

SALIVARY GLANDS AND SALIVA

Number 10

Drug effects on salivary glands: dry mouth

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OBJECTIVE: To identify drugs associated with the complaint of dry mouth.

MATERIALS AND METHODS: MEDLINE was searched for papers 1980–2002 using keywords, oral, mouth, salivary, drugs, dry mouth and xerostomia, and relevant secondary references were hand-searched.

RESULTS: Evidence was forthcoming for a number of xerogenic drugs, especially antimuscarinic agents, some sympathomimetic agents, and agents affecting serotonin and noradrenaline uptake, as well as a miscellany of other drugs such as appetite suppressants, protease inhibitors and cytokines.

CONCLUSION: Dry mouth has a variety of possible causes but drugs – especially those with anticholinergic activity against the M3 muscarinic receptor – are the most common cause of reduced salivation.

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Keywords: oral; drugs; salivary; xerostomia; dry mouth

Introduction

Saliva consists of two components that are secreted by independent mechanisms. First a fluid component which includes ions, produced mainly by parasympathetic stimulation and secondly a protein component released mainly in response to sympathetic stimulation. Salivary gland secretion is mainly under autonomic nervous control, although various hormones may also modulate salivary composition. Secretion appears to be dependent on several modulatory influences which act via either a cyclic AMP or calcium dependent pathway.

The mechanisms and control of salivary secretion have been fully reviewed recently (Turner and Sugiya, 2002). Parasympathetic stimulation produces copious

saliva of low protein concentration while sympathetic stimulation produces little saliva but of high protein concentration and may thus give a sensation of dryness (Carlson, 2000).

Dry mouth

Dry mouth has a variety of possible causes (Table 1). Common habits such as tobacco smoking, alcohol use (including in mouthwashes) and use of beverages containing caffeine (coffee, some soft drinks) can cause some oral dryness. A wide range of drugs can give rise to oral dryness (Di Giovanni, 1990; Sreebny and Schwartz, 1997; Wynn and Meiller, 2001). Indeed, hundreds if not thousands of drugs can be xerogenic: some cause a subjective complaint of dry mouth, many can induce hyposalivation and there appear to be multiple mechanisms whereby drugs can produce xerostomia, but few drugs have been submitted to serious scientific examination. This paper reviews the most commonly reported xerogenic drugs, but comprehensive lists are available in pharmacopoeias and elsewhere (e.g. Madinier *et al*, 1997).

Prevalence of drug-related dry mouth, and at-risk groups

Drugs are the most common cause of reduced salivation (Table 2). A review of the 200 most frequently prescribed drugs (in 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). The drugs most commonly implicated in dry mouth are the tricyclic antidepressants, antipsychotics, atropinics, beta blockers and antihistamines, and therefore the complaint of dry mouth is common particularly in patients treated for hypertensive, psychiatric or urinary problems (Streckfus, 1995).

Dry mouth is a common complaint in the elderly (Vissink *et al*, 1992; Loesche *et al*, 1995) mainly as consequence of the large number of drugs used (Fox, 1998; Narhi, Meurman and Ainamo, 1999) and the high frequency of polypharmacy (Loesche *et al*, 1995; Nederfors, 1996; Fox, 1998). For example, 175

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Table 1 Causes of dry mouth

Iatrogenic
Drugs
Irradiation
Graft vs host disease
Disease
Salivary gland disease
Salivary aplasia (agenesis)
Sjogren's syndrome
Sarcoidosis
Cystic fibrosis
Primary biliary cirrhosis
Infections
HIV
Hepatitis C
Human T lymphotropic virus 1 (HTLV-1)
Dehydration
Psychogenic

Table 2 Drugs associated with dry mouth

Anticholinergic drugs
Tricyclic antidepressants
Muscarinic receptor antagonists for treatment of overactive bladder
Alpha receptor antagonists for treatment of urinary retention
Antipsychotics such as phenothiazines
Diuretics
Antihistamines
Sympathomimetic drugs
Antihypertensive agents
Antidepressants (serotonin agonists, or noradrenaline and/or serotonin re-uptake blockers)
Appetite suppressants
Decongestants and 'cold cures'
Bronchodilators
Skeletal muscle relaxants
Antimigraine agents
Benzodiazepines, hypnotics, opioids and drugs of abuse
H2 antagonists and proton pump inhibitors
Cytotoxic drugs
Retinoids
Anti-HIV drugs such as dideoxyinosine (DDI) and protease inhibitors
Cytokines

home-living elderly patients hospitalized because of sudden worsening of their general health when compared with 252 comparably elderly outpatients, showed that 63% of the hospitalized patients and 57% of the outpatients complained of dry mouth (Pajukoski *et al*, 2001). Dry mouth was more prevalent amongst the hospitalized patients who used several drugs daily. For dry mouth, the strongest explanatory factors were respiratory disease in the outpatients (presumably because of mouth-breathing) and low salivary flow rate in the hospitalized elderly. In all patients however, use of psychiatric drugs was the main cause for dry mouth (Pajukoski *et al*, 2001).

In a larger study, of 1202 individuals, a reduced unstimulated salivary flow (<0.1 ml min⁻¹) and subjective oral dryness were significantly associated with

age, female gender, intake of psychotropics, anti-asthmatics, and diuretics (Bergdahl and Bergdahl, 2000). Subjective oral dryness and reduced unstimulated salivary flow were significantly associated with depression, trait anxiety, perceived stress, state anxiety, female gender, and intake of antihypertensives. Age and medication seemed to play a more important role in individuals with objective evidence of hyposalivation, while female gender and psychological factors were important in individuals with *subjective* oral dryness (Bergdahl and Bergdahl, 2000).

Hypnotics are also commonly used by the elderly. In one study (Wishart, Hodge and Greig, 1981), 53% of respondents had used hypnotics in the previous year, prescription products accounting for 83% (66% benzodiazepines, 11% zopiclone, 4% antidepressants, 2% opioids), while 17% of the products used were over-the-counter (5% herbal, 5% antihistamines, 3% analgesics). Hypnotic use was regular (50% daily) and chronic (mean duration 6 years) and most respondents reported ADRs, mainly dry mouth (30%) (Wishart *et al*, 1981). Prescription drugs used for sleep were perceived to be effective even with long term use, despite mild ADRs such as dry mouth (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, women statistically reporting a higher prevalence of dry mouth than men. Dry mouth was significantly age-related and there was a strong co-morbidity between reported prevalence of dry mouth and on-going pharmacotherapy. Generally, no specific drug or drug-group proved to be especially xerogenic, rather, polypharmacy was strongly correlated to reported symptoms of dry mouth, and there was a significant correlation between increasing dry mouth and the number of medications used (Nederfors, 1996). Unstimulated salivary flow rates were lower amongst older persons who were female or taking antidepressants, and higher amongst smokers or people who were taking hypolipidemic drugs (Thomson *et al*, 2000). Dry mouth severity was higher amongst females, or individuals taking: (1) an anti-anginal, (2) an anti-anginal without a concomitant beta blocker, (3) thyroxine and a diuretic, or (4) antidepressants or anti-asthma 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, Broadley and Beighton, 2001). That is not to say that disease can always be excluded as a cause of dry mouth; for example, saliva secretion is more affected 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.

Finally, the consequences of dry mouth such as caries may be used as a surrogate marker. For example, persons taking three or more prescription medications had a higher Root Caries Index (RCI) than those taking none, one or two drugs, and people who took antidepressants and antiulcer drugs had highest RCI values (Thomson, Slade and Spencer, 1995).

Drugs with actions on salivation

There is usually a fairly close temporal relationship between starting the drug treatment or increasing the dose, and experiencing dry mouth. However, remarkably few studies on drug-related oral dryness have examined salivary flow, much of the data, unfortunately, being based on a subjective complaint of 'dry mouth'.

Mechanisms of action of xerogenic drugs

A number of different mechanisms account for drug-related dry mouth, but an anticholinergic action underlies many. Muscarinic acetylcholine receptors consist of five distinct subtypes. In the periphery, muscarinic acetylcholine receptors mediate cholinergic signals to autonomic organs, but specific physiological functions of each subtype remain poorly elucidated (Matsui *et al.*, 2000). The M3-muscarinic receptors (M3R) mediate parasympathetic cholinergic neurotransmission to salivary (and lacrimal) glands.

Many types of other receptors for endogenous substances in salivary glands exist, suggesting that salivary glands may contain target systems for many drugs. Alpha 1A, beta 1, M3, H2 and some other receptors mediate exocytosis via the cAMP-protein kinase A pathway; NK-1 and M3Rs via another pathway, diacylglycerol and protein kinase C; and gamma amino butyric acid (GABA) and benzodiazepines are involved in decreasing fluid secretion and amylase release elicited by secretagogues (Kawaguchi and Yamagishi, 1995).

Drugs with actions on the cholinergic system

Tricyclic antidepressants

The psychopharmacology of depression is a field that has evolved rapidly in just under five decades. Early antidepressant medications-tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) – enhanced serotonergic or noradrenergic mechanisms or both but unfortunately, TCAs also blocked histaminic,

cholinergic, and alpha1-adrenergic receptor sites, causing ADRs such as dry mouth, weight gain, constipation, drowsiness, and dizziness. Measurement of the inhibitory effect on spontaneous whole mouth and parotid salivation after administration of various antidepressants divides them into (a) isocarboxazide and lithium citrate with minimal salivary effect, (b) zimelidine and nomifensine with slight effect, (c) imipramine oxide and mianserin with moderate effect and (d) maprotiline, nortriptyline, clomipramine, imipramine, and amitriptyline with pronounced effect (Rafaelson *et al.*, 1981). In one study in which stimulated parotid saliva was studied from normal controls and patients on amitriptyline, dothiepin (dosulepine) (TCAs), as well as fluoxetine and paroxetine (selective serotonin re-uptake inhibitors; SSRI), showed TCAs to produce a significant reduction in flow and decrease in [Na⁺] and increase in [K⁺] but the SSRIs produced no such significant changes (Hunter and Wilson, 1995).

Nevertheless, TCAs have been until recently the dominating group used in the treatment of depression. Treatment with a TCA caused more ADRs including dry mouth than did placebo (Hazell *et al.*, 2002) and up to 27% of persons on TCAs have dry mouth (Trindade *et al.*, 1998). Dry mouth, sweating, and increased heart rate constitute a significant and specific enduring burden of imipramine treatment (Mavissakalian, Perel and Guo, 2002).

Men and women may differ in their pharmacokinetic responses to TCAs, in a number of 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.*, 2001) 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 inhibition of cytochrome activity such as with paroxetine could offer a solution (Laine *et al.*, 2001). As discussed below, the newer generation of antidepressants, including the 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 and Overo, 1999; Feighner, 1999).

Muscarinic receptor antagonists used to treat overactive bladder

Normal physiological urine voiding as well as generation of abnormal bladder contractions in diseased states is critically dependent on acetylcholine-induced stimulation of contractile muscarinic receptors on the smooth muscle (detrusor) of the urinary 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 or urinary incontinence (sudden involuntary loss of urine) affects millions of people of all ages and both sexes world wide, with a greater prevalence in women and the elderly. Muscarinic receptor antagonists are currently recommended as first-line therapy for OAB, although a lack of selectivity for bladder receptors may lead to troublesome ADRs, including dry mouth.

Detrusor smooth muscle is endowed principally with M2 and M3 receptors. M2 receptors, via inhibition of adenylyl cyclase, cause smooth muscle contraction indirectly by inhibiting sympathetically (beta-adrenoreceptor)-mediated relaxation. In certain diseased states, M2 receptors may also contribute to direct smooth muscle contraction. From a therapeutic standpoint, combined blockade of M2 and M3 muscarinic receptors would seem to be ideal as this approach would evoke complete inhibition of cholinergically evoked smooth muscle contractions. Antimuscarinic agents such as oxybutynin are the most widely used therapy, but ADRs include constipation, tachycardia and dry mouth. Oxybutynin binds to M3 muscarinic receptors on the detrusor muscle of the bladder, preventing acetylcholinergic activation and relaxing the muscle. Dry mouth is a common side-effect seen with immediate-release (IR) oxybutynin (IR-Oxy) (Hay-Smith *et al*, 2002). A significant lower proportion of patients taking controlled-release oxybutynin have moderate to severe dry mouth or any dry mouth compared with those taking IR oxybutynin (Versi *et al*, 2000).

Extended-release (XR) oxybutynin (Versi *et al*, 2000) uses an osmotic system (OROS) to deliver a controlled amount of oxybutynin chloride into the gastrointestinal tract over a 24-h period when taken once daily. OROS systems are thought to reach the colon, where cytochrome P450-mediated oxidation (oxybutynin's primary metabolic pathway) may be less extensive than in the small intestine. ADRs reported by patients taking XR oxybutynin were dose-related anticholinergic effects, most frequently dry mouth, somnolence, constipation, blurred vision and dizziness (Comer and Goa, 2000). OROS oxybutynin chloride (Oxy-XL), compared with IR-Oxy, showed fewer subjects reporting any ADR, including dry mouth (Gupta and Sathyan, 1999). Saliva output (Gupta and Sathyan, 1999) was significantly higher with Oxy-XL than with IR-Oxy and, accordingly, dry mouth severity was significantly lower with Oxy-XL. The decrease in saliva output and the consequent increase in dry mouth severity correlated with the metabolite R-desethyloxybutynin concentration. Therefore, the reduction in metabolite exposure with Oxy-XL may be a possible explanation for the observed decrease in dry mouth severity with Oxy-XL compared with IR-Oxy. Consequently less dry mouth was observed with Oxy-XL as compared with IR-Oxy (Sathyan, Chancellor and Gupta, 2001). The use of salivary stimulant pastilles does not improve compliance or symptom relief compared with oxybutynin alone (Tincello *et al*, 2000).

Propiverine hydrochloride is a safe and effective antimuscarinic drug used in the treatment of urgency and urge incontinence, as effective as oxybutynin, but with lower severity and incidence of dry mouth (Noguchi *et al*, 1998; Madersbacher *et al*, 1999). Tolterodine is a competitive muscarinic receptor antagonist that shows *in vivo* selectivity for the bladder over the salivary glands compared with oxybutynin. Tolterodine has been generally well tolerated in clinical trials of up to 24-month duration but dry mouth is the most frequent ADR (Jacquetin and Wyndaele, 2001; Layton, Pearce and Shakir, 2001) though few patients (<2%) experience severe dry mouth (Zinner, Mattiasson and Stanton, 2002). Only 3% of patients taking tolterodine discontinued treatment because of dry mouth, compared with 2% of placebo-treated patients (Malone-Lee, Walsh and Maugourd, 2001) and there is a 23% lower incidence of dry mouth reported with once daily XR tolterodine capsules than with twice daily IR tablets ($P < 0.02$) (Clemett and Jarvis, 2001).

Studies directly comparing tolterodine IR with oxybutynin IR have shown similar efficacy but tolterodine IR is significantly better tolerated, particularly with respect to the incidence and severity of dry mouth (Garely and Burrows, 2002). In other studies, dry mouth was reported by 28.1 and 33.2% of participants taking XR oxybutynin and tolterodine, respectively (Appell *et al*, 2001) and fewer patients had dry mouth and withdrew from study because of side effects with tolterodine than oxybutynin (Harvey, Baker and Wells, 2001). Many other newer therapies, including tropsium chloride, can also produce dry mouth (Madersbacher *et al*, 1995) but to verify which antimuscarinic drugs selective for the muscarinic subtypes have the best efficacy and tolerability, comparative clinical trials between M3 selective antagonists and non-selective compounds, such as tolterodine, are required.

Alpha receptor antagonists used to treat overactive bladder

Tamsulosin, a selective alpha 1A-adrenoreceptor antagonist, used in the treatment of urinary outflow obstruction associated with benign prostatic hyperplasia, produced significant improvement in subjective and objective symptoms of urinary outflow obstruction with significantly less dry mouth and dizziness than in patients on terazosin, a less selective alpha antagonist (Lee and Lee, 1997).

Antipsychotics

Long-term drug treatment of schizophrenia with conventional phenothiazine antipsychotics is commonly associated with ADRs including dry mouth. ADRs such as uncomfortable dry mouth, movement disorders, sleep problems and weight gain do not differ between oral and depot forms of fluphenazine enanthate (Moditen) or decanoate (Modecate) (Adams and Eisenbruch, 2000). Newly developed antipsychotic drugs with more potent and selective antagonistic activity against the dopamine D(2) receptor may however, not necessarily

be associated with a lower incidence of ADRs such as dry mouth.

Clozapine is one 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. Clozapine carries a significant risk of serious blood disorders, and patients experience more hypersalivation than those given conventional neuroleptics, but fewer motor side effects and less dry mouth (Wahlbeck, Cheine and Essali, 2000).

Olanzapine is another atypical antipsychotic and appears therapeutically superior to placebo, but with dizziness and dry mouth being more common (Duggan *et al*, 2000). Overall, significantly fewer olanzapine-treated patients (4%) discontinued therapy for an ADR than their clozapine-treated (14%) counterparts (Tollefson *et al*, 2001). Amongst spontaneously reported ADRs however, increased salivation was reported significantly more often amongst clozapine-treated patients, whereas dry mouth was reported more often amongst olanzapine-treated patients (Tollefson *et al*, 2001). Significant correlations have been found for the *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 include quetiapine and risperidone; these may produce dry mouth in 14.5 and 6.9% respectively (Mullen, Jibson and Sweitzer, 2001). ADRs such as dry mouth and dizziness have been shown to be more prevalent in the quetiapine treated group than placebo (Srisurapanont, Disayavanish and Taimkaew, 2000). Tiapride, also an atypical neuroleptic, acts preferentially on D2 and D3 dopaminergic receptors, and is effective against aggressiveness, agitation, delusion and wandering, but with especially less drowsiness, extrapyramidal symptoms, and dry mouth than chlorpromazine (Roger, Gerard and Leger, 1998). Pimiperone dihydrochloride, another atypical neuroleptic, can also produce dry mouth (Potgieter *et al*, 2002).

Donepezil is an acetylcholinesterase inhibitor marketed for treatment of memory loss and behavioural deterioration associated with the acetylcholine deficit of Alzheimer's disease. It is also used for treatment of psychotropic-induced memory loss and constipation. Donepezil reduces dry mouth (Jacobsen and Comas-Diaz, 1999). Lithium may cause dry mouth (Christodoulou, Siafakas and Rinieris, 1977; Chacko *et al*, 1987; Friedlander and Birch, 1990), presumably mainly via its diuretic effect. ADRs are significantly higher in patients on lithium cotherapy with olanzapine and include dry mouth, somnolence, weight gain, increased appetite, tremor, and slurred speech; all greater than those treated with olanzapine alone (Tohen *et al*, 2002).

Diuretics

Diuretic agents and psychotropics were the most commonly used xerostomatic 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). However, analysis of salivary secretions in patients taking furosemide, indicated there were no significant differences in flow rates, total output, total protein, or Na^+ , K^+ , or Cl^- concentrations following drug or placebo, suggesting that the sensation of oral dryness is not solely a function of the quantitative salivary output (Atkinson *et al*, 1989).

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. For example, treatment with clemastine was associated with an excess incidence of dry mouth (6%) (Gwaltney *et al*, 1996). Although ADRs varied from drug to drug, there was some degree of sedation with all old antihistamines and therefore non-sedating antihistamines have been developed, most of which are histamine H1 receptor antagonists. Some of them also have antiserotonin or other actions that oppose allergic inflammation. These antihistamines 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).

Drugs with actions on the sympathetic system

Antihypertensives

The classic centrally acting antihypertensives such as clonidine, guanfacine and alpha-methyl-DOPA (via its active metabolite alpha-methyl-noradrenaline) induce peripheral sympatho-inhibition and a fall in blood pressure as a result of alpha 2-adrenoceptor stimulation in the brain stem. The ganglion blockers and particularly the beta-blockers (beta-adrenoceptor antagonists) may cause dry mouth (Nederfors, 1996) thought to be associated with activation of CNS and salivary gland alpha 2-adrenergic receptors. Centrally acting antihypertensive drugs, or sympatholytics, (reserpine, methyldopa and clonidine) are now little used because of prominent ADRs including dry mouth, sedation, dizziness and oedema.

Treatment with non-selective and beta 1-selective adrenoceptor antagonists compared with placebo showed that salivary composition but not saliva flow rates were affected by the beta-adrenoceptor antagonists, and the most pronounced effects were observed for total protein composition and amylase activity, both being significantly decreased (Nederfors, 1996). In the hypertensive group, however, whole saliva flow rates increased significantly on drug withdrawal and decreased again on re-exposure to metoprolol (Nederfors, 1996).

In the last 15 years it has become possible to produce centrally acting antihypertensives with a selective agonist effect on another class of brainstem receptors in the rostral ventromedulla (RVLM), the imidazoline I₁-receptors. These appear to modulate sympathetic activity and blood pressure without affecting alertness or salivary flow, though they still have some action on alpha 2-receptors. Moxonidine and rilmenidine are examples of this new class. Their ADR profile is better than that of clonidine and alpha-methyl-DOPA, probably because of a weaker affinity for alpha 2-adrenoceptors.

Moxonidine selectively stimulates medullary imidazoline receptors which centrally inhibit sympathetic outflow and potently suppress levels of circulating plasma noradrenaline. Moxonidine is as effective as angiotensin-converting enzyme (ACE) inhibitors (e.g. enalapril and captopril), beta-blockers (e.g., atenolol), calcium-channel blockers (e.g., long-acting nifedipine), and diuretics (e.g. hydrochlorothiazide) in lowering blood pressure. It has superior tolerability, and though dry mouth, symptomatic hypotension, and asthenia are more frequent in moxonidine SR-treated patients than placebo (Dickstein *et al*, 2000), it causes dry mouth or sedation only in a minority (<10%) of patients, significantly less than with the older antihypertensives (Schachter, 1999). Rilmenidine is an imidazoline derivative that appears to lower blood pressure (BP) by interacting with imidazoline I₁ receptors in the brainstem (and kidneys). It is well tolerated, can be taken in combination for greater efficacy, and with low sedation and dry mouth (Reid, 2001). The incidence and severity of ADRs including dry mouth with moxonidine and rilmenidine is lower than for clonidine (van Zwieten, 1999; van Zwieten, 2000).

Angiotensin II converting enzyme inhibitors block this key enzyme in the renin-angiotensin-aldosterone system. However, the ACE enzyme also has a kinase activity. The inhibition of this enzyme may also cause an accumulation of tissue mediators (bradykinin) responsible for a number of ADRs. About 13% of patients on ACE inhibitors complain of dry mouth (Mangrella *et al*, 1998).

Antidepressants (serotonin agonists, or noradrenaline and/or serotonin re-uptake blockers)

Newer antidepressants are essentially serotonin (5-hydroxytryptamine: 5HT) agonists, or block re-uptake of noradrenaline (norepinephrine) and/or serotonin. With the advent of SSRIs as first-line treatments for major depression, there is considerable debate as to whether they are as effective or as potent as the first-generation TCAs or the mixed reuptake inhibitor, venlafaxine, all of which exert considerable effect on noradrenaline reuptake. While often promoted as having significantly less anticholinergic side-effects than the TCAs, dry mouth may still be seen in patients on SSRIs, e.g. fluoxetine, (Ellingrod and Perry, 1994; Shrivastava *et al*, 1994; Hunter and Wilson, 1995; Davis and Faulds, 1996; Boyd, Dwyer and Papas, 1997; Ravindran *et al*,

1997; Trindade *et al*, 1998). However, SSRIs such as paroxetine appear to result in less dry mouth than seen with TCAs (Ravindran *et al*, 1997). Citalopram, the most selective SSRI, a bicyclic phthalane derivative with a chemical structure unrelated to that of other SSRIs and available antidepressants, is well tolerated, with only 15% of patients discontinuing for ADRs. The most common ADRs are nausea, dry mouth, somnolence, insomnia, and increased sweating (Feighner and Overo, 1999).

Venlafaxine is a mixed reuptake inhibitor, inhibiting presynaptic reuptake of serotonin and noradrenaline, but it may produce ADRs including dry mouth, nervous problems (dizziness, somnolence, insomnia) and abnormal ejaculation as well as sweating. Venlafaxine XR capsules have been shown to be effective in short-term treatment of patients with generalized anxiety disorder without major depressive disorder, but common ADRs are nausea, followed by somnolence and 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 reuptake inhibitor of serotonin and noradrenaline, has adverse events (13.8%) which compare favourably with the rates reported for SSRIs, and include nausea, dry mouth, and somnolence (Detke *et al*, 2002). Mianserin, a mainly postsynaptic serotonin 2A agonist, results in minimal ADRs including dry mouth (Dolberg *et al*, 2002). Nefazodone has moderate serotonin selective reuptake blocking properties and direct 5-HT₂ antagonism, which also can enhance 5-HT₁ neurotransmission. The 5-HT₂ antagonist properties may limit serotonin-mediated effects and, as a result, nefazodone may be more anxiolytic than other antidepressants. Nefazodone also moderately inhibits noradrenaline reuptake and blocks alpha 1-adrenergic receptors. Nefazodone as compared with placebo treatment produces dry mouth in 19% vs 13% (Lader, 1996).

Reboxetine, a selective noradrenaline reuptake inhibitor (selective NRI), is as effective as fluoxetine in reducing depressive symptoms but has only a minimal affinity for muscarinic acetylcholine receptors and therefore causes less dry mouth than TCAs, though it produces dry mouth more frequently than placebo (36% vs 16%) (Schatzberg, 2000; Versiani *et al*, 2002). Mirzapine is a noradrenergic and specific serotonergic antidepressant (NaSSA) that acts by antagonizing the adrenergic alpha 2-autoreceptors and alpha 2-heteroreceptors as well as by blocking 5-HT₂ and 5-HT₃ receptors. It enhances, therefore, the release of noradrenaline and 5-HT_{1A}-mediated serotonergic transmission, which may be responsible for a rapid onset of action. Dry mouth, sedation, and increases in appetite and body weight are the most common ADRs (Anttila and Leinonen, 2001).

Bupropion hydrochloride, originally developed as an antidepressant, is a selective re-uptake inhibitor of dopamine and noradrenaline which was found to reduce nicotine withdrawal symptoms and the urge

to smoke, but dry mouth is common (Zwar and Richmond, 2002). A comparison of bupropion sustained release (SR) with the SSRI paroxetine in the treatment of major depression showed headache, insomnia, dry mouth, agitation, dizziness, and nausea in >10% of patients in both groups (Weihs *et al.*, 2000). Dry mouth occurred more frequently with bupropion SR (19%) than with the SSRI sertraline (14%) or placebo (12%), although the differences were not significant (Croft *et al.*, 1999). ADRs experienced with bupropion SR in another study, were not dose-limiting and consisted primarily of dry mouth, insomnia, headache, gastrointestinal upset, tremor, constipation, and dizziness (Roth and Westman, 2001; Semenchuk, Sherman and Davis, 2001). Dry mouth is positively associated with mean bupropion metabolite concentrations, and inversely related to patient weight (Johnston *et al.*, 2001).

Appetite suppressants

A number of appetite suppressants can cause dry mouth. Sibutramine inhibits the uptake of serotonin and noradrenaline, prolonging the sensation of satiety, but may induce dry mouth, headache and fatigue (Richter, 1999; Bray, 2001). Fenfluramine plus phentermine can produce dry mouth in 41% of users (Weintraub *et al.*, 1992). An herbal Ma Huang and Kola nut supplement (containing ephedrine alkaloids/caffeine) used for weight loss can also produce dry mouth (Boozer *et al.*, 2002).

Decongestants and 'cold cures'

Pseudoephedrine is a sympathomimetic drug that acts directly on alpha-adrenergic receptors and may reduce nasal congestion. Cetirizine is the carboxylated metabolite of hydroxyzine, has high specific affinity for histamine H(1) receptors and may reduce congestion. Cetirizine/pseudoephedrine is significantly more effective than intranasal budesonide or placebo at improving nasal obstruction, nasal patency and reducing the volume of nasal secretion, but the most common ADRs are dry mouth, insomnia, headache, somnolence, asthenia and nervousness (Wellington and Jarvis, 2001).

Loratadine plus pseudoephedrine sulphate is superior to placebo in reducing nasal symptoms, rhinorrhoea and nasal stuffiness but dry mouth is reported significantly more often (Kaiser *et al.*, 1998).

Bronchodilators

Antiasthma drugs can be associated with dry mouth, and higher caries experience (Thomson *et al.*, 2002). The most common reported ADR after use of the bronchodilator tiotropium is dry mouth (9.3% vs 1.6% relative to placebo; $P < 0.05$) (Casaburi *et al.*, 2000).

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).

Antimigraine drugs

Rizatriptan, a serotonin agonist used in adolescents for the treatment of migraine, can induce dry mouth in $\leq 5\%$ patients (Winner *et al.*, 2002).

Opioids, benzodiazepines, and drugs of abuse

Opioids are well-recognized causes of dry mouth (Bruera *et al.*, 1999) and atropine, hyoscine and atropinics have long been used to reduce secretions pre-operatively. Females on morphine reported higher ratings of 'coasting (spaced out),' 'heavy or sluggish feeling' and 'dry mouth' (Zacny, 2001). Controlled-release morphine sulphate suppositories are associated with adverse events especially constipation, nausea, anorexia, and dry mouth (Bruera *et al.*, 1999). Tiredness and dry mouth were also reported in 80% after use of dihydrocodeine (Freye, Baranowski and Latasch, 2001). Tramadol, a synthetic, centrally acting analgesic agent with two distinct, synergistic mechanisms of action, acting as both a weak opioid agonist and an inhibitor of monoamine neurotransmitter reuptake, relieves moderate to severe postoperative pain, with similar efficacy to morphine or alfentanil and superior to pentazocine. The most common ADRs (incidence of 1.6–6.1%) are nausea, dizziness, drowsiness, sweating, vomiting and dry mouth (Scott and Perry, 2000). Dry mouth is the only significant side-effect of transdermal scopolamine (hyoscine) (Gordon *et al.*, 2001).

Benzodiazepines, such as diazepam, are used as anxiolytics or hypnotics and may cause slight dry mouth (Conti and Pinder, 1979; Elie and Lamontagne, 1984). Zopiclone, a cyclopyrrolone chemically unrelated to benzodiazepines, is thought to act on a GABA site closely related to, the benzodiazepine-binding site. It is used as an anxiolytic or hypnotic and may produce dry mouth (Wadworth and McTavish, 1993).

Data on any effects on salivation of drugs of abuse are scarce. Cannabis exerts manifold actions including dry mouth (Consroe, Sandyk and Snider, 1986) (Grotenhermen, 1999). Ecstasy, the illegal designer amphetamine-related drug (also known as 'love drug', 'XTC' or 'E': 3,4 methylenedioxy-methamphetamine; MDMA) can produce dry mouth (Peroutka, Newman and Harris, 1988; Milosevic *et al.*, 1999), and both methamphetamine and methadone users appear predisposed to caries (Howe, 1995) (Meaney, 1997). However, despite the sympathomimetic effects of cocaine, there appear to be no data suggesting a relationship between cocaine use and dry mouth.

H2 receptor antagonists and proton-pump inhibitors

The classic triple therapy for eradication of *Helicobacter pylori* is amoxicillin or tetracycline, metronidazole and a bismuth derivative. Addition of an H2-receptor antagonist to these drugs may increase the rate of eradication of *Helicobacter pylori* and shorten the duration, but dry mouth is found in 41% of recipients (Kaviani *et al.*,

2001). Omeprazole may also cause dry mouth (Teare *et al*, 1995).

Cytotoxic drugs

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

Retinoids

Systemic retinoids are well known to cause dryness of the mouth and changes in oral and lip mucosa, as seen with the advent of etretinate (Wishart *et al*, 1981) and 13 cis-retinoic acid (Hennes *et al*, 1984), though there is a paucity of hard data. However, a study to evaluate changes in salivary variables during 3 months treatment with oral isotretinoin showed a significantly lower mean flow rate of stimulated saliva during the period of medication than at baseline (Oikarinen *et al*, 1995).

Anti-HIV drugs

Didanosine (Dodd *et al*, 1992; Valentine, Deenmamode and Sherwood, 1992), and HIV protease inhibitors (Greenwood, Heylen and Zakrzewska, 1998) can cause dry mouth. Protease inhibitor therapy can give rise to oral or peri-oral side effects in a significant proportion of treated patients. Up to 7% may complain of dry mouth (Conant *et al*, 1997; Weir and Wansbrough-Jones, 1997; Porter and Scully, 1998; Cauda *et al*, 1999; Dios and Scully, 2002).

Cytokines

Cytokines such as interferon can have pronounced effects on salivary gland cells *in vitro* (Nagler, 1998) and may be involved in the pathogenesis of salivary disease (Skopouli and Moutsopoulos, 1995). Although for some time now, alpha interferon has been used to treat Sjogren's syndrome (Ferraccioli *et al*, 1996), interferon therapy for the treatment of chronic hepatitis C infection (Cotler *et al*, 2000), can cause significant dry mouth. Interleukin-2 (rIL-2) can also impair salivation when used, for example, for control of nasopharyngeal carcinoma (Chi *et al*, 2001) and major salivary gland dysfunction has been described in patients with haematological malignancies receiving interleukin-2-based immunotherapy postautologous blood stem cell transplantation (Nagler *et al*, 1997). Significant reductions in both the resting and stimulated parotid and submandibular salivary flow rates were observed during IL-2/IFN-alpha immunotherapy, while no hyposalivation was seen in control patients who underwent transplant but did not receive IL-2. Sialochemical evaluation revealed significant increases in potassium and decreases in sodium concentrations in stimulated parotid saliva secreted during IL-2/IFN-

alpha administration, while salivary protein concentrations were unchanged (Nagler *et al*, 1997). Nagler *et al* (2001) also reported significant reductions of resting salivary flow rates, accompanied by significant and multiple compositional alterations in patients with renal cancer after 4 weeks of the combined administration of rIL-2 and recombinant interferon-alpha (rIFN-alpha). This included increases in calcium, magnesium and phosphate concentrations, and reductions in total protein concentration, but no flow rate reduction under stimulated conditions.

Management of drug-induced dry mouth

Apart from avoiding causal drugs, or minimizing exposure to them, attempts have been made to stimulate salivation in patients with drug-induced dry mouth, using salivary stimulants. Yohimbine, an alpha 2-adrenoceptor antagonist, appears more effective than anetholtrithione, in the treatment of dry mouth in patients treated with psychotropic drugs (TCAs or neuroleptics) (Bagheri *et al*, 1997). The use of salivary stimulant pastilles however, appears not to improve compliance or symptom relief when oxybutynin is used (Tincello *et al*, 2000).

Summary

Evidence is available that a number of drugs, especially antimuscarinic agents, some sympathomimetic agents, and agents affecting serotonin and noradrenaline uptake, as well as a miscellany of other drugs such as protease inhibitors and appetite suppressants, may produce subjective dry mouth. Drugs with anticholinergic activity against the M3 muscarinic receptor are the most common reported cause of reduced salivation and efforts are in hand to reduce this activity in newer drugs. Unfortunately, little hard data about the effects of many supposed xerostomia-inducing drugs on salivation are available.

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