



## Adverse drug events in the oral cavity

Anna Yuan, DMD,<sup>a,b</sup> and Sook-Bin Woo, DMD, MMSc<sup>a,b</sup>

Adverse reactions to medications are common and may have a variety of clinical presentations in the oral cavity. Targeted therapies and the new biologic agents have revolutionized the treatment of cancers, autoimmune diseases, and inflammatory and rheumatologic diseases but have also been associated with adverse events in the oral cavity. Some examples include osteonecrosis, seen with not only bisphosphonates but also antiangiogenic agents, and the distinctive ulcers caused by mammalian target of rapamycin inhibitors. As newer therapeutic agents are approved, it is likely that more adverse drug events will be encountered. This review describes the most common clinical presentations of oral mucosal reactions to medications, namely, xerostomia, lichenoid reactions, ulcers, bullous disorders, pigmentation, fibrovascular hyperplasia, white lesions, dysesthesia, osteonecrosis, infection, angioedema, and malignancy. Oral health care providers should be familiar with such events, as they will encounter them in their practice. (Oral Surg Oral Med Oral Pathol Oral Radiol 2015;119:35-47)

A multitude of medications that patients take to control disease also exposes them to the risk for developing reactions to the medications. One definition put forward by Edwards and Aronson in 2000 for “adverse drug reaction” is “an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product.”<sup>1</sup> This definition attempts to address several important issues related to “appreciable harm and unpleasantness” and excludes minor reactions, addresses the issue of medication error, addresses injury from nonpharmaceutical agents (including contaminants and inactive ingredients), and does not assign disease mechanism. The authors make a distinction between an adverse *effect* (adverse outcome attributed to an action of the drug) and an adverse *event* (adverse outcome that occurs when a patient is on the drug but that may not be caused by the drug).<sup>1</sup>

The term used currently that satisfies both regulatory bodies as well as patient safety advocates is “adverse drug event” which includes (1) harm caused by a drug (commonly known as adverse drug reaction), (2) harm caused by appropriate drug use (usually referred to as a *side effect*), and (3) medication errors.<sup>2</sup> This review will focus on common adverse drug events (ADEs), as defined by Nebeker et al.<sup>2</sup> from a clinical perspective. Most fall under the category of side effects, although

whether the patients were significantly harmed by the event is probably subject to interpretation. Although the term “medication” is preferred over “drug,” we are using the term ADE because it is the convention.

Diagnosis is based on history and chronology of the adverse oral reaction. Typically, these changes are detected within weeks or months after taking the medications. Some lesions, such as lichenoid drug reactions, may present asymptotically initially but become symptomatic years later, making the relationship between start of drug use and development of ADE difficult to ascertain. The presence of the oral condition predating the administration of the medication must be excluded, and this may be difficult to determine if the patient has not seen a health care provider in a long time. Resolution should occur after discontinuation of the suspected medication, although this may necessitate the use of topical corticosteroids for inflammatory conditions. Recurrence with rechallenge confirms the diagnosis, although this may not be feasible if the ADEs are unpleasant, severe, or life-threatening. Concurrent medications must be noted.

The benefits of using any particular medication must, of course, always be weighed against the side effects, and some considerations include the necessity for the medication and availability of substitute agents, how severe the side effects are (e.g., asymptomatic oral pigmentation vs highly morbid necrolytic syndromes),

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<sup>a</sup>Division of Oral Medicine, Brigham & Women’s Hospital, Boston, Massachusetts.

<sup>b</sup>Department of Oral Medicine, Infection and Immunity, Harvard School of Dental Medicine, Boston, Massachusetts.

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### Statement of Clinical Relevance

Adverse drug events in the oral cavity are common and will likely increase as newer therapeutic agents are approved. Health care providers should familiarize themselves with such events. This review describes common and uncommon oral mucosal reactions to medications.

**Table I.** Drug-induced oral reactions

|                                  |
|----------------------------------|
| Hyposalivation/xerostomia        |
| Lichenoid reaction/lichen planus |
| Aphthous-like ulcers             |
| Bullous disorders                |
| Pigmentation                     |
| Fibrovascular hyperplasia        |
| Keratosis/epithelial hyperplasia |
| Dysesthesia                      |
| Osteonecrosis of the jaws        |
| Infection                        |
| Angioedema                       |
| Malignancy                       |

the frequency of occurrence of such ADEs, whether the ADE can be eliminated by lowering the dose, and whether the ADE may be easily treated.<sup>1,2</sup>

Drug-induced cutaneous reactions are common and varied in presentation, but only a limited number of reaction patterns occur in the oral cavity. This is likely due to the higher turnover rate in the oral mucosa compared with that on the skin, and this does not allow easy detection of the spectrum of subtle clinical changes on the skin. The oral lesions to be discussed fall into several categories (Table I).

### HYPOSALIVATION/XEROSTOMIA

Medication use is one of the most common causes of both xerostomia and hyposalivation. Many middle-aged and older patients in the United States are on multiple medications (“polypharmacy”), and even medications with small anticholinergic effects may act synergistically in combination to cause oral symptoms of dryness and discomfort (Figure 1). Dry mouth is listed as an adverse effect for over 500 medications.<sup>3</sup> In a systematic review, xerostomia was reported to be one of the most common oral adverse effects associated with over 80% of the 100 most prescribed medications in the United States.<sup>4</sup> The most frequently reported medication classes that result in hyposalivation are antidepressants, antipsychotics, antihistamines, muscarinic receptor and  $\alpha$ -receptor antagonists, antihypertensives (e.g., diuretics,  $\beta$ -blockers, and angiotensin-converting enzyme [ACE] inhibitors), bronchodilators, and skeletal muscle relaxants.<sup>3,5</sup> Other culprits include chemotherapy agents, appetite suppressants, decongestants, antimigraine drugs, opioids, benzodiazepines, hypnotics, histamine 2 (H2) receptor antagonists and proton pump inhibitors, systemic retinoids, anti-human immunodeficiency virus medications, and cytokine therapy.<sup>3,5</sup>

A study of 601 patients reported that older individuals were almost three times more likely to report xerostomia, and patients taking one or more drugs were

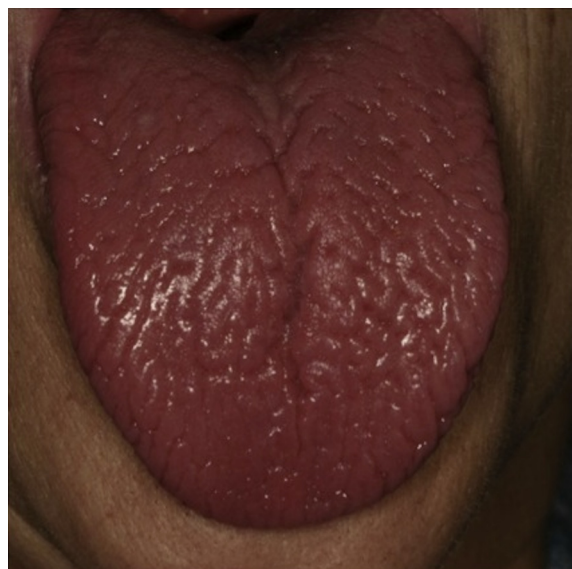


Fig. 1. Hyposalivation from polypharmacy.

more than twice as likely to do so compared with medication-free patients; this prevalence increased with increasing number of medications used (16.7% of patients reported xerostomia with one medication daily vs 33.3% with two to three medications daily vs 36.9% at greater than three medications daily).<sup>6</sup> Persistent hyposalivation can lead to infections, such as candidiasis and dental caries, as well as bacterial sialadenitis.<sup>7</sup> The loss of lubrication also results in erythema and susceptibility of the mucosa to frictional trauma against teeth; discomfort and burning may be profound.

### LICHENOID REACTION/LICHEN PLANUS

One of the most common inflammatory conditions affecting the skin and oral mucosa is lichen planus (LP). LP is an immune-mediated process, where T cells mediate the destruction of the basal cells of the epithelium.<sup>8</sup> Oral LP presents as white striations or papules often associated with erythema or erosion and ulcers, most commonly in a bilaterally symmetric manner, often on the buccal mucosa, tongue, and gingiva.<sup>9</sup> Many medications are known to cause cutaneous lichenoid hypersensitivity reactions (LHRs), which are often difficult to distinguish clinically and histopathologically from idiopathic cutaneous LP.<sup>10,11</sup> Cutaneous LHRs present as skin eruptions characterized by purplish, pruritic keratotic papules and plaques, usually without the classic Wickham striae, on the trunk and extremities instead of the flexural regions.<sup>11-13</sup> It has been postulated that active thiol groups found in the chemical structure of such medications as piroxicam, sulfasalazine, and glipizide play a role in inciting such reactions.<sup>14,15</sup> It is, therefore, likely that these same

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