WHITE PAPER: Need for modifying drug labels to mitigate risk of preventable complications by clarifying oral/dental considerations related to use of certain pharmaceuticals

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ABSTRACT

Purpose: The white paper proposes clarifying the oral/dental considerations related to use of certain medications through the modification of drug labeling materials for relevant pharmaceuticals, inserting brief clauses clarifying that dental caries and periodontal diseases are infections.

Summary: The use of many prescription and over-the-counter medications among individuals with dental infections poses an increased risk of medical complications. Drug labels for these medications indicate the need for cautionary use in the presence of active infection. Such infections include oral infections (e.g., dental caries and periodontal diseases). However, it is a significant problem that most of these drug labels do not specifically mention that dental diseases are bacterial infections. Without such clarification, dental status is seldom considered by prescribing medical professionals, pharmacists, or patients. Many drugs are therefore prescribed for and taken by people whose dental condition can more easily spawn serious complications, avoidable injury, incapacitation, or even potential lethal septicemias. Further, labels for such drugs generally advise about the potential for xerostomia, a side effect of many pharmaceuticals, but do not additionally clarify the potential adverse dental implications of that condition. Consequently, measures to help prevent such complications are therefore not considered or taken.

Conclusion: This white paper advocates for greater patient and health professional understanding of the oral/dental considerations in overall healthcare delivery as a means to reduce unintended patient harm and improve patient well-being. This paper

highlights how the simple addition of current best evidence in medication labeling and instructions for use will lead to improved health outcomes.

A. INTRODUCTION/BACKGROUND

Poor oral health is one of the major health problems facing the nation, especially among the most vulnerable people.[1] Many suffer from oral diseases including periodontal (gum) disease, dental caries (tooth decay), and other serious oral health problems. About 85% of adults aged 18 and older are affected by dental caries in their lifetime.[2] Millions of patients make emergency room visits due to oral health problems, mostly dental caries and abscesses.[i]

Many systemic diseases and conditions affect oral health, and the general health of a patient can often be reflected by examining the oral environment. There has been heightened interest in the literature on the association between oral infection and inflammation along with other chronic systemic diseases. Periodontal diseases have been linked to conditions such as cardiovascular disease,[3,4] diabetes mellitus,[5,6] adverse pregnancy outcomes (e.g., pre-term and low birth weight babies),[7] osteoporosis,[4] HIV/AIDS,[8] and Sjogren's syndrome, among others.[9,10] Some systemic diseases may affect the oral environment and result in complications and symptoms such as xerostomia, a burning sensation in the mouth, candidiasis, periodontitis, bleeding or swollen gums and ulcers.[1,11,12]

Further, oral diseases and conditions have pathogens that also affect many systemic diseases and conditions.[13] Periodontitis has been associated with bacteremia and pathogenesis of diseases in distant sites within the body. An infection in the mouth or tooth can access the blood stream and travel anywhere in the body. Periodontitis is a modifiable risk factor for many systemic diseases and conditions.[14] Dental professionals play an important role in the prevention of many systemic conditions and their

complications through treating and preventing dental problems. Periodontal treatment and maintaining good oral health reduces morbidity and mortality due to respiratory and other diseases.

Impact of Pharmaceuticals

1) Risk of drug facilitated systemic complications from oral infections.

The use of many prescriptions and over the counter medications - including cytotoxic, immuno-suppressant, some psychotropic, and bisphosphonate pharmaceuticals - among individuals with dental infections poses an increased risk of medical complications. “Life threatening infections may follow if maintenance of oral health is neglected during anticancer therapy and if potential oral infection foci are left untreated before immunosuppressive therapy.”[15] Drug-induced immunosuppression predisposes many patients with serious and progressive bacterial dental infections to increased risk for bacteremia and potentially the more severe condition, septicemia.

The oral cavity is an important and significant source of septicemia,[15] one of the top causes of death in the United States affecting about one in three intensive care unit patients.[16,17] One study found that 35% of septicemia of Leukemia patients were traceable to the oral cavity.[18] Neglecting to treat oral infections before immunosuppressive therapy may result in life threatening infections.[15]

2) Risk of dental complications

Many treatments (radiation of head and neck) and medications that are commonly used in treating systemic diseases and conditions can directly or indirectly affect patients' oral health.[1] Many prescription medications have adverse effects on the mouth and associated structures even when used appropriately. Certain medications affect the oral environment through altering plaque composition and adherence, intraoral pH, and salivary flow. The oral mucosa, attached gingiva, and underlying alveolar bone also experience biologic structural and response changes.[19] Xerostomia, dysgeusia, and stomatitis are common side effects of medications.[19,20] The prevalence of drug-induced xerostomia is estimated at about 25 million Americans.[12] "Over 400 medications list dry mouth as a side effect, notably some antidepressants, antipsychotics, antihistamines, decongestants, antihypertensives, diuretics and antiparkinson drugs."[21] Xerostomia is associated with decreased salivary flow rates which are associated with increased incidence of dental caries,[22] and fungal infections.[12] Some prescription drugs can also lead to gingival overgrowth and inflammation.[1]

Function of drug labels to mitigate risks

The appropriate and safe use of medications as they pertain to oral health may depend on the quality, completeness, and clarity of medication information that healthcare professionals and patients receive. This information can be effectively communicated through drug labeling (e.g., label, the wrapping, the package insert and medication guides). Many patients rely on the information on drug labels for directions for safe and appropriate use of medications as some do not receive adequate or any

information from their healthcare providers.[23,24] Drug labeling shortcomings such as non-existent warnings and missing information significantly contribute towards inappropriate and unsafe use of prescription medications. Informed consent, compliance, better health outcomes, and patient safety may be facilitated and enhanced through modifying drug labeling[25] to minimize the difficulty of finding and comprehending information contained on the drug labels.

Problem definition

Currently, drug labels for prescription medications that can facilitate systemic complications from bacterial oral lesions do not clarify that risk, nor do labels for drugs with a xerostomic effect note the risk of that condition potentiating the development and progression of dental diseases. Drug labels of many medications with possible oral health side effects and repercussions indicate the need for cautionary use in the presence of active infection. For example, the medication guide for Infliximab states, “think you have an infection. You should not start taking Infliximab if you have any kind of infection.”[26] However, these labels do not explicitly state that dental caries and periodontal diseases are bacterial infections. Given that most people often do not consider such pathological conditions as infections, dental status is seldom considered by prescribing medical professionals, pharmacists, or patients, and the reference to cautionary use “if you have any kind of infection” goes unheeded.

For example, physicians prescribing immunosuppressive and cytotoxic pharmaceuticals infrequently inquire about a patient’s dental status, seldom request dental clearance before initiating drug therapies, and rarely advise patients about the

importance of maintaining dental health while taking the medication(s) (Wonha Kim, MD, MPH, Loma Linda University Health, 10 September 2015). Without clarification that caries and periodontal diseases are bacterial infections, many drugs are prescribed for and taken by people whose dental condition can more easily spawn serious and potentially lethal septicemias. Consequently, patients can experience avoidable injury or incapacitation. ***Lack of references that dental decay and periodontal diseases are bacterial infections in drug labeling materials is a significant problem.***

Furthermore, individuals taking drugs with a potential xerostomic effect are at increased risk of preventable dental problems without the additional advice that such a condition can contribute to the development and progression of dental diseases. Drug labels for such pharmaceuticals clarify the potential for “dry mouth,” but not the related dental implications and guidance for preventing such complications. While xerostomia may be referenced in the drug labels, the importance of maintaining dental health is not.

The absence of references to relevant oral/dental considerations in drug labeling materials for many medications persist in part due to a lack of integration between dental and medical disciplines and providers. The dental discipline is largely separated from other disciplines and the health care system[1] and many medical personnel have limited awareness and knowledge about the integral relationship of oral health to the treatment and management of many diseases and vice versa. There is limited inter-disciplinary collaboration in the provision of general and oral health care and services. In addition, many patients do not always inform their dentists about their medical conditions.[27]

Proposed Solution

We propose **d*rug labels for all pharmaceuticals with significant known and potential adverse oral / dental considerations should be modified to clarify the oral / dental relationships relevant to the use of these drugs.*** This involves the appropriate insertion of brief clauses clarifying that infections include oral infections. For example, instead of just saying “infection,” the label should be expanded to clarify that infections include dental caries and gum diseases (see Appendix 1 for Infliximab medication guide). This change to the warnings on the label can be achieved through one or both of the following:

a) Drug manufacturers voluntarily making this change for their products, where applicable, without shouldering undue burden. The relevant drug manufacturers can work together with the Food and Drug Administration (FDA) to revise the labels. Each manufacturer has a stake in safe and appropriate use of their products.

b) Federal regulatory agencies could mandate that drug labels include caution about oral side effects and/or clarification about how infections include dental caries and periodontal disease where appropriate.

This simple and yet profound change is not completely new or without precedence. Currently, bisphosphonates represent the only category of pharmaceuticals that focus appropriate attention on dental status. The drug label for Ibandronate (Boniva®), for example, has a specific section on “osteonecrosis of the jaw” with the following statement: “A routine oral examination should be performed by

the prescriber prior to initiation of bisphosphonate treatment. Consider a dental examination with appropriate preventive dentistry prior to treatment with bisphosphonates in patients with a history of concomitant risk factors (e.g., cancer, chemotherapy, radiotherapy, corticosteroids, poor oral hygiene, pre-existing dental disease or infection, anemia, coagulopathy)."[28]

The suggested change has a higher chance of making a meaningful effect on safer and appropriate use of medications if it is complemented by the following actions and measures:

a) Increasing awareness for the general public about the integral relationship of oral health and overall health.
b) Updating the curriculum for health professionals (e.g. medical schools, nursing schools, pharmacy schools, etc.) to increase education about the relationship between oral health and overall health.

Benefits

Increased awareness about the integral interrelationship between oral health and overall health could have a significant impact on the wellbeing of the public and on health professionals. **The proposed modification of drug labeling for all appropriate pharmaceuticals will help to safeguard individuals from the risk of systemic complications seeded by dental infections and, further, reduce the risk of adverse oral / dental side effects from certain drugs, including that which can result from pharmaceutically-induced xerostomia**. Additional meaningful outcomes would include:

i) Improving the appropriate prescribing of medications by clarifying directions for use and the patients' and health care providers' understanding of the oral health implications of certain medicines and diseases.

ii) Increasing medical, dental providers', policy makers', and patients' awareness about the close association between oral and overall health, allowing patients to make better decisions about using or not using a particular drug.

Conclusion

The white paper proposes corrective actions with respect to modifying drug labels by clarifying the oral/dental considerations related to the use of certain pharmaceuticals. In a broader sense, the white paper highlights the need for substantive progress for evolving a truly integrated health care system, calling for the modification of medical and dental standards of care in the management and prevention of many chronic diseases and a close collaboration among all health care providers. In that way, a specific and narrowly-targeted intervention can thus improve the medical care of thousands of patients while establishing a model for the benefits of broader interdisciplinary collaboration.

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[i] That underscores the difficulty many Americans have trying to access dental services. Dental benefits are not provided by Medicare. States (including Washington DC) are not required to cover dental services for adult Medicaid beneficiaries, and as of January 2015, 4 had no benefits, 13 provided only emergency dental coverage, 22 offered a mix of limited benefits, while only 12 had reasonably comprehensive benefits. Consequently, many needy Medicare and Medicaid beneficiaries—people who are at particularly high risk for developing poor oral health—cannot access medically-essential and expensive dental care.