Use Authorization

In presenting this thesis in partial fulfillment of the requirements for an advanced degree at Idaho State University, I agree that the Library shall make it freely available for inspection. I further state that permission to download and/or print my thesis for scholarly purposes may be granted by the Dean of the Graduate School, Dean of my academic division, or by the University Librarian. It is understood that any copying or publication of this thesis for financial gain shall not be allowed without my written permission.

Signature _____

Date _____

California dental hygienists' knowledge, attitudes and practices regarding polypharmacy and off-label drugs

by

Kristen M. Stephens

A thesis

submitted in partial fulfillment

of the requirements for the degree of

Master of Science in Dental Hygiene

Idaho State University

Spring 2017

Copyright (2017) Kristen Stephens

Committee Approval

To the Graduate Faculty:

The members of the committee appointed to examine the thesis of KRISTEN STEPHENS find it satisfactory and recommend that it be accepted.

_____

Tara Johnson, RDH, PhD
Major Advisor

_____

JoAnn Gurenlian, RDH, MS, PhD
Committee Member

_____

Chris Owens, PharmD, MPH
Graduate Faculty Representative

Human Subjects Committee Approval

Idaho State UNIVERSITY

Kristen Stephens <stepkri2@isu.edu>

IRB-FY2016-379 - Initial: Letter of Approval (exempt)

baerralp@isu.edu <baerralp@isu.edu> Wed, Sep 14, 2016 at 2:17 PM
To: stepkri2@isu.edu

September 14, 2016

Kristen Stephens
Dental Hygiene
MS 8048

RE: regarding study number IRB-FY2016-379: CALIFORNIA DENTAL HYGIENISTS' KNOWLEDGE, ATTITUDES AND PRACTICES REGARDING POLYPHARMACY AND OFF-LABEL MEDICATIONS

Ms. Stephens:

I agree that this study qualifies as exempt from review under the following guideline: Category 2: Anonymous educational tests, surveys, interviews, or observations. This letter is your approval, please, keep this document in a safe place.

Notify the HSC of any adverse events. Serious, unexpected adverse events must be reported in writing within 10 business days.

You are granted permission to conduct your study effective immediately. The study is not subject to renewal.

Please note that any changes to the study as approved must be promptly reported and approved. Some changes may be approved by expedited review; others require full board review. Contact Tom Bailey (208-282-2179; fax 208-282-4723; email: humsubj@isu.edu) if you have any questions or require further information.

Sincerely,

Ralph Baergen, PhD, MPH, CIP
Human Subjects Chair

Acknowledgements

I would like to acknowledge my thesis committee for guiding me through this process. This thesis would not have been possible without their invaluable knowledge and expertise.

I would like to thank my family who have supported my education every step of the way. I am lucky to have their undying support and encouragement. I would also like to thank my nieces for the encouragement to set a good example as a Tia, showing them the value of hard work and determination.

Table of Contents

List of Tables

List of Appendices

Abstract

Due to increasing numbers of patients and healthcare professionals utilizing polypharamcy and off-label drugs, it is imperative that dental hygienists are able to recognize and evaluate these situations for comprehensive patient assessment and education. The purposes of this cross-sectional study were to examine knowledge, attitudes, and practices of dental hygienists in California regarding polypharmacy and the use of off-label drugs and to compare those to levels of education, years of experience and types of licensure. Dental hygienists from two local dental hygiene associations in Southern California were surveyed using the online survey tool Qualtrics. Results showed no significant differences in knowledge or practices regarding off-label drugs based on participants' type of licensure, dental hygiene degree, highest degree earned, or years of experience. Attitudes regarding polypharmacy differed significantly based on highest degree achieved. Findings indicate a general lack of knowledge among all participants regardless of educational level, licensure or experience.

Chapter 1: Introduction

Background

According to the Centers for Disease Control and Prevention (2015), the average life expectancy is 78.8 years. While advances in the medical field have allowed for individuals to live longer, an increase in patient age is also connected to coexisting chronic conditions requiring multifaceted individualized patient care. Pharmacological treatment of patients with multiple chronic conditions often consists of polypharmacy, the prescribing of multiple medications (Köberlein et al., 2013).

Kantor, Rehm, Haas, Chan, and Giovannucci (2015) examined nationally representative data from the National Health and Nutrition Examination Survey (NHANES) to analyze the use of prescription drugs from 1999-2000 to 2011-2012. Using a collective sample size of 37,959 individuals, they found that prescription drug use in the U.S. increased from 51% in 1999-2000 to 59% in 2011-2012 and polypharmacy rose from 8.2% to 15%. In fact, Kantor et al. found in the past 30 days, an increase in polypharmacy of 24%-39% in adults aged 65 years and older, 10%-15% in adults aged 40-64, and 0.7%-3.1% in adults aged 20-39 years. An increase in the prevalence of polypharmacy resulting from the increase in comorbidities in the population might be a direct reflection of the practice of evidence based-medicine (EBM) to effectively treat the underlying medical conditions. Evidence-based medicine focuses clinical judgments based on individualized clinical practices, patient values, physiological reasoning and contextual considerations (Ghinea, Lipworth, & Kerridge, 2015). These authors indicated evidence-based decision-making, along with freedom from standardized practice and the use of epidemiological evidence, has led to an

increase in the number of prescriptions written by physicians for drugs utilized for off-label treatment. One study conducted by Radley, Finkelstein and Stafford (2006) found that out of a sample of 725 million drug mentions in 2001, 21% were for off-label use. Additionally, off-label prescribing can be more common in certain populations. For example, a study by Bazzano, Mangione-Smith, Schonlau, Suttrorp, and Brook (2009) showed that 62% of outpatient pediatric visits resulted in the prescription of off-label drugs. While off-label drug use is common worldwide, only 30% of these off-label drug therapies are supported by adequate scientific evidence (Field, 2008). Polypharmacy in combination with the use of off-label drug therapy might affect patient care in multiple facets of medical and dental care alike.

From 1997-2006, under the Food and Drug Administration Modernization Act (FDA, 2009), Congress approved off-label drug promotion allowing pharmaceutical companies to disseminate scientifically valid information related to off-label drug use. In 2009, the FDA (2014b) released provisions under which pharmaceutical companies may distribute journal articles illustrating off-label drug use. While some limitations exist to control the promotion of off-label drugs, it is not illegal to prescribe or use drugs off label.

Due to the increase in off-label drug use, it is highly likely for dental hygienists to come into contact with patients using drugs off-label or to recommend drugs for off-label purposes themselves. Research has shown that cardiac medications, anticonvulsants, and antiasthmatics were among the most commonly prescribed drugs for off-label therapies (Radley, Finkelstrein, & Stafford, 2006). These classes of medications are often reported on the dental patient's health history, requiring a knowledgeable dental hygienist to

properly assess their implications for patient care and appointment modifications. Additionally, due to practical and ethical considerations restricting the ability for clinical drug trials in vulnerable populations, children, elderly individuals, and pregnant women are commonly among those that receive prescriptions for drugs off-label (Ekins-Daukes, Helms, Taylor, & McLay, 2005; Morais-Almeida & Cabral, 2014; Wittich, Burkle, & Lanier, 2012). Drugs may be considered off-label with respect to indications for use, dosage, duration of treatment, and/or age of the recipient.

While scientific evidence shows clinical safety and efficacy for off-label use of certain medications, caution should be taken when assessing the patient's medical history or selecting drugs for patient care, as dental implications or contraindications might be unknown. In light of such a high prevalence of off-label drug use researchers have explored the informed consent and documentation practices among physicians that employ the use of drugs for off-label purposes. Studies assessing the incidence of physicians informing the patients/caregivers that the uses of certain drugs are off-label were low and documentation of reasons for such off-label indications was rare (Culshaw, Kendall, & Wilcock, 2013; To et al., 2013). Ultimately, undocumented side effects or lack of efficacy might arise, making it critical for dental hygienists to be knowledgeable, alert, and attentive to provide the most comprehensive patient care possible.

Statement of the Problem

Off-label prescribing of medications gives freedom to healthcare practitioners to utilize therapeutic options based on the latest evidence. Due to the increasing number of patients and professionals utilizing polypharamcy and drugs off-label, it is imperative that dental hygienists are able to recognize and evaluate these situations for comprehensive

patient assessment and education. To date, there have been insufficient studies published concerning the knowledge, attitudes and practices of dental hygienists regarding polypharmacy and off-label drug recognition and use.

Purpose of the Study

The purpose of this study was to examine the knowledge, attitudes, and practices of dental hygienists in California regarding polypharmacy and drugs used for off-label purposes both in medicine and dentistry.

Professional Significance of the Study

This study addressed the U.S. Department of Health and Human Services (USDHHS, 2015) Healthy People 2020 initiative specifically related to the goal of ensuring the safe use of medical products. Objectives MPS-4 and MPS-5 for this health initiative included increasing the number of safe and effective drugs and reducing the numbers of drug related medical emergencies (USDHHS, 2015). Additionally, this study supports the National Dental Hygiene Research Agenda created by the American Dental Hygienists' Association (ADHA, 2016) by examining the dental hygienist's role in oral health care, specifically as it relates to patient assessment and safety related to polypharmacy and off-label drug use.

Clinical decision-making can be affected by adverse effects of medications both systemically and orally, drug-drug interactions, and informed consent of treatment and treatment modalities. For example, certain cardiac medications are known to cause orthostatic hypotension, a condition caused from a drop in blood pressure while reclining resulting in dizziness or fainting that can occur when sitting or standing up without enough time for blood pressure to return to normal. Also, patients taking medications

that can cause hypertension require that vital signs be monitored closely during dental treatment and caution should be taken when employing the use of vasoconstrictors. Furthermore, fluoride varnish, FDA indicated for the treatment of dentinal hypersensitivity, is used as an anti-caries treatment in the dental office. When products are used in the dental office for off-label indications, one might question the ethics behind not informing the patient that the FDA does not approve this use. These factors might become evident during the initial assessment of the medical history upon review of the medications and during the initial oral examination. Knowledge of the potential treatment modifications necessary when off-label use presents itself might make clinical decision-making more efficient and successful.

Dental hygienists need to be aware of the off-label use of medication for a variety of reasons in order to provide comprehensive care for their patients. Dental hygienists treat numerous patients with complex medical histories taking greater numbers of both prescription and OTC medications. Assessment of patients' health and well-being is a critical component of medical emergency prevention in the dental office as well as best practice as a standard of care. Additionally, providers use drugs off-label during dental therapies. Uncovering the level of knowledge, attitudes and practices of dental hygienists regarding drugs used off-label might establish an unmet need for continuing education or dental journal publications in this area for the provision of safe, thorough oral healthcare services for patients.

Research Questions

1. What are dental hygienists' knowledge levels, attitudes, and practices related to patients' use of off-label drugs and polypharmacy?

2. What are dental hygienists' practices related to the use of off-label drugs in the provision of dental hygiene care?
3. What are the differences in dental hygienists' knowledge, attitudes and practices related to off-label drugs and polypharmacy based on their level of education, years of practice and type of licensure?

Hypotheses.

There is no statistically significant difference between dental hygienists' knowledge, attitudes and practices related to off-label drugs and polypharmacy based on their level of education, years of practice and type of licensure.

Definitions

The following terms are provided with definitions to aid the reader in understanding the key terms of this study.

Polypharmacy: Refers to the "prescribing of many drugs (appropriately)" (Patterson et al., 2014, p. 6). In this study, the term polypharmacy refers to the use of five or more medications by patients seen in the dental office either prescribed by the patient's dentist or physician.

Off-label Drug Use: The use of over the counter and prescription drugs for therapies not stated on the label approved by the U.S. Food and Drug Administration (Dresser & Frader, 2009). In this study, the term off-label drug use describes drugs used in medicine and dentistry for indications not specified on their FDA approved labels that could potentially affect dental patient management.

Dental Hygienist: "The dental hygienist is a primary care oral health professional who has graduated from an accredited dental hygiene program in an institution of higher

education, licensed in dental hygiene to provide education, assessment, research, administrative, diagnostic, preventive and therapeutic services that support overall health through the promotion of optimal oral health." (ADHA, 2014, p. 4). For the purpose of this study, dental hygienists refers to registered dental hygienists practicing in the state of California.

Knowledge: "The understanding of any given topic" (Marías, Glasauer, & Macias, 2014, p. 8). In this study, knowledge refers to the ability of oral health professionals to recognize when drugs are used for off-label purposes and their awareness of their own use of drugs for off-label therapy as measured by a self-designed and validated questionnaire.

Attitudes: "Attitudes are emotional, motivational, perceptive and cognitive beliefs that positively or negatively influence the behavior or practice of an individual" (Marías et al., 2014, p. 10). In this study, attitudes refers to the response of the oral health professional in regards to the patient's use of off-label drugs and the drugs they use in the office off-label.

Practices: "Practices mean the application of rules and knowledge that leads to action" (Lakhan, & Sharma, 2010, p. 102). In this study, practice refers to the oral health professionals' prescribing and use of drugs for off-label therapy in the dental office as well as the assessment of the patient's use of drugs off-label as measured by a self-designed and validated questionnaire.

Prescribe: "Prescribing tasks, which involve pharmacological knowledge, clinical decision-making and practical skill, take place within unpredictable social environments and involve interactions within and between endlessly changing health care

teams" (McLellan et al., 2015, p. 1339). In this study, prescribe refers to the recommendation of drugs for the treatment of various medical/dental conditions as measured by a self-designed and validated survey.

Licensure: "In accordance with state law, licensed individuals are the only persons who meet the minimum qualifications necessary to practice their profession" (ADHA, 2015, para 1). In this study, licensure refers to the type of dental hygiene license possessed by the participants including registered dental hygienist, registered dental hygienist in alternative practice, and registered dental hygienist in extended functions.

Level of Education: "In the United States, higher education is considered to be voluntary studies beyond the high school level" (Learn.org, 2016, para 1). In this study, the variable level of education includes associate degree, baccalaureate degree, masters degree, and doctoral degree.

Years of Practice: "Dental hygienists can apply their professional knowledge and skills in a variety of public and private work settings as clinicians, educators, researchers, administrators, managers, health advocates, and consultants. Clinical dental hygienists may be employed in a variety of healthcare settings including private dental offices, schools, public health clinics, hospitals, managed care organizations, correctional institutions, or nursing homes" (ADHA, 2014, p. 5). In this study, years of practice refers to the number of years the study participants have been licensed as a dental hygienist.

Summary

Although medical advances have contributed to an increase in life expectancy often accompanied by polypharmacy and off-label drug therapy, a large gap in current

research exists in the oral health profession related to this aspect of pharmacology. In order to continue to treat patients safely and effectively in the dental office, further research is needed to assess the knowledge, attitudes, and practices of dental hygienists in regards to off-label drug use. Research has established that off-label drug use is common; however, this remains unstudied in the field of oral health.

Chapter 2: Review of the Literature

Introduction

Medical advances have made it possible for individuals to live long and healthier lives; however, this is often made possible with the help of medications to combat chronic illnesses. Furthermore, the use of multiple medications and medications used for off-label therapies increases the dental hygienist's need for an advanced body of knowledge in aspects of pharmacology related to patient assessment and the provision of treatment.

This literature review will provide a discussion regarding the regulation of off-label drugs and dental hygienists' knowledge, attitudes, and practices associated with off-label drug use and polypharmacy. Subtopics include: (a) a rise in polypharmacy (b) an overview of the existing regulatory structure, (c) rationale for off-label prescriptions, (d) off-label drug use (e) legal implications and, (f) implications for practice. Databases searched for this literature review included PubMed, EBSCOhost, Cochrane Library, Google Scholar, Google database, and Trip Database using combinations of the following search terms: off-label drug use, knowledge, practices, attitudes, ethics, law, common drugs, dentistry, children, pregnancy, adult, elderly, and medical emergencies, dietary and herbal supplements, adverse reactions, polypharmacy, legal implications, informed consent, drug-drug interactions, clinical, FDA, dietary and herbal supplements.

A Rise in Polypharmacy

Dental hygienists are faced with treating an increasing number of patients receiving polypharmacy. As the population ages, there is an increase in the number of medications taken, often times due to the treatment of multiple chronic illnesses. A

repeated cross-sectional analysis conducted in Scotland in 1995 and 2010 obtained from the University of Dundee Health Informatics Centre, analyzed prescribing data for 310,000 adults aged 20 years or older (Guthrie, Makubate, Hernandez-Santiago, & Dreischulte, 2015). In 1995, 50.6% of individuals studied received one or more drugs in the past 84 days and in 2010 this rose to 58.9%. Additionally, polypharmacy rates for the use of 5-9 drugs rose from 9.7% in 1995 to 16.3% in 2010 while the use of 10-14 drugs rose from 1.5% in 1995 to 4.7% in 2010. The authors of this study associated increasing polypharmacy rates with age, and those same implications can be seen in the current dental patient population. Furthermore, the authors concluded that prescribing rates have risen due to an increase in the availability of effective drugs, the implementation of quality improvement interventions, which have streamlined the treatment of many chronic conditions, and changes in patient expectations.

Gu, Dillon, and Burt (2010) reviewed and analyzed United States prescription drug data from the National Health and Nutrition Examination Survey (NHANES) for the year 2007-2008. No minimum or maximum age was identified for inclusion or exclusion from this study. Analysis showed an increase in the use of 1 or more drugs from 43.5% in 1999-2000 to 48.3% in 2007-2008. Additionally, the use of 2 or more drugs increased from 25.4% in 1999-2000 to 31.2% in 2007-2008 and the use of 5 or more drugs rose from 6.3% to 10.7%. In a more recent analysis, Kantor, Rehm, Haas, Chan, and Giovannucci (2015) evaluated prescription drug use in the United States using NHANES data from 1999-2000 to 2011-2012. This study included a sample size of 37,959 adults aged 20 years and older. Kantor et al. found that the incidence of prescription drug use

increased from 51% in 1999-2000 to 59% in 2011-2012. Additionally, polypharmacy rates increased from 8.2% to 15%.

Polypharmacy is a concern among some healthcare professionals due to an increased risk of adverse drug reactions, drug interactions, and medication errors (Jenny et al., 2012). Jenny et al. (2012) surveyed 105 nurses in the Gulf Medical College Hospital and Research Center in Ajman, United Arab Emirates (UAE) regarding participants' attitudes about polypharmacy. The top three negative attributes of polypharmacy identified by this population were increased drug interactions (98.1%), increased adverse drug effects (81.9%), and increased financial burden on patients (69.5%). In fact, only 36.2% stated that polypharmacy prolongs patient's survival and 35.2% stated that it improves the patient's quality of life.

An Overview of the Existing Regulatory Structure and Drug Review

The Federal regulation of drugs can be traced back as far as 1848 and has evolved considerably since 1906 when President Theodore Roosevelt signed the Pure Food and Drugs Act (FDA, 2014a). The Food, Drug, and Cosmetics Act of 1938, including amendments made in 1962, requires that all drugs and medical devices pass FDA approval *for a specific use* (Klein & Tabarrok, 2008). Based on a long process of drug development and review and various phases of clinical trials, the FDA approves drugs and medical devices for specific therapies stated on the FDA-approved label.

Once drugs are FDA approved and on the market they are often utilized for off-label therapies. While controversy exists on the use of drugs for off-label therapies related to prescribing practices, adverse reactions, and lack of evidence to support off-label prescribing, the FDA (2011) stated that it "recognizes that these off-label uses or

treatment regimens may be important therapeutic options and may even constitute a medically recognized standard of care" (p.2). Although the FDA acknowledged the potential benefits of off-label drug therapy, lack of safety and efficacy evaluations for off-label drug therapies remains a concern. Lack of evidence supporting the safety and efficacy of a drug used off-label can result in adverse reactions or potentially ineffective treatment (Eguale et al., 2015). This can put the patient's well-being at risk due to the potential of adverse reactions and the progression of medical conditions. Furthermore, legal implications can arise resulting from a lack of informed consent when using drugs lacking the appropriate FDA indications confirming safety and efficacy (Wittich, Burkle, & Lanier, 2012).

The process of obtaining FDA drug approval can be long and might vary slightly among drugs. Before conducting human studies on a new drug, animal testing and an investigational new drug application are required (FDA, 2014c). These are followed by three phases of clinical studies to determine the safety and efficacy of the new drug (FDA, 2014c). Once the three phases of testing are complete, a new drug application is filed formally asking the FDA to consider the drug for approval. If the FDA considers reviewing the drug for marketing approval, a review team is assigned to evaluate the research and inspect the manufacturing facilities (FDA, 2014c). Once the FDA has endorsed the safety and efficacy of a drug, pharmaceutical companies may begin to market and sell the drug for the approved and specified disease or condition.

Rationale for Off-Label Prescriptions

Chen et al. (2006) stated that among the many reasons for the lack of seeking FDA approval for off-label drug use is the long and expensive drug approval process and

a lack of financial incentives for pharmaceutical companies to receive FDA approval due to the high rate of off-label prescribing already in place. Additionally, they stated financial limitations of government research institutes to fund clinical trials for off-label indications and the limited FDA manpower to review all the possible uses of the drugs already approved for alternative indications can easily discourage pharmaceutical companies. Despite these reasons, most off-label uses have not been sufficiently tested for safety and efficacy in certain populations and medical conditions associated with these populations including children, mentally disabled individuals, and elderly patients, making regulation complicated (Chen et al, 2006). "It is a challenge for regulators to protect patients' safety without interfering with physicians' practice and the pharmaceutical industry's First Amendment rights" (Chen et al, 2006, p. 979).

Ethical and practical considerations are also to blame for the use of off-label medications in certain populations. For example, children, mentally disabled individuals, and some elderly patients are unable to consent to the use of trial or experimental indications and are often excluded from various studies (Chen et al, 2006). Moreover, due to the reasons listed above, in some cases there is a lack of approved medications available to treat certain disorders like dementia, leaving the primary care providers to make evidence-based decisions employing the use of off-label medications.

Off-Label Drug Use

With current increases in polypharmacy and the number of drugs on the market, the identification of off-label uses have become more common. Drug manufacturers benefit financially due to increased opportunities for the use of their drugs. Additionally, physicians have more options to provide effective treatments for patients. Klein and

Tabarrok (2014) surveyed 491 physicians regarding FDA law and found that 94% of participants opposed changes in FDA law that would prohibit the prescription of drugs for off-label uses. The authors also stated that the failure of physicians to consider the prescription of specific drugs for certain off-label uses could be seen as negligence. Amoxicillin was used as an example. Amoxicillin, approved by the FDA for use in treating respiratory tract infections, has been shown to be effective in the treatment of stomach ulcers. Klein and Tabarrok (2014) pointed out that textbooks and medical guides discuss amoxicillin as a potential treatment of stomach ulcers despite the fact that FDA phases II and III trials have not been completed for that specific use.

Common off-label prescribing practices. Literature discussing common prescribing practices of physicians is limited leaving a significant gap in evidence-based knowledge. Strom, Melmon, and Miettinen (1985) stated that 31 of the 100 most common uses of marketed medications were used for indications not initially approved by the FDA. In 2001, Radley et al (2006) analyzed data from the National Disease and Therapeutic Index in an effort to estimate the magnitude of off-label use and whether or not these uses were supported by scientific evidence. They found that cardiac medications, anticonvulsants, and anti-asthmatics were among the most commonly prescribed drugs for off-label therapies. Although the authors were not specific regarding the way in which the drugs were used off-label a few examples were mentioned. Albuterol sulfate, an FDA approved antiasthmatic, is used off-label for the treatment of chronic obstructive pulmonary disorder (COPD) due to the physiologic similarities between the two conditions (Radley et al., 2006). Gabapentin, an FDA approved anticonvulsant, is frequently used off-label to treat chronic nonspecific pain. The authors

did not identify an example of a cardiac medication used off-label. Despite the frequency of these drugs and their off-label use, the biggest disparity between scientifically supported and unsupported use occurred among psychiatric and allergy therapies. In fact, data showed that evidence of clinical efficacy was sparse among the medications with the highest proportion of off-label use. For example, gabapentin was only scientifically supported in 20% of its off-label uses while the other 80% had limited or no scientific support for off-label use (Radley et al, 2006).

Chen, Wynia, Moloney, and Alexander (2009) conducted a survey of 350 general practitioners and psychiatrists to address whether or not they were aware of the FDA labeled indications for the drugs they prescribe. This study showed that general practitioners and psychiatrists correctly identified FDA-approved drug indications about 50% of the time. However, 95% of these same physicians reported knowing the FDA indications of the medications they prescribe and 79% reported FDA labeling is an important factor in their prescribing practices. Currently, there are no studies evaluating dental hygienists' knowledge or practices related to FDA labeling indications for the drugs they utilize in daily practice.

Populations most commonly using drugs off-label. Pediatrics is one area where off-label therapies are frequently prescribed in this population for conditions or age groups not specifically listed on labeling. Due to practical and ethical considerations, clinical trials involving children are rare considering their increased risk of adverse drug reactions (Morais-Almeida & Cabral, 2014). Morais-Almeida and Cabral (2014) conducted a study that involved 1,224 registered prescriptions written for pediatric use in the treatment of asthma, allergic rhinitis, and atopic eczema in pre-school aged children

in Portugal. In this study, 34.5% of the prescriptions were considered off-label due to age, dosage, or clinical indication. For example, nasal topical corticoids were considered off-label due to age with the minimum approved indication being age 6. Fluticasone, cetirizine, levocetirizine, desloratadine, ebastine, ketotifen, and montelukast were all prescribed off-label regarding their approved dosages. Montelukast was prescribed as a single therapy treatment for asthma although it is clinically indicated as adjunctive therapy only. Bazzano, Mangione-Smith, Schonlau, Suttorp, and Brook (2009) analyzed data from the 2001-2004 National Ambulatory Medical Care Surveys in the United States and found that in 7,901 outpatient visits of children ages 0-17, 62% of visits utilized the prescription of off-label drug therapy. Of these prescriptions, 90% of the cardiovascular-renal medications, 80% of pain and gastrointestinal medications, 75% of the pulmonary and dermatologic medications, and 42% of anti-infective uses were considered off-label for either indications or age. The authors of this study stated that while over half of the outpatient visits in the United States result in off-label prescriptions, no longitudinal studies have been conducted despite previous evidence showing an association between off-label prescribing and adverse reactions in the pediatric population.

Ekins-Duakes, Helms, Taylor, and McLay (2005), conducted a study to assess the knowledge and attitudes of primary care physicians regarding off-label prescribing to children. Three hundred forty-six questionnaires were sent out and 202 were completed. Of these 202 participants 31% reported a patient base consisting mostly of children. In this study, 73.7% were familiar with the concept of off-label prescribing but 53.3% were unaware that this practice is commonplace. Of the participants, 79.3% reported off-label prescribing for patients younger than recommended and 25.6% prescribed at higher

dosages while 23.3% prescribed at lower dosages or non-recommended indications. More than 50% of physicians that participated reported that they were concerned by lack of pediatric dosage information and appropriate pediatric formulations. Less than 15% were concerned about side effects, unevaluated efficacy and issues surrounding informed consent.

Similar to pediatric populations, pregnant women are also excluded from clinical trials due to practical and ethical considerations, yet off-label drug use is prevalent in this population. Herring, McManus, and Weeks (2010) analyzed 17,694 prescriptions written for expectant mothers collected from Liverpool Women's Hospital. Herring et al. (2010) found that 84% of these prescriptions were for off-label or unlicensed indications. Additionally, 59% of these off-label drugs carried cautions or specific contraindications for use in pregnancy and 16% were considered high risk. Of the 59% of drugs that carried cautions or specific contraindications were codeine, betamethasone, cyclizine, cefuroxime, and diamorphine. Labetolol, methylodopa, indometacin, temazepam, nifedipine, and morphine were considered high risk for use in pregnancy. Some limitations to this study included the anonymity of the prescribing data resulting in no information related to gestation and history of the pregnancy as well as the reason for the drug therapy.

Second-generation antipsychotic drugs are often prescribed for the treatment of dementia among the elderly population. Kamble, Sherer, Chen, and Aparasu (2010) conducted a study using cross-sectional data from the 2004 National Nursing Home Survey consisting of 1,317,205 elderly patients. Of these patients, 23.5% had received at least one second-generation antipsychotic prescription and 86.3% of these prescriptions

were for off-label indications. Additionally, Kamble et al. (2010) found that of the 86.3% off-label prescriptions, 56.9% were for treatment indications that were considered evidence-based. Patients with psychiatric disorders, regardless of age, were frequently prescribed drugs for off-label indications since this population is often excluded from clinical trials (Wittich et al., 2012). According to Wittich et al. (2012), physicians use these medications for unapproved treatment of psychiatric disorders because these disorders are difficult to study. This difficulty arises due to the crossover of symptoms from one disorder to another.

Off-label drug therapy has become a standard of care in oncology and HIV disease treatment (Henry, 1999). Henry stated that most off-label drug use associated with HIV patient care is related to opportunistic infections. He cited a survey of 1,530 primary care providers who reported 40% of 5,000 prescriptions written were for off-label use. Additionally, participants reported that 81% of HIV patients were treated with at least one drug used for off-label therapy. Oncology often relies on research report publications for off-label therapy recommendations; however, there is often a lag time between when the research is conducted and its publication so many relevant off-label therapies might be excluded from such publications (Henry, 1999). In a study conducted by the United States General Accounting Office it was found that 56% of cancer patients were treated with at least one off-label drug therapy (Henry, 1999).

While the previously mentioned studies provide some insight into off-label prescribing practices, a limitation in the literature is the lack of specificity in regards to the specific drugs being prescribed, and how they were being used off-label. Unfortunately, the information presented in these studies is not specific enough to capture

a true sense of what is really happening in terms of off-label drug use. This lack of information could present a problem for dental hygienists. Their ability to modify dental treatment plans based on the possible adverse effects of off-label uses and prepare for emergency situations might be compromised.

Ethics of off-label drug use. Among the concerns for prescribing drugs off-label is the risk of patient harm through adverse reactions or ineffective treatment (Dresser & Frader, 2009). Drugs used off-label for conditions where little or no approved treatment indications exist in particular patient populations (i.e. children, pregnant mothers, elderly) is highly understudied (Paal, 2009). Drug safety is a major concern in off-label use and continued monitoring is recommended. Factors that might affect the safety of the medication include patient age, range of co-morbidities, polypharmacy, drug-disease interactions, and differences in pharmacokinetics and pharmacodynamics (Paal, 2009). Despite these safety concerns, monitoring is difficult due to a lack of controlled studies and observations.

In order to make the safest and most ethically sound treatment decisions for patients, physicians should base decisions on relevant scientific evidence in order to weigh the potential risk and rewards associated with the treatment options. The previously mentioned study conducted by Chen et al (2009) found that 19% of physicians who prescribed quetiapine for dementia believed that this was an FDA-approved indication for use when, at the time, the drug carried "a black-box warning for increased risk of death compared to placebo in elderly patients with dementia" (p. 1098). Additionally, 33% of the physicians who prescribed lorazepam for patients with chronic

anxiety believed it was FDA approved for this use when, at the time of the survey, there was specific advisement against this use.

Alexander, Gallagher, Mascola, Moloney, and Stafford (2011) also studied a lack of evidence to support off-label drug use. They analyzed data regarding the off-label use of typical and atypical antipsychotic drugs from the IMS National Diagnostic and Therapeutic Index. This retrospective study included data from 1995, 2002, and 2008. In 1995, 97% of the 4.4 million antipsychotics used off-label contained evidence that was uncertain, or had insufficient evidence to support efficacy. In 2002, 81% of the 6.8 million of the off-label uses had uncertain evidence and in 2008, 91% of the 9 million uses had uncertain evidence. Alexander et al. suggested, "when the application of therapies for new and largely untested clinical indications reaches a substantial volume, however, there should be a corresponding obligation to generate evidence that demonstrates the safety and efficacy of the new uses" (Alexander et al., 2011, p. 6).

Evaluating and prioritizing research in off-label indications. Largent, Miller, and Pearson (2009) identified four characteristics that signal the need for increased scrutiny of evidence in terms of prescribing drugs off-label and the levels of evidence needed to guide prescription practices. These characteristics indicating the need for increased scrutiny of evidence included drugs that are new, are associated with high cost, possess novel off-label uses, or contain known adverse effects (Largent et al, 2009). Three levels of evidence were suggested supporting the use of off-label drugs. These included supported, suppositional, and investigational evidence corresponding to the level of certainty based on existing evidence showing a patient would benefit from the off-label treatment. Supported off-label use correlated to a moderate to high level of

certainty in which a drug may be prescribed off-label without concern. Higher levels of evidence, meta-analyses or systematic reviews, reinforce supported off-label use. Suppositional corresponds with a low level of certainty and therefore, risk and benefit analysis should be completed including consultation with colleagues and informed consent from the patients. Higher-level studies are not available to support suppositional evidence. Investigational corresponds with a very low level of certainty so these drug uses should be limited to research protocols due to the unpredictability of benefit to the patient (Largent et al, 2009). Proper evaluation of the evidence is necessary to make the appropriate treatment recommendations and increase the safety of off-label therapies.

In an effort to bring resolution to the barriers in researching off-label drug use, Walton et al. (2008) conducted a study in which they developed a quantitative model for prioritizing research for off-label uses. The model ranked the drugs by volume of off-label use, safety, and cost and market considerations. An estimation of off-label drug usage by indication, from January 2005 through June 2007 in the United States was established by using nationally representative prescribing data. These data were then categorized according to the adequacy of scientific support. Drug safety was analyzed with black box warnings and safety alerts. Cost and market considerations were enumerated by drug cost, date of market entry, and marketing expenditures. These factors were calculated leaving each drug with a numerical value and weighted to generate a priority score. Varying the weightings and model parameters steered a sensitivity analyses. Quetiapine, warfarin, escitalopram, risperiodone, montelukast, bupropion, etc. ranked high in both the base model and sensitivity analysis. According to Walton et al, the high ranking of these drugs indicated the greatest frequency and

inadequacy of evidence suggesting a priority be given to researching off-label use of these drugs. These authors concluded that increasing the potential value of research and policy related to off-label drugs can be accomplished through prioritizing off-label drugs by frequency of usage and inadequacy of the evidence supporting safety and efficacy.

Medical emergencies/adverse reactions. In the previously mentioned study by Guthrie et al. (2015), patients experiencing at least one drug-drug interaction while being treated with polypharmacy rose from 5.8% in 1995 to 13.1% in 2010 and patients experiencing two or more drug-drug interactions tripled from 1.5% in 1005 to 5.6% in 2010. Adverse reactions related to drug-drug interactions is concerning when evaluating the effectiveness and appropriateness of polypharmacy. The addition of drugs used for off-label purposes that have not been adequately studied for the indications in which they are being used can further complicate the potential for drug-drug interactions.

As previously mentioned, children are the recipients of many off-label drug therapies due to the lack of appropriate clinical trials. The reasons drugs may be used or recommended among this population for off-label therapies may be due to age, dosage, or clinical indications. While adverse reactions are a risk of off-label drug therapy among the pediatric population, controversy remains over whether this risk is relative to the risk associated with FDA-approved uses. Commonly prescribed medications have received black box warnings after adverse reactions were documented in children. For example, the antidepressants paroxetine and citalopram contain warnings of suicide in children while cisapride (used for gastric motility) has been linked to life-threatening arrhythmias (Bazzano et al., 2009).

Aspirin, an FDA-approved analgesic, is commonly used for prevention of cardiovascular problems due to its antiplatelet properties. Physician-recommended, long-term, low-dose aspirin therapy could be used as a primary or secondary prevention measure, although it is associated with upper gastrointestinal bleeding (Lin, De Caterina, & García Rodríguez, 2014). Lin et al. conducted a nested case-control study using The Health Improvement Network database and identified 2,049 cases of upper gastrointestinal bleeding and an additional 20,000 controls. Their research showed that the relative risk for upper gastrointestinal bleeding in patients taking low-dose aspirin therapies was higher for primary cardiovascular disease prevention rather than secondary cardiovascular disease prevention. Lin et al. (2014) stated that, compared to primary prevention patients, patients receiving secondary prevention therapy were most often older, more likely to have a history of ulcers, smokers, and use oral corticosteroids, anticoagulants, nonsteroidal anti-inflammatory drugs, and clopidogrel which can increase the risk of upper gastrointestinal bleeding; however, these factors that differentiate primary and secondary prevention patients were adjusted for in the regression models.

A very well-known and well-documented example of adverse effects related with off-label drug use is fen-phen. Fen-phen was a combination of fenfluramine, or dexfenfluramine, and phentermine, both independently indicated and approved by the FDA as an appetite suppressant to be used for a short period of time to aid in weight loss (Gupta & Nayak, 2014). Alone these drugs were only slightly effective, but combined in an off-label indication, exhibited rapid weight loss. The first recorded use of fen-phen was in the early 1980s (Johnson, Sellnow, Seeger, Barrett, & Hasbargen, 2004). Fen-phen gained popularity in the early 1990s after Dr. Weintraub published a series of

articles discussing the effectiveness of this combination drug (Johnson et al., 2004). According to Johnson et al. (2004) an echocardiography technician at MeritCare Medical Center was the first to suspect a link between fen-phen and valvular heart disease in 1994. Never obtaining FDA approval for combined use, fen-phen, was discontinued in 1997 due to the prevalence of the development of heart valve disease (Gupta & Nayak, 2014). This development then required patients with heart valve disease caused by their experiences with fen-phen to take antibiotic prophylaxis prior to their dental visits.

Legal Implications

While the laws and regulations concerning off-label drug use are controversial and sometimes unclear, legal claims have been made against physicians for adverse reactions related to a drugs use off-label (Wittich et al., 2012). According to Wittich et al., "the legal theories used in these lawsuits include unregulated use of a research drug, failure to provide adequate informed consent for an off-label drug use, and medical negligence" (p.986).

Unregulated use of a research drug. When utilizing drugs and medical devices, it is often difficult to differentiate research vs. practice (Riley & Basilius, 2007). When clinical trials begin after obtaining the Investigational New Drug approval by the FDA, institutional review boards are proactive in the protection of human subjects. Once a drug is approved, the FDA has no part in the regulation of off-label uses and physician practice. According to Riley et al. (2007):

> If a physician's use of a drug qualifies as experimental research, the physician has an increased risk of professional discipline and civil liability if such

> experimental use does not comply with the safeguards and oversight of a formal study carefully designed to monitor the drug's safety and effectiveness. (p. 26)

The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research differentiate research and practice based on outcome goals (Riley et al., 2007). Research tests hypotheses, draws conclusions and adds to a knowledge base while practice aims to diagnose, prevent, or treat.

In 2007, Bax Global Inc. was sued in a malpractice case by a patient who was the recipient of an artificial disk inserted into her spine (Riley et al., 2007). The disk was used off-label due to the location of placement in her spine. She argued that since the use was off-label that it was also experimental. The court did not find this use experimental because this off-label placement was widely used in Europe and constituted an easier procedure than the approved use. Riley et al. (2007) stated, based on this case, a physician can avoid professional liability if the patient's needs are foremost and scientific data supporting the off-label use is available.

Informed consent. Unfortunately, there is no court-mandated law that requires a prescribing healthcare provider to disclose information regarding the off-label use of a drug (Wittich et al., 2012). Wittich et al. reported that physicians do not obtain informed consent for off-label use due to concern for unnecessarily frightening patients and the possibility of this information overshadowing more critical patient care issues. In light of such a high prevalence of off-label drug use, researchers have explored the informed consent practices among physicians that employ the use of drugs for off-label purposes. To et al. (2013) conducted a study involving 105 members of the Australian and New Zealand Society of Palliative Medicine providers. This study showed that 26% of

physicians never obtained verbal consent from the patient/caregiver, while 49% sometimes did, and 24% always did. Additionally, 74% never obtained written consent, 23% sometimes did, and 1% always did. When asked about documentation practices, 49% never documented their reasons for off-label prescribing, 38% sometimes did, and 10% always did. Another study conducted by Culshaw, Kendall, and Wilcock (2013) in the United Kingdom involving 332 participants showed that 22% of prescribers do not inform patients that drugs they were prescribing were for off-label indications, while only 3% stated they always do.

Medical negligence. Another legal consideration when utilizing drugs off-label is medical negligence. Wittich et al. (2012) stated that:

> 4 elements of tort law dealing with negligence must be proved before liability can be found to exist: (1) the prescribing physician must have a duty to the patient, (2) that duty must be breached, (3) there must be some injury requiring compensation, and (4) there must be a causal link between the breech and that injury. (p. 987)

Helm (2007), stated that for medical negligence to be ascertained it must be proven that the physician strayed from the standard of practice in the community and FDA regulation of off-label promotion by the manufacturers makes it difficult for the physician to gather information regarding the standard of practice with certain off-label uses.

Implications for Practice

To ensure the safety of the patient in the dental office, dental hygienists should recognize and inquire about medications and conditions for which they are being used, particularly when off-label use is suspected. As previously mentioned, cardiac

medications, anticonvulsants, and anti-asthmatics are among the most commonly prescribed drugs for off-label therapies (Radley et al., 2006). Dental hygienists treat patients taking these medications on a daily basis. Additionally, dental hygienists often treat pediatric, elderly, expectant mothers, and oncology patients, who are all common recipients of off-label drug therapies. The dental hygienist should thoroughly evaluate each patient's medical history to reduce the risk of medical emergencies in the dental office and monitor the patient for signs of possible adverse reactions when using drugs for off-label therapies (Jacobsen & Chavez, 2005). Drugs utilized in the dental office should also be evaluated for possible drug interactions associated with these off-label medications (Jacobsen & Chavez, 2005).

As mentioned previously, the studies discussing off-label prescribing practices and populations using these drugs were not specific in stating the drugs and their uses; therefore, some of the drugs mentioned in these studies were cross referenced with Lexicomp Online. Lexicomp Online is a pharmacy, dental hygiene, and allied health resource that contains drug information and education resources. Individual drugs were searched on the Lexicomp Online database and information was obtained from the monograph section of the drugs webpage. The following are some off-label indications the dental hygienist might see in practice for cardiac medications, anticonvulsants, antiasthmatics and the populations in which they are utilized off-label.

Digoxin, a cardiac glycoside FDA approved for the treatment of heart failure and atrial fibrillation, can be used off-label for fetal tachycardia when administered to a pregnant woman. Digoxin has a narrow therapeutic index; therefore use of this medication should be monitored closely as there is a high risk for adverse reactions, and

drug interactions including the use of caution with vasoconstrictors. Patients using digoxin may have a sensitive gag reflex. Elderly patients are at an increased risk for adverse reactions and should be monitored closely.

Labetolol is an antihypertensive beta-blocker that is FDA approved for the treatment of hypertension in adults aged 18 years and older. Vasoconstrictors must be used with caution in patients taking labetolol and taste perversion may be present. Off-label, labetolol has been used to treat pregnant women in the acute onset of severe hypertension with preeclampsia or eclampsia. Also used off-label in pregnant women is the calcium channel blocker nifedipine. This drug is FDA approved for the treatment of hypertension and the management of angina in adults aged 18 years and older. In pregnant women nifedipine has been used off-label in hypertensive emergencies and to prolong pregnancy when preterm labor occurs. Additionally, this drug is used off-label for the treatment of Raynaud's syndrome, a vascular disorder of the extremities. Dental considerations include gingival enlargement and elderly patients might experience greater hypotensive effects.

Perhaps the most common FDA approved anticonvulsant is gabapentin. Since increasing in popularity for off-label uses, gabapentin is also FDA approved for the treatment of post-herpetic neuralgia in adults. Off-label uses for gabapentin include brachioradial pruritus, chronic cough, diabetic neuropathy, fibromyalgia syndrome, hot flashes, restless leg syndrome, social anxiety disorder, uremic pruritus, and neuropathic and postoperative pain. Dental implications include xerostomia, dry throat and dental abnormalities. Children taking gabapentin might experience central nervous system (CNS) effects such as changes in behavior or thinking, and emotional liability.

Carbamazepine is another FDA anticonvulsant. This drug is also approved to treat trigeminal neuralgia, but has been used off-label for the treatment of restless leg syndrome in adults. Xerostomia is a dental implication. The dental hygienist should watch for latent psychosis, confusion, or agitation in elderly patients utilizing this drug, and in pediatric use the exacerbation of certain seizure types in children with mixed seizure disorders can occur.

Valproate is an FDA approved anticonvulsant also approved for the treatment of mania associated with bipolar disorder and migraine prophylaxis. Off-label, valoproate is also used for the treatment of borderline personality disorder, diabetic neuropathy, post-herpetic neuralgia, and status epilepticus in children and adults. Children under age 2 can be at risk for fatal hepatoxicity and elderly patients may experience an increase in dehydration and sedating effects. The use of valproate in pregnant woman is contraindicated due to an increased risk of congenital malformations. Dental implications include periodontal abscess and taste perversion.

Albuterol and levalbuterol are both $beta_2$ agonist FDA approved for the treatment of bronchoconstriction and are used off-label in this manner for children as this use in not approved in children under the age of 4 years. Xerostomia might occur and children aged 2-14 years of age might experience CNS excitement. Exacerbation of asthma, the condition in which this drug is indicated, might also occur.

Second generation antipsychotics such as risperidone, olanzapine, and quetiapine are all FDA approved for the treatment of schizophrenia and bipolar mania but used off-label to treat psychosis and agitation associated with dementia in elderly patients. Although these three drugs are all used off-label in dementia patients, the drugs carry a

warning stating that studies have shown that elderly patients with dementia-related psychosis treated with antipsychotics are at an increased risk of death compared with placebo. Risperidone is also used off-label for post-traumatic stress disorder (PTSD), major depressive disorder, and Tourette's syndrome. Olanzapine is also used off-label for chemotherapy-related nausea and vomiting, delirium, PTSD, and Tourette's syndrome. Lastly, quetiapine is used off-label for the treatment of obsessive compulsive disorder, delirium in critically ill patients, generalized anxiety disorder, PTSD, and psychosis in Parkinson's disease. Risperidone and quetiapine both require caution with the use of vasoconstrictors and may cause xerostomia (Lexicomp, 2016b).

A thorough review of a patient's medical history and current medications is essential in producing an accurate oral diagnosis and providing safe treatment for patients, especially when administering or recommending drugs in both medical and dental offices. According to Tam et al. (2015), accurate knowledge of patients' medications can help the healthcare provider decipher adverse drug reactions or noncompliance issues, which can aid in uncovering causes for a patient's illness. Additionally, Tam et al. (2015) stated "medication history errors may result in interrupted or inappropriate drug therapy during and following the hospital stay" (p. 510). These authors performed a systematic review analyzing studies discussing the frequency, type, and clinical importance of medication history errors at hospital admission. They reviewed 22 studies that included 3,755 participants. Prescription medication history errors were found in 67% of all cases. Of the cases included, 10%-67% of patients had at least 1 prescription medication history error, which rose to 27%-83% with the inclusion of nonprescription drugs. Additionally, 34%-95% of patients had at least 1 error related

to the identification of prior allergies or adverse drug reactions. Types of errors were considered omission, which described the deletion of a drug used before admission and commission errors, describing the addition of a drug not used before admission. Collectively, 10%-61% of the patients had at least 1 omission error and 13%-22% had at least one commission error resulting in 60%-67% having at least 1 commission or omission error. Of the studies included in this systemic review 5 discussed analyzed intentional and unintentional medication errors and 3 of these 5 studies unintentional medication errors ranging from 19%-75%. In six of the reviewed studies, the researchers reported that 11%-59% of the medication errors committed were clinically important.

Currently unregulated or evaluated by the FDA for safety and efficacy, the use of dietary and herbal supplements has increased among the adult population in the United States from 42% in 1994-1998 to 53% in 2003-2006 (Centers for Disease Control and Prevention, 2011). Due to the lack of FDA regulation and approval, dietary and herbal supplements may be considered off-label since they are void of an FDA approved indication. To assess the prevalence of polypharmacy and the use of dietary supplements Qato et al. (2008) conducted a study using a cross-sectional, nationally representative probability sample of individuals from the United States. This study consisted of 3,005 persons aged 57-85 years and was conducted from June 2005 to March 2006. Of these participants, the investigators found that 81% used at least one prescription medication, 42% used at least one over the counter medication, and 49% used a dietary supplement. Furthermore, 29% of participants used five or more prescription medications. While taking five or more prescription medications, 46% of participants reported the addition of over the counter medications, and 52% reported the concurrent use of dietary

supplements. These authors also stated that 4% were at risk for major drug-drug interactions of which half were due to their use of nonprescription medications. These authors did not state whether or not the patients' physicians were involved in the decision to add over the counter medications and/or dietary supplements to their medication regimen. Patients might decide to self-treat with over the counter medications and/or dietary and herbal supplements without obtaining recommendations or approvals from their primary healthcare provider. Additionally, patients might neglect to mention the use of such products to their medical and oral healthcare providers leading to medication history errors that may result in adverse drug reactions or dangerous drug-drug interactions.

Many dietary and herbal supplements can result in adverse drug reactions and/or drug-drug interactions. Ginseng is used for cardiovascular, central nervous system, and endocrine effects among others but none have been validated by clinical trials (Wynn, Meiller, & Crossley, 2015). Ginseng can increase bleeding and caution should be exercised when using antidiabetic drugs, antipsychotics, nifedipine, and warfarin which are all drugs taken for the conditions in which this supplement is indicated (Wynn et al., 2015). Patients self-medicating with ginseng and taking these drugs might induce a potentially avoidable drug-drug interaction. St. John's Wort is often used in the treatment of depression and this use has been supported by a meta-analysis of clinical trials (Wynn et al., 2015). St. John's Wort interacts with many prescription and nonprescription medications and it is recommended that drugs with a narrow therapeutic index be monitored closely to avoid serious adverse reactions (Wynn et al., 2015).

Additionally, St. John's Wort can cause xerostomia, which can be exacerbated by polypharmacy.

Accurate medication histories and knowledge of medications, over the counter drugs, and dietary and herbal supplements by the dental hygienist can reduce the risk of dangerous drug-drug interactions and can aid in the diagnosis and treatment of the dental effects/adverse drug reactions resulting from the use of certain medications. For example, hyposalivation, an adverse effect of numerous medications, can cause a multitude of problems for those who experience this adverse effect. Xerostomia can cause difficulty in speech, mastication, swallowing, changes in taste, new and recurrent dental caries, etc. and is most commonly caused by polypharmacy-induced salivary hypofunction (Ship, McCutcheon, Spivakovsky, & Kerr, 2007). Pinpointing the direct cause of this condition might help the dental hygienist implement appropriate protocols for the management of the adverse dental effects this condition might cause.

Jacobsen and Chavez (2005) advise oral health professionals to address four questions when treating patients utilizing polypharmacy, which might also prove to be useful for patients taking drugs for off-label purposes. These questions include:

> (1) what are the medical conditions that necessitate the medications, (2) what impact do these medical conditions have on the provision of care, (3) what are the oral side effects of the medications, and (4) how will the patient's current list of medications alter the dentist's prescribing patterns for drugs used in dentistry? (Jacobsen & Chavez, 2005, p.1)

Utilizing this model and asking these questions when evaluating a patient's medication history might be useful in preparing for and/or preventing adverse drug reactions and drug-drug interactions.

Off-label drugs in the dental office. In the dental office, dental hygienists not only see patients who are utilizing drugs for off-label medical purposes, they also employ drugs/medical devices for off-label indications as well. For example, Minimal Intervention (MI) Paste and MI Paste Plus are FDA approved "to be used for cleaning and polishing procedures as part of a professionally administered prophylaxis treatment" (FDA, 2012a). Additional indications include the secondary "management of tooth sensitivity, ultrasonic, post scaling, root planing and bleaching" (FDA, 2012a). The FDA (2012a) has also indicated MI Paste Plus for the relief of dentinal hypersensitivity. MI Varnish is cleared for prescription use as "a fluoride varnish with Recaldent that has a desensitizing action when applied to tooth surfaces" (FDA, 2012a). In 2012(a), the FDA issued a warning letter to the company GC America, the makers of MI Varnish and Paste, stating that they were in violation of the Federal Food, Drug, and Cosmetic Act due to their promotion of these products for off-label purposes. These off-label indications included remineralization claims, the treatment of xerostomia, Sjögrens syndrome, and penetrating and remineralizing sub-surface lesions (FDA, 2012a).

Fluoride varnishes are used in the dental offices for multiple indications including anti-caries treatment. The FDA (2012b) approved indications for fluoride varnish to Dentsply International that include the treatment of hypersensitivity, sealing of dentinal tubules for cavity preparations or on sensitive root surfaces, and as a cavity liner (FDA, 2012b). The use of fluoride varnish for caries prevention is preferred for young children

due to the reduction in risk for over-ingestion, rapid adherence compared to the traditional four minute application with foam and gel applications, and a higher percentage of fluoride with a 5% sodium fluoride varnish compared to a 1.1% sodium fluoride gel or foam (Hawkins et al., 2004). Hawkins et al. (2004) conducted a study assessing costs and patient acceptance of professionally applied topical fluoride varnish versus professional applied topical fluoride foam. A convenience sample of 256 high-risk children from the York Region and city of Hamilton, Ontario, Canada were included in this study. Results showed that the application of fluoride varnish took less time, signs of gagging were lower in the population receiving the fluoride varnish, and the cost per application (including labor costs) was lower per fluoride application. The authors of this study support the use of fluoride varnish over that of fluoride foam. While the use of fluoride varnish is not FDA approved for anti-caries, there are benefits to its' use over that of fluoride foam. To date there have been no studies discussing whether this off-label use is discussed with patients prior to application to obtain informed consent.

Botox is a neuromuscular blocking agent that is FDA (2016) indicated for the treatment of overactive bladder, migraines, spasticity, cervical dystonia, severe axillary hyperhidrosis, and strabismus. More recently, botox has been used off-label in dentistry for the treatment of temporomandibular mandibular joint disorders, bruxism, pathologic clenching, drop the upper lip to reduce the amount of visible attached gingiva, and masseteric hypertrophy (Nayyar, Kumar, Nayyar, & Singh, 2014).

Chlorhexidine gluconate 0.12% (CHX) is an antibiotic oral rinse and topical treatment FDA approved as a skin cleanser for preoperative skin preparation, wound and general skin cleanser for patients, a surgical scrub and antiseptic hand rinse for healthcare

personnel, an antibacterial dental rinse for gingivitis treatment, and in the form of PerioChip an adjunctive therapy to reduce pocket depth in patients with periodontitis (Lexicomp, 2016a). Off-label, CHX has also been used in the treatment of dental caries although the research has been inconclusive. Van Rijkom, Truin, and Van't Hof (1996) conducted a meta-analysis to analyze the effectiveness of CHX in caries prevention. These authors included eight studies in their meta-analysis and found that the overall caries inhibiting effect of CHX treatment in these studies was 46%. More recently, Li and Tanner (2015) conducted a systematic literature review to identify research-based evidence for antimicrobial therapeutic approaches on cariogenic bacteria and early childhood caries. Their systemic review concluded that there is insufficient evidence regarding the efficacy of CHX alone or in combination with fluoride to support their role in reducing cariogenic bacteria.

Used off-label in subgingival irrigation, povidone iodine is FDA approved as a broad spectrum external antiseptic for the prevention or treatment of topical infections associated with surgery, burns, minor cuts/scrapes, or the relief of minor vaginal irritation. Becoming more common in the dental office, dental hygienists use povidone iodine for subgingival irrigation in order to kill periodontopathic bacteria in the periodontal pocket. Hoang, Jorgensen, Keim, Pattison, and Slots (2003) conducted a randomized split mouth study involving 16 participants exhibiting at least one periodontal pocket 6mm or greater harboring periodontal bacteria. A site in each quadrant was randomly chosen to receive either scaling and root planing, scaling and root planing with 10% PVP-iodine subgingival irrigation, subgingival irrigation with 10% povidone iodine, or subgingival irrigation with sterile saline. Microbiological testing was

performed prior to and 5 weeks after the intervention was employed. This study showed that at five weeks post-treatment, scaling and root planing with povidone iodine subgingival irrigation demonstrated a 95% or greater reduction in total bacterial counts in 44% of pockets greater than 6mm. Scaling and root planing alone, povidone-iodine irrigation alone and water irrigation alone resulted in a 95% reduction of total bacteria in only 6%-13% of sites. Pocket depths were reduced by 1.8 mm in the scaling and root planing with povidone iodine irrigation group, 1.6 mm in the scaling and root planing group, and .9mm for the groups with only povidone iodine or water irrigation. There was no significant difference in the reduction of plaque.

Tricyclic antidepressants (TCAs) such as amitriptyline and nortriptyline are all FDA approved for the treatment of depression. While FDA approved in the treatment of depression, these tricyclic antidepressants have been found useful in the treatment of temporomandibular joint disorder (TMD). Cascos-Romero, Vázquez-Delgado, Vázquez-Rodríguez, and Gay-Escoda (2009) conducted a systemic review of 11 articles discussing the effectiveness of tricyclic antidepressants in the treatment of TMD. Cascos-Romero et al. (2009) found that there was sufficient evidence to support the use of tricyclic antidepressants in the treatment of TMD. Caution should be taken in the dental office when using vasoconstrictors on patients using TCAs. Aspiration should be performed to avoid intravenous administration and the dose should be limited to 0.04 mg of epinephrine. Additionally, care should be taken when recommending acetaminophen as TCS levels may increase and acetaminophen levels may decrease when taken together.

Alpha-lipoic acid (ALA) is a natural supplement and is therefore not regulated by the FDA. ALA has been used for the treatment of nerve pain from diabetes or other

diseases, facial pain, weight loss, certain eye conditions, high blood glucose, memory problems, and chronic tiredness. In dentistry, ALA has been studied for the treatment of pain associated with burning mouth syndrome. Cavalcanti and Da Silveira (2009) conducted a randomized double-blind placebo-controlled trial consisting of 38 patients to assess the effectiveness of ALA in treating pain associated with burning mouth syndrome. Half of the participants received capsules containing ALA while the other half received capsules of a placebo. Results showed no significant difference in the reduction of pain associated with burning mouth syndrome. Pain reduction was noted in 22 patients receiving the ALA intervention and 23 patients receiving the placebo. Femiano and Scully (2002) conducted a study also analyzing the effectiveness of ALA in treating burning mouth syndrome. This double blind, controlled study consisted of 60 patients with constant burning mouth syndrome and was conducted for two months. Participants received ALA or the placebo, cellulose starch. These researchers measured participants' symptoms using a visual analogue scale and were assessed at 15-day intervals. Results showed a significant improvement with ALA compared to the placebo with the majority of participants showing at least some improvement after 2 months and maintained for 1 year following treatment by 70% of patients.

Summary

The FDA has worked diligently to establish an appropriate drug review process to ensure proper safety and efficacy of the drugs marketed in the U.S. Advancements in evidence-based medicine, which often encourages the use of off-label drug therapy, has led to the identification of many off-label treatments that have shown to be beneficial to patient care. Despite treatment benefits, concerns for safety and ethical considerations

have been the source of much controversy surrounding the use of drugs off-label. Due to the large gap in existing literature, questions have been raised regarding the knowledge, attitudes, and practices of health professionals who utilize drugs off-label. Additionally, limitations in the literature regarding the specificity of off-label drug indications and how they are used in the population leaves the dental hygienist with limited information regarding these now common practices. More information in this aspect of pharmacology will allow dental hygienists to make appropriate treatment modifications and be properly prepared for any possible adverse effect or medical emergency that might present. This study could provide a basis for further research and continuing education topics relating to the knowledge, attitudes, and practices of dental hygienists regarding off-label drug use.

Chapter 3: Methodology

Design

Overview of study. The purpose of this study was to investigate the knowledge, attitudes, and practices of California dental hygienists related to polypharmacy and off-label drug use. The problem statement, significance of the study, purpose of the study, research questions, and a review of the literature were presented in chapters one and two. This chapter explains the research methodology for this study including the research design, description of the setting, description of the sample, description of the instruments, and procedures for data collection and analysis.

Research Questions

1. What are dental hygienists' knowledge levels, attitudes, and practices related to patients' use of off-label drugs and polypharmacy?
2. What are dental hygienists' practices related to the use of off-label drugs in the provision of dental hygiene care?
3. What are the differences in dental hygienists' knowledge, attitudes and practices related to off-label drugs and polypharmacy based on their level of education, years of practice and type of licensure?

Hypotheses.

There is no statistically significant difference between dental hygienists' knowledge, attitudes and practices related to off-label drugs and polypharmacy based on their level of education, years of practice and type of licensure.

Research method or design. This cross-sectional study utilized a knowledge, attitude, and practice (KAP) survey adapted from a previously conducted study with

permission (Appendix A) from the authors and was administered via an online survey tool. In order to evaluate the magnitude of polypharmacy and off-label drug use among dental hygienists and their knowledge of this aspect of pharmacology a situation analysis was conducted. A situation analysis evaluating oral health professionals, polypharmacy and off-label drug use helped to evaluate areas of need for further research and/or educational programs in this concentration. "A KAP survey is a representative study of a specific population to collect information on what is known, believed and done in relation to a particular topic" (World Health Organization, 2008, p. 6). Due to the gap in current literature, a KAP survey can be an initial assessment of off-label drug use in oral health.

Variables. In this study the dependent variables of dental hygienists' knowledge, attitudes, practice, and the independent variables level of education, years of practice, and type of licensure were examined in relation to polypharmacy and off-label drug use.

Description of Setting

This study was conducted in the fall of 2016. The study utilized an online survey through an online survey tool (Qualtrics). After permission was granted from the Long Beach Dental Hygienists' Association (LBDHA, Appendix B), the Tri County Dental Hygienists' Association (TCDHA, Appendix C) and the ISU Human Subjects Committee, emails were sent to dental hygienists licensed in California through the LBDHA and TCDHA databases requesting participation in the online survey.

Research Participants

Sample description. A convenience sample of 316 dental hygienists practicing in California was utilized for this study; 150 dental hygienists from the LBDHA and 166 dental hygienists from TCDHA.

Sample inclusion and exclusion criteria. Inclusion criteria included current dental hygiene licensure by the state of California. Exclusion criteria included dental hygienists that no longer possess an active license.

Human subjects protection. A proposal for Exempt status was submitted to the Human Subjects Committee and permission was granted to conduct the study prior to the distribution of the survey. A letter (Appendix D) was sent to the sample population explaining the study to the participants and included the researchers' contact information allowing an opportunity for the participants to ask any questions related to the study. A link to the online survey (Appendix E) was embedded in the letter and it explained that completion of the survey signified informed consent. Complete anonymity and confidentiality was maintained. Data obtained from the survey was saved in personal computer files allowing access only to individuals involved with the study. Upon completion of the study, data was stored in a locked cabinet in the Department of Dental Hygiene at ISU and will remain there for seven years, and then destroyed.

Data Collection

Instrument. With permission (Appendix A), a previously designed and validated survey was adapted to obtain quantitative data regarding dental hygienists' knowledge and practices related to polypharmacy and off-label drug use (Hurlbutt, Bray, Mitchell, & Stephens, 2011). The survey (Appendix E) was administered by a questionnaire online through Qualtrics®. The survey included eight questions pertaining to the participant's knowledge, fourteen questions pertaining to attitude and eighteen questions pertaining to practice. Five questions were included to obtain demographic data including type of licensure, years of practice, level of education, and employment setting. The questions

covered topics such as: medical history assessment procedures regarding patients' polypharmacy and off-label drug use, off-label drug usage discussed with patients, knowledge of the use of off-label drug therapies in the dental office, knowledge of FDA indications for drugs used in the dental office, utilization of drugs for off-label purposes in the dental office, and documentation practices. Participants were asked if suspected off-label drug use was investigated upon medical history reviews and if they utilized drugs for off-label use in the dental office.

Validity and reliability. Prior to administration, the survey was tested for reliability by a test/retest method and validity was assessed using a content validity index. The test/retest analysis was used to ensure that the survey yielded consistent results. Six dental hygienists, not taking the survey and belonging to the participating dental hygiene components, were asked to complete the survey. Two weeks after the initial survey was completed, the same participants took the survey again and consistency was evaluated (Appendix F).

A content validity index was used to assess the degree to which the survey content addressed pharmacological subject matter in regards to polypharmacy and off-label drug use. Five subject matter experts were asked to complete a content validity index and a content validity relevance ratio was computed (Appendix G). The survey was revised based on results of the content validity index and reliability tests.

Procedures and protocols. The online survey link was sent to dental hygienists in the LBDHA and TCDHA databases via email and included a cover letter asking for their participation in the survey. An incentive was offered to those who chose to include their email address offering the opportunity to enter a drawing for two Drug Information

Handbooks for Dentistry. Email addresses were separated from the survey. Additional emails (Appendix H) with a link to the online survey were sent out 10, 20, and 30 days after the initial email as a reminder to participate in the survey. Five days after the third email was sent, data collection was completed and data analysis began.

Limitations

Some limitations existed in this study. One limitation was the use of a convenience sample of dental hygienists in the LBDHA and TCDHA database. A convenience sample is typically one in which the researcher can easily access and can be biased (Patten, 2014). By using the LBDHA and TCDHA databases there was bias against other dental hygienists not in the database. Additionally, including only individuals in California created bias against dental hygienists in other states. These limitations along with a small sample size might have compromised the ability to generalize the results of this study to the general population. Another limitation was that this study did not provide evidence of causality and will only identify associations.

The use of an online survey was also considered a limitation of this study. It has been reported that surveys distributed via the Internet may yield a lower response rate than those distributed by mail; however, some studies have shown a positive response rate for online surveys compared to those distributed by mail (Edwards, Dillman, & Smyth, 2014). Edwards et al. conducted a study to compare the response rate, speed, and completeness of surveys sent via the Internet and by mail using 306 potential participants. Participants were randomly assigned a survey via the Internet or mail. These authors found no statistical significance in response rate with 51% of Internet surveys and 53% of the mailed surveys were completed. Conversely, statistical significance was found in

regards to the speed of response being 9.22 days for the internet based survey and 16.43 days for the mailed survey after two rounds of distribution. Lastly, statistical significance was also found in favor of Internet surveys for completeness with 22.51 of the 35 possible items completed on the Internet responses whereas respondents to the mail version of the survey completed 16.88.

Statistical Analysis

Data were collected via the online survey tool, Qualtrics and imported into SPSS version twenty-four. General characteristics were calculated using descriptive statistics and ANOVA was used to assess the differences in attitude, knowledge, and practices of polypharmacy and off-label drugs based on participants' level of education, years of experience, and type of licensure. Significance was set at a value of $p<0.05$.

Summary

This study used a KAP survey via an online survey tool. A convenience sample of dental hygienists was utilized through LBDHA and TCDHA. A content validity index was calculated in order to ensure relevance to the subject matter and a test/retest method was used to establish reliability. Following data collection and analysis, a manuscript was prepared for submission to the *Journal of Dental Hygiene* (Appendix I).

References

Alexander, G. C., Gallagher, S. A., Mascola, A., Moloney, R. M., & Stafford, R. S. (2011). Increasing off‐label use of antipsychotic medications in the United States, 1995–2008. *Pharmacoepidemiology and drug safety*, *20*(2), 177-184.

American Dental Hygienists' Association. (2015). *Licensure.* Retrieved from http://www.adha.org/licensure

American Dental Hygienists' Association. (2016). *National dental hygiene research agenda.* Retrieved from https://www.adha.org/resources-docs/7111_National_Dental_Hygiene_Research_Agenda.pdf

American Dental Hygienists' Association. (2014). *Standards for clinical dental hygiene practice.* Retrieved from https://www.adha.org/resources-docs/7261_Standards_Clinical_Practice.pdf

Bazzano, A. F., Mangione-Smith, R., Schonlau, M., Suttorp, M. J., & Brook, R. H. (2009). Off-label prescribing to children in the United States outpatient setting. *Academic Pediatrics*, *9*(2), 81-88. doi:10.1016/j.acap.2008.11.010

Cascos-Romero, J., Vázquez Delgado, E., Vázquez Rodríguez, E., & Gay Escoda, C. (2009). The use of tricyclic antidepressants in the treatment of temporomandibular joint disorders: Systematic review of the literature of the last 20 years. *Medicina Oral, Patología Oral y Cirugia Bucal*, *14*(1), 3-7.

Cavalcanti, D. R., & Da Silveira, F. R. X. (2009). Alpha lipoic acid in burning mouth syndrome–a randomized double‐blind placebo‐controlled trial. *Journal of Oral Pathology & Medicine*, *38*(3), 254-261.

Centers for Disease Control and Prevention. (2011). *Dietary supplement use among U.S. adults has increased since NHANES III (1988–1994).* Retrieved from http://www.cdc.gov/nchs/data/databriefs/db61.htm

Centers for Diesease Control and Prevention. (2015) *Life expectancy.* Retrieved from http://www.cdc.gov/nchs/fastats/life-expectancy.htm.

Chen, H., Reeves, J. H., Fincham, J. E., Kennedy, W. K., Dorfman, J. H., & Martin, B. C. (2006). Off-label use of antidepressant, anticonvulsant, and antipsychotic medications among Georgia Medicaid enrollees in 2001. *The Journal of clinical psychiatry*, *67*(6), 972-982.

Chen, D. T., Wynia, M. K., Moloney, R. M., & Alexander, G. C. (2009). U.S. physician knowledge of the FDA-approved indications and evidence base for commonly prescribed drugs: results of a national survey. *Pharmacoepidemiology And Drug Safety*, *18*(11), 1094-1100. doi:10.1002/pds.1825

Culshaw, J., Kendall, D., & Wilcock, A. (2013). Off-label prescribing in palliative care: a survey of independent prescribers. *Palliative Medicine, 27*(4), 314-319. doi:10.1177/0269216312465664

Dresser, R., & Frader, J. (2009). Off-label prescribing: A call for heightened professional and government oversight. *Journal of Law, Medicine & Ethics, 37*(3), 476-486.

Edwards, M. L., Dillman, D. A., & Smyth, J. D. (2014). An experimental test of the effects of survey sponsorship on internet and mail survey response. *Public Opinion Quarterly*, *78*(3), 734-750.

Eguale, T., Buckeridge, D. L., Verma, A., Winslade, N. E., Benedetti, A., Hanley, J. A., & Tamblyn, R. (2015). Association of Off-Label Drug Use and Adverse Drug

Events in an Adult Population. *Journal of the American Medical Association Internal Medicine*, 1-9. doi:10.1001/jamainternmed.2015.6058

Ekins-Daukes, S., Helms, P.J., Taylor, M.W., McLay, J.S. (2005). Off-label prescribing to children: Attitudes and experience of general practitioners. *British Journal of Clinical Pharmacology*, *60*(2), 145-149.

Femiano, F., & Scully, C. (2002). Burning mouth syndrome (BMS): Double blind controlled study of alpha‐lipoic acid (thioctic acid) therapy. *Journal of Oral Pathology & Medicine*, *31*(5), 267-269.

Field, R. I. (2008). The FDA's new guidance for off-label promotion is only a start. *Pharmacy and Therapeutics, 33*(4), 220.

Ghinea, N., Lipworth, W., & Kerridge, I. (2015). Evidence, regulation and 'rational' prescribing: the case of gabapentin for neuropathic pain. *Journal of Evaluation in Clinical Practice, 21*(1), 28-33. doi:10.1111/jep.12223.

Gupta, S.K., & R.P., Nayak. (2014). Off-label use of medicine: Perspective of physicians, patients, pharmaceutical companies and regulatory authorities. *Journal Of Pharmacology & Pharmacotherapeutics, 5*(2), 88-92. doi:10.4103/0976-500X.130046

Gu, Q., Dillon, C. F., & Burt, V. L. (2010). Prescription drug use continues to increase: US prescription drug data for 2007-2008. *NCHS Data Brief*, (42), 1-8.

Guthrie, B., Makubate, B., Hernandez-Santiago, V., & Dreischulte, T. (2015). The rising tide of polypharmacy and drug-drug interactions: population database analysis 1995-2010. *BMC Medicine, 13*(1), 1-10. doi:10.1186/s12916-015-0322-7

Hawkins, R., Noble, J., Locker, D., Wiebe, D., Murray, H., Wiebe, P., & ... Clarke, M. (2004). A comparison of the costs and patient acceptability of professionally applied topical fluoride foam and varnish. *Journal Of Public Health Dentistry, 64*(2), 106-110.

Helm, K. A. (2007). Protecting public health from outside the physician's office: A century of FDA regulation from drug safety labeling to off-label drug promotion. *Fordham Intellectual Property, Media & Entertainment Law Journal, 18*, 117.

Henry, V. (1999). Off-label prescribing. *Journal Of Legal Medicine, 20*(3), 365-383.

Herring, C., McManus, A., & Weeks, A. (2010). Off‐label prescribing during pregnancy in the UK: an analysis of 18 000 prescriptions in Liverpool Women's Hospital. *International Journal of Pharmacy Practice, 18*(4), 226-229.

Hoang, T., Jorgensen, M. G., Keim, R. G., Pattison, A. M., & Slots, J. (2003). Povidone-iodine as a periodontal pocket disinfectant. *Journal of Periodontal Research, 38*(3), 311-317.

Hurlbutt, M., Bray, K., Mitchell, T. V., & Stephens, J. (2011). California dental hygienists' knowledge, attitudes and practices regarding herbal and dietary supplements. *The Journal of Dental Hygiene, 85*(4), 285-296.

Jacobsen, P. L., & Chavez, E. M. (2005). Clinical management of the dental patient taking multiple drugs. *Journal of Contemporary Dental Practice, 6*(4), 1-16.

Jenny, J. L., Jenny, C., Jayadevan, S., Jayakumary, M., Mohamed, A., Arun, S., & Mohamed, F. M. (2012). Nurses Opinion on the Attributes of Polypharmacy in Patient Safety. *Acta Medica Iranica, 50*(7), 516-521.

Johnson, C. E., Sellnow, T. L., Seeger, M. W., Barrett, M. S., & Hasbargen, K. C. (2004). Blowing the whistle on fen-phen: An exploration of MeritCare's reporting of linkages between fen-phen and valvular heart disease. *Journal of Business Communication, 41*(4), 350-369.

Kamble, P., Sherer, J., Chen, H., & Aparasu, R. (2010). Off-label use of second-generation antipsychotic agents among elderly nursing home residents. *Psychiatric Services, 61*(2), 130-136.

Kantor, E.D., Rehm, C.D., Haas, J.S., Chan, A.T., Giovannucci, E.L. (2015). Trends in Prescription Drug Use Among Adults in the United States From 1999-2012. *American Medical Association, 314*(17):1818-1830. doi:10.1001/jama.2015.13766.

Klein, D. B., & Tabarrok, A. (2008). Do off-label drug practices argue against FDA efficacy requirements? A critical analysis of physicians' argumentation for initial efficacy requirements. *American Journal of Economics & Sociology*, *67*(5), 743-775. doi:10.1111/j.1536-7150.2008.00597.x

Köberlein, J., Gottschall, M., Czarnecki, K., Thomas, A., Bergmann, A., & Voigt, K. (2013). General practitioners' views on polypharmacy and its consequences for patient health care. *BMC Family Practice, 14*, 119. http://doi.org/10.1186/1471-2296-14-119.

Lakhan, R. & Sharma, M. (2010). A study of knowledge, attitudes and practices (KAP) survey of families toward their children with intellectual disability in Barwani, India. *Asia Pacific Disability Rehabilitation Journal, 21*(2), 01-17.

Largent, E., Miller, F., & Pearson, S. (2009). Going Off-label Without Venturing Off-Course: Evidence and Ethical Off-label Prescribing. *Archives Of Internal Medicine*, *169*(19), 1745-1747 3p. doi:10.1001/archinternmed.2009.314

Learn.org. (2016). *What is higher education?* Retrieved from http://learn.org/articles/What_is_Higher_Education.html

Lexicomp. (2016a). *Chlorhexidine gluconate (Lexi-drugs).* Retrieved from http://online.lexi.com.westcoastuniversity.idm.oclc.org/lco/action/doc/retrieve/docid/patch_f/6584

Lexicomp. (2016b). Lexicomp online. Retrieved from http://online.lexi.com.westcoastuniversity.idm.oclc.org/lco/action/home

Li, Y., & Tanner, A. (2015). Effect of antimicrobial intervention on oral microbiota associated with early childhood caries. *Pediatric Dentistry*, *37*(3), 226.

Lin, K. J., De Caterina, R., & García Rodríguez, L. A. (2014). Low-dose aspirin and upper gastrointestinal bleeding in primary versus secondary cardiovascular prevention: a population-based, nested case-control study. *Circulation. Cardiovascular Quality And Outcomes*, *7*(1), 70-77. doi:10.1161/CIRCOUTCOMES.113.000494

Marías, Y. F., Glasauer, P., & Macias, Y. F. (2014). *Guidelines for assessing nutrition-related knowledge, attitudes and practices*. Food and Agriculture Organization of the United Nations. Retrieved from http://www.fao.org/docrep/019/i3545e/i3545e.pdf

Morais-Almeida, A., & Cabral, A.J. (2014). Off-label prescribing for allergic diseases in pre-school children. *Allergol Immunopathol*, 42(4), 342-347.

McLellan, L., Yardley, S., Norris, B., de Bruin, A., Tully, M. P., & Dornan, T. (2015). Preparing to prescribe: How do clerkship students learn in the midst of complexity? *Advances In Health Sciences Education: Theory And Practice*, *20*(5), 1339-1354. doi:10.1007/s10459-015-9606-0

Nayyar, P., Kumar, P., Nayyar, P. V., & Singh, A. (2014). Botox: Broadening the horizon of dentistry. *Journal of Clinical and Diagnostic Research, 8*(12), ZE25–ZE29. doi.org/10.7860/JCDR/2014/11624.5341

Paal, T. (2009). Monitoring the safety of off-label medicine use. *WHO Drug Information*, *23*(1), 21-22.

Patten, M.L. (2014). *Understanding research methods* (9th ed.). Glendale, CA: Pyrczak Publishing.

Patterson, S.M., Cadogan, C.A., Kerse, N., Cardwell, C.R., Bradley, M.C., Ryan, C., Hughes, C. (2014). Interventions to improve the appropriate use of polypharmacy for older people. *The Cochrane Database Of Systematic Reviews*, *10*CD008165. doi:10.1002/14651858.CD008165.pub3

Qato, D. M., Alexander, G. C., Conti, R. M., Johnson, M., Schumm, P., & Lindau, S. T. (2008). Use of prescription and over-the-counter medications and dietary supplements among older adults in the United States. *Journal of the American Medical Association*, *300*(24), 2867-2878.

Radley, D. C., Finkelstein, S. N., & Stafford, R. S. (2006). Off-label prescribing among office-based physicians. *Archives of Internal Medicine*, *166*(9), 1021-1026.

Riley, J. B., & Basilius, P. A. (2007). Physicians' liability for off-label prescriptions. *Hematology and Oncology News and Issues*, *21*(7), 43.

Ship, J. A., McCutcheon, J. A., Spivakovsky, S., & Kerr, A. R. (2007). Safety and effectiveness of topical dry mouth products containing olive oil, betaine, and xylitol in reducing xerostomia for polypharmacy- induced dry mouth. *Journal of oral Rehabilitation*, *34*(10), 724-732.

Strom, B. L., Melmon, K. L., & Miettinen, O. S. (1985). Post-marketing studies of drug efficacy: Why? *The American Journal of Medicine*, *78*(3), 475-480.

Tam, V. C., Knowles, S. R., Cornish, P. L., Fine, N., Marchesano, R., & Etchells, E. E. (2005). Frequency, type and clinical importance of medication history errors at admission to hospital: A systematic review. *Canadian Medical Association Journal*, *173*(5), 510-515.

To, T. M., Agar, M., Shelby-James, T., Abernethy, A. P., Doogue, M., Rowett, D., & ... Currow, D. C. (2013). Off-label prescribing in palliative care - a cross-sectional national survey of palliative medicine doctors. *Palliative Medicine*, *27*(4), 320-328. doi:10.1177/0269216312464263

U.S. Food and Drug Administration (2014a). *About the center for drug evaluation and research.* Retrieved from http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/default.htm

U.S. Food and Drug Administration. (2016). *Botox label: Highlight of prescribing information.* Retrieved from http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/103000s5252lbl.pdf

U.S. Food and Drug Administration. (2009). *Food And Drug Administration moderization act of 1997.* Retrieved from

http://www.fda.gov/regulatoryinformation/legislation/significantamendmentstothefdcact/fdama/fulltextoffdamalaw/ucm2007426.htm.

U.S. Food and Drug Administration. (2014b). *Good reprint practices for the distribution of medical journal articles and medical or scientific reference publications on unapproved new uses of approved drugs and approved or cleared medical devices.* Retrieved from http://www.fda.gov/regulatoryinformation/guidances/ucm125126.htm.

U.S. Food and Drug Administration. (2011). *Guidance for Industry: Responding to unsolicited requests for off-label information about prescription drugs and medical devices.* Retrieved from http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm285145.pdf

U.S. Food and Drug Administration. (2012a). *Inspections, compliance, enforcement, and criminal investigations.* Retrieved from http://www.fda.gov/iceci/enforcementactions/warningletters/2012/ucm330758.htm

U.S. Department of Health and Human Services. (2015). *Medical product safety - Healthy people*. Retrieved from http://www.healthypeople.gov/2020/topics-objectives/topic/medical-product-safety.

U.S. Food and Drug Administration. (2012b). *Premarket notification: Dentsply international.* Retrieved from http://www.accessdata.fda.gov/cdrh_docs/pdf12/k122331.pdf.

U.S. Food and Drug Administration. (2014c). *The FDA's drug review process: Ensuring drugs are safe and effective*. Retrieved from http://www.fda.gov/drugs/resourcesforyou/consumers/ucm143534.htm.

Van Rijkom, H. M., Truin, G. J., & Van't Hof, M. A. (1996). A meta-analysis of clinical studies on the caries-inhibiting effect of chlorhexidine treatment. *Journal of Dental Research, 75*(2), 790-795.

Walton, S. M., Schumock, G. T., Lee, K.-V., Alexander, G. C., Meltzer, D., & Stafford, R. S. (2008). Prioritizing future research on off-label prescribing: Results of a quantitative evaluation. *Pharmacotherapy*, *28*(12), 1443–1452. http://doi.org/10.1592/phco.28.12.1443

Wittich, C., Burkle, C., & Lanier, W. (2012). Ten Common Questions (and Their Answers) About Off-label Drug Use. *Mayo Clinic Proceedings*, *87*(10), 982-990 9p. doi:10.1016/j.mayocp.2012.04.017

Wynn, R., Meiller, T. F., & Crossley, H. L. (2015). *Drug information handbook for dentistry*. Lexi-Comp: Hudson, OH.

World Health Organization. (2008). Advocacy, communication and social mobilization for TB control: a guide to developing knowledge, attitude and practice surveys. Retrieved from http://apps.who.int/iris/bitstream/10665/43790/1/9789241596176_eng.pdf

Appendix A

From: Michelle Hurlbutt
Sent: Saturday, April 16, 2016 12:21 PM
To: Kristen Stephens
Cc: johntara@isu.edu; gurejoan@isu.edu
Subject: Re: KAP Survey

Of course! Anything to help you!

Sent from my iPhone

Appendix B

From: **Arlene Dale Parker, RDH** lbdhsjobs@gmail.com
Subject: Thesis research
Date: August 30, 2016 at 9:30 PM
To: Kristen Stephens, RDH kstep812000@gmail.com

RE: Kristen Stepehns thesis research
The Long Beach component is will to share research materials and surveys with our members

--
Arlene Parker, RDH
CDHA - Membership Council Chair
http://cdha.org/join-cdha-today

Long Beach Dental Hygienists' Association (LBDHA)
Newsletter, Employment Referrals and Continuing Education Programs
www.lbdhs.org

*MEMBERSHIP MATTERS *

Appendix C

Survey of Tri-County Dental Hygienists

Appendix D

Dear Registered Dental Hygienist:

I am a graduate student at Idaho State University and a practicing dental hygienist in California. I am completing a research project for my thesis on the knowledge, attitudes, and practices of oral health professionals in regards to polypharmacy and off-label medication use. You have been identified as a member of either the Long Beach Dental Hygiene Association or the Tri-County Dental Hygiene Association and therefore, you are being invited to participate in this survey. Research shows there has been a significant increase in the use of medications for off-label purposes as well as in the numbers of medications being used concurrently by a large portion of the population. The purpose of this survey is to identify practicing dental hygienists' knowledge, attitudes and practices regarding off-label medications and polypharmacy.

The Qualtrics survey program is designed to remind non-responders about the opportunity to participate at one and two weeks after the original invitation. Your responses to the survey will be anonymous. Your name will not be collected or appear anywhere on the survey and complete privacy will be guaranteed. Participation is completely voluntary and survey responses will be reported in aggregate form.

The survey can be filled out in approximately 10 to 15 minutes. By completing the survey you consent to participate in the study.

As a token of appreciation, participants who complete the survey and provide their e-mail address will be entered into a drawing for one of two Drug Information Handbooks for Dentistry. If you choose to be entered into the drawing, your e-mail address will be separated from the responses you provide.

If you have any questions about your rights as a research participant you may contact the Idaho State University Institutional Review Board at (208) 282-2179.

For further information regarding this research please contact me at stepkri2@isu.edu. I appreciate your participation and request that your response is returned by 10/18/16.

Survey Link: **(https://isudhs.az1.qualtrics.com/SE/?SID=SV_bmtW0FdjU8FiYFn)**

Thank you so much for your support!
Kristen Stephens RDH, BS
Graduate Dental Hygiene Student

Appendix E

A SURVEY OF CALIFORNIA DENTAL HYGIENISTS' KNOWLEDGE, ATTITUDES AND PRACTICES ON POLYPHARMACY AND OFF-LABEL MEDICATIONS

SECTION 1 – YOUR PRACTICE

These questions concern your professional practice regarding patients taking 5 or more medications and your patients' use of off-label medications (FDA-unapproved uses). When asked a question with percentages, round your answers up or down to the closest 10%.

Please select the ONE BEST ANSWER for each question. Place an "X" in the appropriate response box.

1. In the last month, have you had professional contact with any patients?
    a. Yes
    b. No

Please note: If you responded "No" to question #1, please skip to SECTION 2 – YOUR ATTITUDE.

2. How many hours per week do you spend treating patients? _____

3. Approximately how many patients do you treat in one week?_____

4. What percent of your patients do you estimate are experiencing polypharmacy (patient is currently take 5 or more medications daily)?
    a. 0%
    b. 1%-30%
    c. 31%-50%
    d. 51%-80%
    e. >80%

5. What percent of your patients do you estimate currently use medications for off-label indications (FDA-unapproved uses)?
    a. 0%
    b. 1%-30%
    c. 31%-50%
    d. 51%-80%
    e. >80%

6. In the past 30 days, in what percent of your clinical encounters have you *asked a patient or family member* about potential medication adverse effects?
    a. 0%

b. 1%-30%
c. 31%-50%
d. 51%-80%
e. >80%

7. In the past 30 days, in what percent of your clinical encounters have you *asked a patient or family member* about potential medication interactions?
    a. 0%
    b. 1%-30%
    c. 31%-50%
    d. 51%-80%
    e. >80%

8. In the past 30 days, in what percent of your patient encounters did you identify the patient's use of medications for off-label purposes?
    a. 0%
    b. 1%-30%
    c. 31%-50%
    d. 51%-80%
    e. >80%

9. In the past 30 days, in what percent of your patient encounters did you identify an adverse event from a medication used for off-label purposes?
    a. 0%
    b. 1%-30%
    c. 31%-50%
    d. 51%-80%
    e. >80%

10. In the past 30 days, in what percent of your patient encounters did you identify an interaction between medications used for off-label purposes?
    a. 0%
    b. 1%-30%
    c. 31%-50%
    d. 51%-80%
    e. >80%

11. In the past 30 days, in what percent of your patient encounters did you identify an adverse event from a medication(s) in a patient being treated with 5 or more medications?
    f. 0%
    g. 1%-30%
    h. 31%-50%
    i. 51%-80%
    j. >80%

12. In the past 30 days, in what percent of your patient encounters did you identify an interaction between medications in a patient being treated with 5 or more medications?
    a. 0%
    b. 1%-30%
    c. 31%-50%
    d. 51%-80%
    e. >80%

13. In the past 30 days, in what percent of your patient encounters did you *provide patient handouts* or refer patients/families to specific books, articles or web sites for additional information about the medication(s) the patients was taking?
    a. 0%
    b. 1%-30%
    c. 31%-50%
    d. 51%-80%
    e. >80%

14. In the past 30 days, in what percent of your patient encounters did you *refer the patient to their physician* for additional information about the medication(s) the patients was taking?
    a. 0%
    b. 1%-30%
    c. 31%-50%
    d. 51%-80%
    e. >80%

15. In the past 30 days, in what percent of your patient encounters did you *refer the patient to their pharmacist* for additional information about the medication(s) the patients was taking?
    a. 0%
    b. 1%-30%
    c. 31%-50%
    d. 51%-80%
    e. >80%

16. In the past 30 days, in what percent of your patient encounters did you utilize a medication for an off-label indication as part of the encounter?
    a. 0%
    b. 1%-30%
    c. 31%-50%
    d. 51%-80%
    e. >80%

17. If you stated that you utilized a medication for an off-label indication in the previous question, did you explain the off-label use to the patient?

a. Yes
b. No
c. Don't know

18. Have you attended a continuing education course specifically related to medications in the last year?
    a. Yes
    b. No
    c. Don't know

SECTION 2 – YOUR ATTITUDES AND BELIEFS

These questions reflect your overall confidence in dealing with off-label medications, medical history assessment, and patients being treated with 5 or more medications.
Check the ONE BEST answer that describes how you feel about each statement.

1. If a patient is being treated in the dental office with a medication for an off-label indication, informed consent should be obtained prior to use.

   Strongly disagree Disagree Uncertain Agree Strongly Agree

2. When off-label uses are discovered for medications, FDA approval should be pursued before they are prescribed, recommended, or used for off-label indications.

   Strongly disagree Disagree Uncertain Agree Strongly Agree

3. Off-label prescribing should be illegal.

   Strongly disagree Disagree Uncertain Agree Strongly Agree

4. I feel confident responding to *patients' questions* about medications used for off-label purposes.

   Strongly disagree Disagree Uncertain Agree Strongly Agree

5. I feel confident *initiating discussions* with patients about medications used for off-label purposes.

   Strongly disagree Disagree Uncertain Agree Strongly Agree

6. I feel confident *initiating discussions* with patients about taking 5 or more medications simultaneously.

   Strongly disagree Disagree Uncertain Agree Strongly Agree

7. I can warn patients about *interactions* between commonly used prescription and over the counter medications.

   Strongly disagree Disagree Uncertain Agree Strongly Agree

8. I can readily *record* information about patients' use of off-label medications in the patient record.

   Strongly disagree Disagree Uncertain Agree Strongly Agree

9. I feel confident that my dental hygiene *education* prepared me to manage patients who use medications for off-label purposes.

   Strongly disagree Disagree Uncertain Agree Strongly Agree

10. I feel confident that my dental hygiene *education* prepared me to manage patients who take 5 or more medications.

    Strongly disagree Disagree Uncertain Agree Strongly Agree

11. I feel confident talking with *colleagues* about medications used for off-label purposes.

    Strongly disagree Disagree Uncertain Agree Strongly Agree

12. I feel confident talking with *colleagues* about patient care for those taking 5 or more medications.

    Strongly disagree Disagree Uncertain Agree Strongly Agree

13. I know more about treating patients taking 5 or more medications than many dental hygienists.

    Strongly disagree Disagree Uncertain Agree Strongly Agree

14. I know more about medications used for off-label purposes than many dental hygienists.

    Strongly disagree Disagree Uncertain Agree Strongly Agree

SECTION 3 – YOUR KNOWLEDGE

These questions concern your knowledge of medications used for off-label purposes. Please answer these to the best of your ability, using no outside resources. There is one correct answer for each question. Only check "I don't know" if you have no knowledge of the topic and cannot make an educated guess.

1. Once a medication is FDA approved for a specific indication, it can also be **utilized** for off-label indications.
    a. True
    b. False
    c. I don't know

2. Once a medication is FDA approved for a specific indication, it can also be **marketed** for off-label indications.
    a. True
    b. False
    c. I don't know

3. Which of the following indications is considered off-label for *MI Paste*?
    a. relief of dentinal hypersensitivity.
    b. penetrating and remineralizing white-spot lesions.
    c. cleaning and polishing procedures as part of a professionally administered prophylaxis treatment.
    d. secondary management of tooth sensitivity, ultrasonic, post scaling, root planing and bleaching
    e. all of the above
    f. none of the above
    g. I don't know

4. Which of the following indications is considered off-label for *fluoride varnish*?
    a. treatment of hypersensitive teeth
    b. application as a cavity liner
    c. sealing of dentinal tubules for cavity preparations or on sensitive root surfaces.
    d. an anti-caries treatment
    e. all of the above
    f. none of the above
    g. I don't know

5. Which of the following indications is considered off-label for *povidone iodine*?
    a. relief of miner vaginal irritation
    b. treatment of topical infections associated with surgery, burns, minor cuts/scrapes
    c. prevention of topical infections associated with surgery, burns, minor cuts/scrapes
    d. subgingival irrigation in periodontal pockets
    e. all of the above
    f. none of the above
    g. I don't know

6. The treatment of tempromandibular joint disorder with *Botox* is considered an off-label use.
    a. True
    b. False
    c. I don't know

7. Which of the following indications is considered off-label for *0.12% chlorhexidine gluconate*?
    a. an antiseptic hand rinse for healthcare personnel
    b. an antibacterial dental rinse for gingivitis treatment
    c. an anti-caries treatment
    d. a wound and general skin cleanser for patients
    e. an adjunctive therapy to reduce pocket depth in patients with periodontitis
    f. all of the above
    g. none of the above
    h. I don't know

8. The use of the natural supplement, *alpha-lipoic acid* in the treatment of pain associated with burning mouth syndrome is considered an off-label use.
    a. True
    b. False
    c. I don't know

SECTION 4 – ALL ABOUT YOU

These questions reflect your personal characteristics and are crucial to the survey so the investigator can correlate the findings. We will compile these answers in an overall description of those that complete this survey, but will not report any individual's answers. Your response will remain anonymous and confidential.

1. Highest level of *dental hygiene degree* earned:
    a. Certificate
    b. Associate
    c. Bachelor
    d. Master

2. What type of California dental hygiene license do you have?
    a. RDH
    b. RDHEF
    c. RDHAP
    d. RDH & RDHAP
    e. I no longer have an active California dental hygiene license

3. Highest level of *college degree* earned:
    a. Associate
    b. Bachelor
    c. Master

d. Doctorate

4. How many years have you been a dental hygienist?
    a. < 5 years
    b. 5-15 year
    c. 16-25 years
    d. 26-35 years
    e. 36-45 years
    f. > 45 years

5. Which best describes the type of practice setting you currently work the greatest number of hours per week?
    a. General Dentistry
    b. Periodontics
    c. Education
    d. Public Health
    e. Corporate
    f. Consultant
    g. Alternative Practice
    h. Other:_____
    i. I no longer practice clinical dental hygiene

Appendix F

Summary of Reliability Testing – Stephens Survey

Survey Item	Answered the Same	Answered Differently	Total Percent Consistent	Recommendation
Practice				
1	6		100%	
2	4	2	66.7%	
3	4	2	66.7%	
4	6		100%	
5	5	1	83.3%	
6	3	3	50%	
7	4	2	66.7%	
8	6		100%	
9	5	1	83.3%	
10	4	2	66.7%	
11	4	2	66.7%	
12	3	3	50%	
13	5	1	83.3%	
14	4	2	66.7%	
15	4	2	66.7%	
16	6		100%	
17	6		100%	
18	6		100%	
Attitudes and Beliefs				
1	5	1	83.3%	
2	3	3	50%	
3	5	1	83.3%	
4	3	3	50%	
5	4	2	66.7%	
6	3	3	50%	
7	3	3	50%	
8	6		100%	
9	4	2	66.7%	
10	6		100%	
11	5	1	83.3%	
12	6		100%	
13	4	2	66.7%	
14	6		100%	
Knowledge				
1	6		100%	
2	5	1	83.3%	
3	4	2	66.7%	
4	4	2	66.7%	
5	4	2	66.7%	
6	5	1	83.3%	
7	2	4	33.3%	

8	5	1	83.3%	
All About You				
1	6		100%	
2	6		100%	
3	6		100%	
4	6		100%	
5	6		100%	

Appendix G

Summary of CVI – Polypharmacy and Off-Label Drug Use Survey

Survey Item	Not Relevant	Somewhat Relevant	Relevant	Very Relevant	Total Percent Relevant	Recommendation
Section 1 – Item 1	1		3	1	80%	Keep
Attitude 2	1		3	1	80%	Keep
3	1		3		60%	1 did not answer; technically delete item based on score alone, but majority did find relevant so would keep
4			2	3	100%	Keep
5			1	4	100%	Keep
6		1		4	80%	Keep
7		1		3	60%	Keep; same as 3
8			1	4	100%	Keep
8a		2	2	1	60%	Delete
8b		2	2	1	60%	Delete
9			5		100%	Keep
10			5		100%	Keep
11			5		100%	Keep
12			2	3	100%	Keep
13			2	3	100%	Keep
14		1		4	80%	Keep
15	1	1	3		60%	Delete
Attitudes and Beliefs						
1				5	100%	Keep
2			2	3	100%	Keep
3			1	4	100%	Keep
4			1	4	100%	Keep
5			1	4	100%	Keep
6			1	4	100%	Keep
7			2	3	100%	Keep
8			1	4	100%	Keep
9		1	1	3	80%	Keep
10			2	3	100%	Keep
Knowledge						
1			1	4	100%	Keep
2			2	3	100%	Keep
3				5	100%	Keep
4				5	100%	Keep
5				5	100%	Keep
6				5	100%	Keep

7				5	100%	Keep
8				5	100%	Keep
All About You						
1	1	1	1	2	60%	Delete
2				5	100%	Keep
3		1	1	3	80%	Keep
4				5	100%	Keep
5				5	100%	Keep
6			2	3	100%	Keep
7	2	2	1		20%	Delete
8		3	1	1	40%	Delete

Appendix H

Dear Registered Dental Hygienist,
One week ago, you should have received a survey regarding the knowledge, attitudes, and practices of oral health professionals in regards to polypharmacy and off-label medication use. The Qualtrics survey management software has automatically keyed this email reminder. Your participation in this survey is requested but not mandatory. Participation is both voluntary and anonymous.
This survey can be completed in less than 15 minutes and will provide useful information regarding dental hygienists' knowledge, attitudes and practices with off-label drug use and polypharmacy. Your response is both greatly appreciated, as well as very important to the success of this study.
If you have any questions regarding this survey, please contact me at stepkri2@isu.edu. I appreciate your participation an request that your response is returned by 10/18/16.
Survey Link: (**https://isudhs.az1.qualtrics.com/SE/?SID=SV_bmtW0FdjU8FiYFn**)

Thank you for your participation,
Kristen Stephens, RDH, BS
Graduate Dental Hygiene Student

Appendix I

Author Guidelines

s should be limited. End this section with a clear statement of the purpose of the study, hypothesis or research objectives.

Methods and Materials: Describe the research design (e.g. randomized controlled trial) and procedures (e.g. IRB approval, target population, inclusion/exclusion criteria, recruitment, informed consent, variables to be tested, instruments, equipment, procedures and method of data analysis). Specify the measurements and statistical tests used as well as related levels of significance. Furthermore, assure an adherence to all pertinent federal and state regulations concerning the protection of the rights and welfare of all human and animal subjects.

Results: Summarize all relevant data and study findings. Do not repeat in the text the data reported in tables and figures verbatim, but do refer to the data and emphasize important findings (e.g. Table 1 shows that most of the subjects were African American and between the ages of 12 and 16).

Discussion: Evaluate and interpret the findings. Compare them with those of other related studies. Discuss how they relate to dental hygiene practice, profession, education or research. Include overall health promotion and disease prevention, clinical and primary care for individuals and groups and basic and applied science. Discuss study limitations; implications for dental hygiene practice, education, and research; and recommendations or plans for further study.

Conclusion: State the conclusions, theories, or implications that may be drawn from the study. This section should be one to two paragraphs or can be listed as bulleted points.

Literature Reviews – Limited to 3,000 words (excluding cover page, abstract, references and tables/figures).

A presentation of relevant and primary published material on a specific topic constitutes a comprehensive literature review. Such a review includes a summary and critique of the current status of the topic, and the aspects requiring further study.

Abstract: Literature reviews begin with a non-structured abstract — a brief statement of purpose, content summary, conclusions and recommendations.

Short Reports – Limited to no more than 2,000 words (excluding cover page, abstract, references and tables/figures). Illustrations should be limited to a total of no more than two (e.g. two figures, two tables, or one figure and one table).

The JDH publishes short reports related to dental hygiene. Short reports are limited in scope and should begin with a brief, non-structured abstract that describes the topic.

Text: A concise introduction (which includes a literature review), detailed description of the topic or activity, and discussion, conclusion and recommendations must also be included. References are necessary to support the rationale and methods presented.

A short report may describe a clinical case study, an educational innovation, a research method, a concept or theory, or other current topics.

Clinical Case Study: A report that describes a unique aspect of patient care not previously documented in the literature. Such reports usually focus on a single patient or groups of patients with similar conditions. Suitable topics include, but are not limited to, innovative preventive methods or programs, educational methods or approaches, health promotion interventions, unique clinical conditions, or pathologies and ethical issues.

Theoretical Manuscript: A report that provides a well-supported explanation for natural phenomena that clarify a set of interrelated concepts, definitions, or propositions about dental hygiene care or processes. Such reports provide new knowledge, insight, or interpretation; and discussion, conclusions, and recommendations. These reports begin with a non-structured abstract. At least four keywords are listed at the end of the abstract.

Critical Issues in Dental Hygiene – Limited to 4,000 words (excluding cover page, abstract, references and tables/figures).

The purpose of this category is to highlight challenges and opportunities pertinent to the future directions of the profession of dental hygiene.

Text: Articles in this category should follow the basic structure for text outlined for Original Research Reports.

Innovations in Education and Technology – Limited to 4,000 words (excluding cover page, abstract, references and tables/figures).

The purpose of this category is to feature short reports of innovative teaching applications and techniques as well as new technologies available for increased communication and learning in dental hygiene education.

Text: Articles in this category should follow the

basic structure for text outlined for Original Research Reports.

Manuscript Submission

Authors submitting a manuscript to the JDH should utilize the BenchPress system, located at http://submit-jdh.adha.org/. Specific instructions for submission will be outlined on the BenchPress website. There is no charge for submission. Receipt of submission will be acknowledged by email.

All papers are reviewed by the editor and assigned to three reviewers. The editor reserves the right to return, without review, any manuscript that does not meet JDH criteria for formal review.

The review process takes approximately ten to twelve weeks, depending on the need for authors to make revisions. All reviewer comments, as well as notification of acceptance or rejection, are submitted to the corresponding author. For any questions about the manuscript submission process, contact Staff Editor Josh Snyder at joshs@adha.net.

Manuscript Preparation and Style

Standard usage of the English language is expected. Manuscripts should contain one-inch margins, double spacing and Verdana 10 pt. font. All pages should be numbered, beginning with title page and ending with references.

Title Page: A title page must include: 1) title of article, which should be concise yet informative, 2) first name, middle initial and last name of each author, with academic credentials, 3) each author or coauthor's job title, department and institution or place of employment (if other than academic), 4) disclaimers/disclosures, if any, 5) name, address, all contact information of author responsible for correspondence about the manuscript, and 6) funding sources for the project, equipment, drugs, etc.

Blinding Manuscripts: All information that can identify the author(s) (such as author name, institutional affiliation, IRB approval, acknowledgements, etc.) should be included in the title page. Manuscripts must be blinded and any of the above identifying information should be removed from the text for the review process. If a manuscript is accepted for publication, this information can be added back into the manuscript for publication.

Keywords: When submitting a manuscript, please choose four to six keywords from the list provided by BenchPress. These key words will be used for indexing purposes during the review process. If a manuscript is accepted for publication, a more detailed list of key words can be provided.

National Dental Hygiene Research Agenda: Identify how the study supports a specific topic area and related objective from the National Dental Hygiene Research Agenda (NDHRA). For example: This study supports the objective: Assess strategies for effective communication between the dental hygienist and the client, under Health Promotion/Disease Prevention. NDHRA statements can be found at: http://www.adha.org/downloads/Research_agenda%20-ADHA_Final_Report.pdf

Author Biography: Please include a brief biographical sketch of each author at the end of the cover letter. List names, credentials, titles, affiliations and locations. Example: "Mary B. Jones, RDH, MA, is assistant professor and clinic director, Department of Dental Hygiene; Bill R. Smith, DDS, MEd, is associate professor, Department of Pediatric Dentistry. Both are at the University of Minnesota in Minneapolis."

Disclosure: Authors are obligated to identify any actual or potential conflict of interest in publishing the manuscript. This includes association with a company that produces, distributes or markets any products mentioned, or with funding provided to help prepare the manuscript. Disclosures should appear at the beginning of the manuscript.

Acknowledgments: Be brief and straightforward. Example: "The authors thank Jane Smith, RDH, for her assistance in developing the survey instrument." Anyone making a substantial contribution to the conduct of the research or the resulting report should be appropriately credited as an author.

Acronyms: Spell out abbreviations and acronyms on first mention followed by the abbreviation in parentheses. Limit the overall use of abbreviations in the text.

Medication, Product or Device Names: Throughout the text, use generic, nonproprietary names for medications, products and devices. At the first mention, state the generic name followed in parentheses by the trade name with the register® or trademark™ symbol and the manufacturer's name and city/state.

Example: Chlorhexidine (Peridex®; 3M ESPE, Minneapolis, MN) coded or abbreviated as CHX

Visual Aids

Do not embed tables and figures in the body of the text. These should be provided as separate files, per BenchPress instruction. All tables and figures must be blinded for the review process.

Tables: All tables must have a title that is brief but self-explanatory. Readers should not have to refer to the text to understand a table. The main body of text should not overly depend on the tables. Indicate explanatory notes to items in the table with reference marks (*, #). Cite each table in the text in the order in which it is to appear. Identify tables with Roman Numerals (example: Table I).

Figures: Includes charts, graphs, photographs and artwork. All should include a brief caption and use Arabic numerals (example: Figure 1). Cite each figure in the text in the order in which it will appear.

Photographs: High-resolution digital photos are preferred, with a resolution of at least 300 pixels per inch.

References

The JDH follows National Library of Medicine (NLM) citation style. Please refer to http://www.wsulibs.wsu.edu/quickguides/nlm for specifics.

Each reference should be numbered in the order it first appears in the text. If a source is cited more than once, the first reference number it is given is used throughout. Each reference in the text should be in superscript format. Continuous references should be connected with a dash (example: 7,8-10). ADHA editorial staff does not assume responsibility for verifying references. For more information and detailed examples, please visit the International Committee of Medical Journal Editors at www.icmje.org. Please ensure that every reference cited in the text is also present in the reference list and vice versa. Citation of a reference as "in press" implies that the item has been accepted for publication.

Please list all authors. Capitalize only the first word of the journal article title, and use the NLM journal abbreviations found at www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=journals. If more than six authors are listed, list the first three followed by et al.

Examples of reference citations:

Example Article in a Journal: Michalowicz BS, Hodges JS, DiAngelis AJ, et al. Treatment of periodontal disease and the risk of preterm birth. N Engl J Med. 2006;355(18):1885-1894.

Smith MA, Jones BB. Curette sharpness: a literature review. J Dent Hyg. 1996;77:382-390.

Book citations: Spolarich AE, Gurenlian JR. Drug-induced adverse oral events. In: Daniel SJ, Harfst SA, Wilder RS, ed. Mosby's Dental Hygiene: Concepts, Cases and Competencies. 2nd ed. St. Louis, MO. Mosby/Elsevier Publishing. 2008. p. 259-276.

Internet citations: NLM requires the standard elements of a citation for an Internet resource, with a few modifications. The main elements required:

Polgreen PM, Diekema DJ, Vandeberg J, et al. Risk factors for groin wound infection after femoral artery catheterization: a case-control study. Infect Control Hosp Epidemiol [Internet]. 2006 Jan [cited 2007 Jan 5];27(1):34-7. Available from: http://www.journals.uchicago.edu/ICHE/journal/issues/v27n1/2004069/2004069.web.pdf

Poole KE, Compston JE. Osteoporosis and its management. BMJ [Internet]. 2006 Dec 16 [cited 2007 Jan 4];333(7581):1251-6. Available from: http://www.bmj.com/cgi/reprint/333/7581/1251?maxtoshow=&HITS=10&hits=10&RESULTFORMAT=&andorexactfulltext=and&searchid=1&FIRSTINDEX=0&sortspec=relevance&volume=333&firstpage=1251&resourcetype=HWCIT

Publication

Accepted manuscripts are edited and sent to the principal author for approval of technical accuracy. Editors reserve the right to edit or rewrite copy to fit the style requirements of the JDH. All authors must sign agreements that permit the article to be published and to transfer copyright.

For further information, please contact the JDH by phone at 312-440-8900 or by e-mail at JoshS@adha.net.

Author's Responsibilities

Personal Communications and Unpublished Data

The JDH requires that authors request and receive permission from each person identified in the manuscript as a source of information in a personal communication or as a source for unpublished data. By submitting their manuscripts, authors represent and warrant to the JDH that such permission has been obtained, if applicable. The

JDH strongly recommends that such permissions be in writing and that authors should maintain the signed statements in their records for a reasonable period of time after publication of their work in the JDH. Authors must specify in the manuscript the date of the communication or the data, as well as whether the communication was written or oral.

Example: Additionally, the efforts of the office administrator, with regard to accommodating schedules and financing, could have been a factor (Vaccari, personal communication, April 2008).

Copyright Transfer

The ADHA owns the copyright for all editorial content published in the JDH. An author agreement form, requiring copyright transfer from authors, signed by each author, must be signed before the manuscript is published in the JDH. Manuscripts without a signed author agreement form will not be published until the JDH's Editorial office receives a valid, executed author agreement form from each author. If the manuscript is rejected by the JDH, all copyrights in the manuscript will be retained by the author(s). All accepted manuscripts and their accompanying illustrations become the permanent property of the ADHA and may not be published elsewhere in full or in part, in print or electronically, without written permission from the ADHA's Communications Division.

NIH Open Access Policy

National Institutes of Health Public Access Policy: Authors' Responsibilities – The National Institutes of Health (NIH) Public Access Policy implemented a law passed in December 2007 that affects authors who receive funding from the NIH. As of April 7, 2008, all peer-reviewed articles that arise, in whole or in part, from direct costs funded by NIH, or from NIH staff, that are accepted for publication by a peer-reviewed journal—including JDH—must be deposited with the National Library of Medicine's PubMed Central, in the form of a copy of the manuscript's final version on its acceptance. Please see the following NIH site regarding questions that authors may have about the policy: http://publicaccess.nih.gov.

For JDH papers, when the author deposits the accepted manuscript with PubMed Central, he or she should specify that the manuscript is not to be made available until 12 months after publication (not acceptance). Thereby, the manuscripts will be made publicly available by PubMed Central at the same time that the JDH makes its full text available to the public free of charge.

JDH holds the copyright to all published material except for material authored solely by U.S. government employees. Please see the JDH Author Agreement form (PDF) for further details. The Policy applies to any author of a manuscript that is peer-reviewed, is accepted for publication on or after January 1, 2011, and, arises from one of the following: any direct funding from an NIH grant or cooperative agreement active in Fiscal Year 2008 or beyond, any direct funding from an NIH contract signed on or after April 7, 2008, any direct funding from the NIH Intramural Program or an NIH employee.

SECTION II: Publishable Manuscript

Title Page

California dental hygienists' knowledge, attitudes and practices regarding polypharmacy and off-label drugs

Kristen Stephens, RDH, MS

Tara Johnson, RDH, PhD

JoAnn R. Gurenlian, RDH, MS, PhD

Kristen Stephens is a full-time instructor, Department of Dental Hygiene, West Coast University; Dr. Johnson is Associate Professor, Department of Dental Hygiene, Idaho State University; Dr. Gurenlian is Professor and Graduate Program Director, Department of Dental Hygiene, Idaho State University.

Disclosure: All authors have no conflict of interest.

Direct correspondence and requests for reprints to Kristen Stephens, Department of Dental Hygiene, West Coast University, 1477 S. Manchester Ave., Anaheim, CA 92802; 562-547-7765 phone; kstephens@westcoastuniversity.edu.

No funding sources for project, equipment, drugs, etc.

Abstract

California dental hygienists' knowledge, attitudes and practices regarding polypharmacy and off-label drugs

Purpose: This study examined the knowledge, attitudes, and practices of dental hygienists in California regarding polypharmacy and drugs used for off-label purposes both in medicine and dentistry.

Methods: In a cross-sectional design, knowledge, attitudes, and practices (KAP) related to off-label drugs and polypharmacy were assessed via an online survey tool. The sample included licensed dental hygienists, who were registered with the Long Beach and Tri-County Dental Hygienists' Associations in Southern California, (N=360). Participant characteristics were calculated using descriptive statistics. ANOVA was used to assess differences in knowledge, attitudes and practices when compared to three key variables: highest academic/professional degree, experience and license type.

Results: One hundred seven surveys were returned for a 34% response rate. Over half of respondents (53%) held an Associate degree for their license, most (72%) worked in a general dentistry setting and 46% had practiced 15 years or less. Results revealed very low knowledge levels with 25% of respondents answering zero knowledge items correctly. Furthermore, no significant differences in knowledge and practices related to off-label drugs or polypharmacy were found based on type of licensure, highest degree achieved, or years of experience. However, participants holding a Bachelor degree or higher were significantly more confident ($p=.011$) in discussing polypharmacy with patients and colleagues.

Conclusion: Participants showed a general low-level of knowledge related to off-label drugs and polypharmacy regardless of their level of education, years of experience, or type of dental hygiene licensure. These results indicate a grave need for increasing content in pharmacology in both entry-level programs and continuing education courses.

Key Words: off-label drug use, polypharmacy, dental hygiene assessment, knowledge, attitudes, practices

National Dental Hygiene Research Agenda:

This paper supports the American Dental Hygienists' Association National Dental Hygiene Research Agenda by examining the dental hygienist's role in oral health care, specifically as it relates to patient assessment and safety related to polypharmacy and off-label drug use.

INTRODUCTION

Medical advances of all types have made it possible for individuals to live longer and healthier lives. Similarly, as the population ages, more people are taking increasing numbers of medications (polypharmacy), often times for the treatment of multiple chronic illnesses.[1] Polypharmacy is a concern among some healthcare professionals due to an increased risk of adverse drug reactions, drug interactions, and medication errors.[2] A study evaluating prescription drug use in the United States using NHANES data showed an 8% increase in prescription drug use from 1999-2000 to 2011-2012.[3] Additionally, polypharmacy rates increased from 8.2% to 15%. Polypharmacy, in combination with the use of off-label drug therapy, may affect multiple facets of patient care, in medicine and dentistry alike.

While controversy exists on the use of drugs for off-label therapies related to prescribing practices, increased adverse events, and lack of evidence to support off-label prescribing, the U.S. Food and Drug Administration (FDA) stated it "recognizes that these off-label uses or treatment regimens may be important therapeutic options and may even constitute a medically recognized standard of care."[4] Although the FDA acknowledges the potential benefits of off-label drug therapies, safety, efficacy and approval of drugs being used off label are not required or monitored by the FDA. A lack of regulatory evidence supporting the benefits and potential risks of drugs used for off-label purposes may contribute to rising adverse events or potentially ineffective treatments and remains a concern among healthcare professionals.[5] Adverse drug-drug interactions are especially concerning since polypharmacy has become such a common

aspect of medication regimens. The addition of drugs not thoroughly studied for their off-label indications can further amplify the potential for adverse reactions.

A highly publicized and well-documented example of the association between off-label drug use and the potential for adverse effects was observed with the drug fen-phen. Fenfluramine/dexfenfluramine and phentermine, were individually approved by the FDA as appetite suppressants to be used for a short period of time to aid in weight loss.[6] Alone, these drugs were only slightly effective, but combined and used for the off-label indication of appetite suppression, they exhibited rapid weight loss. The FDA never approved the combination drug fen-phen, and it was discontinued in 1997 due to the number of people who developed heart valve disease.[6] Patients with subsequent valvular disease were recommended to take antibiotic prophylaxis prior to their dental visits.

The use of dietary supplements, such as vitamins, minerals, herbs or other botanicals, has increased among teens and adults of all ages in the US. However, the FDA does not currently regulate or evaluate these supplements for safety and efficacy because they are not intended "to treat, diagnose, prevent or cure diseases".[7] Hence, dietary supplements may be considered off-label since they are void of an FDA approved indication.

In clinical practice, dental hygienists not only see patients who are utilizing drugs for off-label medical purposes, they also employ drugs/medical devices for off-label indications as well. For example, Minimal Intervention (MI) Paste and MI Paste Plus are FDA approved "to be used for cleaning and polishing procedures as part of a professionally administered prophylaxis treatment."[8] Additional indications include the secondary "management of tooth sensitivity, ultrasonic, post scaling, root planing and

bleaching" and for the relief of dentinal hypersensitivity."[8] In 2012, the FDA issued a warning letter to the makers of MI Varnish and Paste, stating that they were in violation of the Federal Food, Drug, and Cosmetic Act due to their promotion of these products for off-label purposes.[8] These off-label indications included treatment of xerostomia due to Sjögrens syndrome and penetration/remineralization of sub-surface lesions in the dentition.[8]

Fluoride varnishes are used in dental settings for multiple indications including anti-caries treatment. The FDA-approved indications for fluoride varnish include the treatment of hypersensitivity, sealing of dentinal tubules for cavity preparations or sensitive root surfaces, and as a cavity liner.[9] Although, the use of fluoride varnish for caries prevention is preferred for young children due to the reduction in risk for over-ingestion, its rapid adherence compared to the traditional four-minute foam and gel applications, and its higher percentage of fluoride (5% sodium fluoride varnish compared to 1.1% sodium fluoride), use of fluoride varnish as an anti-caries treatment is not approved by the FDA.[10] To date there have been no studies identifying whether this off-label use is discussed with patients nor is consent obtained prior to application.

Chlorhexidine gluconate 0.12% (CHX) is an antibiotic oral rinse and skin cleanser approved by the FDA as a preoperative skin preparation, wound and general skin cleanser, surgical scrub and antiseptic hand rinse, dental rinse for treatment of gingivitis, and as an adjunctive therapy to reduce pocket depth in patients with periodontitis.[11] Off label, CHX has also been used in the prevention of dental caries although the research on its efficacy in that capacity has been inconclusive.[12] Used off label in subgingival irrigation, povidone iodine is FDA approved as a broad spectrum external antiseptic for

the prevention or treatment of topical infections associated with surgery, burns, minor cuts/scrapes, or the relief of minor vaginal irritation. This off-label use is becoming more common in clinical practice, and dental hygienists use povidone iodine for subgingival irrigation in order to kill periodontopathic bacteria in the periodontal pocket.[13]

A natural supplement, alpha-lipoic acid (ALA), and therefore not regulated by the FDA, has been used for a myriad of indications including the treatment of nerve pain from diabetes or other diseases, facial pain, weight loss, certain eye conditions, high blood glucose, memory problems, and chronic tiredness. In dentistry, ALA has been studied for the treatment of pain associated with burning mouth syndrome.[14]

While the FDA has worked diligently to establish an appropriate drug review process to ensure the safety and efficacy of drugs marketed in the U.S., advancement in evidence-based medical/dental practice, which often encourages the use of off-label drug therapy, has led to the identification of many off-label treatments that may be beneficial to patient care.[15] Despite obvious benefits to patients, safety and ethical concerns continue to be a source of controversy surrounding the off label use of drugs. Due to the large gap in existing literature, questions have been raised regarding the knowledge, attitudes, and practices of health professionals who utilize drugs off label. Additionally, limitations in the literature regarding the specificity of off-label drug indications and how they are used in the population leaves the dental hygienist with limited information regarding these now common practices. More information in this aspect of pharmacology will allow dental hygienists to make appropriate treatment modifications and to effectively identify adverse effects or medical emergencies that might present. Thus the purposes of this study were two-fold: to examine the knowledge, attitudes, and

practices of dental hygienists in California regarding polypharmacy and drugs used for off-label purposes both in medicine and dentistry; and to identify differences in knowledge, attitudes and practices based on level of education, years of practice and type of licensure. The following research questions guided this study:

1. What are dental hygienists' knowledge levels, attitudes, and practices related to patients' use of off-label drugs and polypharmacy?
2. What are dental hygienists' practices related to the use of off-label drugs in the provision of dental hygiene care?
3. What are the differences in dental hygienists' knowledge, attitudes and practices related to off-label drugs and polypharmacy based on their level of education, years of practice and type of licensure?

It was hypothesized that there is no statistically significant difference between dental hygienists' knowledge, attitudes and practices related to off-label drugs and polypharmacy based on their level of education, years of practice and type of licensure.

METHODS

This cross-sectional study utilized a knowledge, attitude, and practice (KAP) survey and was administered via an online survey tool. Dental hygienists' knowledge, attitudes, and practices were examined in relation to polypharmacy and off-label drug use and compared to their level of education, years of experience, and type of licensure.

A convenience sample of 316 dental hygienists practicing in California was utilized for this study; 150 dental hygiene members of the Long Beach Dental Hygienists' Association (LBDHA) and 166 members of the Tri-County Dental Hygienists Association (TCDHA) were surveyed with permission from the LBDHA and

the TCDHA. Inclusion criteria required current dental hygiene licensure by the state of California and dental hygienists that no longer possess an active license were excluded. This study was reviewed and approved by the Human Subjects Committee, _____ University's Institutional Review Board (IRB-FY2016-379).

A previously designed and validated KAP survey was modified, with permission from the authors, to evaluate dental hygienists' knowledge, attitudes, and practices related to polypharmacy and off-label drug use.[16] The instrument was pilot tested with six practicing dental hygienists for reliability by a test/retest method. Five content experts assessed validity using a content validity index. The survey was revised based on results of these tests and administered online through Qualtrics. The 45-item survey included questions pertaining to demographics (5), knowledge (8), attitudes (14) and practices (18) related to off-label drug use and polypharmacy. Likert-type, multiple choice and ordinal scale questions related to polypharmacy and off-label drugs covered topics such as: discussion with patients, knowledge of therapies used in the dental office, knowledge of FDA-approved indications for drugs used in the dental office, and documentation practices. Participants were asked if suspected off-label drug use was investigated during medical history reviews and if drugs were used for off-label purposes in the dental office.

The LBDHA and TCDHA databases were used to email a cover letter asking for participation, informed consent, and provided an online link to the survey. Three reminder emails were sent, the first ten, twenty, and thirty days following the initial email.

Data were collected online via Qualtrics and imported into SPSS version twenty-three. Participant characteristics were calculated using descriptive statistics and ANOVA

was used to assess the differences in knowledge, attitudes and practices based on participants' level of education, years of practice, and type of licensure. Significance was set at $p \leq 0.05$ for ANOVA analyses.

RESULTS

Demographics

Of the 316 surveys that were emailed, 107 were returned, yielding a response rate of 34%. The majority of respondents had completed an Associate degree for their dental hygiene training (53%) while 42% held a Bachelor degree as the highest college degree earned. The majority of participating dental hygienists (72%) practice in a general dentistry setting and 46% have practiced 15 years or less. All participant characteristics are summarized in Table 1.

Knowledge

Results of knowledge questions related to off-label drug use are presented in Table 2. The mean score for questions answered correctly was 2.28 out of eight. Frequencies for total knowledge scores (Table 3) depict that 25% of participants did not answer any questions correctly, while 74% answered 3 or less questions correctly. Table 4 lays out ANOVA results of key variables analyzed with relationship to participants' knowledge.

Attitudes

Sixty five percent of participants agreed that informed consent should be obtained when using drugs in the dental office for off-label purposes, and half agreed that off-label prescribing should be illegal. Nearly half (44%) believed that FDA approval should be pursued before using medications for off-label purposes. A majority of participating

dental hygienists (69%) felt confident talking about medications used for off-label purposes with colleagues, while 30% were comfortable answering patient questions, and 41% indicated comfort in initiating discussions. Almost half (48%) of respondents did not feel confident their dental hygiene education prepared them to manage patients using medications off label and 15% were uncertain. A large majority (85%) felt confident discussing polypharmacy with colleagues and 63% felt confident initiating discussion with their patients. More than half (66%) of dental hygienists were confident they could inform patients about interactions between commonly used prescriptions and over the counter medications. Sixty-five percent felt confident their dental hygiene education prepared them to manage patients using polypharmacy and 35% were in disagreement or uncertain.

ANOVA results of key variables are compiled in Table 4 showing no significant differences in participant attitudes regarding off-label drugs based on type of licensure, highest degree achieved, or years of experience. Attitudes regarding polypharmacy differed significantly among respondents based on highest degree earned ($p=.011$). Dental hygienists with a bachelor, master or doctoral degree were more confident initiating discussions with patients and talking with colleagues about polypharmcy. These dental hygienists also felt better prepared by their dental hygiene education to manage patients utilizing polypharmacy.

Practices

A total of 18 questions pertaining to practices involving off-label medications and polypharmacy comprised this section of the survey. Twenty-six percent of participants reported attending a continuing education course specifically related to medications

within the last year. A majority of participants (97%) reported seeing patients who use medications for off-label purposes and 68% identified asking patients about off-label medication use. Thirty percent of dental hygienists indicated they use medications for off label during patient care and 39% reported explaining this off-label use to their patients. Many participants reported no history of drug interactions (67%) with off-label medication use and 32% reported no history of any adverse events. All of the dental hygienists surveyed reported seeing patients utilizing polypharmacy. More than half (60%) reported identifying adverse events with their patients related to polypharmacy and 46% reported the identification of drug interactions. Table 5 shows differences in the number of hours per week spent treating patients and the number of patients seen per week based on type of licensure, highest college degree, dental hygiene degree earned, and years of experience.

Accordingly, the null hypothesis was accepted, with the minor exception of the finding that participants were more confident discussing polypharmacy with patients and colleagues based on the highest degree earned ($p=.011$).

DISCUSSION

This study assessed knowledge, attitudes, and practices of California dental hygienists related to off-label drug use and polypharmacy. Results indicate an overall lack of knowledge concerning off-label drugs and their use regardless of participants' licensure, level of education, and/or years of experience. Specifically, hours worked and number of patients seen per week had no bearing on knowledge levels. This finding could be a result of a lack of focus in the subject area of pharmacology, either from

content received during dental hygiene education, or later through continuing education courses.

Current entry-level dental hygiene programs are required to provide instruction in pharmacology as specified in the Accreditation Standards for Dental Hygiene Education Programs mandated by The Commission on Dental Accreditation.[17] However, the standards do not specify the amount or type of instruction that should be delivered related to any topic of pharmacology, particularly polypharmacy or off-label drug use. Likewise, the American Dental Education Association published the ADEA Compendium of Curriculum Guidelines (Revised Edition) Allied Dental Education Programs May 2015-2016 which includes guidelines for pharmacology.[18] Multiple pharmacology topics are included in this revised edition, but no mention is made of polypharmacy or off-label drug use. Textbooks with reference to these topics are very limited. Depending on the text adopted for entry-level dental hygiene programs, inclusion of polypharmacy and off-label drug use is scanty or may not be addressed at all. For example, in Haveles text, "*Basic and Applied Pharmacology for the Dental Hygienist*," 7th edition, off-label drug use is defined and discussed early in the textbook, but rarely referenced in chapters related to various pharmacological categories or with dental hygiene applications although these uses are stated.[19] Therefore, discussions about off-label drug use/polypharmacy and their relevant applications to dental hygiene practice should be included as part of a comprehensive pharmacology curriculum for dental hygienists.

Nearly half of respondents reported that their dental hygiene education did not prepare them to discuss off-label drug use with patients. Findings also showed a lack of confidence when answering patients' questions and initiating discussions about off-label

drug use, signaling dental hygienists may not be sufficiently prepared upon entering the field of practice. Further, education beyond an Associate degree had no impact on knowledge level. Correspondingly, a cross-sectional comparison between pharmacy and medical students in the Netherlands regarding knowledge of basic, applied and clinical pharmacology showed no significant differences in knowledge levels based on number of years of training and education.[20] With regard to continuing education following completion of professional training, only 26% of participants reported that, in the last year, they had attended a course specifically related to medications. These results indicate all dental hygienists, regardless of their level of education and experience, could benefit from a further grounding in pharmacology knowledge.

It is possible that in areas where dental hygienists are able to prescribe drugs more emphasis may be given to this area of pharmacology. In Alberta, Canada, dental hygienists are able to write prescriptions if certain requirements are met. According to the College of Registered Dental Hygienists of Alberta (CRDHA), after completing a CRDHA council approved pharmacy refresher course, dental hygienists may apply for a prescriber identification number.[21] Topics in this course include decision making related to medication use, principles of pharmacology, drugs used in dental hygiene, risk management, drug errors, etc. However, it is unclear if content regarding off-label drug use and polypharmacy is included.[22] Upon successful completion of this course, dental hygienists may prescribe antibiotics, antifungal agents, anti-infective agents, antiviral agents, bronchodilators, epinephrine, fluoride, pilocarpine, and topical corticosteroids "for the purpose of treating oral health conditions, providing prophylaxis and treating emergencies."[23] While knowledge levels of off-label drugs among dental hygienists with

prescription writing privileges is unclear, the CRDHA Guidelines Regarding Prescription and Non-Prescription Drugs in Dental Hygiene Practice, section 1.6, states that those holding a prescriber ID,

> shall not prescribe medications for off-label use unless the drug is part of a research project to investigate use of the drug to treat a documented dental hygiene need. The research project must have received ethics approval from a duly constituted health research ethics board.[24]

If prescription-writing privileges were granted to dental hygienists in the United States, restricting the use of certain medications used off-label would limit several preventive and therapeutic options currently being provided in the dental office during patient care.

There is no literature appraising off-label drug use and polypharmacy in the discipline of dental hygiene; however, Chen, Wynia, Moloney, and Alexander conducted a survey of 350 general practitioners and psychiatrists to address whether or not they were aware of the FDA labeled indications for the drugs they prescribe.[25] Results showed that general practitioners and psychiatrists correctly identified FDA-approved drug indications about 50% of the time. However, 95% of these same physicians reported knowing the FDA indications of the medications they prescribe and 79% reported FDA labeling is an important factor in their prescribing practices. Although knowledge among general practitioners and psychiatrists was considerably higher than that of dental hygienists, the findings parallel those of the current study regarding what general practitioners and psychiatrists thought they knew and what they were able to correctly identify.

A majority of dental hygienists (70%) expressed that in the past 30 days of practice they had not used a medication for off-label therapy and 23% noted they used medication off label in only 1%-13% of patient encounters. Fluoride varnish, considered an off-label anti-caries treatment, is preferred for use in children, is becoming a more commonplace treatment for caries prevention in all age groups and is endorsed by the American Dental Association.[26,27] The fact that only 15% of participants correctly identified the use of fluoride varnish as an anti-caries treatment off-label shows a lack of knowledge of this off-label use of fluoride. This might contribute to the low number of dental hygienists who identified they had used drugs off label in the last 30 days of practice.

Alternately, participants in this survey indicated a familiarity with polypharmacy, and that they could readily identify this drug regimen among their patients. Unlike off-label medication use, a majority (65%) of dental hygienists felt confident their dental hygiene education prepared them to manage patient care for those utilizing polypharmacy. It is unclear if this confidence is related to the entry-level curriculum or clinical experiences following completion of dental hygiene education; however, it can be assumed that the ability to more easily detect polypharmacy among patients increases the perceived knowledge of this aspect of pharmacology. Though participants were more confident in discussing polypharmacy, related adverse effects were rarely noted. Taking into consideration the increased risk of drug-drug interactions and oral side effects associated with polypharmacy, careful assessment of patients' medical histories and knowledge related to adverse effects and precautions for each drug are necessary components of total patient care.

There are, of course, limitations to this study, the foremost of which is the representativeness of the sample. The sample population was not randomly chosen, which may have resulted in reduced variation in data. While this survey provided quantitative data offering insight to knowledge, attitudes and practices, it did not produce the kind of data needed to create a full picture of the factors contributing to the low levels that were identified. Additionally, self-reported data are limited by the fact that they can be independently verified. Some questions were ignored. If questions are not required, there is always a risk they won't be answered. A solution, particularly for online surveys, would be to make answering each item required.

This pilot study points to issues related to knowledge and practice concerning polypharmacy and off-label drug use in dental hygiene practice. Further research on a national level is needed to determine if results can be generalized. In addition, conducting comparative research among dental hygienists who actively prescribe medications would be useful. These practitioners may show a higher level of knowledge and confidence leading to a more global approach to practice. Conducting studies to evaluate medical history assessment procedures and pharmacology practice and knowledge among dental hygienists who actively prescribe drugs versus those who do not prescribe medications would be informative. Lastly, dental hygiene curriculum and continuing education courses should be examined in terms of the depth and breadth of information provided regarding polypharmacy and off-label medication use.

CONCLUSION

The population is living longer, with multiple comorbidities, resulting in a dramatic increase in medications used for off-label indications and polypharmacy. This

cross-sectional study demonstrated California dental hygienists have limited knowledge related to off-label medication use and polypharmacy. Additionally, results indicated no difference in knowledge, attitudes or practices based on type of licensure, highest college degree earned, dental hygiene degree, or years of experience. These findings highlight a grave need for including increased content in pharmacology in both entry-level programs and continuing education courses for practitioners. A solid knowledge base within this discipline may provide more comprehensive care to patients served. More research is needed to study factors that contribute to a positive increase in knowledge, attitudes and practices.

References

1. Köberlein J, Gottschall M, Czarnecki K, Thomas A, Bergmann A, & Voigt K. General practitioners' views on polypharmacy and its consequences for patient health care. BMC Family Practice. 2013; 14:119.
2. Jenny JL, Jenny C, Jayadevan S, et al.(2012). Nurses Opinion on the Attributes of Polypharmacy in Patient Safety. Acta Medica Iranica. 2012;50(7):516-521.
3. Kantor ED, Rehm CD, Haas JS, Chan AT, Giovannucci EL. Trends in Prescription Drug Use Among Adults in the United States From 1999-2012. JAMA. 2015; 314(17):1818-1830.
4. U.S. Food and Drug Administration. Guidance for Industry: Responding to unsolicited requests for off-label information about prescription drugs and medical devices; 2011. Available from http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm285145.pdf. Accessed on March 26, 2016.
5. Eguale T, Buckeridge DL, Verma A, et al. Association of Off-Label Drug Use and Adverse Drug Events in an Adult Population. JAMA Intern Med. 2015;1-9.
6. Gupta SK, & Nayak RP. Off-label use of medicine: Perspective of physicians, patients, pharmaceutical companies and regulatory authorities. J Pharmacol Pharmacother. 2014;5(2):88-92.
7. Centers for Disease Control and Prevention. Dietary supplement use among U.S. adults has increased since NHANES III (1988–1994); 2011. Available from http://www.cdc.gov/nchs/data/databriefs/db61.htm. Accessed March 26, 2016.

8. U.S. Food and Drug Administration. Inspections, compliance, enforcement, and criminal investigations; 2012. Available from http://www.fda.gov/iceci/enforcementactions/warningletters/2012/ucm330758.htm. Accessed April 8, 2016.
9. U.S. Food and Drug Administration. Premarket notification: Dentsply international; 2012. Available from http://www.accessdata.fda.gov/cdrh_docs/pdf12/k122331.pdf. Accessed April 8, 2016.
10. Hawkins R, Noble J, Locker D, et al. A comparison of the costs and patient acceptability of professionally applied topical fluoride foam and varnish. J Public Health Dent. 2004;64(2):106-110.
11. Lexicomp. Chlorhexidine gluconate (Lexi-drugs). Available from http://online.lexi.com.westcoastuniversity.idm.oclc.org/lco/action/doc/retrieve/docid/patch_f/6584. Accessed April 8, 2017.
12. Li Y, & Tanner A. Effect of antimicrobial intervention on oral microbiota associated with early childhood caries. Pediatr Dent. 2015;37(3):226.
13. Perayil J, Menon K S, Fenol A, Vyloppillil R, & Biswas R. (2016). Comparison of the efficacy of subgingival irrigation with 2% povidone-iodine and tetracycline HCl in subjects with chronic moderate periodontitis: A clinico microbiological study. Dent Res J;13(2):98-109.
14. Miziara I, Chagury A, Vargas C, Freitas L, & Mahmoud A. (2015). Therapeutic options in idiopathic burning mouth syndrome: Literature review. Int Arch Otorhinolaryngol;19(1):86-89.

15. Ghinea N, Lipworth W, & Kerridge I. (2015). Evidence, regulation and 'rational' prescribing: The case of gabapentin for neuropathic pain. J Eval Clin Pract;21(1):28-33.

16. Hurlbutt M, Bray K, Mitchell TV, & Stephens J. California dental hygienists' knowledge, attitudes and practices regarding herbal and dietary supplements. J Dent Hyg. 2011;85(4):285-296.

17. Commission on Dental Accreditation. Accreditation standards for dental hygiene education programs. Available from http://www.ada.org/~/media/CODA/Files/dh.pdf?la=en. Accessed January 8, 2017.

18. American Dental Education Association. ADEA compendium of curriculum guidelines (revised edition): Allied dental education programs May 2015-2016. Available from http://www.adea.org/BDEBlog.aspx?id=27917&blogid=27619. Accessed January 8, 2017.

19. Haveles, E. B. (2016). Applied pharmacology for the dental hygienist. 7th ed. St. Louis, Missouri: Mosby, Elsevier Inc.

20. Keijsers CJ, Brouwers JR, de Wildt DJ, Custers EJ, Ten Cate OT, Hazen AC, Jansen PA. A comparison of medical and pharmacy students' knowledge and skills of pharmacology and pharmacotherapy. Br J Clin Pharmacol. 2014;78(4):781-788.

21. College of Registered Dental Hygienists of Alberta. HPA frequently asked questions; 2013. Available from http://www.crdha.ca/legislation/hpa-frequently-asked-questions.aspx. Accessed December 23, 2016.

22. College of Registered Dental Hygienists of Alberta. Learn more about CRDHA dental hygienist prescribing education; 2015. Available from http://www.crdha.ca/media/104984/dh_brochureall_online_feb-2015_final.pdf. Accessed December 23, 2016.
23. College of Registered Dental Hygienists of Alberta; 2015. Restricted activities authorization. Availble from http://www.crdha.ca/media/223266/restricted-activities-authorization-table-updated-dec-2015.pdf. Accessed December 23, 2016.
24. College of Registered Dental Hygienists of Alberta. Guidelines regarding prescription and non-prescription drugs in dental hygiene practice; 2008. Available from http://www.crdha.ca/media/1487/crdha-drug-guidelines.pdf. Accessed December 23, 2016.
25. Chen DT, Wynia MK, Moloney RM, & Alexander GC. U.S. physician knowledge of the FDA-approved indications and evidence base for commonly prescribed drugs: results of a national survey. Pharmacoepidemiol Drug Saf. 2009;18(11):1094-1100.
26. Hawkins R, Noble J, Locker D, Wiebe D, Murray H, Wiebe P, & ... Clarke M. A comparison of the costs and patient acceptability of professionally applied topical fluoride foam and varnish. J Public Health Dent. 2004;64(2), 106-110.
27. American Dental Association. Clinical recommendations for use of professionally-applied or prescription-strength, home-use topical fluoride agents for caries prevention in patients at elevated risk of developing caries; 2013. Available from http://ebd.ada.org/~/media/EBD/Files/ADA_Evidence-

based_Topical_Fluoride_Chairside_Guid.pdf?la=en. Accessed December 23, 2016.

Table 1: Demographics

Characteristic	N	%
Highest Level Dental Hygiene Degree Earned		
Certificate	2	2
Associate	43	53
Bachelor	27	33
Master	9	11
Highest Level College Degree Earned		
Associate	30	37
Bachelor	34	42
Master	16	20
Doctorate	1	1
Type of California License Obtained		
RDH	66	81
RDHEF	6	7
RDHAP	1	1
RDH & RDHAP	8	10
No Longer Have Active License	0	0
Years of Dental Hygiene Practice		
< 5 years	9	11
5-15 year	28	35
16-25 years	14	17
26-35 years	15	19
36-45 years	12	15
> 45 years	3	4
Practice Setting		
General Dentistry	58	72
Periodontics	3	4
Education	11	14
Public Health	3	4
Corporate	2	2
Consultant	0	0
Alternative Practice	0	0
Other	2	2
No Longer Practicing	2	2

Table 2: Responses to Knowledge Questions

Type of Question	Correct		Incorrect/I Don't Know	
	N	%	N	%
FDA Approval and Off-Label Use	37	38.5	59	61.5
Marketing for Off-Label Indications	40	41.7	56	58.3
MI Paste – Off-Label Use	12	12.5	84	87.5
Fluoride Varnish – Off-Label Use	12	12.5	84	87.5
Povidone Iodine – Off-Label Use	27	28.1	69	71.9
Botox – Off-Label Use	55	57.3	41	42.7
0.12% Chlorhexidine Gluconate – Off-label Use	21	21.9	75	78.1
Alpha Lipoic Acid – Off-Label Use	15	15.6	81	84.4

Table 3: Total Knowledge Score

Number of Questions Answered Correctly	Frequency	%	Cumulative %
0	24	25	25
1	8	8.3	33.3
2	26	27.1	60.4
3	13	13.5	74
4	12	12.5	86.5
5	7	7.3	93.8
6	5	5.2	99.0
7	1	1.0	100.0
8	0	0	100.0

Table 4: Comparison of Total Knowledge, Attitude and Practice Scores to Variables – ANOVA

Knowledge		
Variable	**F**	**Sig.**
Type of Dental Hygiene Licensure	1.569	.214
Highest Degree	.709	.495
Dental Hygiene Degree	.592	.556
Years of Experience	2.586	.059

Attitude						
	Off-Label Drug Use		**Polypharmacy**		**Total Attitude**	
Variable	**F**	**Sig.**	**F**	**Sig.**	**F**	**Sig.**
Type of Dental Hygiene Licensure	.050	.825	.762	.385	.653	.422
Highest Degree	.480	.621	4.775	.011*	2.213	.117
Dental Hygiene Degree	.486	.617	1.265	.288	.282	.755
Years of Experience	.359	.783	1.388	.253	.430	.732
Practice						
	Off-Label Drug Use		**Polypharmacy**		**Total Practice**	
Variable	**F**	**Sig.**	**F**	**Sig.**	**F**	**Sig.**
Type of Dental Hygiene Licensure	2.630	.112	1.049	.309	2.347	.132
Highest Degree	.991	.379	.227	.798	2.351	.107
Dental Hygiene Degree	.905	.412	.413	.663	1.939	.155
Years of Experience	.320	.811	.885	.453	.458	.713

*Significance level $p \leq 0.05$

Table 5: Comparison of Extent of Patient Experiences to Variables - ANOVA

	Hours/Week Treating Patients		Number of Patients Treated Per Week	
Variable	**F**	**Sig.**	**F**	**Sig.**
Type of Dental Hygiene Licensure	.475	.493	.074	.786
Highest College Degree	4.753	.012*	2.984	.057
Dental Hygiene Degree	4.976	.010*	3.031	.055
Years of Experience	10.345	.000*	5.394	.002*

*Significance level $p \leq 0.05$