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A comparison of dental practitioners' knowledge of the adverse oral effects of pharmaceuticals; specifically, low-dose methotrexate, diltiazem, cyclosporine, istretinoin, and lisinopril

Melissa Van Witzenburg

Melissa Van Witzenburg
Candidate

Dental Hygiene
Department

This thesis is approved, and it is acceptable in quality
and form for publication on microfilm:

Approved by the Thesis Committee:

Christine Nathe, Chairperson

[illegible]

[illegible]

Accepted:

Dean, Graduate School

Date

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MELISSA VAN WITZENBURG

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THESIS

Submitted in Partial Fulfillment of the
Requirements for the Degree of

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ABSTRACT

There are more than 15, 000 approved prescription and over-the-counter drugs, diagnostics, and intravenous supplementation products in the United States.[1] Due to the increased number of patients using medications it is important that dental providers are aware of common adverse oral complications. The most commonly seen adverse oral effects of medications are xerostomia, gingival hypertrophy, angular cheilitis, and mucositis. The purpose of this study was to examine dental providers, "subjects" knowledge of adverse oral effects of low-dose methotrexate, diltiazem, cyclosporine, isotretinoin, and lisinopril.

Four of the five hypotheses tested demonstrated high P-values, therefore; they were consistent with the null hypothesis. However, these four hypotheses yielded insight into areas of further study.

When evaluating the number of continuing education hours that subjects participate in annually compared to their responses on the survey, a statistically

significant difference was demonstrated. A P-value of 0.022 was obtained, with subjects participating in 26+ hours of continuing education scoring an average of 0.629 higher than those who participate in 25 or fewer hours of continuing education annually.

Data suggests that further studies are needed to evaluate where students are instructed on adverse oral effects in an educational setting and how much time is spent on the subject matter. Other areas of further investigation would include a study of established dental providers and how could their attainment of knowledge improve. Most importantly this data highlights a deficiency in information regarding adverse oral effects. It is crucial that this topic be researched further and dental providers are educated on this subject matter to ensure the highest quality of care to dental patients.

TABLE OF CONTENTS

LIST OF FIGURES x

LIST OF TABLES xi

CHAPTER I INTRODUCTION 1

Statement of the Problem 1

Significance of the Problem 1

Adverse Drug Reactions 2

Oral Effects of Medications 3

Polypharmacy 4

Dental Providers Education 4

Operational Definitions 5

Key Words 7

Hypotheses 7

Assumptions 9

Limitations 9

CHAPTER II LITERATURE REVIEW 10

Methotrexate 10

Side Effects of Methotrexate 11

Low-dose Methotrexate and Mucositis 12

Treatment of Mucositis 14

Diltiazem 14

Side Effects of Diltiazem 15

Diltiazem Induced Taste Aversion 16

Treatment of an Altered Olfactory System 17
Diltiazem and Gingival Hypertrophy 17
Treatment of Gingival Hypertrophy 19
Cyclosporine 20
Side Effects of Cyclosporine 21
Cyclosporine Induced Gingival Hypertrophy 21
Treatment of Cyclosporine-Induced Gingival Hypertrophy 22
Isotretinoin 23
Side effects of isotretinoin 24
Isotretinoin and Cheilitis 25
Treatment of angular cheilitis 26
Lisinopril 27
Side Effects of Lisinopril 28
Lisinopril and Xerostomia 29
Treatment of Xerostomia 30
CHAPTER III METHODOLOGIES 31
Sample Description 32
Research Design 32
Data Analysis 34
Study Approval 36
CHAPTER IV RESULTS 37
CHAPTER V DISCUSSION 52
APPENDIX 1: DATA ANALYSIS 61

APPENDIX 2: PARTICPANT SURVEY 70

REFERENCES 73

LIST OF FIGURES

Figure 1. The number of participants from each demographic group. 39

Figure 2. Percentages of responses for each medication investigated in this study. 41

Figure 3. Total number of correct responses correlating to the highest degree earned. ... 43

Figure 4. Total number of responses correlating to the number of years practicing 44

LIST OF TABLES

Table 1. Demographic statistics for where information is obtained for adverse oral effects of pharmaceuticals. 38

Table 2. One-way ANOVA hypothesis test results for total score earned versus degrees 42

Table 3. One-way ANOVA hypothesis test results for Hypothesis 2. 45

Table 4. One-way ANOVA hypothesis test results for Hypothesis 3. 47

Table 5. Percentage of participants' correct responses for Hypothesis 4. 48

Table 6. Percentage of participants' correct responses for Hypothesis 5. 50

Table 7. Comparison of means between the subjects and the control groups scores. 51

CHAPTER I

INTRODUCTION

It is the responsibility of dental providers to understand the effect that medications have on the oral cavity. Common adverse reactions seen in the oral cavity are xerostomia, gingival hypertrophy, mucositis, angular cheilitis, and distortion of taste. Due to an increase in the number of patients that are taking medications, it is important that dental providers are familiar with commonly prescribed pharmaceuticals. The purpose of this study was to compare dental providers' knowledge of oral manifestations with commonly prescribed medications specifically low-dose methotrexate, diltiazem, cyclosporine, isotretinoin, and lisinopril.

Statement of the Problem

The research questions being investigated were:

1. Are subjects aware of the adverse oral effects of low-dose methotrexate, diltiazem, cyclosporine, isotretinoin, and lisinopril?
2. Does knowledge of the adverse oral effects of the five given medication vary between different demographic groups?
3. How does subjects' knowledge of individual medications compare to the control groups knowledge?

Significance of the Problem

Due to the increased use of pharmaceuticals it is important that dental practitioners are able to identify oral effects of common medications. In 2002, a study published in *The Journal of the American Medical Association* reported that 50 percent of U.S. adults took at least one prescription medication during any given week. The

numbers are even higher for adults over 65 years of age.[2] Six years after this publication, it can be assumed that the number of Americans taking prescription medications is on the rise. This is partly due to the baby boomer era, those of whom are advancing in age and the increase in the medicine available. Of the 94% of patients taking prescription medications, it has been shown that at least one medication may cause an oral side effect or have an implication on dental treatment.[3]

An absence of scientific data on the adverse oral effects of medications exists, making it a challenge to determine the number of patients affected by these reactions. There is also a deficit in research regarding adverse oral effects; it is because of this that the five named medications have been chosen for this study. Newer research studies within the last 10 years have been conducted on the selected medications. Researchers have described specific cases as they relate to a particular oral effect, but generalized data is scarce. Dental and oral manifestations of drug therapy often are nonspecific and can vary in severity and significance.[4]

Adverse Drug Reactions

Drug induced adverse reactions can have an impact on the oral cavity ranging from, mild to severe. An adverse drug reaction is a noxious and unintended response to a medication. Many medications have the potential to cause an adverse reaction in the oral cavity.[5] The clinical manifestation of adverse reactions can be immediate or can appear several weeks after the initiation of treatment. An article published in *General Dentistry* states that, many adverse reactions are mediated by the immune system.[4]

Researchers have proposed three theories on mediated response of the immune system in relation to oral manifestations of pharmacological therapy. The first theory is

that there are IgE–mediated reactions, which occurs when the drug reacts with IgE antibodies bound to mast cells. The second theory proposes that drug related cytotoxic reactions are when the antibody binds to a drug attached to a cell surface. The third theory postulates that when the circulation of antigens lasts for periods of time, this allows for sensitization and antibody production.

In addition to these immunologic responses, non-immunologic factors are overdose and toxicity of the drug itself.[4] Non-immunologic factors include previous adverse reactions, multiple medications, liver and renal disease, and gender. Gender may influence pharmacokinetics, drug utilization, and susceptibility to the presentation/detection of adverse drug reactions. Factors that may explain the higher adverse event rate observed in female patients include pharmacodynamic factors, hormonal influences, reporting bias, and increased use of medicine.[6]

Oral Effects of Medications

The most common oral effects of medications are xerostomia, oral ulcerations/stomatitis, gingival hypertrophy, increased bleeding, angular cheilitis, and alteration of taste. Xerostomia and mucositis can impair a patients ability maintain normal oral function. Normal oral functions include mastication, speech, oral hygiene, and swallowing. In addition, those patients suffering from xerostomia are at an increased risk of developing caries. Other oral effects can be of an esthetic concern, such as gingival hypertrophy and angular cheilitis. The occurrence of gingival hypertrophy/enlargement can also produce areas in which the patient is unable to maintain with regular oral hygiene, thus modifying plaque composition and contributing to secondary inflammation of the periodontal tissues. It is important that dental

providers be familiar with the oral manifestations of adverse drug reactions as more medications become available to the public.

Polypharmacy

Another consideration for dental providers is the practice of polypharmacy. Polypharmacy is common in the elderly due to; multiple chronic medical problems, prescribing of medications by multiple physicians, lack of coordination of care, hospitalization or nursing home placement, severe illness, intake of over the counter medications, vague symptoms, patient pressure to prescribe, and the use of additional medications to manage drug induced conditions.[3,7,8] Polypharmacy has a direct impact on dental providers. It can be difficult to determine what medications are causing an adverse oral effect when a patient presents with polypharmacy. Dental practitioners need to be informed of the doses of medications, the time at which the medication is administered, and any changes in the patients' health. Accurate health histories are necessary because the presence of disease could alter the excretion, absorption, or metabolism of pharmaceuticals.[6] The time at which the medication is administered will allow dental providers and patients to monitor the onset of oral effects. If dental practitioners are aware of the common culprits of oral related side effects, the patients can be properly educated and symptoms can be treated as indicated.

Dental Providers Education

Dental providers' education can vary greatly. Both dental and dental hygiene programs, have a pharmacology course built into the curriculum, however; the number of required credit hours differs between professions and the degree earned.

Dental programs require that students take a four-credit pharmacology course. The coursework discusses the therapeutic, mechanical, and physical mechanisms of actions of classifications of medications. In addition to this, emphasis is given to pharmacological agents that dentists commonly encounter or prescribe and the adverse oral effects. Pharmacology is addressed again when students begin course work for the administration of local anesthetic and nitrous oxide.

Dental hygiene programs have more variance in required pharmacology course compared to dental schools, due to the fact that dental hygiene students can either obtain an associates or bachelors degree. Associate degree programs require that students complete two credits of pharmacology, whereas; a baccalaureate program mandates that students complete three credit hours of pharmacology. Pharmacology courses for dental hygiene students do not focus on writing prescriptions because it is not within the scope of practice. Rather, courses focus on the physiological mechanisms of medications, drug interactions, therapeutic actions, and adverse oral effects that can be detected intraorally. Similar to dental students, pharmacology principles are then discussed when students are instructed on local anesthesia techniques.

Operational Definitions

Cyclosporine:

> A cyclic undecapeptide from an extract of soil fungi. It is a powerful immunosuppressant with a specific action on T-lymphocytes. It is used for the prophylaxis of graft rejection in organ and tissue transplantation.[9]

Diltiazem:

A benzothiazepine derivative with vasodilatation action due to its antagonism of the actions of the calcium ion in membrane functions.[10]

Isotretinoin:

A powerful drug used in the treatment of acne. Four to five months of isotretinoin treatment usually leads to clearing of acne for one year or more after medicine is stopped.[11]

Gingival hypertrophy:

Excessive growth of the gingiva either by an increase in the size of the constitute cells or by an increase in their number.[12]

Lisinopril:

A drug of the angiostensin converting enzyme (ACE) inhibitor class that is primarily used in treatment of hypertension, congestive failure, heart attacks, and also in preventing renal and retinal complications of diabetes.[13]

Methotrexate:

A folic acid antagonist used as an antineoplastic agent; used to treat psoriasis and rheumatoid arthritis.[13]

Mucositis:

Involving the inflammation of the lining of the mouth and digestive tract, and frequently occurs in cancer patients after chemotherapy and radiation therapy. Along with redness and swelling, patients typically experience a strong, burning pain.[14]

Stomatitis:

Inflammation of the mucous membrane of the mouth.[13]

Xerostomia:

A dryness of the mouth from salivary gland dysfunction, often seen in patients with Sjogren syndrome.[15]

Key Words

low-dose methotrexate, diltiazem, cyclosporine, isotretinoin, lisinopril, mucositis, xerostomia, angular chelitis, gingival hypertorphy

Hypotheses

Hypothesis 1: Subjects' knowledge regarding adverse oral effects of investigated pharmaceuticals is greater as the educational level increases.

H_o: There is no significant statistical difference between knowledge and educational levels.

H_a: There is significance statistical difference between knowledge and educational levels.

Hypothesis 2: The longer length of time that subjects have practiced, the less knowledge subjects have regarding adverse oral effects of the investigated medications.

H_o: There is no significant statistical difference between the length of time practicing and knowledge on adverse oral effects.

H_a: There is significant statistical difference between the length of time practicing and knowledge on adverse oral effects.

Hypothesis 3: Subjects that participate in at least twenty-six hours of continuing education will have more knowledge in adverse oral effects of pharmaceuticals, than those that participate in fewer continuing education hours.

H_o: There is no significant statistical difference between the number of hours of continuing education and knowledge.

H_a: There is significant statistical difference between the number of hours of continuing education and knowledge.

Hypothesis 4: Subjects will be knowledgeable regarding adverse oral effects associated with gingival hypertrophy, therefore; answering half of the related questions correctly.

H_o: Subjects will not answer half of the gingival hypertrophy questions correctly.

H_a: Subjects will answer half of the gingival hypertrophy questions correctly.

Hypothesis 5: Senior dental hygiene students at The University of New Mexico will be knowledgeable regarding medications that induce gingival hypertrophy, therefore; answering half of the associated questions correctly.

H_o: Senior dental hygiene students will not answer half the questions regarding gingival hypertrophy correctly.

H_a: Senior dental hygiene students will answer the half questions regarding gingival hypertrophy correctly.

Assumptions

An element that was beyond control during this study design was the occurrence of inaccurate contact information of potential subjects. The assumption of this study design was that New Mexico Board of Dental Health Care had the correct/current addresses for the subjects. It was also assumed that all participants surveyed were all currently residing in New Mexico. However; the potential that subjects may have moved from New Mexico but, maintained a current dental or dental hygiene license existed and therefore should be considered when interpreting the datum. Additionally, in preparing this survey, it was assumed that subjects had prior knowledge of the previously mentioned pharmaceuticals.

Limitations

Limitations of this investigation included the following: 1) subjects mistaking the survey for unsolicited mail; 2) the response rate could have been delayed due to the postal system or time it took to complete the paper survey; 3) this investigation only examined subjects who are licensed in the state of New Mexico, which places geographical limitations on the study; 4) the subjects' ability to maintain an active license in multiple states presents the probability that a small number of states outside of New Mexico may have been represented during this study. Consequently, this study utilized an anonymous survey and therefore, additional states could not be identified and; 5) because New Mexico was the only state examined during this investigation, a limited number of educational institutions were represented in this study.

CHAPTER II

LITERATURE REVIEW

As the number of individuals taking prescription medication increases, so does the risk of oral adverse drug reactions. These oral manifestations affect the oral mucous membrane, saliva production, and taste. In an article titled, "Oral Adverse Drug Reactions to Cardiovascular Drugs" it states, the pathogenesis of oral adverse reactions related to the intake of medications is not well understood, and the prevalence is not known.[6] Due to the lack of research on oral manifestations of adverse drug reactions, dental providers tend to overlook the subtle indications. It is dental practitioners' responsibility to collect accurate health histories and to be aware of commonly prescribed medications and their adverse oral effects. As the majority of the population continues to age and depend on pharmaceuticals, studies will continue to emerge on adverse oral effects.

Methotrexate

Methotrexate is commonly used in the treatment of chronic diseases such as rheumatoid arthritis and psoriasis.[16] Much research has been done on the systemic effects of methotrexate. Comparatively, little has been done on the oral effects. Dental practitioners should be aware of the possible oral effects of low-dose methotrexate that have so far been largely unrecognized.[17]

Methotrexate is classified as an antimetabolite drug.[18] It is an inhibitor of dihydrofolate reductase, an enzyme that reduces folate to an active form where it acts as a co-factor for the production of nucleic acids essential to DNA synthesis. The effect on reducing DNA formation and cell turn over provides both therapeutic properties and

adverse side effects of the medication. Methotrexate traditionally had been used in higher doses in the oncology setting. In the 1970's the FDA approved low doses of methotrexate to be effective in the treatment of rheumatoid arthritis and psoriasis.[19] The primary function of methotrexate when used to control psoriasis is to slow the growth of skin cells; in rheumatoid arthritis methotrexate decreases the immune systems' activity.[18]

Methotrexate can be used either orally or intravenously. In the 1960's the daily oral schedule for methotrexate was found to lead to frequent toxicity and was replaced by a weekly oral dose schedule in the 1970's.[20] Oral administration of methotrexate varies between 15-25mg per week. Should a patient's need exceed 17.5mg per week, the medication is delivered intravenously.[21] Standard practice is to prescribe the lowest most effective dose of methotrexate. If a patient requires regular low doses of methotrexate to remain symptom free, the drug is approved for long-term usage.[22]

It is important that patients inform dental providers that they are undergoing low-dose methotrexate therapy. A study published in the *British Medical Journal* indicated that nitrous oxide, NSAID's, and penicillin increased low-dose methotrexate patients' risk of developing bone marrow suppression.[23] It can be difficult to remember all the medications that one is taking. It is important to encourage patients to keep an updated list of medications with them, as to keep their medical history current.

Side Effects of Methotrexate

Although methotrexate as been regarded as a safe and effective therapy in which to treat chronic illnesses, it potentially can be toxic other areas of the body. The FDA has guidelines in place to minimize patients' risk of toxicity. Methotrexate is metabolized through the liver, which can lead to hepatoxicity. Hepatoxicity can result from long-term

use of methotrexate.[22] A patient taking methotrexate is at a higher risk of developing liver cirrhosis if they have the following risk factors: abnormal kidney function, diabetes, prior liver disease, and/or alcohol consumption.[21]

There are other adverse effects of methotrexate that are less severe and more manageable than liver cirrhosis. These side effects can be seen within 24 hours of taking the medication or throughout the entire treatment. Some of these include: nausea, tiredness, lightheadedness, difficulty sleeping, vomiting, mouth ulcerations, easy bruising or bleeding, fever, or chills. Studies have shown that folic acid supplementation lessens the toxicity and side effects of methotrexate in patients.[24] In a 6-month, double blind, placebo-controlled trial, 7mg of folic acid weekly decreased methotrexate toxicity without affecting the efficacy.[24] Yet, the specific effects of folic acid on methotrexate toxicity are still unclear. Much controversy still remains on the appropriate use in combating the side effects of methotrexate.

Low-dose Methotrexate and Mucositis

According to an article published in *General Dentistry*, erythemas, edema, mucosal shedding, ulceration, and pseudo membrane formation characterize oral mucositis.[25] Discussion of mucositis is needed to understand the oral complications dental professionals encounter when providing care for a patient under going low-dose methotrexate therapy.

There are multiple factors that apply when evaluating the frequency and severity of mucositis: diagnosis, age, level of oral health, and type, dose, and frequency of drug administrations.[26] The patient's risk of developing mucositis increases with exposure time, dosage, and number of previous episodes of mucositis. However, oral

chemotherapeutic agents that interfere with DNA synthesis such as methotrexate have a higher incidence rate of mucositis.

As discussed earlier, DNA replication and the rapid rate of mucosal cell proliferation make the oral mucosa susceptible to mucositis. Much of the research on mucositis is based strictly on observation. Although there are theories and suggestions as to the precise cause of the breakdown of the mucosa, the exact process has not been identified. According to Napenas, et al., mucositis is recognized to result from changes both at the epithelial and subepithelial layers, with evidence of damage to microvasculature (endothelium) and connective tissue that precedes epithelial changes in irradiated oral mucosa.[25] It has been hypothesized that mucositis is a four-phased biologic process: initial, epithelial, ulcerative, and the healing phase.[26] The majority of available research has been directed at evaluating the epithelial phase of mucositis. Studies have shown that antimetabolites are most toxic to the mucosa because they target the DNA synthesis process.[27] It is during the ulcerative phase that patients are prone to infection in which mucositis causes oral complications for the patient. The healing time for mucositis is typically 12-16 days, but depends on the proliferation rate of the mucosa, the reestablishment of the local flora in the oral cavity, and other extraneous factors.[28] These extraneous factors include, but are not limited to, poor oral hygiene, periodontal disease, caries, xerostomia, and nutrient deficiencies. It is important to be able to identify the signs and symptoms of mucositis. The earliest signs and symptoms include: erythema and edema, a burning sensation, and an increased sensitivity to hot or spicy food. The areas of erythema can develop into raised white desquamative patches that become painful ulcerations.[28] Mucositis also compromises the body's defenses against the

invasions of microorganisms from the oral cavity into the bloodstream thus, increasing the risk of systemic infection.[25] This situation can potentially lead to a cascade of events altering the patients overall health. Painful ulcerations in the oral cavity render patients with the inability to eat, drink, or swallow. The areas of the oral cavity that are commonly affected by mucotoxicity are those cells that replicate quickly. In the oral cavity, these are the non-keratinized areas such as: soft palate, cheeks, lips, ventral surface of the tongue, and the floor of the mouth.[28] The remaining areas of the oral cavity are at a reduced risk for mucositis because of a slower cellular rate.

Treatment of Mucositis

Much research has been conducted on possible treatment options for mucositis, however little has proved to eliminate the problem. Studies have indicated treatments provide patients with relief, decrease the severity, or aid in decreasing the risk of developing mucositis. Aside from adequate oral hygiene and frequent visits to the dental provider; folic acid is the most frequently recommended preventative measure for mucositis. A study published by the *Annals Internal Medicine* reports that, a controlled trial shows that folic acid supplementation of 5mg or 27.5mg per week decreases methotrexate toxicity without compromising efficacy.[24] Aside from folic acid, other studies have been conducted on the efficacy of chlorhexadine, hydrogen peroxide, cryotherapy, and a variety of natural herbals in the treatment of mucositis. As researchers discover more information on mucositis, there should be a definitive treatment of choice.

Diltiazem

In a study conducted in 1998, three percent of patients seen in an adverse drug reaction clinic were using cardiovascular drug therapy.[6] The use of calcium channel

blockers emerged in the 1980's. Calcium channel blockers are used in the treatment of cardiovascular disorders including, angina, hypertension, supraventricular arrhythmias, and some forms of myocardial infarction.[28]

Diltiazem, a calcium channel blocker and vasodialator, is commonly used to treat hypertension and angina.[29] Diltiazem, a benzothiazepine, is a calcium antagonist, inhibiting calcium ion entry into smooth muscle cells by a blockade of slow calcium channels.[30] Diltiazem is metabolized through the liver, excreted by the kidneys and the bile. After oral administrations, diltiazem is detectable in the plasma 30-60 minutes after oral administration. When patients are treated for angina, diltiazem assists in reducing the heart rate and blood pressure via dialation of the coronary arteries. Diltiazem works similarly in the treatment of hypertension. Because diltiazem is a vasodilator, blood pressure is reduced; by suppressing the sinoatrial node stimulation.[30]

Side Effects of Diltiazem

Common adverse effects include, gastrointestinal discomfort, swelling, headaches, dizziness, taste aversions, gingival hypertrophy, rash, and fatigue. Diltiazem has shown to have adverse drug interactions with other medications. Co administration of diltiazem with other agents, which follow the same route of biotransformation, may result in the competitive inhibition of metabolism. It is recommended that patients that have been prescribed diltiazem avoid or use extreme caution when taking concomitantly beta blockers, cimetidine, digitalis, and cyslosprine.[31] For this reason, it is vital that patients provide accurate health histories to healthcare providers.

Diltiazem Induced Taste Aversion

It is estimated that the effects of medication on the olfactory system is greatly underestimated.[32] A large number of medications in physician's desk references make note of possible drug interaction with the olfactory senses. According to a study publication in the *Journal of the European Academy of Dermatology and Venereology*, drugs may cause a loss of taste acuity (hypogeusia), distortion in perception of the correct taste of a substance (dysgeusia) or loss of taste sense (ageusia).[5] These effects on the olfactory system cause food to have a bitter, salty, sour, bland, or metallic taste.

Researchers have established two mechanisms of action as the etiology of taste disorders. The first mechanism is the excretion of the drug or its metabolites into the salvia thus interfering with the chemical composition or flow of saliva. The second, is the taste receptor is affected, causing a disturbance in taste.[4] Few studies have been conducted on the effect of medication on the olfactory system because multiple factors have an influence on one's sense of taste. Some explanations include; polypharmacy, orally administered medications that taste bad, secondary effects from other medication, genetics, age, and weight.[32]

Many calcium channel blockers have been reported to alter ones sense of taste, specifically; ditliazem. When a patient experiences a disturbance in taste, symptoms typically dissipate within two to three months after the initiation of the pharmaceutical treatment. If an individual not experiences an alteration in taste, but also xerostomia, this will prolong and complicate the recovery of the olfactory system.[32]

Treatment of an Altered Olfactory System

Due to the limited amount of information on the adverse effects diltiazem on the olfactory system, treatment options are limited. As stated earlier, symptoms usually spontaneously resolve two to three months without any medical intervention. For those patients who do not have a spontaneous recovery, an oral examination and appropriate patient education is vital. Routine dental examinations, proper oral hygiene, and close nutritional balance are fundamental for the maintenance of good taste and smell health.[32] If in addition to altered taste, a patient is experiencing xerostomia it is necessary to provide patients with a saliva substitute. Chlorhexadine is a treatment option for those patients who report a salty or bitter taste. It should be noted that, the effectiveness of chlorhexadine might be secondary to its strong positive charge, however; there is a lack of clinical data.[32] In any case, it is important to be both sympathetic and informative to the patient. Patients who have careers that are reliant on their sense of taste or smell should be informed of the potential side effects of diltiazem. It is the responsibility of healthcare providers to provide this information to patients taking diltiazem.

Diltiazem and Gingival Hypertrophy

Another common adverse oral effect of diltiazem is gingival hypertrophy. Gingival hypertrophy is a fibrotic enlargement of the gingiva that can be induced by various pharmacologic agents through poorly understood mechanisms. In 2002, *The Journal of Clinical Hypertension* reported that, the prevalence of gingival overgrowth with the use of calcium antagonists could be as high as 38%. The study reports it is also 3.3 times more likely to occur in males than females.[33] Calcium channel blockers are one of three classifications of medications that have demonstrated drug-induced gingival

overgrowth. In study conducted by Prisant Herman it was concluded that significant gingival overgrowth occurs in 2.2% of patients on diltiazem therapy.[33]

As stated, the mechanisms by which calcium channel blockers adversely impact the gingiva are poorly understood. Most theories focus on the effect that the drug has on the gingival fibroblast. Not every patient undergoing diltiazem therapy is affected by gingival hypertrophy. It is likely that a variety of factors are responsible such as: genetic predisposition, pharmacokinetic variables, and inflammatory factors.[33] In addition to the above-mentioned risk factors: age, sex, periodontal status, and the presence of plaque also contribute to gingival overgrowth.

It is important that patients who have undergone diltiazem therapy have an understanding of the need for good plaque control. Although researchers do not understand how calcium channel blockers affect the gingiva, they do recognize that poor oral health contributes and can exasperate gingival hypertrophy. Preventing gingival inflammation in patients using calcium channel blockers may help control the degree of drug-induced gingival enlargment.[34] Gingival hypertrophy can range from mild to severe. Gingival hypertrophy primarily affects the interdental papilla and labial gingiva.[13] This usually begins as a diffuse swelling of the interdental papilla; which enlarge and coalesce, leaving a nodular appearance.[28] A study published in the *Journal of Clinical Periodontology* suggests that gingival inflammation has a stronger effect than the drug treatment itself in patients treated with diltiazem. Researchers arrived at this conclusion because of the increased prevalence in gingival inflammation, poor plaque control, and probing depth.[35] The responsibility of educating the patients on this adverse

oral effect rests on dental providers. Dental practitioners must provide patients with both the knowledge and tools to maintain optimum oral health.

Treatment of Gingival Hypertrophy

Gingival hypertrophy is typically visible one to three months after initiation of medicaments. When gingival overgrowth occurs it ranges from mild to severe. Unlike other adverse drug reactions, gingival hypertrophy does not resolve after the medication has been discontinued. Severe gingival overgrowth can obstruct the dentition completely, thus leaving patients incapable of maintaining good oral hygiene. Such changes are unsightly and may result in pain, difficulty eating, and an undesirable breath odor.[34] Gingival overgrowth can cause both physical and emotional pain. For patients affected by severe gingival hypertrophy, the only treatment option is surgical intervention.

There is a 34% reoccurrence rate for drug-induced gingival hypertrophy.[36] For many years, the standard of care was performing a scalpel gingivectomy to reduce gingival overgrowth. Recent studies have emerged comparing the results and postoperative discomfort of scalpel and laser gingivectomies. In a study published in the *Journal of Clinical Periodontology*, researchers compared post-operative pain and recurrence rates after having scalpel and laser gingivectomies. Results yielded that gingival overgrowth reoccurrence was significantly greater in patients who had a scalpel gingivectomy when compared with the laser gingivectomy.[36] Initial results suggest that new "gold standard" for gingivectomies is to complete the procedure with a laser technique. This technique does present its own disadvantages. The first disadvantage is the cost, the second being post operative discomfort for patients. Aside from surgical interventions, chlorhexadine mouth rinse has been reported to reverse recurrent gingival

overgrowth following gingivectomies. A study in mice indicated it may have a role in limiting but not preventing gingival overgrowth.[27,37,38]

It is important for dental providers to educate patients on the risk of gingival hypertrophy. Because researchers can only theorize on what causes gingival overgrowth, patients should be aware of the correlation between poor oral hygiene and drug-induced gingival overgrowth. Patients may need to be put on more frequent recalls to allow the gingival tissues to be monitored closely.

Cyclosporine

In the 1900's physicians began performing organ transplants. Cyclosporine is an immunosuppressant drug that prevents or interferes with the host's immunologic response to the foreign protein substances from the organ donor. Pharmacological therapy is of fundamental importance in situations where correct and prompt administration can improve the quality of life and survival as witnessed in transplant recipients.[39]

Cyclosporine is commonly known to be used in the conjunction with organ transplants involving skin, heart, kidney, pancreas, bone marrow, small intestine, and lungs.[40] Cyclosporine can be used to treat rheumatoid arthritis, psoriasis, and inflammatory bowel disease. Cyclosporine is absorbed through the gastrointestinal system. Bioavailability and peak serum concentration levels vary from patient to patient.[27] An initial dose 15mg of cyclosporine should be administered 4 to 12 hours prior to transplantation. The dose is then decreased 5% per week until a maintenance dose of 5-10mg/kg/day is reached.[40] The exact mechanism of action of cyclosporine is not known. Experimental evidence suggests that the effectiveness of cyclosporine is due to

specific and reversible inhibition of immunocompetent lymphocytes.[40] It is recommended that patients taking cyclosporine have routine blood work completed to monitor plasma levels and both liver and kidney function.

Side Effects of Cyclosporine

As with all medications, cyclosporine has adverse side effects and drug interactions. Hypertension is a common adverse effect of cyclosporine therapy, therefore, increasing the patients' risk of developing gingival overgrowth. Transplant recipients are prescribed many medications to suppress the immune system but to combat adverse side effects due to polypharmacy. Patients should avoid specific classifications of drugs particularly, NSAIDs, antineoplastic, gastrointestinal agents, calcium channel blockers, specific antibiotics, antifungals, and anticonvulsants.[40] Because of the use of polypharmacy with transplant patients, it is crucial that patients and providers are aware of these common adverse effects and drug interactions. If medication is to be co-administered with cyclosporine, an in-depth review of contraindications is required.

Cyclosporine Induced Gingival Hypertrophy

Like diltiazem and other calcium channel blockers, gingival hypertrophy is a frequent oral complication of cyclosporine. Ten to thirty percent of patients on cyclosporine therapy experience gingival overgrowth.[41] According to a study published in, *Progress in Transplantation*, the dose and plasma level were significant risk factors for the development and extent of gingival hypertrophy.[42] Similar to diltiazem, gingival hypertrophy is typically seen around the dental papilla. Cyclosporin-induced gingival overgrowth is usually seen in the anterior segments of the mouth and on facial surfaces of the teeth. Overgrowth is usually confined to the attached gingiva but may extend

coronally and interfere with the occlusion, mastication, and speech without altering the periodontium.[27] As with diltiazem, gingival hypertrophy ranges from mild to severe; in severe case two-thirds or more of the tooth structure can be obstructed.

One study evaluated the risk of gingival hypertrophy when cyclosporine was taking in a solution versus a capsule. The effects of both preparations on the gingival tissue demonstrated that gingival overgrowth was observed in 37% of the patients taking the cyclosporine solution, compared to 43% dosed with capsules.[43] As previously stated, the pathogenesis of gingival overgrowth is still unknown. Researchers have hypothesized that cyclosporine-induced gingival hypertrophy is due to the indirect and direct effects of cyclosporine on fibroblasts and the extra cellular components of the lamina propria.[27]

Treatment of Cyclosporine-Induced Gingival Hypertrophy

Treatment of cyclosporine-induced gingival hypertrophy would be the same as it is for diltiazem. The treatment options for patients experiencing drug-induced gingival overgrowth are limited. Early studies have shown that chlorhexadine is an effective treatment modality for plaque control, thus aiding in the prevention of gingival hypertrophy. Drug intervention has shown to be successful in the regression of gingival hypertrophy. Two medications in particular have been the focus of such studies, metronidazole and azithromycin.[42] The mechanism in which gingival overgrowth responds to azithromyacin is unclear, however; researchers found that there is a reduction in anaerobic bacteria and spirochetes.[42] Surgical intervention is an option that is utilized in cases where esthetic appearance is the concern, but patients can experience post-operative discomfort, bleeding, and reoccurrence.

As with diltiazem, educating the patient about the adverse oral side effects is a key component to dental treatment. More frequent dental visits can be recommended, however; an intensive course of plaque control and removal of gingival irritants have shown to have little effect on the development of gingival overgrowth.[27] Although studies have suggested that meticulous plaque control may not prevent gingival overgrowth, patients are encouraged to maintain optimal health as to not exasperate the overgrowth. Optimal oral health is important when minimizing adverse oral effects, but it is also a key component to maintaining the patients' overall health.

Isotretinoin

The Food and Drug Administration (FDA) approved isotretinoin, which is in the retinoid family, in 1982. Isotretinoin or *Accutane* is the most frequently prescribed medication in the treatment of moderate to severe nodulocystic acne. Acne is a multifaceted dermatological disorder of the sebaceous glands, affecting 90-100% of adolescents with varying degrees of severity.[44] In *Dermatology Nursing* it states that, the number of prescriptions for acne have increased 2.5-fold in the United States between 1992 and 2000.[45,46] The side effects of isotretinoin can range from mild to life altering, but isotretinoin is the most effective pharmaceutical agent used for managing nodulocystic acne or treatment-resistant acne.[47] Clinical improvement in nodular acne patients occurs in association with a reduction in sebum secretion. The decrease in sebum secretion is temporary and is related to the does and duration of treatment with *Accutane*, and reflects a reduction in sebaceous gland size and an inhibition of sebaceous gland differentiation. Nodulocystic acne is the most severe type of acne; it has the potential to produce lifelong disfiguring scares.[44] When this type of scarring occurs the

effects can be devastating leading to embarrassment, anxiety, poor self- esteem, and depression.

Isotretinoin is widely accepted as the treatment of choice because it is the only acne medication that impacts all four major pathophysiologic factors of acne. However, this is also the most potent drug. Isotretinoin significantly decreases the dimensions and sebum production of the sebaceous glands, reverses the effect of androgens on these structures, thus changing keratinocyte maturation and adhesion, and represses the inflammatory component of acne and comedone production.[45,48,49] Studies have been conducted as to the efficacy of conventional and intermediate dosages of istotretinoin.

Recommended dosage by the FDA is 0.5-2.0mg/kg, this is dosage is considered to be conventional dosaging. Intermediate or long-term dosaging of isotretinoin is when the recommended cumulative dosage is taken over a period of time, totaling 120-150 mg/kg.[50] In prescribing intermediate dosaging, studies have shown that it is effective in minimizing adverse drug reactions and in treating treatment-resistant acne. In a study conducted in Turkey, researchers investigated the response of acne when treated with both intermittent and conventional isotertinoin therapy. Results yielded that intermittent isotretinoin therapy successfully treated mild to moderate acne and that there was a significant reduction in adverse effects.[51]

Side effects of isotretinoin

Patients taking isotretinoin are at risk of developing adverse drug reactions. These reactions can affect various systems in the body including: the mucocutaneous, ophthalmologic, teratogenicity, neuromuscular, and the gastrointestinal system. Teratogenicity is the most potent of the adverse reactions, for this reason, the use of

isotretinoin may be limited, either by the patients' choice or the prescribing physician. All patients taking istotretinoin will experience at least one side effect. As with any medication it is important that medical providers clearly and concisely explain these risks to the patient. Mucocutaneous effects are the most common adverse reactions of isotretinoin; these are tolerable, treatable, and the mildest. Patients typically present with mucosal dryness, of the nasal and oral cavity, eyes, and skin. Two thirds of patients undergoing isotretinoin therapy report nosebleeds due to mucosal dryness and 100% of patients experience cheilitis.[49] It is vital that women who are pregnant or plan on becoming pregnant inform their medical provider. Approximately one-fourth of all exposed fetuses have birth defects when iostretinoin is used in conjunction with pregnancy.[49] Once treatment has been completed there are no long-term effects on fertility. It is important to remember that the severity and frequency of adverse effects of isotretinoin is dose dependant.

Isotretinoin and Cheilitis

Angular cheilitis is the most frequently witnessed oral complication of isotretinoin. For this reason, it is important that dental providers are able to identify and educate patients on this common side effect. Angular cheilitis is an inflammatory condition that occurs in one or both angles of the mouth. This condition typically presents with erythema, painful cracking, scaling, bleeding, and ulceration at the corners of the mouth.[52] Previous studies have shown that 100% of all patients taking isotretinoin experience cheilitis; if a patient does not exhibit this side effect the patient is non-compliant.

The etiology of angular cheilitis is very broad and at times can be difficult to identify the causative agent. This mucosal condition can be indicative of an idiopathic cause, various nutritional deficiencies, allergic reactions, fungal infections, and trauma. Because cheilitis can be caused by a multitude of factors, the treatments vary greatly.

Due to an inconsistency in the etiology of cheilitis, dental practitioners need to gather accurate information. All changes in a patients' health history should be updated to include new diagnoses and medication, including dosages. Dental providers should investigate how long the lesions have been present, periodicity, previous treatment, and the reoccurrence rate. It is also pertinent to evaluate the patients' daily nutrition. Nutritional deficiencies especially of iron and B vitamins are important in the development of angular cheilitis. After collecting the appropriate information from patients the severity of angular cheilitis is classified into three categories; type I (mild), type II (moderate), and type III (severe).[52]

Treatment of angular cheilitis

The treatment of angular cheilitis is dependent on the etiology. For drug-induced cheilitis, many times a lubricant is the only recommendation. Studies have shown by simply applying a moisturizer or petroleum jelly to the cracks, this provides patients with relief. If symptoms persist or worsen then a topical medication can be applied to the area. Four percent of patients with cheilitis did not respond to topical moisturizers and required topical corticosteroids.[45,53] In another study that was published in the *Journal of the American Academy of Dermatology*, researchers investigated that effect of Vitamin E supplementation on angular cheilitis. Results did not fully reveal the efficacy of Vitamin E on isotretinoin-induced cheilitis; more studies will be needed in the future to determine

the benefits.[54] Because this type of angular cheilitis is pharmacologically induced, it is not considered to be a contagious lesion. Patients should be encouraged to maintain a healthy oral cavity in order to reduce the risk of reoccurrence. If dental providers are unable to obtain an accurate health history or inaccurate information as to the origin of the lesion, angular cheilitis should be treated as an infectious lesion.

Lisinopril

It is predicted that by the year 2025 the number of adults with hypertension is to exceed 1.5 billion worldwide.[55,56] Lisinopril was approved in the 1990's and is commonly used in the treatment of hypertension, heart attacks, and congestive heart failure. This medication is routinely seen in dental practices for the control of hypertension. As the population continues to age the number of patients on antihypertensive therapy will continue to rise.

Lisinopril is an angiotension-converting enzyme (ACE). Unlike other ACE inhibitors, lisinopril has notable properties. It is hydrophilic, it has a long half-life and tissue penetration, and the liver does not metabolize it.[57] Unlike the majority of pharmaceuticals, lisinopril is not metabolized but is excreted unchanged through the urine. The usual dosage is once a day because of the long half-life of lisinopril, which is typically an accumulation of 12 hours. A single daily dose allows for an improvement in patient compliance. Studies in the United States and Europe have concluded that around 25% of all hypertensives and 50% of all treated patients have controlled blood pressure.[55] The typical dosage is 2.5 mg for sensitive patients to 40mg. It is recommended that lower dosages be used in patients with higher-grade renal impairment. Dosages up to 80 mg per day have been used in patients that are more tolerant of the medication.[57]

To lower blood pressure, many effective treatment regimes are available and a lower blood pressure has been shown to be associated with a decrease in cardiovascular risk.[58] The FDA reports that, two dose-response studies utilizing a once daily regimen were conducted in 438 mild to moderate hypertensive patients that were not on a diuretic. Blood pressure was measured 24 hours after dosing. An antihypertensive effect of lisinopril was seen with 5mg in some patients. However, in both studies blood pressure reduction occurred sooner and was greater in patients treated with 10, 20, or 80 mg of lisinopril.[59] Pharmacological therapy is important for patients with hypertension, but nonpharmacological treatments can also aide in the reduction of ones' blood pressure. Nonpharmacological interventions include; smoking cessation, dietary changes, weight control, decrease in sodium and alcohol consumption, and daily exercise.

Side Effects of Lisinopril

As with any medication, lisinopril is known to have common adverse reactions. The most frequent side effects include cough, diarrhea, loss of taste, nausea, xerostomia, drowsiness, and headaches.[57] Generally, many of the side effects patients report when taking lisinopril are both mild and transient. In clinical trials, patients with hypertension treated with lisinopril, discontinued therapy due to clinical adverse experiences in 5.7% of the patients. The overall frequency of adverse experiences could not be related to total daily dosage within the recommended therapeutic dosage range.[54] Dental practitioners are concerned with the loss of taste and xerostomia due to its adverse effect on the oral cavity.

Lisinopril and Xerostomia

Hyposalivation (xerostomia) is defined as unstimulated whole saliva rates of 0.1 mL/min and stimulated rates of 0.7 mL/min.[1] Saliva contain 99% water and 1% proteins, enzymes, and electrolytes.[60] Patients may or may not be aware of a decrease in salivation; it is only after xerostomia begins to interfere with daily functions that one notes a change.

Xerostomia can occur as a result of medications' effect on the sympathetic and parasympathetic nervous system. According to an article in *Compendium*, other drug-induced causes of xerostomia may be the result of a reduction of blood volume (diuretics) and antihypertensiveagents.[1] Although this research will focus on the adverse oral effects of pharmaceuticals, it should be noted that systemic diseases have a direct impact on salivary flow. When dental practitioners investigate the etiology of xerostomia, providers need to review the medications patients take but also any systemic disease processes. As with any adverse oral effect, xerostomia can be overlooked if the appropriate questions and information is not gathered. Xerostomia can have a negative impact on patients' nutritional intake and quality of life, but typically is not distinguished until there has been a 50% reduction in salivary flow.

Patients who have xerostomia are at an increased risk of developing caries and oral infections. It is typical that as saliva production decreases so does patients' oral hygiene. With an increase in plaque, acid, and bacteria those with xerostomia are at increases risk of developing candida albicans. This infection presents with erythema and atrophy of tongue, or a white, cheesy substance that may bleed when removed.[60] The oral tissue is at an elevate risk of tearing when gauze, instruments, and saliva ejectors are

placed in the mouth. Dental practitioners should use caution when working in the oral cavity of a patient with xerostomia.

Treatment of Xerostomia

Xerostomia is a condition that has no cures, but there are options available to patients to help manage the symptoms and prevention techniques. Dry mouth products come in a variety of forms including, gum, mints, toothpaste, mouth rinse, lozenges, lubricants, and sprays. Patients should be advised to avoid products containing alcohol; as alcohol has a drying effect. It is vital that dental practitioners educate patients on their increased risk of dental caries and oral infections. Patients suffering from xerostomia can be placed on a prescription fluoride treatment or toothpaste. Additional fluoride will aid in remineralization of the tooth structure. Because of the increased risk of caries, patients need to be provided with nutritional counseling, regarding cariogenic food and noncariogenic food. In an article in *The Consultant Pharmacist* it states that sipping water throughout the day also may offer relief for affected patients. Ice chips can also provide moisture and possibly alleviate symptoms.[60] Dental practitioners play a large role in managing xerostomia. They must provide patients with accurate information and product recommendations.

CHAPTER III

METHODOLOGIES

The purpose of this study was to examine New Mexico dental practitioners' knowledge of the adverse oral effects of low-dose methotrexate, diltiazem, cyclosporine, isotretinoin, and lisinopril. The study included an assessment of where this knowledge is obtained.

This study examined New Mexico dental practitioners' knowledge of adverse oral effects of low-dose methotrexate, diltiazem, cyclosporine, iostretinoin, and lisinopril. An informed consent and survey was sent to all licensed dentists and dental hygienists in New Mexico; we will refer to these participants as "subjects". The subjects' contact information was obtained from New Mexico Board of Dental Health Care; this information was kept on file at The University of New Mexico's Dental Hygiene Division. Subjects in New Mexico were selected by a convenience census. Those who were interested and qualified to participate in the adverse oral effects study were asked to complete a survey. By returning the anonymous survey in the envelope provided subjects agreed to participate in the study. Exclusion criteria were as follows: subjects who had either a suspended or inactive license; those subjects not wishing to complete the survey and therefore not providing informed consent; and subjects who were unable to understand the survey.

Senior dental hygiene students at UNM were used as the control group. These students have taken a general pharmacology course within the last year and provided a comparison group. Senior dental hygiene students were presented information on methotrexate, diltiazem, cyclosporine, and lisinopril (this drug classification is addressed,

but not lisinopril specifically). Accutane (isotrenion) is not addressed in this course. Throughout the students' education, adverse oral reactions to pharmaceuticals are also discussed in oral pathology, periodontology, and clinical courses. Exclusion criteria were as follows: senior students who are not present the day the survey was distributed and those not wishing to participate, therefore; not providing informed consent.

Sample Description

All subjects from New Mexico (2,148) received a copy of the survey and consent letter in the mail. Both male and female subjects ranged in age, experience, number of continuing education hours completed, and educational background. In addition to the dental providers, senior dental hygiene students (23 students) at UNM participated in the study. This allowed for internal control of the study when evaluating medications that induce gingival hypertrophy.

Research Design

The research was designed as a descriptive survey study. The selection of subjects was a process of convenience census; every dental provider in the state of New Mexico was sent an informed consent letter and a survey in the mail. The questionnaire was identified with a survey number and consisted of ten questions which included two questions about each medication; one true/false and one multiple-choice question:

1. Diltiazem-induced gingival hypertrophy commonly appears on the attached gingiva.
2. Diltiazem is used to treat which common medical condition?
3. Low-dose methotrexate can be used in the treatment of autoimmune diseases such as, arthritis and psoriasis.

4. Which are the MOST COMMON adverse oral side effects associated with low-dose methotrexate.
5. Isotretinoin (Accutane) causes angular cheilitis in patients using this medication.
6. Isotretinoin (Accutane) is used in the treatment of which condition?
7. Patients taking lisinopril do not report symptoms of xerostomia until saliva production has been reduced by 100%.
8. Lisinopril-induced xerostomia increases patients' risk of developing what oral manifestation?
9. When a patient has cyclosporine-induced gingival hypertrophy, this overgrowth is noted primarily in the posterior interdental papilla.
10. Which is a common pharmacological use of cyclosporine?

Demographic information was collected, which included: educational institution attended, years in practice, continuing education hours completed, and the dental providers' credentials. The purpose of the anonymous survey was to compare knowledge of the five medications being studied. In addition, results were compared between demographic groups. These variations included years of experience, degree earned, number of continuing education hours participated in each year, and type of dental provider.

The same subjects participated throughout the study. Senior dental hygiene students at UNM served as the control group during the investigation of Hypotheses 4 and 5. The control group's responses were not computed for Hypotheses 1, 2, and 3 because it was assumed during the investigation that they would have been most familiar

with gingival hypertrophy when compared to other adverse oral effects. The control group completed the same survey as the subjects.

Data Analysis

After all the results from the study had been gathered, Minitab Release 14.20 (2005) statistical software was used to analyze the data. A descriptive analysis of all data was conducted. For there to be a statistical significance, a P-value of < 0.05 was required. While evaluating the data, a two-sample t-test was used to determine whether two population means were equal, and a one-way ANOVA was used to compare the means of two or more samples/groups. Since five individual hypotheses were examined during this study, specific data analysis for each hypothesis will be discussed.

Two different data analyses were performed on the respondent sample in order to summarize the collected data. First, each of the correct and incorrect number of responses was tallied for each question. Secondly, responses to questions corresponding to each medication (one true/false and one multiple choice question) were tallied. For purposes of calculating the data, the answers were coded to express either a correct or incorrect response. An incorrect response with coded with the number *zero*, one correct response was coded with a number *one*, and two correct responses were coded with a number *two*. This coding system does not specifically identify which of two responses were answered incorrectly. For both, an analysis of the mean, standard error of the mean, and standard deviation were calculated.

Hypothesis 1: Subjects' knowledge regarding adverse oral effects of investigated pharmaceuticals is greater as the educational levels increase.

To test this hypothesis, the total number of correct responses was compared to the highest degree earned. A one-way ANOVA was used to explore any significant differences in knowledge based on degrees.

Hypothesis 2: The longer length of time that subjects have practiced, the less knowledge subjects have regarding adverse oral effects of the investigated medications.

The total number of correct responses was compared to the number of years practicing. The number of years practicing ranged from 0-30+ years. A one-way ANOVA was used to explore any significant differences in knowledge based on years of experience.

Hypothesis 3: Subjects who participate in at least twenty-six hours of continuing education will have more knowledge in adverse oral effects of pharmaceuticals than those who participate in fewer continuing education hours.

To test this hypothesis, the total number of correct responses for those subjects participating in twenty-five hours or fewer of continuing education hours was tallied. The same tally for subjects participating in at least twenty-six hours of continuing education was completed. A one-way ANOVA was used to explore any significant difference in knowledge based on continuing education.

Hypothesis 4: Subjects will be knowledgeable regarding adverse oral effects associated with gingival hypertrophy, therefore; answering half of the related questions correctly.

The total number of incorrect and correct scores was tallied (using the coding system previously mentioned) from questions one and nine. Descriptive statistics were used to analyze the data for the testing of this hypothesis. The mean, standard error of the mean, and standard deviation was calculated. The result of these calculations provided an average score for subjects' knowledge of gingival hypertrophy.

Hypothesis 5: Senior dental hygiene students at The University of New Mexico will knowledgeable regarding medications that induce gingival hypertrophy, therefore; answering half of the associated questions correctly.

To test this hypothesis, the total number of incorrect and correct responses was tallied for questions one and nine (using the established coding system previously discussed), and descriptive statistics were calculated. This hypothesis utilized the control group and the sample group. A two-sample t-test was used to compare the distribution of the mean, standard error of the mean, and standard deviation between the control and sample groups.

Study Approval

The Human Research Review Committee (HRRC) at UNM approved this study. The associated study number of HRRC# 08-443 can be referenced for this research study. In addition, the letters of consent and participant surveys also had the approval of the HRRC. In returning the completed survey, New Mexico dental providers and UNM senior dental hygiene students provided an informed consent for this research.

CHAPTER IV

RESULTS

A total of 2,148 surveys were mailed to subjects in New Mexico; this consisted of 1,083 dentists and 1,010 registered dental hygienists. Twenty-three senior dental hygiene students at UNM also participated in this study as a control group. Two hundred and eighty-four surveys were completed and returned by the requested date of November 10, 2008. Twenty-three completed surveys were returned after the deadline; these subjects' responses were not included with the computations of the final data.

The survey used in this research classified dentists and registered dental hygienists as "subjects." Of the participants, 145 (51.1%) were dentists and 139 (48.9%) were registered dental hygienists. Participants were asked to provide demographic information including: with what type of dental practice they were associated, how many years they have practiced, and the highest degree they have earned. This information provided a comparison for the number of correct responses to the demographic information.

The subjects in this survey are likely representative of practicing dental providers in the state of New Mexico. Due to subjects' ability to maintain an active license but live in different states, there exists the possibility that a small number of other states may be represented in this study.

The survey that subjects completed for this research study inquired about how they obtain information regarding adverse oral effects of pharmaceuticals. Subjects were asked to select which of the options applied to them. The options that participants could select were *websites*, *newspapers*, *journals*, *conferences*, *seminars*, and *other*. Subjects

reported that the use of journals was the primary source for information on adverse oral effects of pharmaceuticals. Table 1 illustrates where subjects obtain information regarding adverse oral effects.

Table 1. ***Demographic statistics for where information is obtained for adverse oral effects of pharmaceuticals.***

Where subjects obtain information on pharmaceuticals		
Source	Number of Participants	**Percentage**
Websites	129	**45.5%**
Newspapers	35	**12.3%**
Journals	223	**78.5%**
Conferences	166	**58.4%**
Seminars	194	**68.3%**
Other	101	**35.5%**

Additional demographic information collected from respondents included the number of years they have practiced, the highest degree they earned, the number of continuing education hours in which they participate yearly, and where they obtain information regarding adverse oral effects from pharmaceuticals. The tested hypotheses in this study explore subjects' knowledge of adverse oral effects based on the number of years practicing, highest degree earned, and annual continuing education hours. These results are discussed further with each associated hypothesis.

Respondent sample data observations and descriptive statistics:

A response rate of 13.2% was found due to 284 of the 2,148 survey recipients responding. In addition, 23 surveys were received after the stated deadline. This increased the response rate to 14.4%; however, because this was a time sensitive investigation, the responses from these 23 subjects were not calculated into the final data. Of the student control group, 100% of the control group responded. Figure 1 illustrates the percentage of dentists, dental hygienists, and students participating in the study. Participants were asked to identify the type of dental practice with which they were associated. It was found that 84.5% worked in general dentistry. The remaining dental specialties had a significantly smaller percentage of representation in this study. These percentages varied from 1.8% to 4.7%.

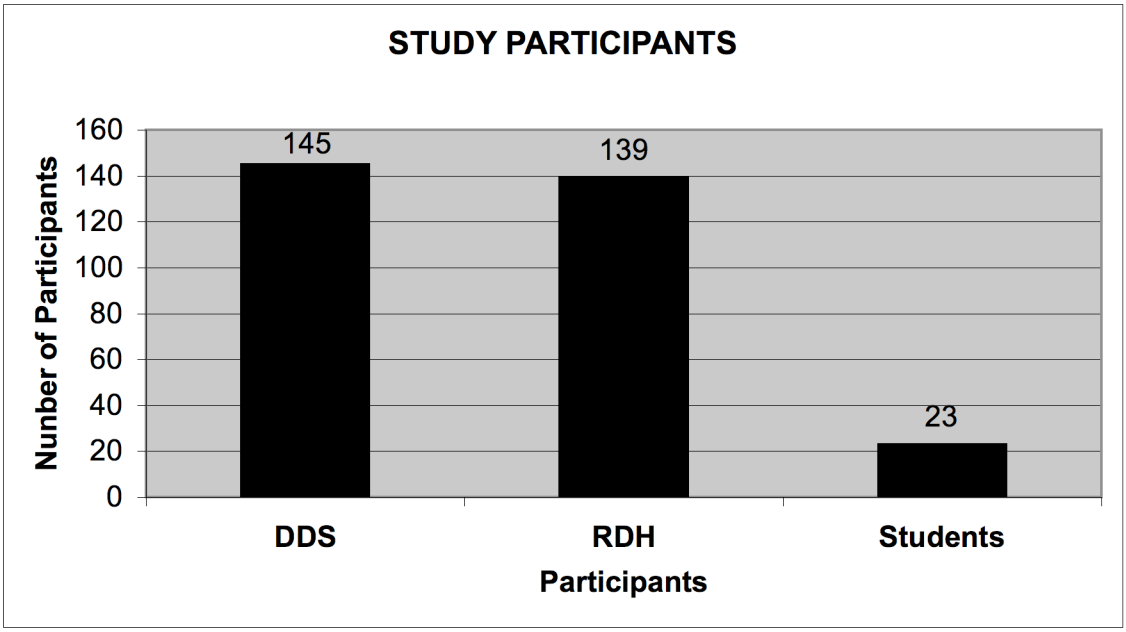


Figure 1. **The number of participants from each demographic group.**

A descriptive summary of the data collected for each medication was calculated. Each medication being researched had one true/false and one multiple-choice question associated with it. The responses were coded with a zero, one, or two; *zero* if both answers were incorrect or no answer was given, *one* if one answer was incorrect, and a *two* if both answers were correct. Subjects' knowledge regarding oral health complications and medications were evaluated during this study. Diltiazem-induced gingival hypertrophy commonly appears on the attached gingiva.

1. Diltiazem is used to treat which common medical condition?
2. Low-dose methotrexate can be used in the treatment of autoimmune diseases such as, arthritis and psoriasis.
3. Which are the MOST COMMON adverse oral side effects associated with low-dose methotrexate.
4. Isotretinoin (Accutane) causes angular cheilitis in patients using this medication.
5. Isotretinoin (Accutane) is used in the treatment of which condition?
6. Patients taking lisinopril do not report symptoms of xerostomia until saliva production has been reduced by 100%.
7. Lisinopril-induced xerostomia increases patients' risk of developing what oral manifestation?
8. When a patient has cyclosporine-induced gingival hypertrophy, this overgrowth is noted primarily in the posterior interdental papilla.
9. Which is a common pharmacological use of cyclosporine?

Figure 2 illustrates the subjects' responses for each medication. In the diagram, each medication has three corresponding sections demonstrating no correct answers, one correct answer, or two correct answers, respectively. This analysis and coding system did not identify which of the two questions were answered correctly.

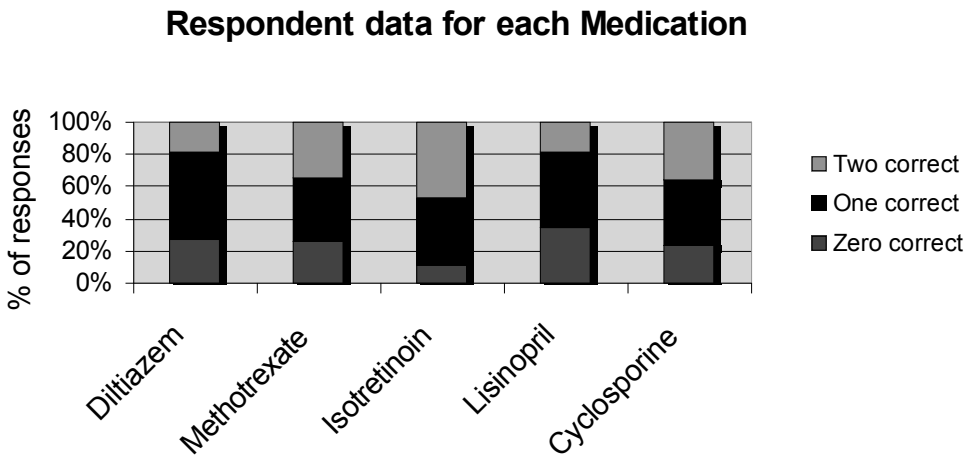


Figure 2. **Percentages of responses for each medication investigated in this study.**

Hypothesis 1: Subjects' knowledge regarding adverse oral effects of investigated pharmaceuticals is greater as educational levels increase.

A one-way ANOVA was used to appraise if there was a difference between educational levels and knowledge of the five predetermined medications by comparing the total number of correct responses to the degrees earned. The control group's data was not used in this analysis because their data was only relevant to hypotheses four and five. A dot plot was generated to display the dispersion of the subjects' correct responses. The dot plot represented in Figure 3 displays the participants' correct responses in correlation to the highest degree earned. The majority of dental providers answered eight or fewer

questions correctly. The dot plot departs slightly from normality with a slight skew to the left; however, this is not severe enough to doubt the results of the ANOVA test. An individual 95% confidence interval was calculated for the mean based on the pooled standard deviation. The means of the levels of educational degrees are centered on 5.3 with a spread from one to ten. The ANOVA test (Table 2) yielded a P-value of 0.196, which is greater than alpha; therefore, it is concluded that there was no significant difference in knowledge of adverse oral effects based the highest degree earned, and Hypothesis 1 was supported.

Table 2. ***One-way ANOVA hypothesis test results for total score earned versus degrees***

One-way ANOVA for Hypothesis 1

Hypothesis 1:
Subjects knowledge regarding adverse oral effects of investigated pharmaceuticals is greater as educational levels increase

Degree	Number of Subjects	Mean	**P-Value**
Associates	52	4.885	
Bachelors	70	5.486	
DDS	131	5.374	
Masters	24	5.417	
PhD	4	7.500	
			0.196

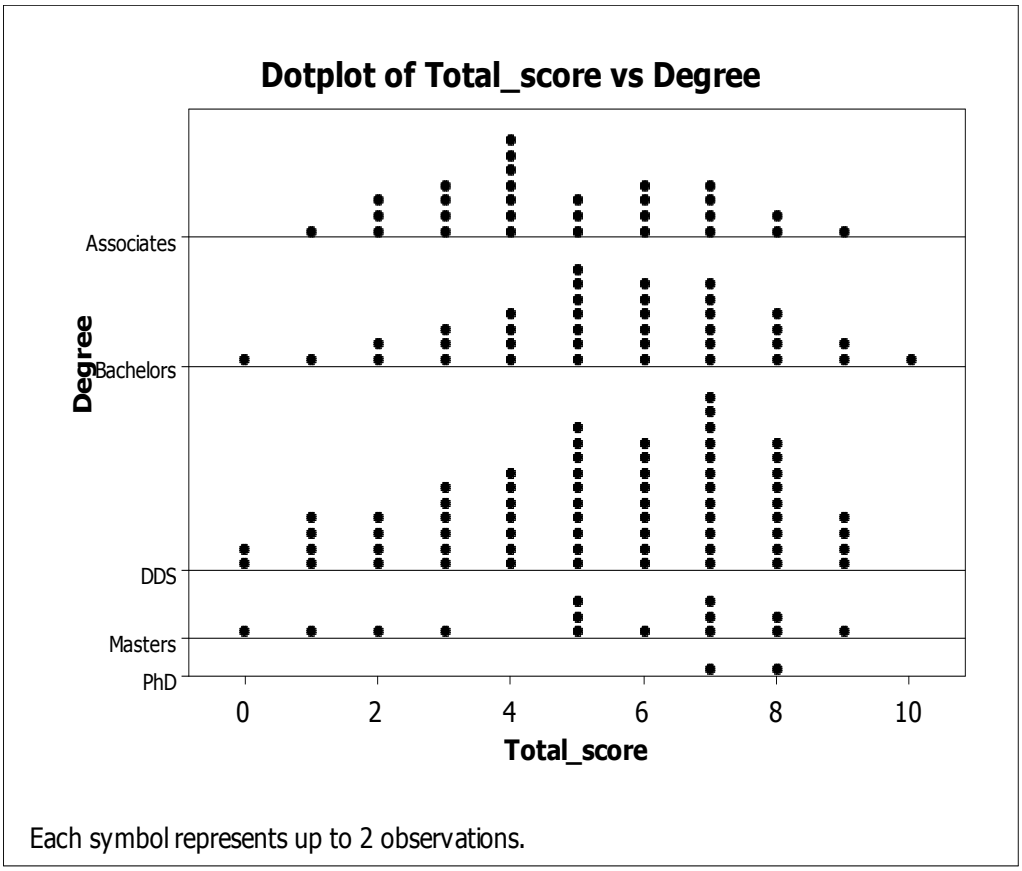


Figure 3. **Total number of correct responses correlating to the highest degree earned.**

Hypothesis 2: The longer length of time that subjects have practiced, the less knowledge subjects have regarding adverse oral effects of the investigated medications

A one-way ANOVA was used to test this hypothesis by comparing the total numbers of correct responses to the number of years the subject respondents have been practicing. The control group's data was not used in this analysis because their data was useful for questions regarding gingival hypertrophy. On the survey, dental practitioners were able to select from 0 years to more than 30 years practicing. As with the previous hypothesis, an individual 95% confidence interval for the mean based on pooled standard deviation was calculated; all means varied from 5.037-6.333 with a spread from zero to

ten. The dot plot (Figure 4) is used to illustrate the distribution of data. A slight skew to the left can be witnessed, but this is not severe enough to dispute the results of the ANOVA hypothesis test. The one-way ANOVA test revealed a P-value of 0.661, which is greater than set alpha (Table 3); therefore, there was no significant difference in knowledge of adverse oral effects for the five investigated pharmaceuticals based on years practicing.

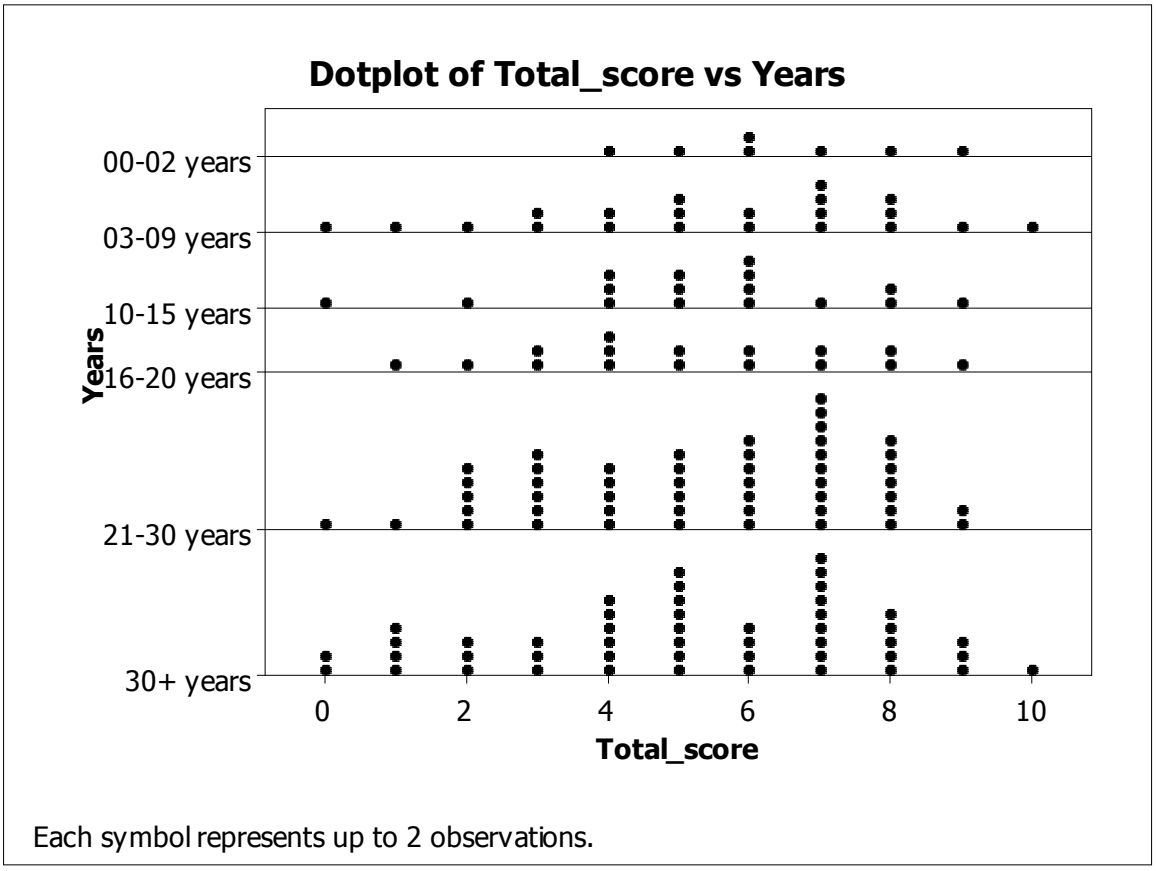


Figure 4. **Total number of responses correlating to the number of years practicing.**

Table 3. ***One-way ANOVA hypothesis test results for Hypothesis 2.***

One-way ANOVA for Hypothesis 2			
Hypothesis 2: The longer length of time subjects have practiced the less knowledge they will have regarding adverse oral effects of medications			
Years practicing	Number of Participants	Mean	**P-Value**
0-2	9	6.333	
3-9	36	5.583	
10-15	28	5.393	
16-20	27	5.037	
21-30	95	5.358	
30+	88	5.136	
			0.661

A regression model was used to test an alternative to Hypothesis 2. This regression model compared the number of years practicing with the total score. A large P-value of 0.178 was obtained, which is consistent with the slope (-0.12335) and is not different from zero. When responses were displayed graphically the data was representative of a normal curve, but it is slightly skewed to the left with no difference from zero. Thus, the number of years practicing does not predict the total score; however, the negative slope of -0.12335 which is the means's difference from zero, suggests that the longer dental practitioners have been practicing, the less they know about adverse oral effects of pharmaceuticals.

Hypothesis 3: Subjects that participate in at least twenty-six hours of continuing education will have more knowledge in adverse oral effects of pharmaceuticals than those that participate in fewer continuing education hours.

A one-way ANOVA was used to explore any significant statistical difference in dental providers' knowledge based on the number of hours of continuing education. The total number of correct responses for those subjects participating in twenty-five hours or fewer of continuing education hours was tallied. The same was tallied for respondents participating in at least twenty-six hours of continuing education. The control group's responses were not factored in for this analysis because their responses were used during the investigation of drug-induced gingival hypertrophy. An individual 95% confidence interval for mean based on the pooled standard deviation was calculated, with the two means centered around 5.3 with a spread ranging from zero to ten. The one-way ANOVA hypothesis test (Table 4) revealed a statistically significant difference ($p = 0.022$). Tukey's HSD test was used to verify the results of the one-way ANOVA test, thus confirming that there was a statistical difference between participants that participated in twenty-five hours or fewer or continuing education and those that participated in at least twenty-six hours of continuing education annually. Those participating in at least twenty-six hours of continuing education scored an average of 0.629 higher than those who had fewer hours.

Table 4. ***One-way ANOVA hypothesis test results for Hypothesis 3.***

One-way ANOVA for Hypothesis 3			
Hypothesis 3: Subjects that participate in at least twenty-six hours of continuing education will have more knowledge in adverse oral effects of pharmaceuticals than those that participate in fewer continuing education hours.			
Number of CE hours	Number of Participants	Mean	**P-Value**
25 or fewer hours	176	5.084	
26+ hours	115	5.713	
			0.022

Hypothesis 4: Subjects will be knowledgeable regarding adverse oral effects associated with gingival hypertrophy, therefore; answering half of the related questions correctly.

Descriptive statistics (mean, standard error of the mean, and standard deviation) were used to test this hypothesis. The total number of incorrect and correct answers for questions one and nine were tallied. The answers were coded with a *zero*, *one*, or *two*, corresponding to an incorrect answer/no response, one correct response, and two correct responses, respectively. This coding system does not identify which of the two questions subjects answered correctly. Table 5 illustrates the distribution of responses from the subjects. A mean score of 0.6632 suggests that the subjects did not know about gingival hypertrophy as it relates to diltiazem and cyclosporine in context of the two posed questions.

Table 5. ***Percentage of participants' correct responses for Hypothesis 4.***

Two Samples t-test

Hypothesis 4:
Subjects will be knowledgeable regarding adverse oral effects associated with gingival hypertrophy, therefore; answering half of the related questions correctly.

Number of Correct Responses	Number of Participants	**Percentage**
0	129	**45.26**
1	123	**43.16**
2	33	**11.58**

Average score = **0.6632**

Standard Deviation = **0.6757**

Upon closer examination of both questions one and nine on the survey, which explore diltiazem and cyclosporines' implication on the gingival tissue, a total of two hundred seventy-five participants answered these questions. For both questions, the participants could select one of three options: *true*, *false*, or *I don't know*. In question one, which states, "Diltiazem-induced gingival hypertrophy commonly appears on the attached gingiva," 45% of subjects answered *true* and 28% responded *I don't know*. However, only 27% answered *false,* which was the correct answer. In question nine, "When a patient has cyclosporine-induced gingival hypertrophy, this overgrowth is noted primarily in the posterior interdental papilla," 10% answered *true* and 48% *I don't know*. These were both the incorrect choice. The correct response was *false,* which 42% of

subjects correctly answered. This suggests that subjects performed worse than expected even if they had randomly guessed the correct answer.

Hypothesis 5: Senior dental hygiene students at The University of New Mexico will be knowledgeable regarding medications that induce gingival hypertrophy, therefore; answering half of the associated questions correctly.

Descriptive statistics (mean, standard error of the mean, and standard deviation) were used to test this hypothesis. The total number of incorrect and correct responses were tallied for questions one and nine for the twenty-three student participants.

1. Diltiazem-induced gingival hypertrophy commonly appears on the attached gingiva.
2. When a patient has cyclosporine-induced gingival hypertrophy, this overgrowth is noted primarily in the posterior interdental papilla.

Both true/false questions answers were coded using the same system described in Hypothesis 4: *zero*, *one*, and *two*. Table 6 demonstrates the percentage distribution of responses from the control group for questions regarding gingival hypertrophy. The mean score of 0.435 suggests that the control group did not have knowledge regarding gingival hypertrophy. As with the subjects that participated in this study, data suggests that the control group scored worse than expected even if they had randomly guessed the correct answer.

Table 6. ***Percentage of participants' correct responses for Hypothesis 5.***

Two Samples t-test

Hypothesis 5:
Senior dental hygiene students at The University of New Mexico will knowledgeable regarding medications that induce gingival hypertrophy, therefore; answering half of the associated questions correctly.

Number of Correct Responses	Number of Participants	**Percentage**
0	15	**65.22**
1	6	**26.09**
2	2	**8.70**

Average score = **0.435**

Standard Deviation = **0.662**

A two-sample t-test was used to compare the scores of the control and sample group. A 95% confidence interval was calculated with an upper limit of 0.0654 and a lower limit of -0.526, which includes zero. The control group scored lower on these two questions than the subjects with a mean difference of -0.230 (Table 7). However, this difference was not statistically significant with a p-value of 0.196.

Table 7. ***Comparison of means between the subjects and the control groups scores.***

Two Sample t-test

Comparison Of Results For Hypotheses 4 and 5:

Group	Number of Participants	**Mean**
Students (control)	23	**0.435**
Dental providers (sample)	284	**0.665**
		Mean difference = **-0.230**

CHAPTER V

DISCUSSION

To the investigators' knowledge, this is the first study that has been conducted regarding subjects knowledge on the five specific medications evaluated during this investigation. Many times, patients do not report adverse oral effects to dental providers because the effects are subtle or they are associated with other systemic or oral conditions. Because of this, there is a minimal amount of research on pharmaceuticals' adverse effects on the oral cavity.

All subjects held a current license and were selected for this study by means of a convenience census. Subjects were sent a time sensitive, 10-question survey and letter of consent in the mail. Two hundred eighty-four of the 2,148 survey recipients participated in this investigation. Subjects in this study were either dentists or dental hygienists; of the total number of participants 51% were dentists and 49% were dental hygienists. In addition, 23 senior dental hygiene students at UNM were utilized as a control group for questions on the survey pertaining to gingival hypertrophy. It was the assumption of this investigative team that the control group would be most knowledgeable regarding this particular adverse oral effect because of their student status. At UNM, students are required to take a pharmacology course prior to their senior year.

Data analysis techniques during the collection of data included the use of descriptive statistics, two sample t-tests, and one-way ANOVAs. An alpha level of 0.05 was established to determine whether or not a statistically significant difference could be declared. From the data analysis performed, it was deemed that four of the five hypotheses' were not supported as a result of a high p-value. However, one hypothesis

did demonstrate a statistically significant difference, therefore ruling in favor of the alternative hypothesis.

Hypothesis 1: Subjects knowledge regarding adverse oral effects of investigated pharmaceuticals is greater as educational level increases.

When analyzing this hypothesis, the assumption was that the education levels are ranked in a hierarchy, beginning at an associates' degree and increasing to a Ph.D. Table 3 illustrates that out of the 284 providers, four participants responded that they had obtained a Ph.D. (three DDS and one RDH); these responses did not alter the results for this hypothesis. Subjects' level of knowledge regarding adverse oral effects does not increase with an increase in the levels of education. The associated dot plot (Figure 3) clearly illustrates that subjects' responses are reasonably evenly distributed amongst the various educational levels. The majority of subjects (excluding subjects with a Ph.D.) answered eight or fewer of the survey questions correctly; these observations are confirmed by a pooled standard deviation of 2.264. Thus, the shape of the bell curve is much wider than it would be had the number of correct responses been densely populated around higher levels of education. Results for this hypothesis suggest that dental providers do not obtain more knowledge regarding adverse oral effects of pharmaceuticals as they continue to move up the educational ladder. Instead, results simply suggest that oral effects are addressed during one's initial education, unlike the preliminary thought that the more education one has, the more educators address adverse oral effects in educational institutions.

Future studies could compare dentists and dental hygienists knowledge of adverse oral effects. Unfortunately, this hypothesis was not examined during this investigation.

Research results also suggest that future studies could include an investigation of both dental and dental hygiene educational programs. Focusing on the timeframe and courses during which one's education of adverse oral effects is addressed could provide insight to areas where more education is needed. An investigation into the effectiveness of a dental-specific pharmacology course could provide additional useful information. In the future, this study could be expanded to compare the effectiveness of specific dental pharmacology courses versus a biomedical pharmacology course.

Hypothesis 2: The longer length of time that subjects have practiced, the less knowledge subjects have regarding adverse oral effects of the investigated medications

It was the assumption of this hypothesis that knowledge of adverse oral effects is associated with experience. A p-value larger than alpha was obtained, indicating that there was no significant difference in knowledge of the predetermined medications and oral health implications based on years practicing. An alternative regression model was analyzed to compare the total score versus the number of years practicing. Again, the large p-value continued to demonstrate that there was no significant difference in knowledge of the five investigated pharmaceuticals' oral effects based on years. A slight variation to the left in the normal bell curve, with a slope of -0.12335, indicates that the longer the subjects have been practicing, the less they know about adverse oral effects of the five named pharmaceuticals. It should be mentioned that this was not a statistically significant difference, but it suggests the need for future studies.

An investigation of dental providers' knowledge and use of other key factors pertaining to dentistry could be investigated; including the adverse oral effects of pharmaceuticals, instrumentation techniques, product recommendations, integration of

advanced technology, and the implementation of evidence-based dentistry. These results could indicate that the longer subjects practice, the less they keep up with current research, technology, or procedures. It may be assumed from the compiled data that patients may not be receiving the most current information, thus potentially compromising the quality of patient education. An evaluation of technique, procedures, and research that are provided to patients from providers who have been practicing dentistry for longer periods may beneficial to both patients and providers. This could provide insight on how to motivate and update those practitioners who have been practicing for extended lengths of time. The government mandating the use of electronic medical and dental records may initiate a renewed sense of exploration and technology in the field of dentistry. It is the expectation of patients that they receive current quality and evidenced-based dental care.

Hypothesis 3: Subjects that participate in at least twenty-six hours of continuing education will have more knowledge in adverse oral effects of pharmaceuticals than those that participate in fewer continuing education hours.

Through the use of a one-way ANOVA, a small P-value of 0.022 was obtained. This was indicative of a statistically significant difference in knowledge of the specially named medications and their associated oral manifestations based on the number of continuing education hour's subjects participated in yearly. The difference between subjects participating in at least twenty-six hours versus twenty-five or fewer hours was 0.629. The specific reason for this difference is not known.

Assumptions can be made to account for this difference regarding those subjects that participate in at least twenty-six hours of continuing education per year. It could be

that these subjects enrolled in continuing education courses that addressed pharmaceuticals and their implications on the oral cavity. Even if these courses do not address adverse oral effects specifically, it is plausible that this topic would be briefly addressed in pharmacology seminars. The majority of states require that both dentists and dental hygienists participate in continuing education in order to maintain an active license. The state of New Mexico requires that dentists and dental hygienists complete a minimum of sixty (DDS) and forty-five hours (RDH) per triennial renewal cycle.[61] New Mexico mandates that a specific number of courses be taken at seminars/conventions, whereas other hours can be obtained from journals and on-line coursework. This factor could account for the significant difference between twenty-five or fewer and at least twenty-six continuing education hours participated in annually.

This difference in scores can also be associated with Hypothesis 2. It is plausible that the same subjects who have been practicing longer and performed slightly worse on the survey participated in fewer continuing educations hours. This assumption provides opportunities for further studies; investigation into the correlation between the length of time practicing and the number of continuing education hours would be useful in accounting for the difference discovered in this study. Perhaps an evaluation into the effectiveness of continuing education from journals, periodicals, and on-line courses would be useful. The results from an investigation could provide insight and change to the current regulations set forth by the New Mexico Board of Dental Health Care.

Hypothesis 4: Subjects will be knowledgeable regarding adverse oral effects associated with gingival hypertrophy, therefore; answering half of the related questions correctly.

Two questions in this investigation addressed medications that induce gingival hypertrophy, both of which were true/false questions:

1. Diltiazem-induced gingival hypertrophy commonly appears on the attached gingiva.
2. When a patient has cyclosporine-induced gingival hypertrophy, this overgrowth is noted primarily in the posterior interdental papilla.

In the consent letter, subjects were instructed that they were not required to answer a question if they did not understand it or did not feel comfortable. Of the 284 surveys returned, 275 subjects answered both questions 1 and 9. In question number one, the survey inquired as to if diltiazem-induced gingival hypertrophy commonly appears on the attached gingiva. Seventy-three percent of subjects either responded *true* or *I don't know*; the correct response was *false*. Statistically, this indicated that this question was exceptionally difficult for subjects. For question nine, 58.1% of subjects answered it incorrectly, while 41.8% answered it correctly. This question presented less difficulty for the subjects than question one.

An average score of 0.6632 does not suggest that subjects in New Mexico knew about gingival hypertrophy in the context of the two posed questions. In fact, subjects scored worse on these two questions statistically than they would have if they had simply guessed. If subjects had guessed at random, 25% would have answered both questions incorrectly, 50% answered one question correctly, and 25% answered both questions correctly. Gingival hypertrophy is commonly taught in educational settings, as this can complicate dental treatment, oral health, and have an aesthetic impact on the patient. It is important that dental providers be familiar with the characteristic appearances and

location of gingival hypertrophy. This data may suggest that more education is needed in this area to assist in educating dental providers of this commonly witnessed adverse oral effect. This education can be in a variety of forms including articles, research, seminars, and information from pharmaceutical companies. It should be acknowledged that the sole responsibility of providing and obtaining information regarding gingival hypertrophy does not fall primarily on dental providers. Research can be done by pharmaceutical companies to assist in determining the number of patients on drug therapies that induce gingival hypertrophy and how frequently it occurs. Pharmaceutical companies also have the opportunity to educate dental providers on the likelihood of this condition occurring. Dental providers should take the initiative to investigate medications that the patient is taking. This will not only educate providers on adverse oral effects, but also allow them to provide the patient with the appropriate education and information regarding any adverse oral effects they may be experiencing or could experience.

Hypothesis 5: Senior dental hygiene students at The University of New Mexico will be knowledgeable regarding medications that induce gingival hypertrophy, therefore; answering half of the associated questions correctly.

Similar to the fourth hypothesis, questions one and nine were used to investigate this hypothesis. The percentage of the control group that responded incorrectly with answering either *true* or *I don't know* to question one was 78.2%, whereas the correct response was *false*. In questions nine, 73.9% of the control responded *true* or *I don't know*; the correct answer was *false*, with 26.1% answering correctly. The control groups average score is 0.435, which suggests that they did not have knowledge of gingival hypertrophy in the context of the posed questions. Similarly to the subjects, the control

group performed worse than expected had they simply guessed the correct response at random. Students scored lower than the dental providers did, but not significantly worse.

It was the expectation during this study that the control group would score higher on the questions pertaining to gingival hypertrophy than the subjects. The control group would have been educated on this adverse oral effect throughout their course work at UNM. Currently, dental hygiene students take a general pharmacology course that includes other branches of healthcare. An evaluation into the effectiveness of a pharmacology course specifically designed for dental professionals may be of interest to UNM and other educational institutions. These results yield insight to areas of further study regarding adverse oral effects. Implementing a discussion regarding gingival hypertrophy into other dental hygiene courses at UNM may assist in increasing students' knowledge of this adverse oral complication as it relates to diltiazem and cyclosporine.

In conclusion, statistical data suggests that further studies are needed to evaluate the occurrence of these adverse oral effects, in addition to assess the deficiencies in dental providers' knowledge of adverse oral effects. This investigation offers insight to areas where there is a lack of information for both students and dental providers. Future studies can be implemented to evaluate the educational process for both dental and dental hygiene students in regards to pharmacology and adverse oral effects. However, to adequately educate students, a key factor will be further investigation into the occurrence rate of adverse effects and which medications are more prevalent for causing an adverse response. As dental providers, patients seek medical advice and guidance; the lack of information and knowledge on adverse oral effects may be a disservice to the patient.

This study is indicative of what is needed and of what is yet to come in the investigation of adverse oral effects of pharmaceuticals.

Respondent data analysis:

Tally for Discrete Variables: s01

s01	Count	Percent
0	210	73.94
1	74	26.06
N=	284	

Tally for Discrete Variables: s02

s02	Count	Percent
0	98	34.51
1	186	65.49
N=	284	

Tally for Discrete Variables: s03

s03	Count	Percent
0	81	28.52
1	203	71.48
N=	284	

Tally for Discrete Variables: s04

s04	Count	Percent
0	180	63.38
1	104	36.62
N=	284	

Tally for Discrete Variables: s05

s05	Count	Percent
0	144	50.70
1	140	49.30
N=	284	

Tally for Discrete Variables: s06

s06	Count	Percent
0	43	15.14
1	241	84.86
N=	284	

Tally for Discrete Variables: s07

s07	Count	Percent
0	120	42.25
1	164	57.75
N=	284	

Tally for Discrete Variables: s08

s08	Count	Percent
0	208	73.24
1	76	26.76
N=	284	

Tally for Discrete Variables: s09

s09	Count	Percent
0	169	59.51
1	115	40.49
N=	284	

Tally for Discrete Variables: s10

s10	Count	Percent
0	81	28.52
1	203	71.48
N=	284	

Tally for Discrete Variables: d1_Diltiazem

d1_Diltiazem	Count	Percent
0	76	26.76
1	156	54.93
2	52	18.31
N=	284	

Tally for Discrete Variables: d2_Methotrexate

d2_Methotrexate	Count	Percent
0	75	26.41
1	111	39.08
2	98	34.51
N=	284	

Tally for Discrete Variables: d3_Isotretinoin

d3_Isotretinoin	Count	Percent
0	33	11.62
1	121	42.61
2	130	45.77
N=	284	

Tally for Discrete Variables: d4_Lisinopril

d4_Lisinopril	Count	Percent
0	97	34.15
1	134	47.18
2	53	18.66
N=	284	

Tally for Discrete Variables: d5_Cyclosporine

d5_Cyclosporine	Count	Percent
0	68	23.94
1	114	40.14
2	102	35.92
N=	284	

Descriptive Statistics: d1_Diltiazem, d2_Methotrexate, d3_Isotretinoin, d4_Lisinopril, d5_Cyclosporine

Variable	Mean	SE Mean	StDev
d1_Diltiazem	0.9155	0.0396	0.6672
d2_Methotrexate	1.0810	0.0461	0.7776
d3_Isotretinoin	1.3415	0.0402	0.6774
d4_Lisinopril	0.8451	0.0422	0.7113
d5_Cyclosporine	1.1197	0.0454	0.7657

Tally for Discrete Variables: Total_score

Total_score	Count	Percent
0	8	2.82
1	12	4.23
2	18	6.34
3	25	8.80
4	36	12.68
5	43	15.14
6	40	14.08
7	51	17.96
8	34	11.97
9	15	5.28
10	2	0.70
N=	284	

Descriptive Statistics: Total_score

Variable	Mean	SE Mean	StDev
Total_score	5.303	0.137	2.305

Hypotheses:

1. The higher levels of education mean an increased level of knowledge regarding adverse oral effects of pharmaceuticals.

Results: There are no significant differences in knowledge based on degree.

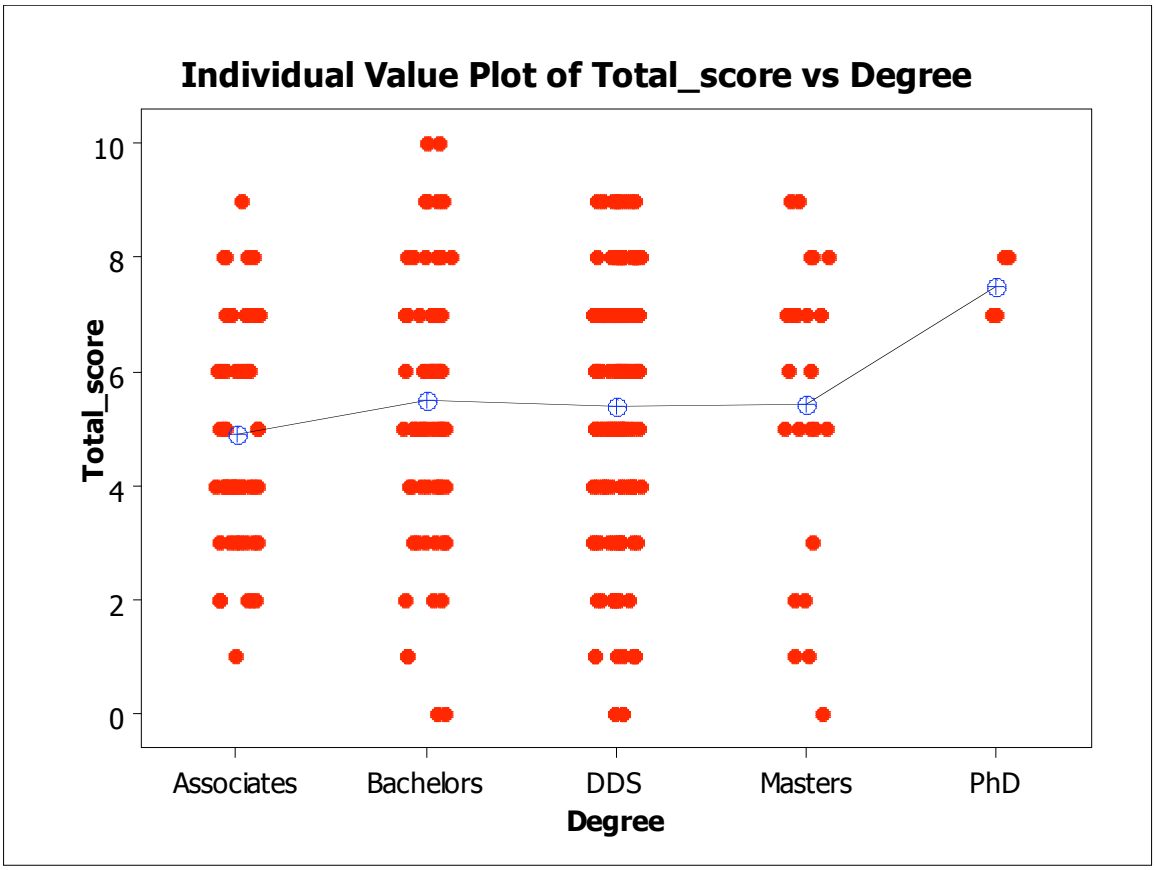
One-way ANOVA: Total_score versus Degree

Source	DF	SS	MS	F	P
Degree	4	31.22	7.80	1.52	0.196
Error	276	1414.30	5.12		
Total	280	1445.52			

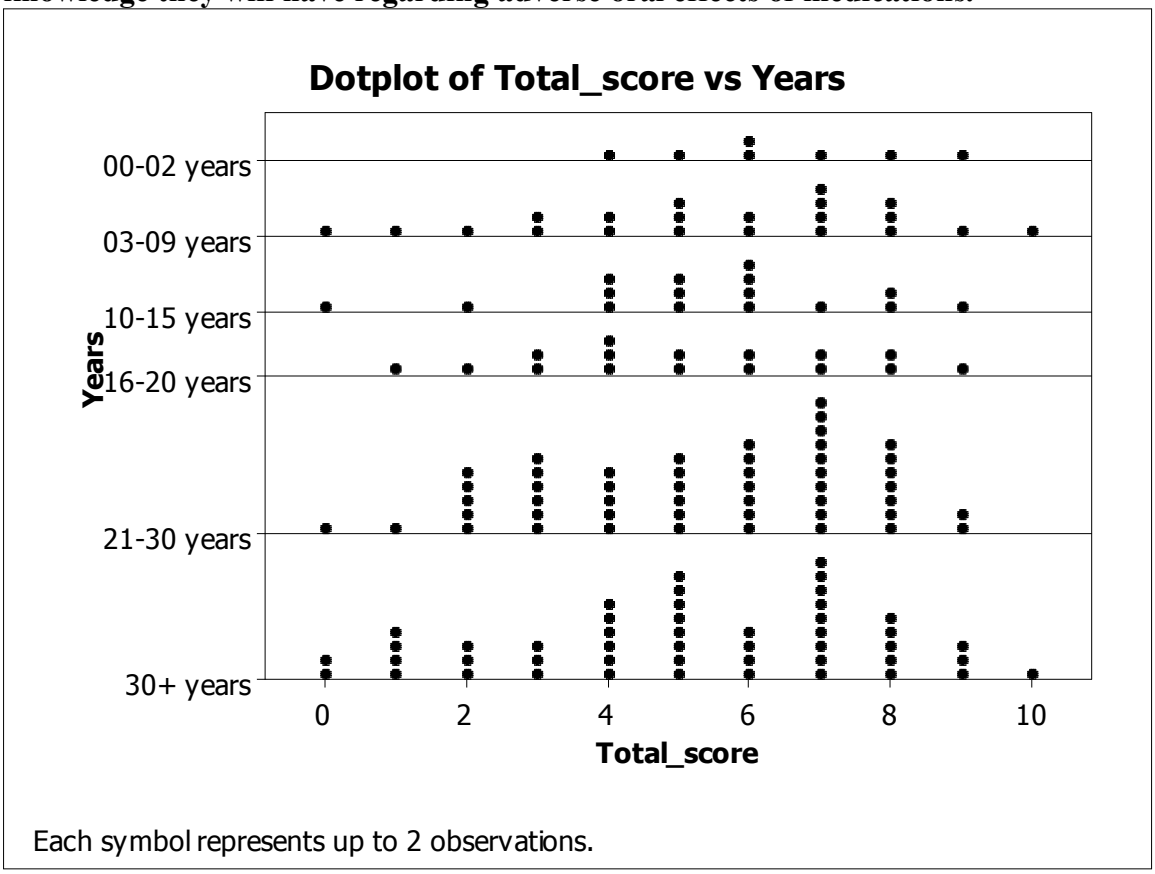
S = 2.264 R-Sq = 2.16% R-Sq(adj) = 0.74%

Level	N	Mean	StDev	Individual 95% CIs For Mean Based on Pooled StDev
Associates	52	4.885	1.947	(----*---)
Bachelors	70	5.486	2.276	(---*--)
DDS	131	5.374	2.325	(--*-)
Masters	24	5.417	2.636	(-----*-----)
PhD	4	7.500	0.577	(--------------*--------------)
				4.5 6.0 7.5 9.0

Pooled StDev = 2.264


Individual Value Plot of Total_score vs Degree
Total_score
10
8
6
4
2
0
Associates
Bachelors
DDS
Masters
PhD
Degree

2. The longer period of time that dental providers have practicing, the less knowledge they will have regarding adverse oral effects of medications.



Results: There are no significant differences in knowledge based on years.

One-way ANOVA: Total_score versus Years

```
Source   DF       SS    MS     F      P
Years     5    17.15  3.43  0.65  0.661
Error   277  1458.59  5.27
Total   282  1475.74

S = 2.295   R-Sq = 1.16%   R-Sq(adj) = 0.00%

                                 Individual 95% CIs For Mean Based on
                                 Pooled StDev
Level         N   Mean  StDev  --------+---------+---------+---------+-
00-02 years   9  6.333  1.500        (--------------*--------------)
03-09 years  36  5.583  2.430        (-------*------)
10-15 years  28  5.393  2.061     (--------*-------)
16-20 years  27  5.037  2.192  (-------*--------)
21-30 years  95  5.358  2.226         (----*---)
30+ years    88  5.136  2.464       (---*----)
                                 --------+---------+---------+---------+-
                                       5.0       6.0       7.0       8.0

Pooled StDev = 2.295
```

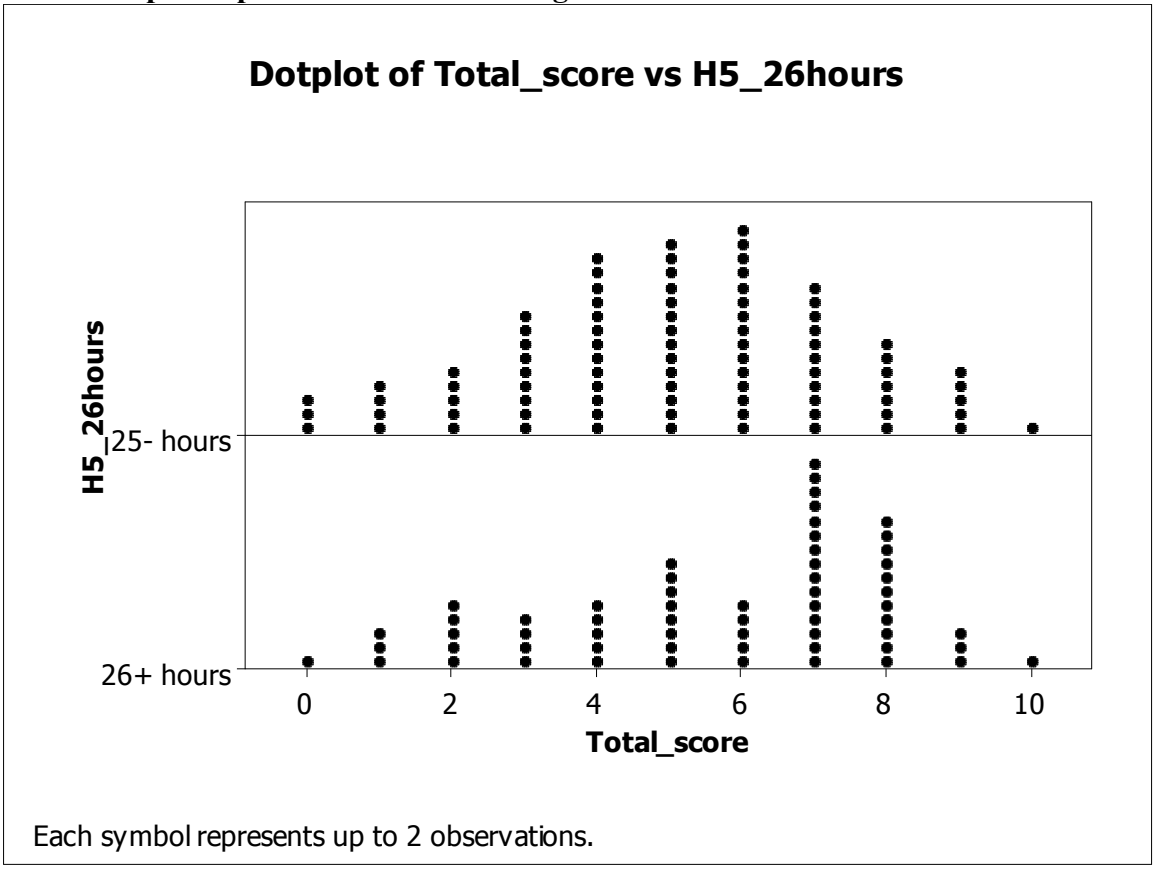
Regression Analysis: Total_score versus C

```
The regression equation is
Total_score = 5.88 - 0.123 C

Predictor      Coef  SE Coef      T      P
Constant     5.8777   0.4332  13.57  0.000
C          -0.12335  0.09124  -1.35  0.178

S = 2.28425   R-Sq = 0.6%   R-Sq(adj) = 0.3%
```

3. Dental providers that participate in at least twenty-six hours of continuing education will have more knowledge in adverse oral effects of pharmaceuticals than those that participate in fewer continuing education hours.



Results: There is a significant difference in knowledge based on continuing education hours 26+ versus 25-, scoring an average of 0.629 higher.

One-way ANOVA: Total_score versus H5_26hours

```
Source       DF       SS     MS     F      P
H5_26hours    1    26.96  26.96  5.32  0.022
Error       280  1420.36   5.07
Total       281  1447.32

S = 2.252   R-Sq = 1.86%   R-Sq(adj) = 1.51%


                              Individual 95% CIs For Mean Based on
                              Pooled StDev
Level        N   Mean  StDev  -----+---------+---------+---------+----
25- hours  167  5.084  2.216  (---------*---------)
26+ hours  115  5.713  2.305                 (-----------*-----------)
                              -----+---------+---------+---------+----
                                 4.90      5.25      5.60      5.95

Pooled StDev = 2.252
```

4. Dental providers will be able to answer half the questions with adverse oral effects associated with gingival hypertrophy.

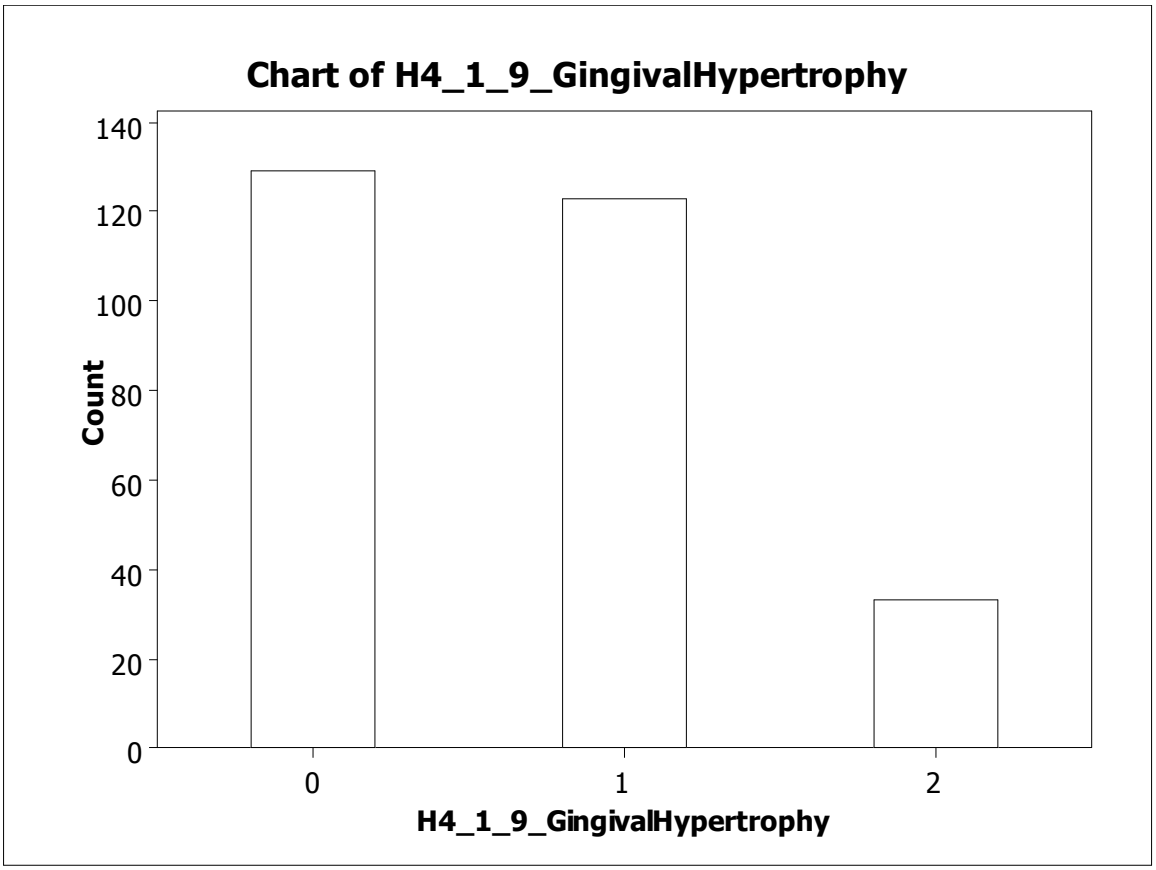
Results: Average score is 0.6632, which does not suggest that they know about Gingival Hypertrophy in the context of the two posed questions. In fact, they did worse than expected if they simply guessed at random (which would have 0.25 0's, 0.5 1's, and 0.25 2's)!

Tally for Discrete Variables: H4_1_9_GingivalHypertrophy

```
H4_1_9_GingivalHypertrophy  Count  Percent
                         0    129    45.26
                         1    123    43.16
                         2     33    11.58
                       N=    285
```

Descriptive Statistics: H4_1_9_GingivalHypertrophy

```
Variable          N*    Mean  SE Mean   StDev  Minimum      Q1  Median      Q3  Maximum
H4_1_9_GingivalH   0  0.6632   0.0400  0.6757   0.0000  0.0000  1.0000  1.0000   2.0000
```



5. Senior dental hygiene students at The University of New Mexico will be able to answer half the questions regarding medications that induce gingival hypertrophy.

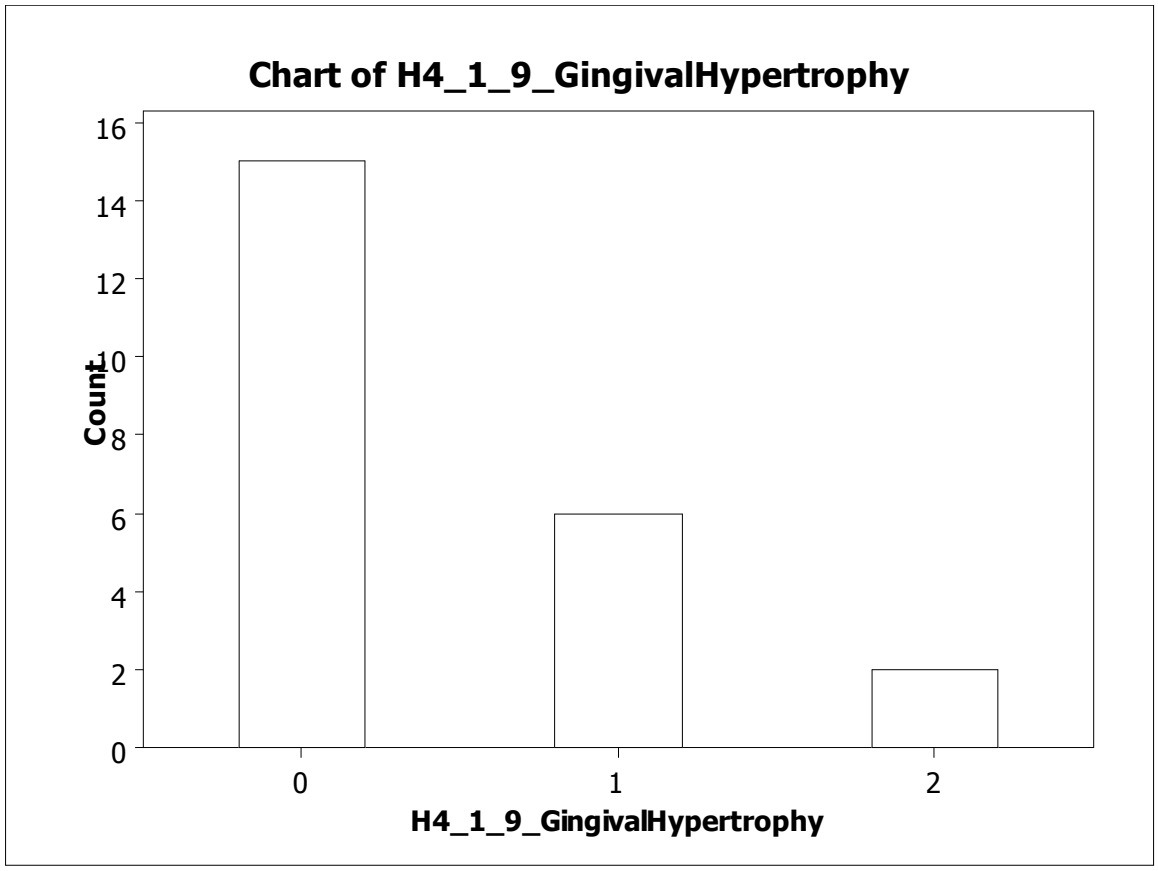
Results: Average score is 0.435, which does not suggest that they know about Gingival Hypertrophy in the context of the two posed questions. In fact, they did worse than expected if they simply guessed at random (which would have 0.25 0's, 0.5 1's, and 0.25 2's), and even worse than the practitioners (but not significantly worse)!

Tally for Discrete Variables: H4_1_9_GingivalHypertrophy

H4_1_9_GingivalHypertrophy	Count	Percent
0	15	65.22
1	6	26.09
2	2	8.70
N=	23	

Descriptive Statistics: H4_1_9_GingivalHypertrophy

Variable	N*	Mean	SE Mean	StDev	Minimum	Q1	Median	Q3	Maximum
H4_1_9_GingivalH	0	0.435	0.138	0.662	0.000	0.000	0.000	1.000	2.000



Two-Sample T-Test and CI: H4_1_9_GingivalHypertrophy, Group

```
Two-sample T for H4_1_9_GingivalHypertrophy

Group      N   Mean  StDev  SE Mean
Control   23  0.435  0.662     0.14
Sample   284  0.665  0.676    0.040


Difference = mu (Control) - mu (Sample)
Estimate for difference:  -0.230710
95% CI for difference:  (-0.526906, 0.065486)
T-Test of difference = 0 (vs not =): T-Value = -1.60  P-Value = 0.121  DF = 25
```

APPENDIX 2: PARTICPANT SURVEY

Demographic Information: **Survey #:**

What type of dental provider are you?

- ☐1 Dentist
- ☐2 Registered Dental Hygienist

What type of dental practice are you associated with?

- ☐1 General
- ☐2 Orthodontic
- ☐3 Oral Surgery
- ☐4 Pediatric
- ☐5 Endodontic
- ☐6 Periodontal

How many years have you been practicing?

- ☐1 0-2 years
- ☐2 3-9 years
- ☐3 10-15 years
- ☐4 16-20 years
- ☐5 21-30 years
- ☐6 30+ years

What is the highest degree earned?

- ☐1 Associates
- ☐2 Bachelors
- ☐3 DDS
- ☐4 Masters
- ☐5 Ph.D.

How many hours of continuing education do you participate in each year?

- ☐1 5-10 hours
- ☐2 11-15 hours
- ☐3 16-20 hours
- ☐4 21-25 hours

☐$_5$ 26-30 hours
☐$_6$ 31+ hours

Where have you obtained information on adverse oral effects of pharmaceuticals that patients may present with on their medical histories? (Circle all that apply)

☐$_1$ Websites
☐$_2$ Newspaper
☐$_3$ Journals
☐$_4$ Conferences
☐$_5$ Seminars
☐$_6$ Other _____

<u>Adverse oral effects questionnaire:</u> Please check the BEST answer.

1. Diltiazem-induced gingival hypertrophy commonly appears on the attached gingiva.

   ☐$_1$ True ☐$_2$ False *** ☐$_3$ I do not know

2. Diltiazem is used to treat which common medical condition?

   ☐$_1$ Hypertension ***
   ☐$_2$ Pulmonary embolism
   ☐$_3$ Cardiac arrest
   ☐$_4$ Bronchitis
   ☐$_5$ I do not know

3. Low-dose methotrexate can be used in the treatment of autoimmune diseases such as, arthritis and psoriasis.

   ☐$_1$ True *** ☐$_2$ False ☐$_3$ I do not know

4. Which are the MOST COMMON adverse oral side effects associated with low-dose methotrexate.

   ☐$_1$ Mucositis and oral ulcerations ***
   ☐$_2$ Candidiasis and leukoplakia
   ☐$_3$ Xerostomia and mucositis
   ☐$_4$ Candidiasis and xerostomia
   ☐$_5$ I do not know

5. Isotretinoin (Accutane) causes angular cheilitis in patients using this medication.

☐$_1$ True *** ☐$_2$ False ☐$_3$ I do not know

6. Isotretinoin (Accutane) is used in the treatment of which condition?

☐$_1$ Psoriasis
☐$_2$ Nodular acne ***
☐$_3$ Sjrogen's Syndrome
☐$_4$ Migraine headaches
☐$_5$ I do not know

7. Patients taking lisinopril do not report symptoms of xerostomia until saliva production has been reduced by 100%.

☐$_1$ True ☐$_2$ False *** ☐$_3$ I do not know

8. Lisinopril-induced xerostomia increases patients' risk of developing what oral manifestation?

☐$_1$ Mucositis
☐$_2$ Leukoedma
☐$_3$ Candida albicans ***
☐$_4$ Oral Ulceration
☐$_5$ I do not know

9. When a patient has cyclosporine-induced gingival hypertrophy, this overgrowth is noted primarily in the posterior interdental papilla.

☐$_1$ True ☐$_2$ False *** ☐$_3$ I do not know

10. Which is a common pharmacological use of cyclosporine?

☐$_1$ Hypertension
☐$_2$ Cancer
☐$_3$ Osteoporosis
☐$_4$ Organ transplants ***
☐$_5$ I do not know

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