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Off-label Prescribing: Pediatrician Beliefs and Experience

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Dedication

This Dissertation is dedicated to my mother, Evelyn Herbst. Thank you, Mom, for showing me the importance of dedication, even when faced with seemingly insurmountable adversity.

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Abstract

Off-label Prescribing: Pediatrician Beliefs and Experience

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When a health authority approves a drug for marketing, they approve the drug for use in the population tested by drug manufacturer. However, once the drug is on the market, a physician may legally prescribe the drug in whatever manner they feel is appropriate for their patients. When the drug is prescribed in a manner outside of the marketing approval, it is prescribed in an off-label manner. Off-label prescribing is prevalent in many populations, including up to 80% of the drug prescribed to children.

The purpose of this study was to determine the beliefs and experience of pediatricians toward this practice. A total of 167 pediatricians answered an 11 question survey regarding their beliefs and experience with off-label prescribing. The results indicated that pediatricians are concerned with the safety and efficacy of drugs that are prescribed in an off-label manner and they believe that more references should be available to determine the best medicines to prescribe to their patients. In addition, respondents are concerned about the

legal liabilities, patient complaints, and insurance coverage related to off-label prescribing.

As this study is the first to determine the beliefs and experience of pediatricians toward off-label prescribing, the results provide a foundation for pediatricians to develop effective guidance and improve their clinical judgment when prescribing medicines off-label.

Chapter I

Introduction

Background of the Problem

Prior to marketing a medicine to a specific population, pharmaceutical manufacturers must submit evidence to a regulatory health authority indicating that the medicine is both safe and effective for that population. The evidence required by the health authority includes data from tests in humans, which are collectively known as clinical trials. If the results from the clinical trials indicate that the benefits of the medicine outweigh the risks, the regulatory authority generally approves the medicine for the specific indication, population, route of administration and dosage studied in the clinical trial. However, once the medicine is approved for a single indication, population, route of administration and dosage, any physician may legally choose to prescribe the drug in a manner not approved by the regulatory authority (Cohen, 1997).

When a medical practitioner prescribes a drug for an indication, dose, population or route of administration not indicated on the drug's label (i.e. in a manner not approved by a regulatory authority), they have prescribed the drug in an "off-label" manner. Many people believe that because medicines prescribed

off-label are not tested in a clinical trial that the patients may be at a higher risk for safety concerns or that the medicine may not be effective for the prescribed use (Cohen, 1997).

There is some research that indicates that even though they prescribe medicines off-label, some physicians may not be aware of the practice of off-label prescribing. For example, the results of one study indicate that about 1 in 4 physicians were not familiar with off-label prescribing, and that only 40% of physicians knowingly prescribed medicines off-label (Ekins-Daukes, Helms, Taylor & McLay (2005)). This lack of off-label prescribing practices combined with the fact that many medications may not have sufficient evidence to support its usage in the manner it was prescribed, could limit health care management options and or put patients at increased risk for adverse effects resulting from the management practices implemented.

Additional risks exist when the patient receiving the off-label medicine is a child because children have more active physiological changes than adults (Cohen, 1997). However, up to 80% of medicines prescribed to children are off-label (Pandolfini & Bonati, 2005; Shah, et al., 2007). Although there are no studies that indicate exactly why off-label prescribing is so prevalent in this population, Conroy (2002) argues that the pediatricians who are aware of the practice and knowingly prescribe medicines off-label may do so because information on the proper use of the medicine is not available. O'Reilly & Dalal (2003) further suggest that a pediatrician may prescribe a medicine off-label because there is a lack of adequate information regarding the appropriate use,

safety and efficacy of the medicine, a medical practitioner's fear of litigation if the medicine they prescribe is not approved for the use prescribed, whether the patient has insurance coverage for the preferred medicine or whether a patient has complaints regarding the use of off-label medicines to treat their disease.

The information is not available because, often, drug manufacturers do not perform clinical trials in a certain population, such as children, because the cost of performing the research outweighs the potential marketing value – the pediatric population is relatively small compared to the adult population for most diseases. To encourage drug manufacturers to perform clinical trials in the pediatric population, in 1997, the FDA enacted the pediatric exclusivity program. This program allowed the FDA to grant an extra six months of patent rights to companies that performed clinical trials in children. For many medicines, an extra six months of patent exclusivity could mean up to half a billion dollars in additional sales of the medicine and more than cover the cost of the research.

While the purpose of this program was to encourage pharmaceutical companies to perform more clinical trials in children, thus enabling physicians to have more information on how to prescribe the medicine in the pediatric population. While the program incentives successfully encouraged pharmaceutical manufacturers to perform over 250 additional studies in children between 1998 and 2004, there was no incentive for the manufacturer to publish the study results. Benjamin, et al. (2006) found that the clinical trial results were published in peer-reviewed journals less than half of the time. Thus the lack of published results restricts the establishment of evidence-based practice. Often,

the drug studied may have been on the market for a while and the manufacturers may not believe that publication was a worthwhile investment of resources. Therefore, any negative results or results that are not published or do not lead to a change in the drug's label, may never reach the physician prescribing the medicine to determine the appropriate use of the medicine for their patient (Benjamin, et al. 2006).

Unfortunately, even if proper pediatric prescribing information is available, it may not be present in the medical drug references most often utilized by physicians. Therefore, physicians may not be aware of the proper current use of a medicine. For example, greater than 70% of the entries in the *Physicians Desk Reference (PDR)*, a popular reference used in the United States, have either no pediatric dosing information or an explicit statement saying that safety and efficacy in children has not been determined (Blumer, 1999). Moreover, the results of a survey given to 500 family physicians in Canada indicated that the reference used by 87% of the physicians, the *Compendium of Pharmaceuticals and Specialities*, did not reflect the current pediatric standard of care (Matsui, Jardine, Steer, Cukernik & Rieder (2003)).

Another concern with off-label prescribing is insurance coverage. Many prescription benefit companies will reimburse patients only for drugs that have been approved by the FDA for the use in which they were prescribed (O'Reilly & Dalal, 2003). In situations where off-label treatments may be more effective than approved drugs, reimbursement issues can hinder a physician's ability to effectively treat a patient. Patients in these situations may be forced to pay out-

of-pocket for their drugs or be treated with drugs that may be less effective for their situation.

Accordingly, physicians also fear litigation when prescribing a medicine off-label (Hill, 2005; O'Reilly & Dalal, 2003). Although off-label prescribing is legal, physicians must use their professional judgment, based on the scientific literature and their personal experience, when choosing to prescribe a medicine in an off-label manner. If a physician is sued for prescribing a medicine off-label, it is his/her responsibility to prove that prescribing the medicine was most appropriate choice for their patient. Some commonly used references may not have the complete prescribing information for a medicine so proving proper use of the medicine may be difficult. Therefore, even if a physician believes that an off-label medicine may be more appropriate for their patient, they may fear litigation and possibly withhold a better treatment from their patient (O'Reilly & Dalal, 2003).

Physicians also want to please their patients when prescribing medicines. Lowe-Ponsford & Baldwin (2000) surveyed 200 psychiatrists to determine how common off-label prescribing was in their specialty and to ascertain whether or not they felt sufficient prescribing guidelines were available. Although 65% of respondents had prescribed medicine off-label in the last month, only four percent had received complaints from their patients regarding the off-label prescribing. The respondents did not indicate the context of the specific complaints but the authors believe that, based on respondent comments,

whether a patient complains about the use of a drug off-label may be another factor that influences physicians to prescribe a medicine off-label.

Most importantly, previous studies report that off-label treatments can lead to a higher incidence of adverse drug reactions (ADRs). Turner, Nunn, Fielding, and Choonara (1999) found that patients who were prescribed a drug off-label had a 1.5 times greater chance of an ADR than those who were prescribed drugs according to their marketing license. Choonara and Conroy (2002) argue that because children have a significantly different physiologic and metabolic makeup than adults, medicines may severely affect their physical and metabolic status. In fact, the results of a survey of 257 hospital-based pediatricians indicated that about half of pediatricians were concerned about efficacy and safety of off-label medicines (McLay, Tanaka, Ekins-Daukes & Helms (2006)). Therefore, patient safety concerns in the pediatric population are paramount.

Purpose of this Study

Because the physician ultimately decides what medicine to offer what patient, it is important that their perspectives of off-label prescribing practices are understood. This is especially important in the treatment of children, whose maturing bodies may be more sensitive to the medicine's effects. The results from this study will provide an understanding of factors that influence a pediatrician's decision to prescribe a medicine off-label and thus may lead to strategies for promoting more informed off-label practices amongst pediatricians.

Research Question

What factors influence a pediatrician's decision to prescribe medicines off-label?

Hypotheses

- Pediatricians will report that the primary factors that influence their decision whether or not to prescribe a medicine off-label are:
    - lack of appropriate references
    - concerns about patient safety.
- Pediatricians will report that the secondary factors that influence their decision whether or not to prescribe a medicine off-label are:
    - legal concerns
    - insurance coverage
    - patient complaints.

Chapter II

Review of Literature

A license to market a medicine in the United States is given to a pharmaceutical manufacturer only after they provide sufficient data to the FDA that the medicine is safe and effective for a particular use in humans. The process for gathering these data to submit to the FDA is outlined in the first section of this literature review.

Once the product license is granted by the FDA to the manufacturer, physicians may legally prescribe the medicine in any manner, whether or not it is indicated on the product license. If the medicine is prescribed outside of its product license, it is prescribed in an off-label manner. The second section of this literature review describes the prevalence of off-label prescribing in many populations, including children, the target population of this study.

Although off-label prescribing is, in many cases, the standard of care for some patients and diseases, there are risks associated with the practice, especially for the pediatric population. The third portion of the literature review describes these concerns and risks from both the patient and physician point of view.

The final portion of this literature review explains the FDA efforts to encourage pharmaceutical manufacturers to collect data about the use of their medicines in children with hopes that the additional data collected from these studies can allow physicians to make more informed decisions about the use of the medicine in this population.

The Drug Development and Approval Process

When a drug manufacturer develops a new medicine, it must be approved by the FDA prior to marketing in the United States. FDA approval is given only when a manufacturer can prove that the benefits of the drug outweigh the risks and that the drug is safe and effective for human use. In order to determine the safety and efficacy of a drug, a drug manufacturer must perform several tests using the drug. The results of these tests allow the FDA to determine whether or not the drug should be approved for use. Blumer (1999) and Kaitin & Healy (2000) describe how the typical drug development process encompasses several unique steps: pre-clinical testing, clinical testing, approval and post-marketing. Figure 1, which is based on their research, summarizes the cost, time and resources required for each step of the drug development process and how the steps relate to one another.

Pre-clinical testing. Once a chemical entity that has some beneficial effects on a disease target is discovered, a drug manufacturer performs pre-clinical tests using the molecule. These tests, which usually last between 3 and 6 years, are performed using various laboratory and animal models and their purpose is to determine initial safety and efficacy profiles of the medicine.

Clinical testing. If the results from the pre-clinical tests indicate that the medicine is safe and effective, a drug manufacturer may apply for an FDA Investigational New Drug Application (IND). Approval of the IND allows the manufacturer to begin clinical trials. There are three phases of clinical trials during the clinical testing portion of the drug development process. The three phases together can last from 2-6 years.

Phase I clinical trials. The first time the medicine is tested in humans is during phase I clinical trials. The purpose of phase I clinical trials are to determine the safety, pharmacokinetics and pharmacodynamics profiles of the medicine. Therefore, the participants in these trials are healthy volunteers and not patients who need the medicine for therapy. Typically 20-100 participants are involved in phase I trials.

Phase II clinical trials. The first time the medicine is tested in patients who have the disease to be treated is during Phase II clinical trials. The primary purpose of phase II trials is to determine the efficacy profile of the medicine. Dosing, kinetics and metabolism of the medicine are further studied in these trials. Typically, 100-500 patients are enrolled in these studies.

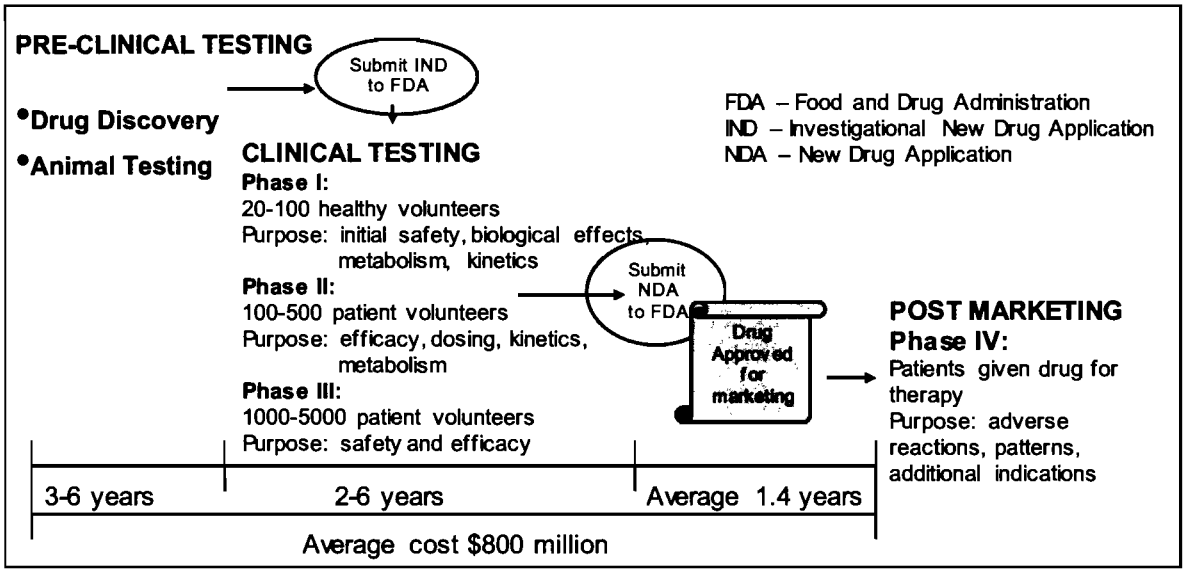
Phase III clinical trials. The purpose of phase III clinical trials is to further evaluate the safety and efficacy of the medicine in patients with the disease to be treated. Phase III clinical trials involve many more participants than in the previous two phases, typically 1,000 to 5,000 patients.

New Drug Application and approval process. Once the manufacturer has enough data to support marketing the medicine, they must submit a New

Drug Application (NDA) to the FDA. The NDA contains the data gathered from both the preclinical and clinical tests performed. The FDA takes an average of 1.4 years to grant approval to the manufacturer. Once the medicine is approved by the FDA, the manufacturer can legally market the medicine in the United States, but only for the population(s) and indication(s) tested in clinical trials with positive results.

Post marketing (Phase IV clinical trials). As clinical trials are performed over a specific and relatively short duration with a relatively small population, the safety and efficacy profiles of the medicine may not be fully known at the time the medicine is approved. Once a medicine is on the market, a manufacturer may choose to (and sometimes may be forced to by the FDA) perform phase IV clinical trials to further evaluate the medicine for the already approved use or new uses once it is on the market. The results of these clinical trials are often used to expand the information on the original label, with FDA approval.

Figure 1. The steps of the typical drug development process, their relationship to one another, their purpose, and the average time, cost and patients required for each step.



Prevalence of Off-label Prescribing

A medicine is prescribed off-label when it is prescribed outside of its product license with respect to the dosage, age, indication and/or route of administration. Determining the prevalence of off-label prescribing can be difficult for a researcher because all of these factors may not be known to the researcher at the time of the study. For example, a researcher may be able to easily determine if the dosage was prescribed according to the product label by comparing the label to the dosage given, but it may be difficult, due to privacy laws, for a researcher to determine the age or indication of the patient who received the medicine.

Studies conducted in various populations determined that medicines are prescribed off-label 20-90% of the time. The majority of these studies reviewed only one or two conditions for determining whether or not a medicine was prescribed off-label (e.g. only indication or only patient age or both). In addition, the literature suggests that the greatest prevalence of medicines prescribed off-label is to patients in the hospital and to children with serious or rare diseases (O'Reilly & Dalal, 2003).

Patient location. When comparing the prevalence of off-label prescribing between in-patients and out-patients, research suggests that the lowest percentage of off-label prescribing occurs in the outpatient setting. Radley, Finkelstein and Stafford (2006) performed a retrospective analysis of United States prescribing data to determine the rate of off-label prescribing among office-based physicians. The researchers reviewed prescription data from the National Disease and Therapeutic Index (NDTI), a national survey that requires office-based physicians to report all diagnoses and drug therapies for every patient encounter during two randomly selected consecutive workdays. Of the total of 725 million prescriptions analyzed, the authors found that 21% (150 million) were prescribed off-label due to the indication they were used to treat. In addition, the authors determined that out of the 150 million prescriptions, only 27% had strong scientific support for the use in which they were prescribed.

On the other hand, in the largest study of off-label prescribing in the United States pediatric population to date, Shah, et al. (2007) reviewed prescriptions from a database containing demographic information, diagnoses

and procedures for all patients discharged from 31 pediatric hospitals in the United States. In order to determine the prevalence of off-label prescribing, the authors compared the patient's age with the FDA approved age range for any indication of the medicine. Out of a total of 355,409 patients, 297,592 (78.7%) received at least one medicine off-label indicating that off-label prescribing is especially prevalent in the pediatric inpatient population.

Patient diagnosis. The prevalence of off-label prescribing can vary due to the patient's disease, regardless of their age. Sugarman, Fletcher and Feldman (2002) reviewed 7 years of data from a United States National Center for Heath Statistics survey to determine the prevalence of off-label prescribing for dermatologic diseases in adults. For approximately 200 million office visits where the primary and only diagnosis was dermatologic, the researchers compared the patient's diagnosis to the medication prescribed to determine whether the medicine was prescribed off-label. Depending on the diagnosis, up to 73% of prescriptions were prescribed off-label.

Loder and Biondi (2004) prospectively studied off-label prevalence rates in an adult specialty headache practice in the United States over a 30-day period. During the study, physicians were instructed to record the medication(s) prescribed and whether they were prescribed according to the FDA-approved package insert. In total, 379 eligible prescriptions were written during the study period and 178 (47%) were prescribed off-label.

Researchers report similar results regarding the prevalence of off-label prescribing in different diseases in the pediatric population as well. Johnson and

Clark (2001) performed a prospective study of medicines prescribed by child and adolescent mental health practitioners in England over a six month period. When prescribing a new medicine to their patient during the study period, the prescribing clinician recorded the age of the child, the drug prescribed, the maximum dosage prescribed and the condition being treated. Out of the 478 new medicines prescribed during the study period, 39% were prescribed off-label.

Conroy, Newman and Gudka (2003) also prospectively studied pediatric off-label drug use in the United Kingdom. However, they reviewed prescription data for pediatric oncology inpatients and outpatients of a medical center during a 4 week period. During the study period, the researchers collected the patient's hospital number, age, weight, surface area, diagnosis, drugs administered, formulation, date and route of administration, dose, frequency and indication for use. Although they collected more data on their patients than Johnson and Clark (2001), which would allow them to determine that a medicine was prescribed off-label for more reasons (e.g. route of administration) they found that only 26% of the medicines prescribed were off-label.

Lastly, 't Jong, Eland, Sturkenboom, van den Anker and Stricker (2004) retrospectively reviewed a random sample of patient data from a database of prescription data from a group of 150 general practitioners in The Netherlands to determine the prevalence of off-label prescribing of respiratory drugs given to children during a one year period.. The data reviewed included the name of the medicine, dosage, indication and patient age. Of the of 5,253 respiratory drugs

issued to 2,502 patients during the study period, only 20.3% were off-label, even less than the prevalence found in the Conroy et al. and Johnson and Clark studies.

The results of each study reviewed vary significantly because the authors of each study used different methods for determining whether a medicine was prescribed off-label. Also, the duration of the study, whether it was retrospective or prospective, the location of the physicians, and the specific disease studied explain the variance as well. In any case, these studies indicate that off-label prescribing is prevalent in a variety of geographic locations (United States, United Kingdom, and The Netherlands), indications (dermatology, headache, mental health, oncology, and respiratory diseases) and patient populations (adults and children).

Patient age. The prevalence of off-label prescribing can also vary depending on the age of the child. Schirm, Tobi, & de Jong-van den Berg (2003) analyzed the outpatient pharmacy records for over 19,000 children aged 16 and younger in the Netherlands to determine the age of children most likely to receive a medicine off-label. The authors first compared the medicine's label to the age of the child to determine if the child was at least the minimum age for use and then they grouped the results by age (0-1, 2-5, 6-11, and 12-16 years) to determine the proportions of off-label prescribing per each group. In a total of 66,222 prescriptions, 20.6% were prescribed off-label and children aged 12-16 years old received the greatest percentage of medicines off-label (27.4%) and children aged 2-5 received the least percentage of medicines off-label (16.4%).

Conversely, Conroy, McIntyre & Choonara (1999) determined that off label drug use is more prevalent in neonates than any other age group. These authors prospectively collected patient demographic data, diagnosis, and prescription information for all patients admitted to a neonatal intensive care unit in the United Kingdom over a 13 week period. In order to determine whether the medicine if the medicine was prescribed off-label, the researchers compared the patient age, dose, indication and route of administration to several drug reference sources. Of a total of 455 prescriptions issued during the study period, 249 (54.7%) were prescribed in an off-label manner and many were off-label for more than one reason.

Limitation of prevalence studies. Although varied, the results of studies described in this section indicate that off-label prescribing is prevalent across many diagnoses, patient populations, and locations. The variance is at least partially due to the methods followed during the study to determine the prevalence of off-label prescribing. For example, some researchers only have access to the patient age and name of medicine prescribed (e.g. Schirm et al., 2003). In this case, if the medication was prescribed off-label because the dosage did not match the dosage information on the product license, its use would not be considered off-label. Because of this limitation, the results of most of the studies presented in this section likely underestimate the magnitude of off-label drug use.

Concerns of Off-label Prescribing

While off-label prescribing is legal, it is important for patients and physicians to understand all the risks and benefits of the practice. The following section outlines the concerns identified in the literature regarding this practice.

Physician knowledge. According to the FDA, physicians are required to be well informed about the proper use of a medicine and prescribe it only when the use is based on "firm scientific rationale or on sound medical evidence" (http://www.fda.gov/oc/ohrt/irbs/offlabel.html, Accessed March 18, 2007). Drug prescribing manuals, pharmacies, the FDA, and pharmaceutical companies are all commonly used sources of information regarding the proper use of a medicine. However, according to Blumer (1999), the *Physicians Desk Reference (PDR)*, which is the most recognized information source for practitioners in the United States, is not the best reference. The *PDR* contains only the drug's package insert, or label. It does not contain any information on off-label uses, or in-depth information regarding the safety or tolerance of a medicine. More specifically, the *PDR* contains either no pediatric dosing information or explicitly states that the safety and efficacy of the medicine in children have not been determined. Therefore, a physician may have difficulty being well informed about the proper use of a medicine and ensuring the use is based on sound medical evidence.

Ekins-Daukes, et al. (2005) prospectively surveyed 346 doctors in 80 outpatient practices in Scotland to determine their attitudes and experience with off-label prescribing to children. Of the 202 (58%) surveys returned, over 70% indicated that the doctors are familiar with off-label prescribing and 40%

knowingly prescribe off-label. These results indicate that there are still many physicians that are not aware of the practice. Interestingly, almost all doctors surveyed indicated that development of pediatric formulations and clearer dosage information were the best means to reducing off-label prescribing indicating that they believe that the current references are not complete.

Lastly, Radley, et al. (2006) analyzed prescription data from the 2001 National Disease and Therapeutic Index (NDTI), a quarterly survey of about 3,500 US office-based physicians regarding their clinical activity. The authors studied the prescribing patterns of the NDTI top 100 prescribed medicines as well as 60 additionally randomly selected medications. Using the patient's diagnosis, they categorized the prescriptions as prescribed according to the FDA approved label, off-label with strong scientific support, or off-label with limited or no scientific support. They found that of the 575 million prescriptions in the studied sample, 150 million (21%) were prescribed off-label and 109 million (73%) medicines prescribed off-label had little or no scientific support.

The results of these studies indicate that although physicians are required to prescribe medicines based on their knowledge and expertise, they may not always have adequate information to assist them when prescribing a medicine. If physicians cannot rely on approved and published information to make proper prescribing decisions, then they may subject their patients to unnecessary or improper treatment.

Patient safety. Patient safety is also a concern when prescribing a medicine off-label. If the FDA has not approved the medication for the

prescribed indication, age, dosage or route of administration, then the patient may experience unknown side effects or the medicine may not work as intended. Often, children, especially infants, may not be able to swallow a medicine via the approved route of administration; for example, a tablet versus a liquid. Therefore, physicians may prescribe a formulation which is not commercially available and the consequences of the different formulation may not be fully known. Also, physiologically, pediatric patients react differently to drugs when compared to adults (Cohen, 1997); side effects are of special concern when a medicine, approved for adults, is prescribed to children. In these situations, physicians must prescribe a medicine off-label to the child and the side effects could produce unintended results for the patient. (Conroy, 2002)

Results of several studies suggest that off-label treatments can lead to a higher incidence of side effects. Neubert, et al (2004) found that patients treated with off-label medicines had a much higher risk of developing unwanted side effects, or adverse drug reactions (ADRs). These researchers prospectively evaluated patient charts from a German hospital pediatric ward over an 8-month period. Out of a total of 170 patients given 740 prescriptions, 195 medicines were prescribed off-label. Of these, 46 ADRs were detected in 31 patients, an overall ADR rate of 17.4%. Patients that received at least one medicine off-label experienced at least one ADR more frequently than patients who received a medicine only in a licensed manner (28.3% vs 7.8%), almost 4 times greater chance.

Interestingly, these authors also found that when the physician prescribed a medicine in an off-label manner, they were more likely to recognize the associated ADR than when the ADR was associated with a medicine prescribed in an approved manner (43.8% vs 64.3%). This is an important finding because it shows that when the physicians prescribed the medicine off-label, they had increased their awareness level for ADRs, possibly because they were prescribing the medicine off-label.

A few years earlier, Turner, Nunn, Fielding, and Choonara (1999) had similar findings in their 13 week prospective study of prescriptions in children's hospital wards in the United Kingdom. Of 4,455 prescriptions given to 936 patients during the study period, 1,574 (35%) were off-label. ADRs occurred with 6% of the medicines prescribed off-label but only with 3.9% of the licensed medicines, accounting for an increased risk of about 1.5.

Horen, Montastruc and Lapeyre-Mestre (2002) reported similar, although less alarming, results in their prospective study of pediatric drug prescribing among 39 office-based physicians in France over a 4 month period. In this study, 42% of the 1419 patients received at least one off-label prescription and of those prescriptions, 20 ADRs were reported, with the incidence of ADRs for off-label medicines occurring 2.0% of the time versus 1.4% medicines that were prescribed according to their label. Most likely, there were much fewer ADRs reported in this study versus the studies done in the hospital because the medicines prescribed in the hospital are more powerful as the diseases treated in the hospital are much more serious.

If an ADR does occur, physicians may be reluctant to report the ADR when the medicine was prescribed for an off-label use (Conroy, 2002). Also, without knowing the ADRs that occur in patients on a widespread basis, physicians may unknowingly subject their patients to ADRs.

Litigation. Researchers indicate that physicians fear legal complications if they prescribe a medicine off-label if their patient has an adverse reaction to the medicine or if the medicine is ineffective for the indication prescribed. Blum (2002) explains that physicians must be very careful to ensure that the information they use to prescribe a medicine to their patients is up to date and scientifically valid. As explained previously, the *PDR*, while a common reference, becomes quickly out-of-date and does not include any information about off-label prescribing. If a physician is unsure about the safety or efficacy of a medicine when prescribed off-label, they may hold back valuable treatments for the patient just because the medicine is not approved in the manner it was prescribed (O'Reilly & Dalal, 2003).

Hill (2005) explains that if a physician did not prescribe the best medicine for their patient, whether the medicine is prescribed off-label or not, the physician could be held liable for any side effects that occur. Several legal cases have sided with patients claiming that physicians have not used good judgment when prescribing medicines off-label. If a physician is unsure about the latest off-label research, they may choose to not prescribe medicines off-label, which could mean that a highly effective treatment is withheld from the patient. In order to be protected from legal liabilities, physicians must rely on information and guidance

from "a respected body of medical knowledge." However, as indicated above, finding a reference that is appropriate is not always easy or feasible for the physician (Hill, 2005).

Insurance reimbursement. When a physician prescribes a medicine off-label, the patient may have difficultly getting reimbursement for the medicine. Many prescription benefit companies will reimburse patients only for medicines that have been approved by the FDA for the use in which they were prescribed (O'Reilly & Dalal, 2003). In situations where off-label treatments may be more effective than approved medicines, insurance reimbursement issues can hinder a physician's ability to effectively treat a patient. Patients in these situations may be forced to pay out-of-pocket for their medicines or be treated with medicines that may be less effective for their needs.

Patient complaints. Lastly, as patients become more educated about healthcare, they may be more likely to complain to their physician about the use of a medicine in a manner that is not indicated on the medicine's label. Physicians, however, want to please their patients. Lowe-Ponsford & Baldwin (2000) surveyed 200 psychiatrists to determine how common off-label prescribing was in their specialty and to ascertain whether or not they felt sufficient prescribing guidelines were available. Although 65% of respondents indicated that they prescribed medicines off-label in the last month, only four percent had received complaints from their patients regarding the off-label prescribing. Although the result is not very significant and the respondents did not indicate what the exact complaint was, based on respondent comments, the

authors believe that patient complaints are another concern that may influence physicians to prescribe a medicine off-label. If patients complain, a physician may be less likely to prescribe a certain medicine to their patients, even if the medicines prescribed off-label can benefit the patients more than those prescribed in a manner indicated on the label.

New Regulations

To encourage manufacturers to perform more clinical trials in the pediatric population, which would lead to more data about the risks and benefits of the use of a specific medicine in this population, in 1997, the FDA enacted the pediatric exclusivity program. This program allows the FDA to grant a patent extension to a manufacturer if they conduct pediatric clinical trials with their medicines. Fortunately, there have been over 100 changes made to product labels due to the new data available on the use of the medicine in the pediatric population.

According to Benjamin, et al. (2006) dissemination of all clinical trial results has been limited. Their study suggests that the results of clinical trials with positive results are much more likely to be reviewed by the FDA and published. These researchers found that positive labeling changes were made for only 50% of the studies submitted to the FDA and that results from only 45% of studies performed were published in peer reviewed journals. These results indicate that although the new regulation has been successful in encouraging manufactures to perform pediatric clinical trials, the results from the studies are not being published in a manner to ensure physicians understand all the risks and benefits of a particular medicine before prescribing it to their patients.

Pediatrician Opinion

While off-label prescribing is prevalent in many patient populations and there are many factors associated with the practice, few researchers studied physician knowledge and attitudes regarding the practice. Moreover, no research is available which explains whether physicians treating children have the same factors, knowledge and beliefs regarding the practice as physicians that treat adults. This study will add to the body of knowledge regarding off-label prescribing in the pediatric population.

Summary

The practice of prescribing medicines to children in a manner that has not been approved by a regulatory agency (off-label prescribing) can have significant effects on the patient, their family and the healthcare community. This literature review described the process a manufacturer must follow to receive marketing approval for a medicine, reviewed the prevalence of off-label prescribing in both the general and pediatric populations and evaluated several concerns of off-label prescribing.

Physicians, who are ultimately responsible for providing medicines to patients, must be able to provide patients and their families with adequate, balanced information on the benefits and risks of all treatment options, whether the options are approved for the prescribed use or not. In order for this to occur, physicians must be aware of the risks and benefits of off-label prescribing. In addition, they must be able to adequately describe it to their patients. Only when both the physician and the patient are properly informed can they both decide on

the best treatment method. Therefore, it is important to understand the reasons why physicians choose to prescribe medicines off-label to children. The results of this study will provide the background knowledge needed to develop strategies to ensure that the medication decisions being made for pediatric patients are the most effective and evidence-based.

Chapter III

Methods

Subjects

All members of the New Jersey chapter of the American Academy of Pediatricians (AAP/NJ) and the Tennessee chapter of the American Academy of Pediatricians (TNAAP) with an email address registered with their respective organization were asked to participate in the study. The American Academy of Pediatrics (AAP) is a national organization that is "committed to the attainment of optimal physical, mental, and social health and well-being for all infants, children, adolescents and young adults" (http://www.aap.org/about.html, Accessed April 30, 2008). They provide membership opportunities to pediatricians, pediatric medical subspecialists and pediatric surgical specialists.

TNAAP and AAP/NJ offer benefits and have membership similar to AAP, but at the state level. The members of these organizations were chosen as subjects for this study because TNAAP and AAP/NJ are the largest groups that represent the pediatric profession in their respective states. Surveying two states allowed for a greater number of respondents and enabled the researcher to determine if pediatrician understanding of off-label prescribing differs based on

geographic practice location. These particular two states were chosen due to geographic convenience for the researcher while also representing different regions of the United States.

The AAP/NJ has 2,184 members and 1,806 of the members have an email address registered with the organization. TNAAP has 1,100 members and 864 of the members have a working email address registered with the organization. Not having a working email address registered with either TNAAP or AAP/NJ when the survey was distributed was the only exclusion criterion for this study. In order to achieve a medium effect size of .3, a power of .8 and an alpha of .05, a minimum of 143 respondents were required (Erdfelder, Faul & Buchner, 1996; Portney & Watkins (2000)).

Design and Variables

This study was a between respondents, descriptive survey design.

Independent variables. The eight independent variables were the answers to the demographic questions. The answers to these questions collected general information about the respondents in order to help gain information which could account for the answers given for the dependent variables.

The independent variables are the following: (1) name of state in which the respondent practices medicine [New Jersey, Tennessee or other], (2) name of country in which the respondent attended medical school, (3) name of country in which the respondent completed first residency, (4) name of country in which the respondent completed fellowship, (5) name of country in which the

respondent obtained board certification, (6) whether the respondent was a pediatric generalist, surgical specialist or medical specialist, (7) number of years the respondent has been a practicing physician and (8) the type of environment the respondent works in [solo practice, group practice, teaching or non-teaching hospital].

Dependent variables. The thirty-two dependent variables were the answers to the five research questions. The frequency of use of the 12 references, 11 therapeutic categories and 5 age ranges identified in the first three research questions each had five levels of responses on a Likert scale: (1) regularly, (2) often, (3) sometimes, (4) rarely and (5) never. The percent of medicines prescribed in the last year had 5 possible responses (none, 1-25%, 26-50%, 51-75%, and 76-100%). The last three dependent variables, the legal concerns, patient complaints and personal opinion about off-label prescribing, had 6 levels of responses on a Likert scale: (1) strongly agree, (2) agree, (3) neutral, (4) disagree, (5) strongly disagree and (6) I do not prescribe medicines off-label.

Instrumentation

There are currently no available surveys published to determine pediatrician attitudes and beliefs towards off-label prescribing. Therefore, the researcher developed an eleven item survey based on the literature that describes factors that may influence physicians to prescribe medicine off-label (Conroy, 2002). Prior to use, in the current study, the survey was distributed to ten experts in healthcare and research associated with Seton Hall University for

face validation. Expertise was defined as possessing a terminal doctoral degree in healthcare or a related field, twenty or more years of experience in research and the title of Associate Professor or greater. The process utilized for validation and the changes made to the survey due to the validation process are described in Appendix A and was based on the Delphi method as described by Hyrkas, Appelqvist-Schmidlechner, & Oksa (2003), Powell (2003) and Rubio, Berg-Weger, Tebb, Lee, & Rauch (2003).

Structure of the survey. The final version of the survey is contained in Appendix B. The survey contained four sections: (1) instructions, (2) research questions, (3) demographic questions and (4) an open-ended question.

The instructions contained a brief consent statement and definitions of terms used in the survey. The terms defined were off-label, regularly, often, sometimes, rarely, never, strongly agree, agree, neutral, disagree, and strongly disagree. The consent statement indicated that by submitting a completed survey, the participant allowed the researcher to use the answers for research purposes.

The second section of the survey contained 5 questions about the knowledge, practice and concerns of pediatricians regarding off-label prescribing. The first question in this section asked participants to report on the frequency of use of 12 different medical references when choosing to prescribe a medicine to their patients. The second question asked participants to indicate their use of medicines off-label over the last month for 11 different therapeutic categories. The third question asked participants to indicate their use of medicines off-label

for 5 different patient age ranges. For each of these first three questions, the participants were instructed to choose one of the following previously-defined choices on a Likert scale: (1) regularly, (2) often, (3) sometimes, (4) rarely and (5) never.

The fourth question asked respondents to report on the percentage of medicines they prescribed off-label in the last year, ranging from 0 to 100% in five categories (i.e. none, 0-25%, 26-50%, 51-75%, and 76-100%). The final question in this section contained three individual statements for which participants were asked to report their beliefs about off-label prescribing with regard to legal liabilities, patient complaints, and whether off-label prescribing should be allowed. The possible responses for these questions were: (1) strongly agree, (2) agree, (3) neutral, (4) disagree, (5) strongly disagree and (6) I do not prescribe medicines off-label.

The third section consisted of 5 demographic questions. The following information was collected about the respondents via multiple choice answers: state in which they practiced medicine, whether specialist or generalist, years working as a pediatrician, and working environment. In addition, the pediatricians were asked to provide the name of the country where they attended medical school, completed residency, completed fellowship and obtained board certification.

The final section of the survey consisted of one open-ended question which gave the participants an opportunity to share any additional information about off-label prescribing.

Data Collection

The survey was hosted on SurveyMonkey (www.surveymonkey.com), a secure website for creating and hosting web surveys. The participants were required to log on to the website via a unique Universal Resource Locator (URL) to access the survey. SurveyMonkey.com ensured that there were no duplicate responses from the same IP address which prevented participants from completing the form multiple times.

Confidentiality and anonymity were maintained as no personal, identifiable information about the participants was collected. Participants were unable to view the responses of other participants or any summary of responses which could cause bias or pose as a potential influence.

Prior to obtaining approval of the research protocol by the Institutional Review Board (IRB) for Human Subjects Research at Seton Hall University, the researcher contacted the Executive Director of the TNAAP and the President of the AAP/NJ to determine their interest in participating in the study. Both organizations agreed to participate and provided the researcher with written approval for their participation. The written approval indicated that the TNAAP and AAP/NJ staff agreed to be the conduit between the researcher and the subjects by distributing the survey to all members of their associations that have an email address registered with their association. They also agreed to send two reminders, one at two weeks and one at four weeks after the initial invitation, to all individuals who received the initial invitation (Appendices C and D).

Following approval by the IRB (Appendix E), the researcher developed and sent emails (Appendices F, G and H) to the Executive Directors of the TNAAP and AAP/NJ asking them to forward the email to all members of their association with email addresses registered with their respective associations. The emails briefly explained the purpose of the study and invited the recipients to complete the survey. The emails included a link for the subjects to click on which brought them to a website, which included the survey instructions, applicable definitions and the survey. If the email recipient chose to participate, they completed the survey on-line and submitted their responses to the Survey Monkey host location.

The first email was sent to both individuals by the researcher on May 14, 2009, the second email was sent May 31, 2009 and the final email was sent on June 15, 2009. While data collection was ongoing, all information collected was stored on SurveyMonkey.com and only the researcher had access to this information. The survey was available for access from May 14, 2009 to July 6, 2009. After July 6, 2009, the researcher downloaded the survey answers directly from the survey website and saved it to two USB drives, one which remained in a locked, secure cabinet in the researcher's home office and one which remained in a locked, secure cabinet in the researcher's professional office. After analyzing the data using SPSS, the researcher saved all information related to the study on a CD, in a locked cabinet, in the researcher's home office. No other people had access to the data.

Data Analysis

Data obtained from each of the submitted surveys were coded and downloaded to the Statistical Package for Social Sciences (SPSS) Version 17.0 for data analysis. Prior to analyzing the data, the questions utilizing a Likert scale were coded. Questions 1-3 were coded as follows: 1= regularly, 2=often, 3=sometimes, 4=rarely and 5=never. Question 5 was coded as follows: 1=strongly agree, 2=agree, 3=neutral, 4=disagree, 5=strongly disagree and 6=I do not prescribe medicines off-label.

Statistical analysis. The researcher analyzed the data using both descriptive and non-parametric statistics. With descriptive statistics, the researcher was able to describe the central tendency and variability of the data to describe the population (Portney & Watkins, 2000), in this case, the factors that may affect off-label prescribing. Specifically, frequencies and / or percentages were reported to examine trends in the following independent variables: years of practice, specialty, practice type, country educated and practice location. The results of these tests enabled the researcher to describe the demographics of the population surveyed. Means and frequencies were calculated to examine trends in the following dependent variables: off-label prescribing concerns, percentage of drugs prescribed off-label in the last year, therapeutic categories of off-label prescriptions, references used, and age range(s) of patients.

Two non-parametric statistics, the chi-square test of association and Spearman's rho, were used to analyze the relationships of the variables in this study. The chi-square test examines the association between the variables and cross tabulations were used to describe the association of many variables at one

time. Spearman's rho, used to determine relationships among ordinal data, was used to analyze the relationships between the dependent variables in this study (Portney & Watkins, 2000).

The Chi Square tests analyzed relationships between the independent and dependent variables (e.g. whether or not pediatricians educated outside of the United States prescribe more medicines off-label than those educated in the United States). The Spearman's rho tests analyzed the relationships between the dependent variables (e.g. whether or not pediatricians with more concerns about off-label prescribing prescribe medicines off-label less often than pediatricians that have less concerns about off-label prescribing).

An alpha level of $p \leq .05$ was considered significant for all statistical tests (Portney & Watkins, 2000).

Analysis of responses to open ended question. The qualitative data received from the last question of the survey were analyzed for emergent themes, which were then compared with the quantitative data received from the other survey questions. In addition, keyword analysis and topic grouping was used to analyze the response to the open ended question in order to develop future research questions and enable the researcher to interpret the qualitative data with respect to the quantitative data.

Chapter IV

Results

Study Sample

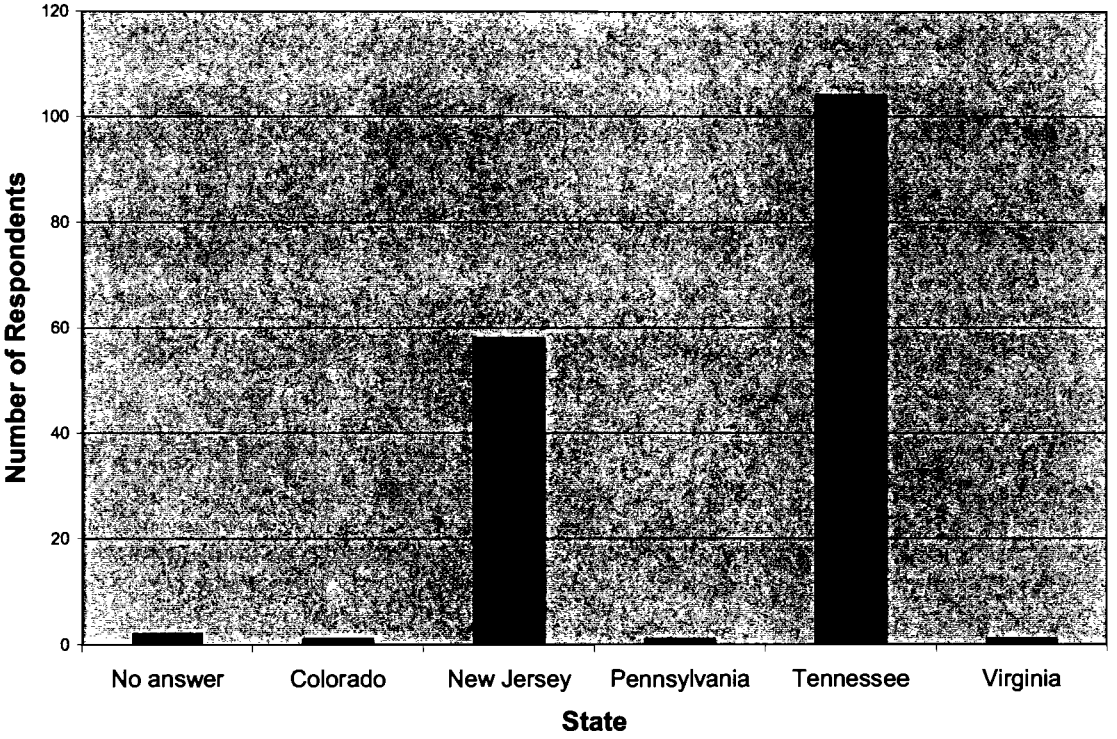
Of the 2670 email requests to participate in the survey, a total of 167 individuals accessed the survey and responded to at least one survey question (response rate = 6.25%). As indicated earlier, 143 responses were required based on the power analysis. Because respondents were not required to provide answers to all survey questions, all surveys submitted, regardless of whether all questions were answered, were included for analysis.

Demographic characteristics of the study sample. The demographic characteristics of the study sample (years in practice, specialty, practice type, country educated and location of practice) were analyzed using means, standard deviations and frequencies. The demographics of the study sample were then compared to the questions regarding off-label use to determine if there are any relationships between the demographics and beliefs and practices regarding off-label prescribing.

Almost two-thirds of the respondents indicated that they practice medicine in Tennessee (n=104, 62.3%), 58 (34.7%) indicated that they practice in New

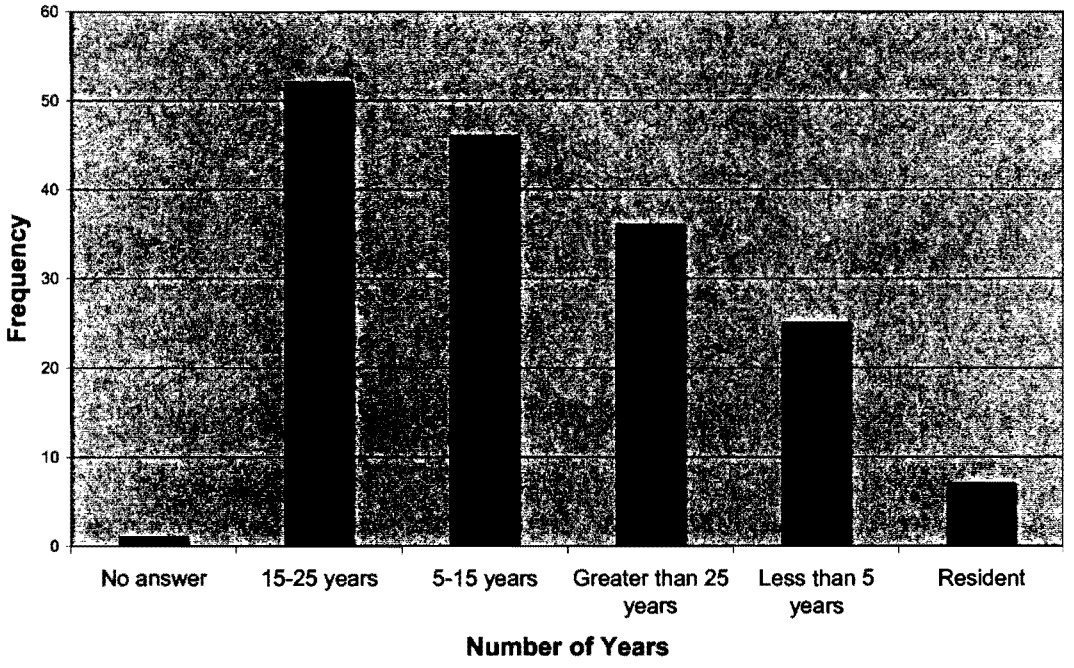
Jersey, 3 respondents (1.8%) indicated another state and 2 respondents (1.2%) did not respond to the question (Figure 2).

Figure 2. State in which respondents practice medicine



The number of years, post residency, that the respondent has been a practicing physician is shown in Figure 3. Twenty-five (15%) respondents had less than 5 years of experience, forty-six (27.5%) had 5-15 years of experience, fifty-two (31.1%) had 15-25 years of experience and thirty-six (21.6%) had over twenty-five years of experience. Seven respondents (4.2%) indicated they were residents and one respondent (0.6%) did not answer the question.

Figure 3. Number of years respondent has been a practicing physician (post residency)



Regarding pediatric specialty, the majority (n=119, 71.3%) of respondents reported that they were pediatricians, with no specialty. Forty respondents (24%) indicated that they were pediatric medical subspecialists, and 3 respondents (1.8%) indicated that they were pediatric surgical specialists. One respondent (0.6%) indicated that they were an administrator in a pediatric hospital and one respondent indicated that they were a pediatric resident. Three respondents did not answer this question.

Regarding their working environment, six percent of respondents (n=10) indicated they worked in a solo practice, 51.5% (n=86) in a group non-hospital based practice, 7.8% (n=13) in a non-teaching hospital based practice and 33.5% (n=56) in a teaching-hospital based practice. Because respondents were allowed to select more than one answer, the total number of responses for this question exceeds the total number of respondents.

The majority of the respondents reported that they attended medical school in the USA (n=145, 86.8%). The remainder of the respondents attended medical school in 14 other countries which are listed in Table 1.

Table 1. Country in which respondents attended medical school

Country	Frequency	Percent
No answer	1	0.6
Brazil	2	1.2
Colombia	2	1.2
Czech Republic	1	0.6
Germany	1	0.6
Grenada	2	1.2
India	3	1.8
Jordan	1	0.6
Lebanon	1	0.6
Mexico	1	0.6
Nigeria	2	1.2
Pakistan	1	0.6
Philippines	2	1.2
Saint Kitts	1	0.6
USA	145	86.8
West Indies	1	0.6
Total	167	100

One hundred sixty three (97.6%) respondents indicated that they completed their first residency in the USA. One respondent did not answer the question and three other respondents indicated that they completed their first residency in other countries, namely Brazil, India and Lebanon.

About half of respondents (n=76, 45.5%) indicated not applicable to the question regarding where they completed their fellowship. Twenty-one respondents (12.6%) did not provide an answer to this question and 70 respondents indicated that they completed their fellowship in the USA. As fellowships are not required in all medical specialties, the response to this question was not surprising.

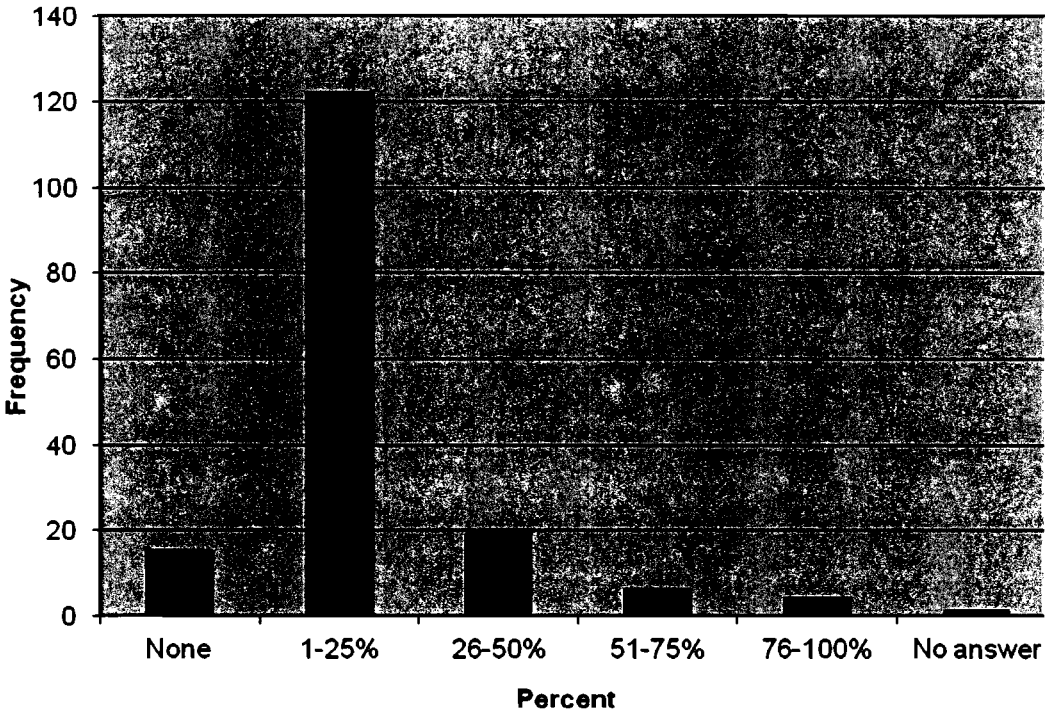
The majority of respondents also indicated that they obtained board certification in the USA (n=155, 92.8%). The remainder of the respondents either indicated not applicable (n=9, 5.4%) or did not provide a response to this question (n=3, 1.8%).

Overall, therefore, the study population reflects general pediatrician population in the United States in terms of specialty, practice type, number of years respondents practiced medicine, and the country in which the respondents attended medical school, completed first residency and completed their first fellowship and was Board Certified (Smart, 2009).

Frequency of Off-label Prescribing

Figure 4 indicates that almost three quarters of the respondents (73.1%) prescribed medicines off-label 1-25% of the time in the last year.

Figure 4. Frequency of percent of off-label prescriptions in the last year



Use of References for Medication Prescribing

Respondents reported that, most often (43% indicated regularly used), they use reference manuals to determine which medicines to prescribe to their patients (mean 1.92, indicating an average ranking of often) and that they use unpublished research least often (49% indicated never used) for determining whether to prescribe a medicine to their patients (mean 4.41, indicating an average ranking between rarely and never).

The other references, ranked from greatest to least used, are as follows: published, peer-reviewed research (mean 1.96), medicine's label (mean 2.01), previous experience (mean 2.01), group/ hospital/ facility / office's experience

(mean 2.20), peer recommendations (mean 2.46), pharmaceutical representative (3.54), patient's insurance company (mean 3.59), patient/ guardian's request (mean 3.61), published, not-peer reviewed research (mean 3.68), and patient / guardian's suggestion (mean 3.74).

Interestingly, the references with the least consistency in use (highest standard deviation) were the medicine's label and the patient's insurance company, with standard deviations of 1.078 and 1.191, respectively. Table 2 provides detailed information on the number of respondents who used each referenced resource to determine whether to prescribe a medicine to their patients and their individual means and standard deviations.

Table 2. Materials respondents use to determine whether or not to prescribe medicine to their patients

I use the following to determine whether or not to prescribe medicine to my patients:	N	Mean	Standard deviation
The medicine's label	162	2.01	1.078
Published, peer-reviewed research	164	1.96	0.929
Reference manuals	166	1.92	0.956
Published, not peer-reviewed research	161	3.68	0.885
Unpublished research	162	4.41	0.665
My previous experience with the medicine	164	2.01	0.95
My group/ hospital/ facility / office's experience with the medicine	163	2.2	0.995
Peer recommendations	163	2.46	0.884
Information from a pharmaceutical representative	162	3.54	0.985
The patient's insurance company	161	3.59	1.191
The patient / guardian's suggestion	163	3.74	0.736
The patient / guardian's request	162	3.61	0.798

Off-label Prescribing by Therapeutic Area

Of all the therapeutic areas included in the survey, respondents reported that they prescribe antibiotic medicines in an off-label manner, most often (mean 3.63, indicating an average ranking between sometimes and rarely) and insulin,

least often (mean 4.90, indicating an average between rarely and never but very close to never).

The other therapeutic areas, which were ranked from greatest to least prescribed off-label, are as follows: anti-asthmatic (mean 3.75), anti-histimine (mean 3.80), dermatologic (mean 3.90), analgesic (mean 3.96), rhinological (mean 4.23), expectorant and anti-tussive agents (mean 4.27), otologic (mean 4.44), psycholeptic and psychoanaleptic (mean 4.48), and anti-epileptic (mean 4.51).

The therapeutic area with the highest noted standard deviation was anti-asthmatic, at 1.294. This indicates that this therapeutic area had the most variability in response around the mean. The therapeutic area with the least variability was insulin, .361, indicating little variability in responses around the mean. Table 3 indicates the frequency that the respondents prescribe medicines off-label for each therapeutic area and their individual means and standard deviations.

Table 3. Medicines prescribed off-label in various therapeutic areas once per month, at minimum (total n= 164)

Therapeutic area	N	Mean	Standard Deviation
analgesic	164	3.96	1.164
anti-asthmatic	164	3.75	1.294
anti-epileptic	164	4.51	0.825
antibiotic	163	3.63	1.176
anti-histimine	162	3.8	1.098
dermatologic	162	3.9	1.061
expectorant and anti-tussive agents	163	4.27	0.889
insulin	164	4.9	0.361
otologic	164	4.44	0.736
psycholeptic and psychoanaleptic	163	4.48	0.958
rhinological	163	4.23	0.938

Off-label Prescribing by Age

When asked what age ranges respondents prescribed medicines off-label to in the last month, there was no significant difference in the means and standard deviations for the different age ranges provided less than 18 years of age. The mean for less than one year old was 3.52, for 1-5 years old was 3.43, for 6-12 years old was 3.50, and for 13-17 years old was 3.55, which all indicate an average ranking between sometimes and rarely. The standard deviations

were 1.320, 1.136, 1.116 and 1.093, respectively, which indicates that there was some variability around the mean for these age ranges.

For patients 18 years and older, the mean was 4.07, indicating an average ranking of 4.07, between rarely and never, and the standard deviation was .944, indicating less variance around the mean than for all other age ranges.

Off-label Prescribing Beliefs

Regarding their beliefs about off-label prescribing, with a mean of 2.90, respondents reported that they felt slightly concerned about legal liabilities or were neutral in their response. The standard deviation, however, was 1.288, indicating some variance around the mean.

Respondents indicated that they disagree that they are concerned about patient or guardian complaints when they prescribe a medicine off-label or were neutral in their response (mean 3.59). The standard deviation for this question was 1.110, indicating some variability around the mean.

Respondents indicated that they believe that physicians should be allowed to legally prescribe medicines off-label, as the mean for the question "I believe that physicians should not be legally allowed to prescribe medicines off-label" was 4.23, with the average ranking between disagree and strongly disagree. The standard deviation was 1.118, indicating some variability around the mean.

Nonparametric Statistical Analysis

The Chi-square test of association was used to analyze relationships between the dependent and independent variables using cross tabulations.

Spearman's Rho was used to analyze the relationships between the dependent variables. Only the analyses that met the criteria for statistical significance of $p \leq .05$ are described in this section.

The first set of analyses conducted were to determine if there was a relationship between the state in which the respondent practiced medicine and the following dependent variables: materials respondents use to determine whether to prescribe a medicine to their patient, medicines in various therapeutic areas respondents prescribed off-label in the last month, respondents beliefs regarding off-label prescribing and the percent of medicines the respondents prescribed off-label in the last month.

Regarding materials used to determine whether to prescribe a medicine to their patients, there was a significant relationship between state in which the respondents practiced medicine and the medicine's label ($p=.021$), the respondent's group/ hospital/ facility / office's experience with the medicine ($p=.021$) and peer recommendations ($p=.000$).

The only therapeutic area in which the respondent's state and whether the respondent prescribed medicines off-label in that therapeutic area in the last month had a statistically significant relationship was for analgesic medicines ($p=.006$). The only belief that had a statistically significant relationship with the respondent's state was legal liabilities ($p=.011$).

The second set of analyses conducted were to determine if there was a relationship between the therapeutic area of medicines prescribed off-label and the pediatric specialty (pediatrician, medical subspecialist or surgical

subspecialist) of the respondent. For this analysis, two therapeutic areas met the criteria for statistical significance of $p \leq .05$: whether the respondent prescribed expectorant and anti-tussive agents off-label in the last month ($p=.011$) and anti-histimine medicines ($p=.010$).

For all these associations, the results must be interpreted with caution, as there were numerous cells that had a count of less than 5 responses per cell and with such a small number of responses, the results may not be indicative of the beliefs of the general population.

Qualitative Analysis

Since there is little research available which looks at off-label prescribing from the prescriber's point of view, the last question of the survey asked respondents to include any additional information they would like the researcher to consider about off-label prescribing. The themes that emerged from the responses allowed the researcher to put the quantitative responses into context as well as develop further avenues to pursue when studying off-label prescribing (Graneheim & Lundman, 2004).

A total of 40 respondents provided comments to the last question of the survey. The responses were grouped into seven categories based on keywords within the responses.

The first category contained a total of 13 responses that indicated that either the respondent was a specialist and the majority of the medicines they prescribe are off-label or that the respondent was a general pediatrician that relied heavily on specialists for prescribing medicines off-label to their patients.

An example of a response in this category was "I do weight heavily the off-label use of medications by pediatric subspecialists in deciding whether it is either safe or efficacious to use a particular medication. It would seem that the subspecialists are the first to choose a drug for off-label use. If it is successful in the patients I have referred to them, and if I see increasing numbers of patients being treated that way, I am more likely to try it off-label myself."

The second category contained 11 responses in which respondents indicated that they believe that the majority of the off-label prescribing that they engage in is related to the age of their patient. They further indicated that they rely on evidence-based data on adults to assist them in determining whether they should prescribe a medicine to their child, indicating that they attempt to use an evidence-based approach to making their prescribing decisions.

The third category that emerged from respondents' comments supported a disappointment with the lack of evidence-based data regarding the use of many medications in the pediatric population. Specifically, five respondents indicated that while they do not like prescribing off-label to their patients, they feel forced to because of the lack of approved medications in this population. An example of a response in this category was "it is difficult to find enough drugs approved for the less than 12 month old."

The fourth category contained responses from 4 respondents. These respondents indicated that they prescribe only certain medicines off-label to their patients given they can based their prescribing decision on their previous experience with the medication thus supporting that prior knowledge does play a

key factor in prescribing practices. An example of a response in this category was "I prescribe hydroxyurea to children with sickle-cell disease on a regular basis because, based on my experience, it is effective for these patients."

Interestingly, only two respondents indicated that they do not inform the patient or their guardian when they prescribe medicines off-label to them and also do not discuss the medication risks and potential other options of care. This suggests that communication may be factor in decision making for some physicians.

Only, one respondent indicated that they were not aware what medicines were off-label anymore. Two respondents provided non-content specific responses to this question: one further clarified their use of the word rarely for responding to the survey questions and one respondent indicated that their answers to the survey may have been different if they were still practicing medicine.

Summary

A total of 167 individuals provided answers to an on-line survey regarding their beliefs and practices toward off-label prescribing.

The hypotheses that pediatricians would report that the primary factors that influence their decision whether or not to prescribe a medicine off-label are a lack of appropriate references and concerns about patient safety and the secondary factors that influence their decision whether or not to prescribe a medicine off-label are legal concerns, insurance coverage and patient complaints were not fully supported by the results of this study.

Interestingly, respondents indicated that they use reference manuals most often, with published, peer-reviewed research a close second. These results are promising because, as indicated in chapter 2, the problem with reference manuals is that they may not contain the most up-to-date research regarding a medicine and published, peer-reviewed research is the best way to supplement. Additionally, this may offer support that physicians are aware of the need to practice in an evidenced based manner using the currently available evidence to support and direct their clinical decision making.

However, given the significant variance (1.078) in the use of the medicine's label for prescribing information, one must question their practices as the drug's label contains the most up-to-date information about the health authority-approved uses for the medicine. Thus, this finding may suggest that some respondents may not be prescribing a medicine in a manner not approved by a health authority.

Regarding their beliefs about off-label prescribing, respondents did not feel strongly about the legal liabilities or patient complaints related to off-label prescribing but did believe that physicians should legally be allowed to prescribe a medicine off-label.

Yet, given that almost two-thirds (73%) of respondents indicated that, in the last year, they prescribed medicines off-label less than 25% of the time and none of the therapeutic areas listed in the survey supported that they prescribed off-label medications regularly or often, off-label prescribing does not seem to be prevalent in this physician population. Taken together, this data suggests that

pediatricians prefer to practice autonomously using and evidence-based approach which may explain why they do not prescribe medicines off-label a significant portion of the time regardless of practice setting.

Considering that most of the respondents were not medical or surgical specialists and many worked in an outpatient facility, the overall results of the study are not surprising. As indicated in chapter 2, medicines are prescribed off-label more often for the more serious, specialized diseases where the patient is typically seen in the hospital or by a specialist (O'Reilly and Dalal, 2003) and, therefore, the pediatricians working in these areas are more likely to prescribe medicines off-label and have concerns about the practice.

While the results of the quantitative questions within the survey provided valuable insight into the beliefs and practices of pediatricians toward off-label prescribing, the answers to the qualitative question were similarly revealing. Many respondents indicated that they believed that the references currently available were inadequate and that, often, pediatricians rely on specialists to prescribe medicines off-label. This finding is also in line with previous research that indicates that generalists often do not prescribe medicines off-label (O'Reilly and Dalal, 2003).

The qualitative findings of this study support previous literature that indicates that there is a need for more research in the pediatric population. In addition, the results indicate that pediatricians are concerned about the safety and efficacy of the medicines they prescribe to their patients and would like to have evidence-based results prior to prescribing a medicine to their patient.

Certainly if a medicine is prescribe in the manner indicated on its label, then that means that it has been tested and found to be safe and effective.

As the results of this study indicate, pediatricians have concerns about prescribing a medicine off-label because information about the proper use of the medicine may not be available. With the absence of evidence-based research, pediatricians must utilize their critical thinking skills and develop practice based-evidence to determine the best medicine to treat their patient (Horn & Gassaway, 2007).

Chapter V

Discussion and Conclusions

The purpose of this study was to determine pediatrician beliefs toward off-label prescribing and the factors that may influence their decision to prescribe a medicine off-label. The results of this study indicate that pediatricians prescribe medicines off-label and most reported that they do so no more than 25% of the time. Respondents also indicated that some pediatricians have little experience with off-label prescribing and, often, there are no references, based on evidence –based practice, that clearly define how medicines should be prescribed off-label.

The results of this exploratory study set the stage for the initial dialogue regarding off- label prescribing practices in the pediatric population in a scholarly venue. While this contribution, in of itself, is important to the practice of health care in the United States, this work sheds light on the importance of the health care community specifically physicians, who as autonomous practitioners have the right and privilege to prescribe medications off-label, to practice their craft using the best available evidence.

Two key factors that can be used to support evidenced based practice which resonate from the findings of this study are the importance of practice based evidence and ongoing training for health care professionals.

Practice-based Evidence

One way to address the lack of evidence-based practice is to develop guidelines based on observed current practices. Horn and Gassaway (2007) describe this method as practice-based evidence (PBE). PBE is developed by a multisite, trans-disciplinary Clinical Practice Team whose responsibility is to analyze patient data within their practice to develop guidelines for members of their clinical team. The team does not need to publish the data or rely on others to approve their guidelines; they just need to ensure there is observable evidence to justify the processes suggested.

Other benefits of PBE are that the data that is analyzed is based upon patient treatments and therapeutic outcome data that is normally collected in medical practice and therefore, does not require patient consent. Also, the guidelines developed can be modified quickly based on new information, evidenced based observations or treatment outcome data. Thus, health care team does not need to wait for regulatory approval or the publication of evidence-based practices; the team can re-train and improve their practices as necessary based upon PBE.

Training

Training is another issue that was highlighted in the results of this study. Many physicians felt that additional training is needed to determine the risks and benefits related to off-label prescribing as well as when the practice is appropriate or not. The issue is how to develop training that will be effective., Generally, after the completion of their internship, any and all training that a physician receives is through continuing medical education (CME) (Davis, 1998). Several studies (Holm, 1998; Fox & Bennett, 1998; Mathers, Challis, Howe & Field, 1999; Grol, 1992; Bashook & Parboosingh, 1998) present theories for how to effectively and efficiently provide CME to physicians as well as how to change a physician's prescribing behavior through CME (Denig, Wahlstrom, Chaput de Saintonge, Haaijer-Ruskamp, 2002; Gill, Makela, Verneulen, Freemantle, Ryan, Bond, et al, 1999).

Interestingly, Verniga, Denig, Zwaagstra, and Haaijer-Ruskamp (2000) studied the effects of cognitive feedback on a physician's choice of treatment for patients with asthma and urinary tract infections. Their parallel, randomized controlled study included 24 already existing pharmacotherapy counseling groups in the Netherlands, each with about 7 physicians per group. The researchers provided half of the groups with national guidelines, case studies and individual and group feedback on the prescribing choices made for the treatment of asthma and half of the groups received this information of urinary tract infections (UTIs). Each set of groups acted as a control group for each condition. Lastly, the researchers collected the 6 months of prescribing data

before the intervention and 6 months of prescribing data after the intervention to determine whether there were any changes in prescribing behaviors.

While the results of this study showed some improvement in prescribing behaviors, they showed no significant improvement in participants' knowledge. The intervention for the asthma groups did not, on average, improve participants' knowledge of the condition, yet there was an 11% to 68% improvement for the treatment of different patients with asthma (e.g. treating with inhaled vs. oral steroids). For the UTI groups, there was little improvement in knowledge of the disease or treatment choices but there was a significant effect on the duration of treatment (decreased from an average of 6.07 to 4.29 days on treatment.) This suggests that although physicians may have sufficient knowledge about a condition, providing them with approved guidelines and feedback on appropriate prescribing can improve their prescribing behavior.

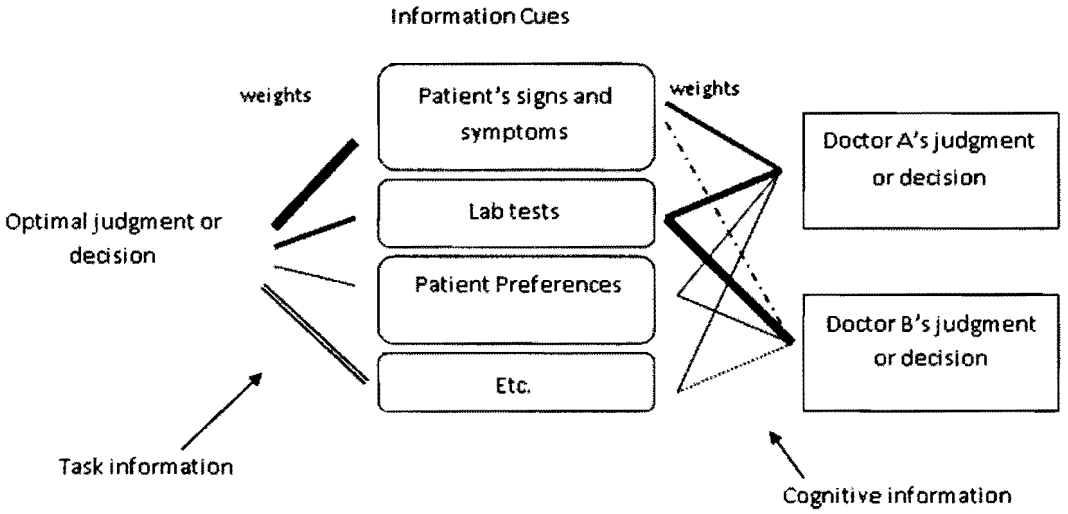
Another way to change pediatrician prescribing behavior is described by Fox and Bennett (1998) and is based on adult learning theory. They suggest that in order to influence a change in physician behavior, physicians need to first identify the deficiencies in their own knowledge and experience and then critically evaluate the new information to influence the change. Ultimately, the physicians must believe that they need to change their behavior in order to effectively practice. They explain that the motivation comes from a physician who estimates where they should be in terms of knowledge or skills and then compares it to what they actually know or do. Surprisingly, only if the physician discovers a discrepancy do they become motivated to learn and address that gap in their

knowledge. Thus, leaving change in the hands of the physician who may not be aware of their limitations, but who has the right and privilege to prescribe off - label. Hopefully, if more research is made available that describes the risks and benefits of off-label prescribing as well as off-label practicing patterns, physicians may self-reflect upon their knowledge of, comfort of and current off-label practices and see it as an area to improve their prescribing practices.

Clinical Judgment Analysis

Once PBE is established and effective training programs are developed, a pediatrician, or any health care professional, ultimately needs to include the new practices into their decision making processes for prescribing. The Clinical Judgment Analysis model, as described by Denig, Wahlstrom, Chaput & Haaijer (2002), indicates one way in which PBE and training would influence prescribing decision making practices. The Clinical Judgment Analysis model (Figure 5) indicates that there are several informational cues that enable a physician to make a decision. These cues can be a patient's signs or symptoms, laboratory test results, patient preferences, etc. The model suggests that each individual physician weighs the relative importance of each of the information cues differently based on their knowledge of what the optimal decision is versus their own personal experience or knowledge and then makes the final judgment or decision.

Figure 5. Clinical Judgment Analysis Model



As suggested above and further explained by Denig, et al (2002), the key to clinical judgment analysis is the knowledge and expertise of the physician regarding the specific decision that needs to be made. The authors believe that the Clinical Judgment Analysis Model looks behind the outcome of a decision to the underlying decision process and combines ideas from adult learning, behavioral change and decision making theory to improve prescribing decisions. Both PBE and effective training could lead a physician to support their final prescribing decision because they can assist them in reflecting on the influence and relevance of the information cues. If off-label prescribing is included as an additional informational cue in the clinical judgment model then it can further support a physician in making a better prescribing decision for their patient.

Finally, the authors suggest that educators could develop a set of case studies with informational cues for physicians to analyze. Using the case study approach further insight on the physicians use of the cues in order to make prescribing decisions could be explored and thus further support the adult learning process via feedback to the physician. In the literature it has been suggested that through this direct feedback that physicians learned and were able to make changes to their prescribing behavior. These findings support the possibility that case studies can be effectively used in a similar fashion to inform and educate the decision making practices of pediatricians with regard to off-label practices. Specifically, physicians could be provided with a set of case studies, based on PBE, which present various situations where off-label prescribing may be necessary. Then, through the analysis of the case studies,

pediatricians could determine the best options for their patients, thus creating PBE and establish effective training on that practice.

Overall, the results of our study and those in the literature support that while no single strategy can change a physician's behavior, the most successful strategies are based on the theories of adult learning and behavioral change that require physicians to critically think about and analyze their decisions. Clearly, these findings further explain our data in a meaningful manner and offer insight into future directions for research and education. Given that the respondents of this study indicated that they had varying levels of years of experience practicing medicine and the absence of significant differences in off-label prescribing practices among the different levels of experience one might suggest that a CME course that included an element for developing their critical thinking skills, could assist pediatricians, at all levels of experience, in critically reviewing and assesses all e evidence available to support that use, whether it is EBP or PBE.

Limitations

The respondents that completed the survey represented a convenience sample of volunteers who learned about the survey through their membership of either the AAP/NJ or TNAAP. While about two-thirds of the respondents indicated that they practice medicine in TN and about one-third in NJ, the survey results may not be representative of the views or practices of other pediatricians who are members of these organizations or, furthermore, of those that practice medicine in NJ or TN.

One of the limitations of this study was the difference in size between the number of specialists and general pediatricians. As the qualitative results indicated, some generalists rely on the specialists to prescribe medicines off-label. Since 119 of the respondents were general pediatricians and only about 45 of the respondents were specialists, it was not ideal to calculate group differences since the sizes of the groups were so disparate.

Another limitation involved the use of an anonymous, on-line survey to collect the data. Although Surveymonkey.com prevented the same person from answering the survey using the same computer by blocking their IP address after they completed the survey, this could have been circumvented by use of an alternate computer. The anonymity also prevented the researcher from verifying the answers from each of the respondents. Specifically for the questions that required respondents to recall their prescribing patterns over the last month or the last year, chart verification could have yielded more accurate results. The questions which used a Likert scale assumed that the categories had equal intervals between them, which is unlikely. Lastly, the use of a survey inherently is a limitation because surveys only collect perceptions / opinions and may not accurately reflect the behaviors of the respondents.

Future Research

The purpose of this research study was to determine the beliefs and factors that may influence a pediatrician to prescribe medicines off-label. The results of this study should be used to encourage pediatricians to seek more guidance and training on the best use of off-label prescribing practices. The

results of future research involving a larger population, face to face interviews with pediatric specialists or chart reviews could further support the findings of this study.

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Appendix A

Off-label Prescribing of Medicines in Children: Survey Validation

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Table of Contents

Abstract

Published literature indicates that the prescribing of off-label medicines to children is common. However, few researchers have surveyed pediatricians to determine their attitudes and beliefs toward this practice and no surveys used in these studies have been validated by research and healthcare experts. The purpose of this research project was to develop and validate a survey that will be used to determine the attitudes and beliefs of New Jersey pediatricians towards off-label prescribing. Ten experts were asked to comment on the appropriateness, clarity and sequence of the survey questions. Seven experts responded to the request. Overall, only minor changes were incorporated into the survey.

Introduction

A medicine that is prescribed off-label is prescribed in a manner that has not been approved by a health authority. Although off-label prescribing is legal, many researchers have expressed concerns about the use of medicines in this manner, indicating that medicines prescribed off-label may not be safe and/or effective. These concerns are especially common in the pediatric population because of the significant physiological changes occurring in the pediatric population (Cohen, 1997).

Several studies have been performed globally to indicate the prevalence of off-label prescribing in the pediatric population. Results of these studies indicate that up to 63% of medicines prescribed to children are off-label (Pandolfini & Bonati, 2005). Researchers suggest several reasons for the widespread use of off-label medicines in this population such as lack of resources to perform clinical trials in this population (Conroy, 2002) and lack of appropriate references and training on how to properly medicate children (Matsui, Jardine, Steer, Cukernik & Rieder, 2003). However, only two studies indicate the attitudes and beliefs of physicians towards this practice (Ekins-Daukes, Helms, Taylor & McLay, 2004 and McLay, Tanaka, Ekins-Daukes & Helms, 2006). Because the physician ultimately provides the prescription to the patient, it is important that their perspectives of off-label prescribing are properly understood by those wanting to make changes to this practice.

The Elkins-Daukes et al and McLay et al studies include the results of a survey given to over 200 general practitioners in Scotland indicating their attitudes and beliefs towards off-label prescribing. However, neither study details the methods used to develop and validate the survey tool used to collect the study data. Therefore, it is important that a survey used to determine the attitudes and beliefs of pediatricians towards off-label prescribing is developed and properly validated by experts in research and healthcare.

Methods

A survey consisting of instructions, 5 research questions, 5 demographic questions and 1 open ended question for additional comments was developed based on the review of published research in the area of off-label prescribing to children (Appendix 1). Each question contains multiple choice, Likert-scale or open ended answers. Validation of the sequence, appropriateness, completeness and clarity of the survey questions was obtained by mailing printed copies of the survey to ten experts in healthcare and research affiliated with Seton Hall University. Expertise were defined as possessing a terminal degree in healthcare or related field, 20 or more years of experience in research and a title of associate professor or greater.

Along with a copy of the survey, an introduction letter (Appendix 1) was provided which included a brief summary of the purpose of the study, definitions of terms and references used in the survey, and the researcher's contact

information in case the expert had questions about the survey. The experts were asked to answer 2-4 questions per survey question, each allowing the expert to report whether the sequence, appropriateness, completeness and clarity of the questions were suitable for the study. Each question for the experts contained two possible answers – yes and no. If the response was no, the experts were asked to provide suggestions for improvement. A self-addressed stamped envelope was included along with the survey and the experts were asked to return completed surveys back within 2 weeks of receipt. Seven responses were received within the study timeframe. Overall, only a few questions have been changed due to the survey validation results. The final survey can be found in Appendix 2.

Results

Analysis

Below are summaries of the responses per question. Only responses received by two or more experts (29% or more) were considered for revision.

Survey Instructions

Five experts (71%) believed that the survey instructions were both appropriate and clear. Two experts (29%) did not comment on the appropriateness or clarity of the survey instructions. No experts believed that the instructions should change in any manner; therefore, the instructions remained unchanged in the final version of the survey.

Question 1. The purpose of question 1 was to determine the reference(s) pediatricians use to prescribe medicines to their patients. The experts were asked whether the question was appropriate for the study, clear, in the correct sequence and complete. All but one expert provided answers for this question.

Six respondents (86%) believed question 1 was appropriate for this survey. Only one respondent believed that question 1 was not clear. Two experts (29%) believed that the sequence of the statements in question 1 were not suitable. Both experts suggested that the list be presented in order from least scientific / evidence-based to most scientific / evidence-based. Because two experts reported this opinion, meeting the previously set criteria for making changes to the survey, the sequence of the answers for this question has been changed in the final version of the survey.

Two experts believed that additional references should be added to question 1. One expert suggested that the *Merck Manual* be added to the list and the other believed that Personal Digital Assistants (PDAs) should be added. Because these suggestions do not meet the previously set criteria of two experts providing the same suggestion, the reference list will remain unchanged in the final version of the survey.

Question 2. The purpose of question 2 was to determine the therapeutic categories pediatricians most often prescribe medications in an off-label manner. The experts were asked whether the question was appropriate for the study, clear, in the correct sequence and complete. One expert (14%) did not provide answers for this question.

Six experts (86%) believed that question 2 was appropriate for this survey. Only one expert (14%) believed that question 2 was not clear. Because this response was received by only one expert, the question will remain unchanged.

One respondent (14%) believed that the therapeutic areas should be presented in alphabetical order. Four experts (57%) suggested that additional categories should be added to the question. The suggestions included anti-anxiety, anti-inflammatory, and a section for Other. One expert questioned the use of psychotropic, however, did not explain why so no changes are being made to this term. The suggested categories have not been added to the final version of the survey because only one expert made the suggestion for each therapeutic category.

Question 3. The purpose of question 3 was to determine the age ranges treated by the pediatricians who complete the survey. The experts were asked whether the question was appropriate for the study, clear, and in the correct sequence. Two experts (29%) did not provide answers for this question.

Five (71%) experts believed that this question was both appropriate and in the correct sequence for this survey. Only one expert (14%) believed that question 3 was not clear. Because this response was received by only one expert, the question will remain unchanged in the final version of the survey.

Question 4. The purpose of question 4 was to determine the percent of medicines the pediatrician prescribed off-label in the last year. The experts were asked whether the question was appropriate for the study, clear, and in the correct sequence. Two experts did not provide answers for this question.

Five experts (71%) believed that this question was both appropriate and in the correct sequence for this survey. Three experts (43%) believed that question 2 was not clear. One expert asked whether this question needs to be qualified by age group as in question 3. One expert suggested to change the ranges for choices b-e from 1-25, 25-50, 50-75 and 75-100% to 1-5, 5-10, 10-25, and >25% and another expert suggested to change the ranges to 1-25, 26-50, 51-75 and 76-100%.

Although none of these suggestions were made by more than one expert, the criteria established for making changes to the final version of the survey, the final version will be changed to reflect the latter suggestion. This change ensures that the answers are distinct from one another.

Question 5. The purpose of question 5 was to determine the beliefs that pediatricians have about off-label prescribing. The experts were asked whether the question was appropriate for the study, clear, in the correct sequence and complete. One expert did not provide answers for this question.

Five (71%) experts believed that this question was appropriate for this survey. Because only one expert (14%) believed that changes should be made to the question, the question will remain unchanged.

Six (86%) experts believed that the question was both clear and in the correct sequence. Two experts (29%) made suggestions for additional statements to be added to this question. The first suggestion was to add questions regarding the ethical implications of off-label prescribing (e.g. patient safety, informed consent) and the second was to add a statement saying "I

believe that patients should receive pharmacotherapy that presents the best outcome opportunity regardless of label use." Because the suggestions for this question were not received by two or more experts, meeting the previously defined criteria, this question will remain unchanged.

Question 6. The purpose of question 6 was to determine in which state the pediatrician practices medicine. The experts were asked whether the question was appropriate for the study, clear, and in the correct sequence. Two experts (29%) did not provide answers for this question. The remaining experts (71%) believed that this question was appropriate, clear and in the correct sequence for this survey.

Question 7. The purpose of question 7 was to determine the country the pediatrician attended medical school, completed residency, completed fellowship and obtained board certification. The experts were asked whether the question was appropriate for the study, clear, in the correct sequence and complete.

One expert (14%) did not provide answers for all questions; two experts (29%) did not provide responses for the last question. Six experts (86%) believed that the question was appropriate, clear and in the correct sequence for the survey. Two experts (29%) believed that additional options should be added to this question. One expert suggested that an option is added to allow for more than one residency. The other expert suggested to add an option to determine whether the pediatrician is a currently a licensed practitioner. Because both of these suggestions were made by only one expert each, the final version of the survey will remain unchanged.

Question 8. The purpose of question 8 was to determine whether the respondent is a general pediatrician, pediatric medical specialist or pediatric surgical specialist. The experts were asked whether the question was appropriate for the study, clear, in the correct sequence and complete.

Two experts (29%) did not provide answers for the questions regarding appropriateness; the remainder of the experts (71%) did believe that the question was appropriate. Two experts (29%) did not comment on the clarity of this question and four experts did believe that the question was clear. One expert believed that choices b & c should include a section for the respondents to write in their specific specialty. However, since this comment was received by only one expert, question 8 will remain unchanged.

Four (57%) experts did not answer the question about sequence, while the remainder of the experts did believe that the question was in the correct sequence. None of the experts provided suggestions for additional options to this question.

Question 9. The purpose of question 9 was to determine the number of years the respondent has been a practicing physician. The experts were asked whether the question was appropriate for the study, clear, and in the correct sequence.

One expert (14%) did not provide a response for this question. Six experts (86%) believed that this question was appropriate and in the correct sequence. Two experts (29%) did not believe that this question was clear. One expert suggested that the words "post residency" be added to the question. Although

only one expert provided this comment, this phrase will be added to the final version of this survey to ensure that survey respondents all use the same definition for practicing physician.

One expert questioned whether practice experience, specifically for pediatricians who have been practicing for 5-15 years, would skew the results of this study; however, this expert did not provide a suggestion for improvement. Because this response was received from only one expert, the final survey will remain unchanged.

Question 10. The purpose of question 10 was to determine the working environment of the survey respondent. The experts were asked whether the question was appropriate for the study, clear, and in the correct sequence.

Two experts (29%) did not provide an answer for the question about appropriateness. The remainder of the experts, however, did believe that this question was appropriate for this survey. One expert did not provide a response for the questions about clarity or sequence. Four experts (57%) believed that the question was clear; two experts (29%) provided suggestions for improving the clarity.

Specifically, one expert believed that option b (group practice) should be separated into 3 categories – 2-10, 11-25 and greater than 25 doctors. The other expert suggested that an additional option be included for "other." Because neither suggestion was provided by two or more experts, this question will remain unchanged in the final version of the survey.

Question 11. The purpose of question 11 was to determine whether the pediatricians have any additional information about off-label prescribing to share with the researcher. The experts were asked whether the question was appropriate for the study, clear, and in the correct sequence.

Two experts (29%) did not answer the question about appropriateness; three experts (43%) did not answer the questions about clarity and sequence. The remainder of the experts believed that this question was appropriate (71%), clear (57%) and in the correct sequence (57%). Therefore, this question will remain unchanged.

Additional suggestions. Experts were also provided the opportunity to make additional suggestions to improve the survey. One expert believed that an additional question could be added on the policy of off-label use in the given organization. The expert believed that the policies of the pediatrician's organization may have a larger impact on prescribing practices of the pediatrician than the individual pediatrician's attitudes and beliefs toward off-label prescribing. Because this comment was received by only one expert, no changes will be made to the final version of the survey based on this comment.

An additional suggestion provided by an expert was that the research question uses the term influence, implying causality, and that this survey does not measure causality. No changes will be made to the final version of the survey based on this comment because it was received by only one expert.

Results Summary

Only three changes were made to the survey based on the input from the experts. The first change was to the sequence of the answers in question 1. In the final version of the survey, the answers will be provided in order from most scientific to least scientific, as suggested by two experts.

Another change was made to improve the clarity of the answers for question 4. Instead of overlapping the choices (i.e. 1-25, 25-50, 50-75 and 75-100), the final version of the survey will provide clearly distinct possibilities for the respondent (i.e. 1-25, 26-50, 51-75 and 76-100).

The wording of question 9 was changed to improve the clarity as well. The words "post residency" will be added to the final version of the survey to ensure that all respondents answer the question in the same manner.

Appendix 1 contains the introduction letter and survey that was sent to the experts. Appendix 2 contains the final version of the survey, based on the responses from the experts. Overall, the survey did not change greatly from its initial format. The information that was changed between the two versions is indicated in italics.

Conclusion

The purpose of this paper was to describe the development and validation of a survey to be used to determine New Jersey pediatrician attitudes and beliefs towards of off-label prescribing. The survey was developed after a thorough review of published literature describing the issues associated with off-label

prescribing. Validation of the survey was performed by experts in healthcare and research to ensure that the survey was appropriate, clear and information was presented in the proper sequence.

Survey validation allows the researcher to ensure that the survey will adequately capture the appropriate information necessary to conduct the research. Overall the experts believed that the survey was clear and appropriate and that the questions were presented in the correct sequence. Only minor changes were made to the final version of the survey and all were made to improve the clarity of the survey. All changes are highlighted in Appendix 2.

Appendix 1

Survey Sent to Experts

September 12, 2006

Dear Healthcare Educator:

I am a doctoral student at Seton Hall University in the School of Graduate Medical Education. Your name was provided to me as an expert in healthcare and research by Dr. Genevieve Pinto-Zipp, chair, Graduate Programs in Health Sciences. I would appreciate your input on the appropriateness, clarity and sequence of the questions in the attached survey. After the final version of the survey has been developed, a sample of pediatricians in New Jersey will be invited to participate in its completion, via email, over the internet.

The purpose of the study is to determine the factors influencing pediatricians in prescribing medicines off-label. Off-label prescribing occurs when a physician prescribes a medicine in a manner where the dosage, age, indication and/or route of administration have not been approved by a health authority (not indicated on the medicine's label).[1] While off-label prescribing is a

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[1] Conroy, S. (2002). Unlicensed and off-label drug use: issues and recommendations. *Pediatric Drugs, 4* (6), 353-359.

legal and widely accepted practice, up to 33% of children in the community, up to 60% of children in a pediatric hospital ward and up to 63% of children in a neonatal hospital ward receive medicines off-label. [2]

Please provide your responses and comments in the grey box below each question on the enclosed survey. Please also use the following definitions when providing your feedback:

Appropriate: The survey question and answers are suitable for this study.

Clear: The survey question and answers are easy to understand.

Sequence: The survey questions and answers are presented in a logical order.

Your thoughtful response to this request should take no longer than 20 minutes. Please return your comments in the enclosed envelope, addressed to Joann DeBerto, secretary, Seton Hall Graduate Programs in Health Science, no later than **September 26, 2006**. If you would like to complete your review electronically, please email your request to me at herbstel@shu.edu. Upon completion of the data analysis, the final results of the study will be provided to you.

Sincerely,
Elizabeth G. Evola

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[2] Pandolfini, C. & Bonati, M. (2005). A literature review on off-label drug use in children. *European Journal of Pediatrics, 164*, 552-558.

Survey Instructions

By completing this survey, you consent for the researcher to use your answers for research purposes. Please use the following definitions when responding to the survey questions:

Off-label: A medicine prescribed in a manner where the ***dosage***, ***age***, ***indication*** and/or ***route of administration*** are not indicated on the medicine's label (have not been approved by a health authority).[3]

Regularly: I perform this activity greater than 75% of the time.

Often: I perform this activity greater than half but less than 75% of the time.

Sometimes: I perform this activity greater than 25% but less than half of the time.

Rarely: I perform this activity less than 25% of the time.

Never: I do not perform this activity.

Are these instructions appropriate for this survey, yes or no?
If no, what are your suggestions for improvement?
Are these instructions clear, yes or no?
If no, what are your suggestions for improvement?

Survey Questions

[3] Conroy, S. (2002). Unlicensed and off-label drug use: issues and recommendations. *Pediatric Drugs, 4* (6), 353-359.

1) I use the following to determine whether or not to prescribe medicine to my patients:

	Regularly	Often	Sometimes	Rarely	Never
Reference Manuals (e.g. Physicians Desk Reference (PDR))					
Patient / guardian suggestion					
Patient / guardian request					
Patient insurance company					
My previous experience with the medicine					
My group/ hospital/ facility/ office's experience with the medicine					
The medicine's label (prescribing information)					
Published research					
Unpublished research					
Peer recommendations					
Information from pharmaceutical representative					

Is Question #1 appropriate for this survey, yes or no?
If no, what are your suggestions for improvement?
Is Question #1 clear, yes or no?
If no, what are your suggestions for improvement?
Is Question #1 in the correct sequence, yes or no?
If no, what are your suggestions for improvement?
Are there any other references that should be included in the list in Question #1, yes or no?
If yes, name them here.

2) Once per month, at minimum, I prescribe medicines in the following categories in an *off-label* manner.

	Regularly	Often	Sometimes	Rarely	Never
Dermatologics					
Otologics					
Psycholeptic and psychoanaleptics					
Analgesics					
Rhinologicals					
Antihistamines					
Expectorants and anti-tussive agents					
Anti-epileptics					
Anti-asthmatics					
Antibiotics					
Insulin					

Is Question #2 appropriate for this survey, yes or no?
If no, what are your suggestions for improvement?
Is Question #2 clear, yes or no?
If no, what are your suggestions for improvement?
Is Question #2 in the correct sequence, yes or no?
If no, what are your suggestions for improvement?
Are there any other medicinal categories that should be included in the list in Question #2, yes or no?
If yes, name them here.

3) Once per month, at minimum, I prescribe medicines to patients in the following age ranges in an *off-label* manner.

	Regularly	Often	Sometimes	Rarely	Never
Less than 1 year old					

1-5 years old					
5-12 years old					
13-18 years old					
Greater than 18 years old					

Is Question #3 appropriate for this survey, yes or no?
If no, what are your suggestions for improvement?
Is Question #3 clear, yes or no?
If no, what are your suggestions for improvement?
Is Question #3 in the correct sequence, yes or no?
If no, what are your suggestions for improvement?

4) In the last year, what is the percent of medicines that you prescribed off-label?
   a) None
   b) 1- 25 %
   c) 25 - 50%
   d) 50 - 75%
   e) 75 - 100%

Is Question #4 appropriate for this survey, yes or no?
If no, what are your suggestions for improvement?
Is Question #4 clear, yes or no?
If no, what are your suggestions for improvement?
Is Question #4 in the correct sequence, yes or no?
If no, what are your suggestions for improvement?

5) Although the practice of medicine allows for physicians to prescribe medicines off-label, please complete the following section with regard to your beliefs about off-label prescribing.

	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree	I do not prescribe medicines off-label.
When I prescribe a medicine off-label, I am concerned about the legal liabilities.						
When I prescribe a medicine off-label, I am concerned that patients (or their guardians) will complain.						
I believe that physicians should not be legally allowed to prescribe medicines off-label.						

Is Question #5 appropriate for this survey, yes or no?
If no, what are your suggestions for improvement?
Is Question #5 clear, yes or no?
If no, what are your suggestions for improvement?
Is Question #5 in the correct sequence, yes or no?
If no, what are your suggestions for improvement?
Are there any other options that should be included in the list in Question #5, yes

or no?
If yes, name them here.

6) In what state do you practice medicine?

a) New Jersey
b) Other _____

Is Question #6 appropriate for this survey, yes or no?
If no, what are your suggestions for improvement?
Is Question #6 clear, yes or no?
If no, what are your suggestions for improvement?
Is Question #6 in the correct sequence, yes or no?
If no, what are your suggestions for improvement?

7) In which country did you:

	United States	If outside United States, enter name of country.	Not applicable
Attend Medical School?			
Complete Residency?			
Complete Fellowship?			
Obtain Board Certification?			

Is Question #7 appropriate for this survey, yes or no?
If no, what are your suggestions for improvement?

Is Question #7 clear, yes or no?
If no, what are your suggestions for improvement?
Is Question #7 in the correct sequence, yes or no?
If no, what are your suggestions for improvement?
Are there any other options that should be included in the list in Question #7, yes or no?
If yes, name them here.

8) Are you a: (please choose only one answer)

a.) Pediatrician
b.) Pediatric medical subspecialist
c.) Pediatric surgical specialist

Is Question #8 appropriate for this survey, yes or no?
If no, what are your suggestions for improvement?
Is Question #8 clear, yes or no?
If no, what are your suggestions for improvement?
Is Question #8 in the correct sequence, yes or no?
If no, what are your suggestions for improvement?
Are there any other options that should be included in the list in Question #8, yes or no?
If yes, name them here.

9) How many years have you been a practicing physician?

a. Less than 5 years
b. 5-15 years
c. 15-25 years
d. greater than 25 years

Is Question #9 appropriate for this survey, yes or no?
If no, what are your suggestions for improvement?
Is Question #9 clear, yes or no?
If no, what are your suggestions for improvement?
Is Question #9 in the correct sequence, yes or no?
If no, what are your suggestions for improvement?

10) What type of environment do you currently work in? (please choose all that apply)

a.) Solo practice
b.) Group practice
c.) Hospital based practice – non-teaching
d.) Hospital based practice - teaching

Is Question #10 appropriate for this survey, yes or no?
If no, what are your suggestions for improvement?
Is Question #10 clear, yes or no?
If no, what are your suggestions for improvement?
Is Question #10 in the correct sequence, yes or no?
If no, what are your suggestions for improvement?

11) Please provide any additional information about your off-label prescribing practices for the researcher to consider.

Is Question #11 appropriate for this survey, yes or no?
If no, what are your suggestions for improvement?
Is Question #11 clear, yes or no?
If no, what are your suggestions for improvement?
Is Question #11 in the correct sequence, yes or no?
If no, what are your suggestions for improvement?

In the space below, please provide any additional suggestions for this survey. Thank you for your time in completing this survey.

Please send any additional comments to me using the enclosed envelope or email me at herbstel@shu.edu.

Appendix 2

Final Survey

Survey Instructions

By completing this survey, you consent for the researcher to use your answers for research purposes.

Please use the following definitions when responding to the survey questions:

Off-label: A medicine prescribed in a manner where the ***dosage***, ***age***, ***indication*** and/or ***route of administration*** are not indicated on the medicine's label (have not been approved by a health authority).[4]

Regularly: I perform this activity greater than 75% of the time.

Often: I perform this activity greater than half but less than 75% of the time.

Sometimes: I perform this activity greater than 25% but less than half of the time.

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[4] Conroy, S. (2002). Unlicensed and off-label drug use: issues and recommendations. *Pediatric Drugs, 4* (6), 353-359.

Rarely: I perform this activity less than 25% of the time.

Never: I do not perform this activity.

Survey Questions

1) I use the following to determine whether or not to prescribe medicine to my patients:

	Regularly	Often	Sometimes	Rarely	Never
Reference Manuals (e.g. Physicians Desk Reference (PDR), etc.)					
Published research					
Unpublished research					
The medicine's label (prescribing information)					
My previous experience with the medicine					
My group/ hospital/ facility/ office's experience with the medicine					
Peer recommendations					
Information from pharmaceutical representative					
Patient insurance company					
Patient / guardian suggestion					
Patient / guardian request					

2) Once per month, at minimum, I prescribe medicines in the following categories in an *off-label* manner.

	Regularly	Often	Sometimes	Rarely	Never
Analgesics					
Anti-asthmatics					
Anti-epileptics					
Antibiotics					
Antihistamines					
Dermatologics					

Expectorants and anti-tussive agents					
Insulin					
Otologics					
Psycholeptic and psychoanaleptics					
Rhinologicals					

3) Once per month, at minimum, I prescribe medicines to patients in the following age ranges in an *off-label* manner.

	Regularly	Often	Sometimes	Rarely	Never
Less than 1 year old					
1-5 years old					
5-12 years old					
13-18 years old					
Greater than 18 years old					

4) In the last year, what is the percent of medicines that you prescribed off-label?
   a) None
   b) 1- 25 %
   c) *26* - 50%
   d) 51 - 75%
   e) 76 - 100%

5) Although the practice of medicine allows for physicians to prescribe medicines off-label, please complete the following section with regard to your beliefs about off-label prescribing.

	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree	I do not prescribe medicines off-label.
When I prescribe a medicine off-label, I am						

concerned about the legal liabilities.						
When I prescribe a medicine off-label, I am concerned that patients (or their guardians) will complain.						
I believe that physicians should not be legally allowed to prescribe medicines off-label.						

6) In what state do you practice medicine?
   a) New Jersey
   b) Other _____

7) In which country did you:

	United States	If outside United States, enter name of country.	Not applicable
Attend Medical School?			
Complete First Residency?			
Complete Fellowship?			
Obtain Board Certification?			

8) Are you a: (please choose only one answer)
   a.) Pediatrician
   b.) Pediatric medical subspecialist
   c.) Pediatric surgical specialist

9) How many years have you been a practicing physician (*post residency*)?
   a.) Less than 5 years
   b.) 5-15 years
   c.) 15-25 years
   d.) Greater than 25 years

10) What type of environment do you currently work in? (please choose all that apply)

   a.) Solo practice
   b.) Hospital based practice – non-teaching
   c.) Hospital based practice – teaching

11) Please provide any additional information about your off-label prescribing practices for the researcher to consider.

Appendix B

Final Survey

Survey Instructions

By completing this survey, you consent for the researcher to use your answers for research purposes.

Please use the following definitions when responding to the survey questions:

Off-label: A medicine prescribed in a manner where the *dosage*, *age*, *indication* and/or *route of administration* are not indicated on the medicine's label (have not been approved by a health authority).[5]

Regularly: I perform this activity greater than 75% of the time.

Often: I perform this activity greater than half but less than 75% of the time.

Sometimes: I perform this activity greater than 25% but less than half of the time.

Rarely: I perform this activity less than 25% of the time.

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[5] Conroy, S. (2002). Unlicensed and off-label drug use: issues and recommendations. *Pediatric Drugs, 4* (6), 353-359.

Never: I do not perform this activity.

Strongly Agree: I agree most or all of the time.

Agree: I agree some of the time.

Neutral: I neither agree nor disagree.

Disagree: I disagree some of the time.

Strongly Disagree: I disagree most or all of the time.

Survey Questions

1. I use the following to determine whether or not to prescribe medicine to my patients:

	Regularly	Often	Sometimes	Rarely	Never
The medicine's label (prescribing information)					
Published, peer-reviewed research					
Reference Manuals (e.g. Physicians Desk Reference (PDR), etc.)					
Published, not peer-reviewed research					
Unpublished research					
My previous experience with the medicine					
My group/ hospital/ facility/ office's experience with the medicine					
Peer recommendations					
Information from pharmaceutical representative					
Patient insurance company					
Patient / guardian suggestion					
Patient / guardian request					

2. Once per month, at minimum, I prescribe medicines in the following categories in an *off-label* manner.

	Regularly	Often	Sometimes	Rarely	Never
Analgesics					
Anti-asthmatics					
Anti-epileptics					
Antibiotics					
Antihistamines					
Dermatologics					
Expectorants and anti-tussive agents					
Insulin					
Otologics					
Psycholeptic and psychoanaleptics					
Rhinologicals					

3. Once per month, at minimum, I prescribe medicines to patients in the following age ranges in an *off-label* manner.

	Regularly	Often	Sometimes	Rarely	Never
Less than 1 year old					
1-5 years old					
5-12 years old					
13-18 years old					
Greater than 18 years old					

4. In the last year, what is the percent of medicines that you prescribed off-label?

   - None
   - 25 %
   - 26 - 50%

- 51 - 75%
- 76 - 100%

5. Although the practice of medicine allows for physicians to prescribe medicines off-label, please complete the following section with regard to your beliefs about off-label prescribing.

	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree	I do not prescribe medicines off-label.
When I prescribe a medicine off-label, I am concerned about the legal liabilities.						
When I prescribe a medicine off-label, I am concerned that patients (or their guardians) will complain.						
I believe that physicians should not be legally allowed to prescribe medicines off-label.						

6. In what state do you practice medicine?

- New Jersey

- Tennessee
- Other _____

7. In which country did you:

	United States	If outside United States, enter name of country.	Not applicable
Attend Medical School?			
Complete First Residency?			
Complete Fellowship?			
Obtain Board Certification?			

8. Are you a: (please choose only one answer)
   - Pediatrician
   - Pediatric medical subspecialist
   - Pediatric surgical specialist
   - Other _____

9. How many years have you been a practicing physician (post residency)?
   - Less than 5 years
   - 5-15 years
   - 15-25 years
   - Greater than 25 years
   - I am a resident
   - None of the above

10. What type of environment do you currently work in? (please choose all that apply)
    - Solo practice
    - Group non-hospital based practice
    - Non-teaching hospital based practice
    - Teaching hospital based practice

11. Please provide any additional information about your off-label prescribing practices for the researcher to consider.

Appendix C

TNAAP Approval

November 4, 2008

Dear Ms. Catherine M. Fenner:

I am a doctoral candidate at Seton Hall University, School of Health and Medical Sciences and my dissertation topic is pediatric off-label prescribing practices.

The purpose of my dissertation research is to determine pediatrician off-label prescribing practices. Off-label prescribing occurs when a physician prescribes a drug in a manner where the dosage, age, indication and/or route of administration are not approved by a health authority (not indicated on the drug's label) (Conroy, 2002).

This confirms our conversation on <<date>>, that you will send an email invitation to complete an online survey, which I created and validated (Appendix 1), to the membership of the American Academy of Pediatrics, Tennessee Chapter (TNAAP). The survey will be placed on www.formsite.com, a survey-hosting website, which allows the members of your organization to complete it online and anonymously. The completion of the survey should take no longer than 10 minutes and will be available on the website for two months.

I will send you the initial invitation (Appendix 2) for your membership once the Seton Hall University Institutional Review Board (IRB) has approved my study. In addition, two weeks and four weeks after the initial invitation is sent, I will provide you with a follow-up invitation (Appendix 3) for all members of TNAAP who received the initial email.

As a token of my appreciation, please contact me at the email address below and I would be pleased to provide the results of my study to you or your membership, when available. Thank you, in advance, for your assistance with this study.

Sincerely,

Elizabeth G. Evola

ElizabethEvola@yahoo.com

865 824 9433

If you concur with this request, please sign and date this letter and return the original copy to me in the envelope provided. Again, thank you for your interest in the project.

Catherine M. Fenner, Executive Director

11/11/08

Date

Appendix D

NJAAP Approval

November 12, 2008

Dear Dr. Segarra:

I am a doctoral candidate at Seton Hall University, School of Health and Medical Sciences and my dissertation topic is pediatric off-label prescribing practices.

The purpose of my dissertation research is to determine pediatrician off-label prescribing practices. Off-label prescribing occurs when a physician prescribes a drug in a manner where the dosage, age, indication and/or route of administration are not approved by a health authority (not indicated on the drug's label) (Conroy, 2002).

This confirms our conversation on November 12, 2008, that you will send an email invitation to complete an online survey, which I created and validated (Appendix 1), to the membership of the New Jersey Chapter of the American Academy of Pediatrics (AAP/NJ). The survey will be placed on www.formsite.com, a survey-hosting website, which allows the members of your organization to complete it online and anonymously. The completion of the survey should take no longer than 10 minutes and will be available on the website for two months.

I will send you the initial invitation (Appendix 2) for your membership once the Seton Hall University Institutional Review Board (IRB) has approved my study. In addition, two weeks and four weeks after the initial invitation is sent, I will provide you with a follow-up invitation (Appendix 3) for all members of TNAAP who received the initial email.

As a token of my appreciation, please contact me at the email address below and I would be pleased to provide the results of my study to you or your membership, when available. Thank you, in advance, for your assistance with this study.

Sincerely,

Elizabeth G. Evola

ElizabethEvola@yahoo.com

865 824 9433

If you concur with this request, please sign and date this letter and return it to me. Again, thank you for your interest in the project.

Dr. Michael Segarra

AAP/NJ President

November 13, 2008

Appendix E

Seton Hall University IRB Approval

REQUEST FOR APPROVAL OF RESEARCH, DEMONSTRATION OR RELATED ACTIVITIES INVOLVING HUMAN SUBJECTS

All material must be typed.

PROJECT TITLE: *Off-label Prescribing: Pediatrician Beliefs and Experience*

CERTIFICATION STATEMENT:

In making **this application**, I(we) certify that I(we) have read and understand the University's policies and procedures governing research, development, and related activities involving human subjects. I (we) shall comply with the letter and spirit of those policies. I(we) further acknowledge my(our) obligation to (1) obtain written approval of significant deviations from the originally-approved protocol BEFORE making those deviations, and (2) report immediately all adverse effects of the study on the subjects to the Director of the Institutional Review Board, Seton Hall University, South Orange, NJ 07079.

Elizabeth Evola

RESEARCHER(S) OR PROJECT DIRECTOR(S) — DATE 1/21/09

**Please print or type out names of all researchers below signature.
Use separate sheet of paper, if necessary.**

My signature indicates that I have reviewed the attached materials and consider them to meet IRB standards.

RESEARCHER'S ADVISOR OR DEPARTMENTAL SUPERVISOR — DATE 1/21/09

Please print or type out name below signature

The request for approval submitted by the above researcher(s) was considered by the IRB for Research Involving Human Subjects Research ~~at the~~ in March 2009 ~~meeting.~~

The application was approved ✓ not approved ___ by the Committee. Special conditions were ___ were not ✓ set by the IRB. (Any special conditions are described on the reverse side.)

Mary F. Ruzicka, Ph.D. — DATE 3/25/09

DIRECTOR,
SETON HALL UNIVERSITY INSTITUTIONAL
REVIEW BOARD FOR HUMAN SUBJECTS RESEARCH

Appendix F

Initial Survey Invitation

Dear Pediatrician:

I am a Doctoral Candidate at Seton Hall University in the School of Health and Medical Sciences and I am studying pediatric off-label prescribing practices. You are receiving this email via the email distribution of the New Jersey or Tennessee chapter of the American Academy of Pediatrics.

The purpose of the study is to determine pediatrician off-label prescribing practices. Off-label prescribing occurs when a physician prescribes a drug in a manner where the dosage, age, indication and/or route of administration have not been approved by a health authority (not indicated on the drug's label) (Conroy, 2002).

The survey has been designed so that you can complete it anonymously via the following link: <link will be included here>. It should take no longer than 10 minutes of your time.

Your assistance is greatly appreciated and your response can be provided anonymously and will be kept confidential. As a token of my appreciation, please contact me at the email address below and I will provide the results of my study to you, when available.

Sincerely,

Elizabeth G. Evola

ElizabethEvola@yahoo.com

Appendix G

Two week follow-up Survey Invitation

Dear Pediatrician:

This email is a follow-up to an email that you received two weeks ago. I am a Doctoral Candidate at Seton Hall University in the School of Health and Medical Sciences and I am studying pediatric off-label prescribing practices. You are receiving this email via the email distribution of the New Jersey or Tennessee chapter of the American Academy of Pediatrics.

If you have already responded to my survey, I thank you very much for your time. If not, I would greatly appreciate it if you could assist me in my research by completing the short survey. As I explained in my previous email, I am looking to determine the attitudes and beliefs of pediatricians towards off-label prescribing, a practice that occurs when a physician prescribes a medicine in a manner that has not been approved by a health authority (i.e. not indicated on the drug's label) (Conroy, 2002).

The survey allows you to complete it anonymously via the following link: <link will be included here>. It should take no longer than 10 minutes of your time.

Your assistance is greatly appreciated. If you have already responded to my survey, again, I thank you very much for your time.

Sincerely,

Elizabeth G. Evola

ElizabethEvola@yahoo.com

Appendix H

Four week follow-up Survey Invitation

Dear Pediatrician:

This email is a follow-up to an email that you received about one month ago. I am a Doctoral Candidate at Seton Hall University in the School of Health and Medical Sciences and I am studying pediatric off-label prescribing practices. You are receiving this email via the email distribution of the New Jersey or Tennessee chapter of the American Academy of Pediatrics.

If you have already responded to my survey, I thank you very much for your time. If not, I would greatly appreciate it if you could assist me in my research by completing the short survey. As I explained in my previous email, I am looking to determine the attitudes and beliefs of pediatricians towards off-label prescribing, a practice that occurs when a physician prescribes a medicine in a manner that has not been approved by a health authority (i.e. not indicated on the drug's label) (Conroy, 2002).

The survey allows you to complete it anonymously via the following link: <link will be included here>. It should take no longer than 10 minutes of your time.

Your assistance is greatly appreciated. If you have already responded to my survey, again, I thank you very much for your time.

Sincerely,

Elizabeth G. Evola

ElizabethEvola@yahoo.com