Title

Putting Pediatric Off Label Prescribing on the Map: A Study to Understand which Children, Medications and Physicians are Involved in Prescribing Drugs for Unapproved Uses

Author

Bazzano, Alicia Theresa Francesca

Publication Date

2012

Peer reviewed|Thesis/dissertation

UNIVERSITY OF CALIFORNIA

Los Angeles

Putting Pediatric Off-Label Prescribing on the Map: A Study to Understand which Children, Medications and Physicians are Involved in Prescribing Drugs for Unapproved Uses

A dissertation submitted in partial satisfaction of the requirements for the degree Doctor of Philosophy in Health Services

by

Alicia Theresa Francesca Bazzano

2012

ABSTRACT OF DISSERTATION

Putting Pediatric Off-Label Prescribing on the Map: A Study to Understand which Children, Medications and Physicians are Involved in Prescribing Drugs for Unapproved Uses

by

Alicia Theresa Francesca Bazzano
Doctor of Philosophy in Health Services
University of California, Los Angeles, 2012
Professor Robert Brook, Chair

Background. Prescribing medications for an indication or age outside of the terms of U.S. Food and Drug Administration (FDA) approval is called off-label prescribing. In children, off-label prescribing has resulted in drug disasters and increased adverse events and has been the subject of recent legislation promoting medication study. Off-label prescribing appears to be a very common pediatric practice; nonetheless, the pharmacoepidemiology of off-label prescribing has not been systematically studied and could inform approaches to interventions.

Methods. The National Ambulatory Medical Care Surveys (NAMCS), a nationally representative population-based sample of U.S. outpatient medical visits collected by the Centers for Disease Control and Prevention (CDC) were utilized over a four-year period (2001-2004). We evaluated an estimated 312 million prescription visits by children 0-17 years old (based on a sample of 7901 prescription visits). FDA-approved age and indication were compared to the to

the child's age and diagnoses. Descriptive and regression analyses were used to determine epidemiological characteristics and predictors of: (1) pediatric off-label prescribing in general, (2) prescribing to infants and toddlers (0-3 yrs; *n*=81 million visits) and (3) off-label prescribing for age versus off-label prescribing for indication.

Results. Sixty-two percent of U.S. outpatient pediatric prescription visits included off-label prescribing, with 25% (95% CI: 23%, 27%) including off-label prescribing for age and 53% (95% CI: 50%, 56%) off-label prescribing for indication. Approximately 96% of cardiovascular-renal, 86% of pain, 80% of gastrointestinal, and 67% of pulmonary and dermatologic prescriptions were off-label. Anti-infectives, upper respiratory and pulmonary medications were much more commonly prescribed off-label for indication (41%, 52%, and 61%) than for age (6%, 16%, and 24%). For infants and toddlers, off-label prescribing occurred in 65% of prescription visits (52.7 million), with a higher risk of exposure to off-label prescribing for age than older children. Physician specialists were 14% (95% CI: 7%, 20%) more likely to prescribe off-label for age than general pediatricians or family physicians. Most top prescribed off-label medications have remained unchanged over time.

Conclusions. Despite legislation resulting in studies and labeling changes of pediatric medications, the majority of pediatric outpatient visits involve off-label prescribing, across all medication categories, to the youngest children, and especially by physician specialists, and with medications that are off-label for indication; this exposure is disproportionate compared to adults. Many off-label prescriptions are for medications with unproven benefit or safety concerns. FDA policies should be strengthened to require prioritized study of all medications commonly prescribed off-label; mandate patient registries to assess off-label prescribing over time; and provide physicians more accessible prescribing information. Medical education and

prescribing incentives and tools should target the most commonly off-label prescribed drugs. Future research should determine outcomes, causes, and appropriateness of off-label prescribing to children.

The dissertation of Alicia Theresa Francesca Bazzano is approved.

Rita Mangione-Smith

Gerald Kominski

Paul Chung

Robert Brook, Committee Chair

University of California, Los Angeles

2012

DEDICATION

This dissertation is dedicated to my children, Aurelio, Alessandro and Annabella. It is also dedicated to all of the other children in the U.S. and throughout the world who receive medications that have not been studied or approved for pediatric use. It is my great and immodest hope that this work will inspire change to decrease off-label prescribing to children.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ACKNOWLEDGMENTS

I would like to acknowledge my family, especially my loving husband, Ari Zeldin, and my mother, Gail Bazzano. I have always known that Ari, as our family's superhero, had my back. He cajoled and teased and did everything in his power to get this dissertation out of me. Luckily, my Mom was the one from whom I inherited the persistence and optimism to finish this project--she has shaped my work and life in so many other ways too. I owe them both thanks especially for taking our children to Sequoia National Park through a road closure at midnight so that I could complete the writing.

I am grateful to my children, Aurelio, Alessandro and Annabella, all born while I was working on this project, for their presence in reminding me why I should persevere. I am also appreciative that they allowed me the time stolen from them to complete this work. I wish I could give it back to them.

I am grateful to my sisters, Lydia and Alessandra, who went down this road before me. They both lifted me up during difficult times in writing and their examples led the way to this eighth doctorate in our family of five.

I am grateful to Rita Mangione Smith, M.D., M.P.H. for getting me off to a great start in scholarship, seeing me through all of the research and much of the writing, and spending a great deal of time and mental energy with me. Dr. Mangione-Smith is a gracious and amazing mentor and I am very lucky to have been under her wing for quite a long time.

I wish to thank my dissertation chair, Robert Brook, M.D., Sc.D., for so many years of inspiration and guidance. Dr. Brook's challenging and respectful method of teaching sharpened my reasoning skills and brought me to an understanding that there are often many right answers. He has taught lessons about science as well as about life and I feel so fortunate to have been

mentored by such an extraordinary person. The inspiration for this research and dissertation came from the Robert Wood Johnson Clinical Scholars Program that Dr. Brook headed at UCLA. Being a Clinical Scholar was one of the most important experiences of my life, transforming my thinking from linear to multi-modal and inspiring me to become a physician-scientist and hopefully a community leader.

I am grateful to past and present committee members, Stuart Schweitzer, Ph.D. and Gerald Kominski, Ph.D., who have contributed their expertise and their good-natured encouragement to improve my work. They have been steadfast in supporting me. Thanks to Paul Chung, M.D., M.P.H., who at the last minute agreed to join my committee and generously gave of his time and expertise in reviewing this dissertation.

To Matt Schonlau, Ph.D., a wonderful team member, supporter and friend, I owe a great deal of thanks for tremendous statistical expertise over these years and more importantly for gracefully coaxing me into continuing when I did not believe I could and then cheering me on until I was done.

To Marika Suttorp, M.S., I am incredibly grateful for many hours of formative statistical work on a demanding data set.

Special thanks go to Sonja Brion, M.D., whose friendship has sustained me for 19 years and whose clinical practice and practical ideas inspired much discourse that led to interesting points in the papers.

I would like to thank Sumner Yaffe, M.D., posthumously, for his contributions to my understanding of the field of pediatric clinical pharmacology, of which he is one of the founders and major contributors.

This research was generously supported and guided by the University of California, Los Angeles, Robert Wood Johnson Foundation Clinical Scholars Program and the STAR Program in the Department of Pediatrics. I wish to thank all of my colleagues and the staff in those programs for their contributions of time, friendship and skills.

VITA

EDUCATION

1997-1998 **University of California, Los Angeles, School of Public Health**
Masters in Public Health in Health Services, awarded June 1998

1993-1997 **University of California, Los Angeles, School of Medicine**
Doctor of Medicine, awarded May 1997

1993 Bioethics Intern; **Bioethics Resource Center, Office of the Director, Clinical Center, National Institutes of Health (NIH)**, Bethesda, MD

1987-1992 **Tulane University, Newcomb College**, New Orleans, LA
Bachelor of Science in Psychology, awarded May 1991
Bachelor of Arts in Philosophy, awarded May 1992

POSTGRADUATE TRAINING

2004-2007 **UCLA Specialty Training and Advanced Research (STAR) Fellowship**
Department of Pediatrics, UCLA David Geffen School of Medicine

2002-2004 **UCLA Robert Wood Johnson Clinical Scholars Program**
Clinical Scholar, Department of Pediatrics, UCLA David Geffen School of Medicine

1998-2001 **Cedars-Sinai Medical Center, Residency Training Program in Pediatrics**
Resident House Officer, UCLA David Geffen School of Medicine

PROFESSIONAL EMPLOYMENT

2010-present **Achievable Clinic, A Community Clinic for People with Developmental Disabilities and Their Families**
Chief Medical Officer

2006-present **Westside Regional Center, Department of Clinical Services**
Chief Physician, Consulting

2003-present **Harbor/UCLA Medical Center, Department of Emergency Medicine, Division of Pediatric Emergency Medicine**
Clinical Faculty, Pediatric Emergency Medicine

2001-2008 **Children's Hospital Los Angeles, Department of Pediatrics, Division of Emergency and Transport Medicine**
Attending Staff, Emergency Medicine/Transport; Pediatric Sedation Service

2001-2002 **St. John's Well Child Center**, Los Angeles, CA
Pediatric Provider, Per Diem

2001 **Dr. Alan Klein, A Medical Corporation**, Los Angeles, CA
Locum Tenens Pediatrician, November-December

RESEARCH FUNDING

2011-2014 Principal Investigator, California Mental Health Services Act Grant,
L.A. Transition-Age Youth Service Integration Project
Total award: $345,836

2011-2014 Principal Investigator, California Mental Health Services Act Grant,
Tool for Assessing Quality (TAQ) of Mental Health Care for People with Developmental Disabilities
Total award: $311,125

2011-2012 Co-Principal Investigator, HRSA Affordable Care Act: Health Center Planning Grant P04CS22998-01-00
The Achievable Clinic: A Community Clinic for Individuals with Developmental Disabilities and Their Families
Total award: $80,000

2010-2011 Co-Principal Investigator, NINR ARRA Funding: R21 NR0113322008-2011
PM-PREP: Peer Mentored Preparedness for Adults with Developmental Disabilities
Sub-award: $110,000

2008-2011 Principal Investigator, California Mental Health Services Act Grant
Los Angeles Mental Health and Developmental Disabilities Education Program
Total awarded: $377,268

2009-2010 Principal Investigator, Nordstroms Grant, *awarded $5,000*, Saucony Run for Good Grant
Families in Motion Program
Awarded $10,000

2008-2009 Principal Investigator, State Council on Developmental Disabilities, Community Program Developmental Grant
Teen Live Well and Get Fit Program
Total awarded: $88,957

2007-2009 Principal Investigator, Robert Ellis Simon Foundation Grant
Mindfulness Based Stress Reduction Program for Parents/Caregivers of Children with Developmental Disabilities
Total awarded: $56,000

2006-2008 Co-Investigator, Westside Regional Center, Intramural Grant
Understanding Knowledge, Attitudes and Treatment Practices of Parents of Children with Autism
Total awarded: $26,000

2005-2007 Co-Investigator, California Department of Developmental Services Wellness Grant
Health and Fitness Lifestyle Community Intervention for the Developmentally Disabled.
Total awarded: $128,604

2004-2006 Co-Investigator, California Department of Developmental Services Wellness Grant
Diabetes Management and Prevention for Consumers Living Semi-Independently: Improving Long Term Outcomes with a Comprehensive Diabetes Care Model.
Total Awarded: $152,308

MANUSCRIPTS

Bazzano, A., Zeldin, A. Schuster, E., Barrett, C., & Lehrer, D. (2012). Vaccine beliefs and practices of parents of children with autism spectrum disorders. *American Journal on Intellectual and Developmental Disabilities, 117*(3), in press.

Zeldin, A., & **Bazzano, A**. (2010, October). Mental retardation. *eMedicine by WebMD*. Available at http://emedicine.medscape.com/article/1180709-overview

Bazzano, A., Zeldin, A., Shihady, I., Garro, N., Allevato, N., Lehrer, D., & WRC Project Oversight Team. (2009). Outcomes of the healthy lifestyle change program for adults with developmental disabilities. *American Journal of Preventive Medicine*, 37(6 Suppl 1), 201-208.

Bazzano, A., Mangione-Smith, R., Schonlau, M., Suttorp, M., & Brook, R. (2009). Off-label prescribing to children in the United States. *Academic Pediatrics, 9*(2), 81-88.

Zeldin, A., Ratanawongsa, B., & **Bazzano, A**. (2007). Cerebral palsy. *eMedicine by WebMD*. Available at http://www.emedicine.com/NEURO/topic533.htm

Bazzano G, Terezakis N, Attia H, **Bazzano A**, Dover R, Fenton D, Mandir N, Celleno L, Tamburro M, & Jaconi S. (1993). Effect of retinoids on follicular cells. *Journal of Investigative Dermatology,* 101(1 Suppl):138S-142S.

ABSTRACTS/PRESENTATIONS

Bazzano, A., Jamora, J., Chen, W., Forte, J., Schuster, E., & Lehrer, D. (2011). Promoting healthy weight and nutrition among children with developmental disabilities: A pilot of the families-in-motion community-based intervention. Poster presented at the American Public Health Association meeting, Washington, D.C.

Bazzano, A., Schuster, E., Spatzier, A., Webb, P., Schallert, L., & Lehrer, D. (2011). The Los Angeles mental health and developmental disabilities education program: A cross-systems collaborative addressing the needs of individuals with dual diagnosis. Presented at the Association of University Centers on Disability conference, Washington, D.C.

Bazzano, A. (2011). The Los Angeles mental health and developmental disabilities education (LAMHaDDE) program. Presented at the Health Education Practice conference, Los Angeles, CA.

Bazzano, A. (2011). L.A. caring for individuals with developmental disabilities. Invited presentation to the L.A. Care Health Plan, Los Angeles, CA.

Bazzano, A., Jimenez, N., Chen, W., Garro, N., Schuster, E., Forte, J., & Lehrer, L. (2010). Teen scene program: Pilot of a community-based health intervention for teens with developmental disabilities. Presented at the American Public Health Association meeting, Denver, CO.

Bazzano, A., Wolfe, C., Zylovska, L. Wang, S., Schuster, E., Barrett, C., & Lehrer, D. (2009). Stress-reduction and improved well-being following a pilot community-based participatory mindfulness-based stress-reduction (MBSR) program for parents/caregivers of children with developmental disabilities. Presented at the American Public Health Association meeting, Philadelphia, PA.

Bazzano, A., Shihady, I., Garro, N., Lehrer, D., & Zeldin, A. (2008). Lifestyle modification following the healthy lifestyle change program, a novel community-based intervention for adults with developmental disabilities. Presented at the American Public Health Association meeting, San Diego, CA.

Zeldin, A., Barrett, C., Schuster, E., Lehrer, D., & **Bazzano, A**. (2008). Immunization practices among parents of children with autism and their relationship to immunization beliefs. Poster presented at the Pediatric Academic Societies meeting, Honolulu, HI.

Zeldin, A., Shihady, I., Garro, N., Lehrer, D., Eis, J., Bazzano, L., & **Bazzano, A**. (2008). Weight loss and dietary improvements following the healthy lifestyle change program, a community-based intervention for adults with developmental disabilities. Presented at the American Society for Nutrition meeting at Experimental Biology 2008, San Diego, CA.

Bazzano, A., Shihady, I., Garro, N., Lehrer, D., & Zeldin, A. (2008). Exercise effects of the healthy lifestyle change program, a novel intervention for adults with developmental disabilities. Presented at the American Heart Association meeting, Colorado Springs, CO.

Bazzano, A., Mangione-Smith, R., Suttorp, M., Schonlau, M., & Brook, R. (2007). National rates and predictors of off-label prescribing to infants and toddlers: Publication 7900.18. Presented as a poster at the Pediatric Academic Societies meeting, Toronto, CA.

Bazzano, A., Shihady, I., Garro, N., Lehrer, D., & Zeldin, A. (2006). The healthy change program: An intervention to decrease obesity and diabetes for adults with developmental disabilities. Presented at the Department of Developmental Services Wellness Conference, San Diego, CA.

Bazzano, A., Mangione-Smith, R., Schonlau, M., Suttorp, M., & Brook, R. (2005). Off-label prescribing to children: How often, what medications, and who gets them? Presented as a Platform Session at the meeting of the Pediatric Academic Societies, Washington, D.C.

Bazzano, A., Mangione-Smith, R., Yaffe, S., Schonlau, M., Suttorp, M., Laouri, M., McGlynn, E., & Brook, R. (2004). Understanding off-label prescribing to children. Presented at the annual meeting of the Robert Wood Johnson Clinical Scholars Program, Tucson, AZ.

Bazzano, A., Slavin, S., & Wilkes, M. (1998). Sexual assault: A medical school curricular intervention. Presented at the meeting of the American Association of Medical Colleges, New Orleans, LA.

CERTIFICATIONS/LICENSURE

American Board of Pediatrics	Board Certified, 2001, recertified 2008
Medical Board of California	License # A70658
Current	BLS, ACLS, PALS, and NRP certifications

PROFESSIONAL ORGANIZATIONS

American Academy of Pediatrics, Fellow	Academy Health
American Society for Bioethics and Humanities	American Medical Women's Association
American Public Health Association	Food and Drug Law Institute

PROFESSIONAL COMMITTEES

2010-present	California State Committee for the Protection of Human Subjects, Member
2004-present	Southern California Bioethics Committee Consortium member; 2004-2006 Legislative Reporter
2001-2009	Los Angeles County Medical Association/Los Angeles County Bar Association Ethics Committee member; 2004-2006 Legislative Liaison
2002-2008	University of California Los Angeles Bioethics Committee member
2002-2007	Children's Hospital Los Angeles Ethics Resource Committee member

HONORS AND AWARDS

2011	STAR Award for Outstanding Service, Westside Regional Center
2000	Good Beginnings Outstanding Resident Award for NICU Service
1997	Alpha Omega Alpha Honor Medical Society Membership
	Dean's Scholar Award for Outstanding Medical Student Thesis
1992	*Cum laude* honors in Psychology and Philosophy
1987-1992	Tulane University Dean's List and Tulane Scholar

CHAPTER 1: INTRODUCTION AND SPECIFIC AIMS

A Case Study

Anne was a 5-year-old girl needing an MRI of her brain to evaluate a possible seizure. Anne's parents were very concerned that the MRI would make her very anxious. They told her regular pediatrician of their concerns and, in response, the pediatrician prescribed Soma™ (carisoprodol), a muscle relaxant, telling Anne's mother to give her one-fourth tablet on the morning of the MRI. Anne's parents tried to cut the pill into quarters and gave it to Anne about one hour before the MRI, but they weren't sure that she took exactly one-fourth. When Anne arrived at the MRI suite, she was anxious and agitated. Due to the previously prescribed Soma, the attending physician did not provide further sedation. About halfway through the MRI, Anne became very sleepy--so somnolent that she had to remain in recovery for two extra hours, having her heart rate, blood pressure, respiratory rate and oxygen saturation monitored continuously. The attending physician shared with Anne's parents that Soma is a medication that has not been studied for use in children and does not have U.S. Food and Drug Administration (FDA) approval for use in children. In adult post-marketing studies, carisoprodol was associated with increased risk of seizures and sedation. Anne's parents asked, "How does this happen? Why did our pediatrician prescribe this medication for Annie?"

Prescribing Medications in an Unapproved Manner

When the FDA gives a license for a drug in the U.S., it is given for a certain indication in a certain sub-population. Once a drug is approved for any age group or indication, the FDA does not regulate the prescribing of the drug by physicians. A physician is able to use the medication for another age group, indication, dosage, population, or by a route of administration that is

different from that for which the drug was approved. The FDA considers such use part of the "practice of medicine" by the physician and does not interfere, but does state that the physician using a medication for a non-approved use has a "responsibility to be well-informed about the product and to base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product's use and effects" (U.S. Food and Drug Administration [FDA], 2011b). The prescribing of medicine that is used in circumstances other than the specific approved use, and thus has not been tested or approved by the FDA, is commonly called off-label or unlabeled prescribing (American Academy of Pediatrics Committee on Drugs [AAP], 1996). This may include the prescribing of a medication in an age, indication, dosage, route or manner that is not approved by the FDA.

Off-Label Prescribing in Adults

Off-label prescribing for an unapproved indication (or diagnosis) is widespread among physicians caring for adults (Radley, Finkelstein, & Stafford, 2006). Sometimes the scientific and clinical trial evidence clearly supports use and the medication label lags behind the available data. Physicians may be following the "standard of care" by prescribing medications for those off-label indications. This is the case, for example, in prescribing the tricyclic antidepressant amitriptyline for neuropathic pain (Saarto & Wiffen, 2007). Amitriptyline was originally studied and approved for depression but subsequent trials have shown its usefulness in diabetic neuropathy (Max et al., 1992) and other neuropathic pain syndromes. The makers of amitriptyline have not gotten FDA approval for any of these indications and FDA cannot require it; but physicians, who are aware of the evidence, prescribe the medication legally to patients.

On the other hand, studies indicate that 73-79% of off-label prescribing is for indications that do not have strong supporting evidence, such as a randomized clinical trial (Eguale et al.,

2012; Radley et al., 2006). Proponents of off-label prescribing describe this off-label prescribing without evidence of safety or efficacy as "innovative prescribing" and point to new approved drug uses that were discovered through this prescribing (Demonaco, Ali, & Hippel, 2006). However, this "innovative prescribing" has been found to be a challenge to quality of care and concerning for increased patient risk of adverse events with uncertain benefits (Ansani et al., 2006).

Off-Label Prescribing in Children

In adults, medications are often studied for safety and efficacy for one condition and then used for a different condition. In children, it has been estimated that up to two-thirds of medications on the market have never been tested for safety or efficacy and had no labeling for children (Demonaco et al., 2006). Moreover, we have very little knowledge in the U.S. about the magnitude of off-label prescribing to children--in other words, how commonly those untested and unlabeled drugs are prescribed.

Studies in Europe and the U.S. indicate a great deal of off-label prescribing in hospitalized children and certain subspecialties. For example, in Italy, a national study of hospitalized children found that 89% were exposed to off-label prescribing, mostly due to unapproved dosing/frequency (50%) and less often indication (7%) or age (7%) (Pandolfini et al., 2002). A multinational European study of prescribing in hospitals revealed that 46% of prescriptions were off-label or unlicensed, exposing 67% of pediatric patients, with substantial variation among hospitals and medications (Conroy et al., 2000).

In the U.S., the first study in the general pediatric inpatient setting found that 7% of medications were used off-label in a single hospital (Thompson & Helfin, 1987). Eiland and Knight (2006) subsequently found that one-third of prescriptions for hospitalized children in a

single teaching facility were off-label. In a 2007 report of patients in 31 children's hospitals across the U.S., Shah et al. (2007) found that 79% were prescribed medications that were off-label for age. In the pediatric emergency department setting, 43% of children received medications that were off-label for age (McKinzie, Wright, & Wrenn, 1997). Yoon and colleagues used prescription claims data and found that half of cardiovascular medications were prescribed to children younger than the labeled age (Yoon, Dombkowski, Rocchini, Lin, & Davis, 2007) despite less expensive on-label alternatives. Studies have also indicated that a large portion of psychotropic medication prescribing to children is off-label and without adequate testing in children (Pathak, West, Martin, Helm & Henderson, 2010; Zito et al., 2008).

European rates of off-label prescribing to children in the outpatient setting vary widely between countries, from 14% of prescriptions to Swedish children (Olsson, Kimland, Pettersson, & Odlind, 2011) to 26% in U.K. pediatric offices (Ekins-Daukes, Helms, Simpson, Taylor, & McLay, 2004) to 56% in a study of French pediatricians (Chalumeau et al., 2000). Data from Europe should be taken with caution, since prescribing practices may differ from the U.S. and especially in the U.K., with the National Health Service and its formulary, which restricts prescribing of certain medications.

The current literature has begun to describe the epidemiology of off-label prescribing to children in the U.S. and elsewhere. A few studies, like Shah's, have generated national data, but most have concentrated on single categories of medication, specialties, cities or hospitals. However, the vast majority of prescribing and medication utilization in children occurs in the outpatient rather than the inpatient setting. To date, no national studies have assessed how often and under what circumstances children are prescribed medications off-label at office visits in the

U.S. nor have studies addressed off-label prescribing for age in comparison with off-label prescribing for indication.

Why is Off-Label Prescribing Important?

Unlike in adult medicine, off-label prescribing to children is worrisome not only for concerns that the medication we give a child might not work (or efficacy concerns), but also that the medication might not be safe. In one ironic example, newborns who are exposed to sedative benzodiazepines (in itself off-label; Roche Pharmaceuticals, Inc., 2008a) and develop respiratory depression may receive the antidote flumazenil off-label as well without a proper, age-appropriate understanding of the effects, adverse events or dosing of either medication (Genentech, 2010).

Children who receive off-label prescriptions have a 2 to 3 times higher relative risk of adverse events (Horen, Montastruc, & Lapeyre-Mestre, 2002) and increased serious adverse events (Conroy, 1996) than children who received labeled medications. Because the medications have not been tested or approved, physicians may have few supports for prescribing. As clearly illustrated in Anne's case study, dosages are extrapolated from adults, drugs are formulated as pills and must be cut into pieces or liquefied, and drug interactions have not been studied. Further, no information is accruing for these prescriptions, which makes the next prescribing episode just as experimental (risky) as the last.

Children are not Little Adults and Infants are not Little Children when it Comes to Prescribing

Children of different ages react very differently to medications, and medications have differential effects based on age and physiology. Children have basic physiological differences

from adults, including heart rates that in the newborn period are more than twice as fast as in adults, and decrease to adult rates in the pre-teen years; blood pressures that are much lower than adults and may remain so until late adolescence; higher metabolic rates; and much larger head and skin surface area than adults. Pharmacodynamics (i.e., how medications affect the body) clearly diverge between children and adults. For example, sedating medications like benzodiazepines and diphenhydramine sometimes have a "paradoxical effect" on children and actually cause agitation and increased activity levels (Roche Pharmaceuticals, Inc., 2008b). Other medications may result in side effects unique to pediatrics, such as the tetracycline antibiotics, which cause tooth discoloration and dysplasia (Barr Laboratories, Inc., 2011). Differences in pharmacokinetics (i.e., how the body affects medications) between children and adults span all four stages of drug disposition: absorption, distribution, metabolism and excretion. When an infant ingests a drug, absorption patterns are affected by prolonged stomach-emptying time, decreased gastric acidity and larger small intestine surface area compared with those in adults (Novak & Aleen, 2007). Drugs may be more rapidly absorbed, such as beta-lactam antibiotics in young infants or more slowly, such as the anti-epileptic drug phenytoin (Woo, 2004). Children have thinner, more permeable skin and a much larger skin surface area relative to adults. If medications are absorbed through the skin, such as in topical preparations, greater absorption into the systemic circulation is a risk. For example, when infants and children have been exposed to high-potency topical steroids for diaper dermatitis or eczema, systemic absorption and adrenal axis suppression has led to Cushing's syndrome and deaths (Tempark et al., 2010). Infants' and children's higher body composition of water can affect drugs that are hydrophilic by increasing their volume of distribution and conversely affects lipophilic drugs by decreasing their volume of distribution (Alcorn & McNamara, 2003). In comparison to

adults, infants also have lower levels of serum proteins, which are needed for drug binding. Drug toxicities may result as the unbound form is increased in the circulation (Kearns & Reed, 1989). Over the course of a child's physiologic development, dramatic changes in intestinal microflora and hepatic enzymes occur (Rice & Barone, 2000). Maturation of drug metabolizing enzymes is variable and delayed maturation can result in decreased drug metabolism and toxicity, such as in the case of the antibiotic gentamicin, which requires therapeutic drug monitoring and reduced dosing frequency in the neonate (Rao, Srinivasjois, Hagan, & Ahmed, 2011). Finally, drug excretion through the kidneys is reduced in infants compared to that in children and adults due to decreased renal blood flow and tubular function (Novak & Aleen, 2007).

With all of the differences between children and adults, it might be surprising that the primary means of determining medication doses for children is by adjustment based on simply comparing adult body weight to the child's body weight. This is especially common when prescribing medications that have not received FDA approval for children (Steinbrook, 2002). Because neonates, infants and children exhibit physiological immaturity and vast differences in responses to medications, the weight-based method of determining dosing has led to poor outcomes, including overdose leading to toxicity and under-dosing leading to ineffectiveness (Alcorn & McNamara, 2003). Infants and young children are likely at the greatest risk of poor outcomes with this off-label prescribing, given their developmental vulnerability, furthest deviation in physiology from adults, and the severe lack of testing in this age group. Understanding the differences between children and adults in terms of pharmacokinetics and pharmacodynamics may lead one to consider why pediatric medications have not historically been tested for children.

Policy Context: The History of the FDA and Studying Medications for Children

The history of food and drug law is intimately intertwined with medication prescribing to children. In 1937, 107 Americans, mostly children, died due to a liquid preparation of the antibiotic sulfanilamide that was made with diethylene glycol (more commonly known as "antifreeze"; U.S. Food and Drug Administration [FDA], 1981). As a direct result of this pediatric tragedy, the Federal Food, Drug and Cosmetic Act of 1938 was enacted to ensure that medications are tested for safety before marketing (Federal Food, Drug and Cosmetic Act, 1938). Toxicity studies were required on all new medications to be sold in the U.S. Additionally, direct advertising was prohibited for use beyond the FDA-approved labeling. This fundamentally changed the role of the FDA from an after-event policing agency to a pre-marketing consumer regulatory agency. However, despite the children's drug-caused deaths from sulfanilamide, older medications and studies on children were excluded from these safety requirements. In 1962, thalidomide, a popular medication prescribed for a number of uses, including the prevention of morning sickness in pregnancy, was found to cause birth defects in thousands of European babies--20% of those who were exposed to the drug (McBride 1961). Following the thalidomide disaster, the Kefauver-Harris Drug Amendments were enacted to ensure the efficacy of medications before marketing (Federal Food, Drug and Cosmetic Act Amendments, 1962). The process of pre-clinical and human clinical trials was established, including phase I safety studies to determine safety and pharmacokinetics; phase II trials to determine safe dosing range; and phase III trials to determine efficacy and adverse events. In the 1960s, the antibiotic, chloramphenicol, caused the deaths of many newborns who developed "gray baby syndrome" as a result of hepatic and renal toxicity (Weiss, Glazko, & Weston, 1960). Subsequently, the FDA contracted with the National Academy of Sciences and the National Research Council in 1966 to

evaluate the effectiveness of 4000 medications approved based on safety alone between 1938 and 1962, establishing the FDA's role in surveillance and contracting for research studies. Nonetheless, the vast majority of these medications were never tested for children. In 1979, when pediatric information was mandated on drug labeling and prescribing information, "Safety and effectiveness have not been established in children" was included on most of those labels. In response to growing awareness of concerns regarding off-label prescribing to children, FDA allowed an easier path to pediatric labeling, requiring only establishment of a pediatric dosing regiment for medications in which the disease course was similar to adults (Coté, Kauffman, Troendle, & Lambert, 1996). In addition, the FDA in 1994 issued the "pediatric final rule," mandating that some drugs be tested for pediatric use. This rule came under scrutiny and was eventually overturned. However, in 2002, Congress acted to pass the Best Pharmaceuticals for Children Act (BPCA) and established significant incentives for testing in children (Best Pharmaceuticals for Children Act, 2002). Specifically, drug manufacturers were given an extension of six months market exclusivity in both children and adults before generics would be allowed. In addition, a list of drugs needing study was mandated to be published and the legislation provided for a foundation to fund the study of generic drugs. This was followed in 2003 by the Pediatric Research Equity Act (2003) that reinstated the pediatric rule and required that new molecular entities with an expected use in pediatrics be tested on children. In 2007, the BPCA was renewed and strengthened. The FDA's authority to make written requests was reaffirmed, a pediatric committee was convened to oversee drug development, and funding for study of generic drugs was increased.

Challenges to Improving Research and Labeling of Medications for Children

Even with these efforts to increase research, many challenges exist to studying pediatric medications. A reluctance to test medications on children is longstanding and originates with the cost of trials, scientific challenges, practical barriers, and historical ethical concerns regarding including children in clinical trials. Pharmaceutical manufacturers have generally viewed children's medications as a small portion of market share, given that adults take medications much more frequently and continuously than children (FDA, 2011a). It is hoped that the lack of perceived financial benefit was obviated to a certain degree due to the BPCA's exclusivity incentive (Roberts, Rodriguez, Murphy, & Crescenzi, 2003). Because children display such a wide range of age-dependent clinical responses to medications, trials must include measures that span age-ranges. For example, adult obesity is defined as having a body mass index (weight/height ratio) of 25 or more. In children, the BMI limit changes based on age and must be expressed as a z-score or percentile to describe difference from the average child. For mental health drugs, outcome measures must address age-dependent expressions of behavior. For example, an angry five year-old may throw a tantrum whereas an angry teenager may engage in vandalism. Clinical trials are more challenging to carry out in children than adults. Age-appropriate equipment, personnel with training in performing procedures on children, and family-centered environments are all needed (FDA, 2011a). Procedures that may seem standard to adults, such as drawing blood or obtaining urine, may be much more challenging in children. Other procedures, such as obtaining a computerized tomography (CT) scan, may entail increased risk in children compared with adults. Nonetheless, recent pediatric pharmaceutical networks and others have developed age-appropriate methods to address these scientific and practical issues. Finally, until recently, children were not included in clinical trials due to ethical concerns of

coercion. While adults may offer informed consent to participate in trials, children may not fully understand the risks, benefits and alternatives of the research and thus generally do not provide informed consent (Steinbrook, 2002). To ensure protection, the U.S. Office for Human Research Protections (OHRP) considers children a "vulnerable population" and requires special research regulations for children participating in studies (U.S. Department of Health and Human Services [HHS], n.d.). Overall, though barriers do exist, newer methodologies and protections have made the inclusion of children in clinical trials significantly more feasible.

Recent FDA policy measures have increased drug testing for children and labeling changes are occurring (Roberts et al., 2003), but limitations have been noted by academicians and the government (U.S. Government Accountability Office [GAO], 2011). The BPCA legislation is restricted, as FDA has only one opportunity to make a written request and this is negotiated with the drug companies. Responses to written requests are voluntary and no consequence occurs should study not be undertaken. In addition, only those medications that are thought to be profitable are likely to be tested (Walton et al., 2008) and even in the face of a 6-month exclusivity incentive, a pharmaceutical company may not wish to risk negative clinical trial results affecting drug sales for the lifetime of a medication (Stafford, 2008). For off-patent medications, of which there are many, a very small budget (approximately $2 million) substantially limits the ability of NIH to conduct trials on more than a few medications (Berenzy, Smith, & Benjamin, 2011).

The Utility of Understanding the Pharmacoepidemiology of Off-Label Prescribing to Children

Given the barriers to research and labeling of medications for children, it appears as though not every medication used off-label in children will be studied in a timely fashion. As a

result, prioritization of which drugs to be studied and in what populations and circumstances becomes a necessity until all medicines are required to be scrutinized for safety and efficacy in children.

Even after testing, the results may not be transmitted to the label and moreover the physicians prescribing may not become aware of the labeling change (Gazarian, 2003). When alternative labeled medications are available, physicians may continue to prescribe in an off-label manner (Pandolfini, Campi, Clavenna, Cazzato, & Bonati, 2005). In this case, understanding which physicians are prescribing to which children and under what circumstances may facilitate incentives and support for prescribing on label.

Beyond the Label: Physician Prescribing Practices and Theory

The complexity of physician off-label prescribing behavior indicates that a theoretical basis is useful in order to appropriately inform study. A prominent theory emerging on physician prescribing behavior is the Theory of Planned Behavior (Ajzen, 1991), which has its origins in the school of Social Learning and Theory of Reasoned Action (Bandura, 1998). It assumes that individuals have rationally processed information in order to decide on and carry out a behavior. Behavioral attitudes, perceived social norms and perceived behavioral control determine one's intention to act which in turn results in behavior. The major constructs are defined below:

- *Attitudes* are the individual's beliefs about and evaluation of the outcomes of his/her behavior; for example, whether the results of prescribing would be favorable based on past experience.
- *Subjective Norms* are the perceived social pressure to perform or not perform the behavior, or whether primary care physicians generally approve of prescribing medications for subspecialty issues and whether the physician is motivated by that approval.
- *Perceived Behavioral Control* is a person's belief of the ease or difficulty of the behavior or how much power she thinks she has over the behavior and how much is controlled by

outside factors. For example, whether health maintenance organization (HMO) policies would direct prescribing of a certain medication.

These theories have been increasingly applied to provider behavior with significant empirical success.

In some studies, an augmentation of this theory includes factoring in the patient and encounter, the organization and practice, and environment as independent factors that determine provider behavior (Rashidian & Russell, 2011). This may account for features of behavior that are not intended or that are outside of the physician's perceptions of factors that determine his/her behavior. A compilation of these factors was influential in the development of the current model.

Conceptual Model of Off-Label Prescribing

The components of theory may be used as a basis for concepts that may describe off-label prescribing (see Figure 1). For example, attitudes of the physician about off-label prescribing behavior may be affected by her background, available decision support and specific drug knowledge. Where and when the physician trained and practices may affect social norms. Risk aversion may influence the physician's perceived behavioral control.

Patient factors also have a role in decision-making. These characteristics work through their influence on physician beliefs, perceptions and behavior and include patient demographics and disease severity. For example, social norms may influence physicians toward prescribing off-label to a child with cancer for which there may be no on-label alternative.

Visit characteristics also may play a role in prescribing. One example of how the concept of perceived behavioral control is operationalized is sharing care. For example, if a physician shares care with another, she may feel she has less control over the prescribing.

Finally, health systems may have a direct or indirect effect on physicians' prescribing, which could be due to behavioral beliefs, norms within the organization, such as prescribing guidelines, or perceived power within the organization and therefore, perceived control.

Although not all of these factors may be studied at once, this framework assisted in selecting data sources that would include some of the factors.

Finding Data Sources for Off-Label Prescribing

Since no publicly available national databases specific to off-label prescribing exist, we explored the National Ambulatory Medical Care Survey (Centers for Disease Control and Prevention [CDC], 2012). This database constitutes a national probability sample survey conducted by the Centers for Disease Control and Prevention that can be used for national prescribing estimates. The intent of the survey is to provide information on content of U.S. health care visits and it uses a chart abstraction format that does include prescribing information. Specifically, physician offices participate yearly by completing a one page encounter form on approximately 30 randomly selected visits during one week. This form includes data on patient demographics, reason for the visit, diagnostic work up, up to three diagnoses, up to six medications, follow-up, and payment source. In addition, NAMCS includes some information on physician and health system characteristics.

Thus, many factors desirable for study in the conceptual model are included in NAMCS. Given that the study was not originally intended to evaluate off-label prescribing, not all factors that may be part of the decision to prescribe medications off-label are included.

Specific Aims of the Three Papers

There is a need to understand the scope of off-label prescribing so as to serve as a basis for policy and practice decisions. If off-label prescribing to children is an infrequent practice or restricted to certain types (e.g., indication or age) or patient, physician and medication characteristics, targeting those factors for study would be a reasonable approach. If off-label prescribing to children is ubiquitous or shows little variation across medications, prescribers or patients, a second look at the acceptability and rationale for off-label prescribing may be in order.

The specific aims of these three papers are as follows:

1. To determine the frequency of off-label prescribing to U.S. children and to determine which patient, physician, and visit characteristics are associated with off-label prescribing
2. To assess the pharmacoepidemiology of off-label prescribing to infants and toddlers
3. To compare frequencies and characteristics of off-label prescribing for age with off-label prescribing for indication in children.

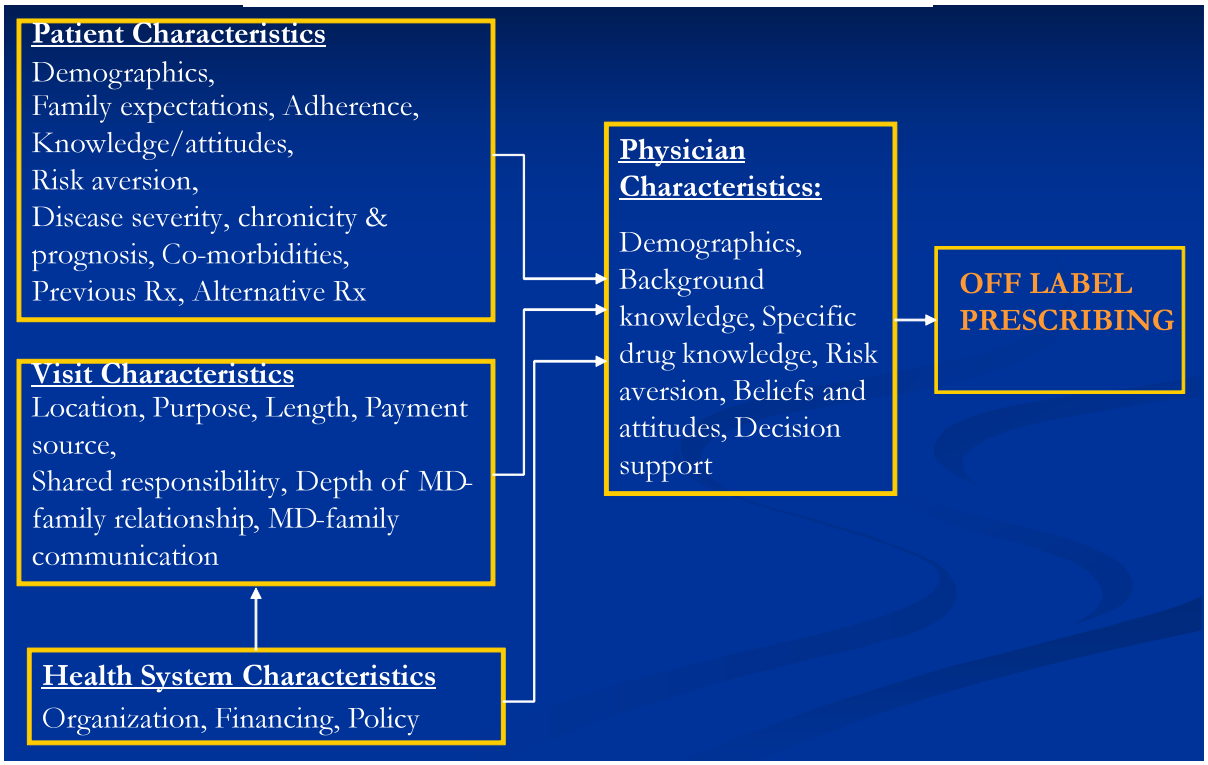

Figure 1. Conceptual model of factors influencing off-label prescribing to children.

References

Ajzen, I. (1991). The theory of planned behavior. *Organizational Behavior and Human Decision Processes, 50,* 179-211.

Alcorn, J., & McNamara, P. J. (2003). Pharmacokinetics in the newborn. *Advanced Drug Delivery Reviews, 55*(5), 667-686.

American Academy of Pediatrics Committee on Drugs (AAP). (1996). Unapproved uses of approved drugs: The physician, the package insert, and the Food and Drug Administration: Subject review. *Pediatrics, 98,* 143-145.

Ansani, N., Branch, R., Fedutes-Henderson, B., Smitherman, T., Weber, R. J., Skledar, S., . . . Sirio, C. (2006). United States medical practice summary: Innovative off-label medication use. *American Journal of Medical Quality, 21*, 246.

Bandura, A. (1998). Health promotion from the perspective of social cognitive theory. *Psychology & Health, 13,* 623-649.

Barr Laboratories, Inc. (2011). *Tetracycline hydrochloride capsule* [Package insert]. Pomona, NY: Author.

Berenzy, K., Smith, P. B., & Benjamin, D. K. (2011). Future of the NICHD Pediatric Trial Network. *e-Journal of Neonatology Research*, 1(2), 109-111.

Best Pharmaceuticals for Children Act. (2002). Pub L No. 107 109, 115 Stat 1408.

Centers for Disease Control and Prevention (CDC). (2012). *Ambulatory health care data.* Retrieved from http://www.cdc.gov/nchs/ahcd.htm

Chalumeau, M., Treluyer, J., Salanave, B., Assathiany, R., Cheron, G., & Crocheton, N. (2000). Off-label and unlicensed drug use among French office based paediatricians. *Archives of Disease in Childhood, 83,* 502-505.

Conroy, S. (1996). Association between license status and medication errors. *Archives of Disease in Childhood, 3,* 305-306.

Conroy, S., Choonara, I., Impicciatore, P., Mohn, A., Arnell, H., Rane, A., . . . van den Anker, J. (2000). Survey of unlicensed and off-label drug use in paediatric wards in European countries. European Network for Drug Investigation in Children. *British Medical Journal, 320*(7227), 79-82.

Coté, C. J., Kauffman, R. E., Troendle, G. J., & Lambert, G. H. (1996). Is the "therapeutic orphan" about to be adopted? *Pediatrics, 98*, 118-123.

Demonaco, H. J., Ali, A., & Hippel, E. (2006). The major role of clinicians in the discovery of off-label drug therapies. *Pharmacotherapy, 26,* 323-332.

Eguale, T., Buckeridge, D. L., Winslade, N. E., Benedetti, A., Hanley, J. A., & Tamblyn, R. (2012). Drug, patient, and physician characteristics associated with off-label prescribing in primary care. *Archives of Internal Medicine, 16,* 1538-3679.

Eiland, L., & Knight, P. (2006). Evaluating the off-label use of medications in children. *American Journal of Health-System Pharmacy, 63,* 1062-1065.

Ekins-Daukes, S., Helms, P. J., Simpson, C. R., Taylor, M. W., McLay, J. S. (2004). Off-label prescribing to children in primary care: Retrospective observational study. *European Journal of Clinical Pharmacology, 60*(5), 349-533.

Federal Food, Drug and Cosmetic Act (1938). PL 75-717, 52 Stat 1040.

Federal Food, Drug and Cosmetic Act Amendments (1962). PL 87-781, 76 Stat 780.

Gazarian, M., Kelly, M., McPhee, J. R., Graudins, L. V., Ward, R. L., & Campbell, T. J. (2006). Off-label use of medicines: Consensus recommendations for evaluating appropriateness. *Medical Journal of Australia, 185*(10), 544 548.

Genentech. (2010). *Romazicon prescribing information*. South San Francisco, CA: Author.

Horen, B., Montastruc, J., & Lapeyre-Mestre, M. (2002). Adverse drug reactions and off-label drug use in paediatric outpatients. *British Journal of Clinical Pharmacology, 54*, 665-670.

Kearns, G. L., & Reed, M. D. (1989). Clinical pharmacokinetics in infants and children: A reappraisal. *Clinical Pharmacokinetics, 17,* S29-S67.

Max, M. B., Lynch, S. A., Muir, J., Shoaf, S. E., Smoller, B., & Dubner, R. (1992). Effects of desipramine, amitriptyline, and fluoxetine on pain in diabetic neuropathy. *New England Journal of Medicine, 326*(19), 1250-1256.

McBride, W. G. (1961). Thalidomide and congenital abnormalities: Letter to the editor. *The Lancet, 2*, 1358.

McKinzie, J. P., Wright, S. W., & Wrenn, K. D. (1997). Pediatric drug therapy in the emergency department: Does it meet FDA-approved prescribing guidelines? *American Journal of Emergency Medicine, 15,* 118-121.

Novak, E., & Aleen, P. J. (2007). Prescribing medications in pediatrics: Concerns regarding FDA approval and pharmacokinetics. *Pediatric Nursing, 33,* 64-70.

Olsson, J., Kimland, E., Pettersson, S., & Odlind, V. (2011). Paediatric drug use with focus on off-label prescriptions in Swedish outpatient care: A nationwide study. *Acta Paediatrica, 100*(9), 1272-1275.

Roche Pharmaceuticals Inc. (2008a). *Ativan prescribing information* [Package insert]. Nutley, NJ: Author.

Roche Pharmaceuticals Inc. (2008b). *Valium* [Package insert]. Nutley, NJ: Author.

Pandolfini, C., Campi, R., Clavenna, A., Cazzato, T., & Bonati, M. (2005). Italian paediatricians and off-label prescriptions: Loyal to regulatory or guideline standards? *Acta Paediatrica, 94*(6), 753-757.

Pandolfini, C., Impicciatore, P., Provasi, D., Rocchi, F., Campi, R., Bonati, M., & Italian Paediatric Off-Label Collaborative Group. (2002). Off-label use of drugs in Italy: A prospective, observational and multicentre study. *Acta Paediatrica, 91*, 339-347.

Pathak, P., West, D., Martin, B. C., Helm, M. E., & Henderson, C. (2010). Evidence-based use of second-generation antipsychotics in a state Medicaid pediatric population, 2001-2005. *Psychiatric Services, 61*(2), 123-129.

Pediatric Research Equity Act of 2003. Pub L No. 108 155, 117 Stat 1936.

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

Rao, S. C., Srinivasjois, R., Hagan, R., & Ahmed, M. (2011). One dose per day compared to multiple doses per day of gentamicin for treatment of suspected or proven sepsis in neonates. *Cochrane Database of Systematic Reviews, 11*, CD005091.

Rashidian, A., & Russell, I. (2011). Intentions and statins prescribing: Can the theory of planned behaviour explain physician behaviour in following guideline recommendations? *Journal of Evaluation in Clinical Practice, 17,* 749-757.

Rice, D., & Barone, S., Jr. (2000). Critical periods of vulnerability for the developing nervous system: Evidence from humans and animal models. *Environmental Health Perspectives, 108*, 511-533.

Roberts, R., Rodriguez, W., Murphy, D., & Crescenzi, T. (2003). Pediatric drug labeling: Improving the safety and efficacy of pediatric therapies. *Journal of the American Medical Association, 290*, 905-911.

Saarto, T., & Wiffen, P. J. (2007). Antidepressants for neuropathic pain. *Cochrane Database of Systematic Reviews, 4,* CD005454.

Shah, S. S., Hall, M., Goodman, D. M., Feuer, P., Sharma, V., Fargason, C. Jr., . . . Slonim, A. D. (2007). Off-label drug use in hospitalized children. *Archives of Pediatrics & Adolescent Medicine, 161*(3), 282-290.

Stafford, R. S. (2008). Regulating off-label drug use-rethinking the role of the FDA. *New England Journal of Medicine, 358,* 1427-1429.

Steinbrook, R. (2002). Testing medications in children. *New England Journal of Medicine, 347*(18), 1462-1470.

Tempark, T., Phatarakijnirund, V., Chatproedprai, S., Watcharasindhu, S., Supornsilchai, V., Wananukul, S. (2010). Exogenous Cushing's syndrome due to topical corticosteroid application: Case report and review literature. *Endocrine, 38,* 328-334.

Thompson, D., & Heflin, N. R. (1987). Frequency and appropriateness of drug prescribing for unlabeled uses in pediatric patients. *American Journal of Hospital Pharmacy, 44,* 792-794.

U.S. Department of Health and Human Services (HHS). (n.d.). *Special protections for children as research subjects*. Retrieved from http://www.hhs.gov/ohrp/policy/populations/children.html

U.S. Food and Drug Administration (FDA). (1981). *Sulfanilamide disaster.* Retrieved from http://www.fda.gov/AboutFDA/WhatWeDo/History/ProductRegulation/SulfanilamideDisaster/default.htm

U.S. Food and Drug Administration (FDA). (2011a). *Drug research and children*. Retrieved from http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm143565.htm

U.S. Food and Drug Administration (FDA). (2011b). *Regulatory information.* http://www.fda.gov/RegulatoryInformation/Guidances/ucm126486.htm. Accessed April 12, 2012

U.S. Government Accountability Office (GAO). (2011). *Pediatric research: Products studied under two related laws, but improved tracking needed by FDA*. Retrieved from http://www.gao.gov/products/GAO-11-457

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

Weiss, C. F., Glazko, A. J., & Weston, J. K. (1960). Chloramphenicol in the newborn infant. A physiologic explanation of its toxicity when given in excessive doses. *New England Journal of Medicine, 262*, 787-794.

Woo, T. M. (2004). Pediatric pharmacology update. Essential concepts for prescribing. *Advance for Nurse Practitioners, 12*(6), 22-27.

Yoon, E. Y., Dombkowski, K. J., Rocchini, A., Lin, J.-J., & Davis, M. M. (2007). Off-label utilization of antihypertensive medications in children. *Ambulatory Pediatrics, 7*, 299-303.

Zito, J. M., Derivan, A. T., Kratochvil, C. J., Safer, D. J., Fegert, J. M., & Greenhill, L. L. (2008). Off-label psychopharmacologic prescribing for children: History supports close clinical monitoring. *Child and Adolescent Psychiatry and Mental Health, 2*, 24.

CHAPTER 2: OFF-LABEL PRESCRIBING TO CHILDREN IN THE UNITED STATES OUTPATIENT SETTING

Abstract

Objective. The aim of this study was to determine the frequency of off-label prescribing to children at U.S. outpatient visits and to determine how drug class, patient age, and physician specialty relate to off-label prescribing.

Methods. Data from the 2001 through 2004 National Ambulatory Medical Care Surveys (NAMCS) consisted of a sample of 7901 outpatient visits by children aged 0 through 17 years in which prescriptions were given, representative of an estimated 312 million visits. We compared FDA-approved age and indication to the child's age and diagnoses. We used multivariate logistic regression to determine adjusted differences in probabilities of off-label prescribing.

Results. Sixty-two percent of outpatient pediatric visits included off-label prescribing. Approximately 96% of cardiovascular-renal, 86% of pain, 80% of gastrointestinal, and 67% of pulmonary and dermatologic medication prescriptions were off-label. Visits by children aged <6 years had a higher probability of off-label prescribing (P<.01), especially visits by children aged <1 year (74% adjusted probability). Visits to specialists also involved a significantly increased probability (68% vs. 59% for general pediatricians, P<.01) of off-label prescribing.

Conclusions. Despite recent studies and labeling changes of pediatric medications, the majority of pediatric outpatient visits involve off-label prescribing across all medication categories. Off-label prescribing is more frequent for younger children and those receiving care from specialist pediatricians. Increased dissemination of pediatric studies and label information may be helpful to guide clinical practice. Further research should be prioritized for the

medications most commonly prescribed off-label and to determine outcomes, causes, and appropriateness of off-label prescribing to children.

Introduction

Off-label prescribing occurs when a child receives a medication that has not received FDA approval for the child's age or diagnosis. Off-label prescribing is concerning because of lack of information on medication safety, efficacy, and proper use in children (e.g. dosing, interactions). Furthermore, off-label prescribing has been associated with adverse drug events (Horen, Montastruc, & Lapeyre-Mestre, 2002; Ufer, Kimland, & Bergman, 2004). Recent legislation gave FDA authority to require evaluation of certain new drugs for children and to encourage evaluation of others through patent extensions (Best Pharmaceuticals for Children Act, 2002; Pediatric Research Equity Act of 2003). As a result, the FDA has reported an increase in the number of medications approved for use in children (Roberts, Rodriguez, Murphy, & Crescenzi, 2003). Nonetheless, little published information is available on how often physicians prescribe medications off-label to children, which types of medications physicians prescribe, which children receive these off-label medications, and which physicians are prescribing off-label.

Worldwide reported rates of off-label prescribing to children range from 11% to 79% (Chalumeau et al., 2000; Ekins-Daukes, Helms, Simpson, Taylor, McLay, 2004; McIntyre, Conroy, Avery, Corns, & Choonara, 2000; Roberts et al., 2003; Shah et al., 2007). One recent U.S. study reported that 79% of children admitted to tertiary care children's hospitals received off-label prescriptions (Shah et al., 2007). This study and others have described variation in off-label prescribing across drug category and patient age, but methodology and results are inconsistent, with some indicating, for example, that respiratory medications are most often

prescribed off-label (Horen et al., 2002) and others concluding that topical preparations are most often prescribed off-label (Ufer, Rane, Karlsoon, Kimland, & Bergman, 2003). Studies also differ with regard to age of children receiving off-label medications (Ekins-Daukes et al., 2004; Schirm, Tobi, & de Jong van den Berg, 2003). Some studies indicate that physician specialists prescribe off-label to children more frequently (Schirm et al., 2003). Prior investigations have been limited by small sample size (Bajcetic et al., 2005), single U.S. or international geographic location (Eiland & Knight, 2006; McKinzie, Wright, & Wrenn, 1997), examination of prescribing for a single or limited set of conditions (Chen, Reeves et al., 2006; Yoon, Dombkowski, Rocchini, Lin, & Davis, 2007), exclusive focus on the inpatient setting (Eiland & Knight, 2006); Shah et al., 2007) and lack of control for other potential explanatory variables (Yoon et al., 2007).

Research and policy interventions may benefit from understanding which children receive which medications off-label at outpatient visits. Educational interventions could be better targeted if the types of physician specialists who most often prescribe off-label were known. Because most prescribing to children occurs during office visits, we chose to study outpatient prescribing. Thus, our study seeks to answer the following questions: (1) what is the frequency of off-label prescribing for age and indication to U.S. children in the outpatient setting? (2) what is the relationship between off-label prescribing and drug category, patient age, and physician specialty?

Methods

Data Sources

We used data from the 2001 through 2004 National Ambulatory Medical Care Surveys (NAMCS; Cherry, Burt, & Woodwell, 2003), conducted by the Centers for Disease Control and

Prevention (CDC), National Center for Health Statistics, to provide nationally representative information on the content of office-based physician visits in the U.S. NAMCS used a 3-stage probability design that sampled geographic areas, then practicing physicians within geographic areas, then patient visits among physicians. The design included sampling weights, which permit estimations at the national population level and comparisons among subgroups. NAMCS took a random sample of all U.S. non-federally employed physicians (excluding anesthesiologists, radiologists, and pathologists) who are primarily engaged in "office-based patient care" as classified by the American Medical Association or the American Osteopathic Association, which compile lists of all licensed physicians regardless of organizational affiliation. In 2001 through 2004, 5501 physician offices (64%-70% of those eligible) participated in the NAMCS by completing a one page encounter form on a systematic random sample of approximately 30 patient visits during a randomly assigned 1-week period (Cherry et al., 2003). This form included data on patient demographics, reason for the visit, diagnostic workup, diagnoses (up to three), medications (up to six), and follow-up. Non-response rates for NAMCS data are generally less than 5%. We analyzed visits from the NAMCSs by children aged <18 years during which a medication available by prescription was given (prescription visits). Visits were excluded if the following treatments were given: vaccines, vitamins, over-the-counter medications, nutritional products, nonspecific treatments (e.g. "antibacterial agent"), non-medications (e.g. infant oil, soap), and rarely prescribed medications (e.g. chloramphenicol, domperidone).

Dependent Variable: Off-Label

We constructed dichotomous variables describing whether or not the visit involved off-label prescribing. A visit was considered off-label for age or indication if at least one prescription at the visit was off-label for age or indication. A prescription was off-label for

age when the child's age was less than the youngest FDA-approval age for the drug regardless of indication. A prescription was considered off-label for indication when none of the visit diagnoses corresponded to an FDA-approved indication. FDA-approved indications were converted to International Classification of Disease, 9th Revision, Clinical Modification codes (World Health Organization [WHO], 2006), which were cross-matched with the NAMCS physician diagnosis variable to ensure inclusion of all plausible diagnoses. For consistency across data years, we used the latest available medication prescription information obtained from the label (also known as the package insert), Physician's Desk Reference (Physician's Desk Reference, n.d.), FDA website (Center for Drug Evaluation and Research, Food and Drug Administration [CDER, FDA], n.d.), or other compendia (Micromedex, 2004) as of September 1, 2007. For generic equivalents for which children's prescribing information was unavailable, branded drug data were substituted.

The frequency of off-label prescribing at visits was defined as the number of visits in which at least one off-label medication was prescribed. The proportion of visits with at least one off-label prescription was determined by dividing the visits in which an off-label prescription was provided by the total number of visits in the sample. Frequencies and proportions for specific age groups and drug categories were derived using the same general method.

Key Independent Variables

Patient Age

We categorized patient ages as follows: infant (aged <1 year), toddler (aged 1 to <2 years), preschool (aged 2 to <6 years), school age (aged 6 to <12 years), and adolescent (aged 12 to <18 years). This classification closely follows FDA age categories.

Drug Category

We reviewed all NAMCS drug names for accuracy, combining drugs (e.g., Azma-cort and Azmacort) that had been missed by NAMCS to ensure precise drug counts. We used NAMCS drug categories, based on National Drug Code (NDC) Directory classifications, which broadly categorize drugs by their uses. Medication names and NDC classifications are searchable on the CDC website (National Center for Health Statistics [NCHS], n.d.). We did not change drug category based on potential off-label uses of a medication. For example, diuretics were included as cardiovascular-renal medications, even though they might be used off-label for neonatal chronic lung disease. We reclassified some NAMCS drug categories due to sample size limitations and drug similarities. Specifically, we combined anti-parasitics with antimicrobials, and from the respiratory tract category, we separated upper respiratory drugs (i.e., otic, cough, cold, and allergy preparations) from pulmonary drugs (e.g. asthma medications). We performed bivariate analyses but did not include the drug category variable in our multivariate modeling because our regressions were at the visit level rather than prescription level.

Physician Specialty

NAMCS includes 15 self-reported physician specialties, which are based on American Medical Association and American Osteopathic Association categories. We collapsed the variable, simplifying specialties to include family medicine/general practice, general pediatricians, and all other specialties (adult and pediatric).

Covariates

Initial model covariates were derived from existing empiric literature (Schirm et al., 2003; ‘t Jong, Eland, Sturkenboem, van der Anker, & Stricker, 2003) and theory on physician prescribing behavior (Carrin, 1987), and included the following patient characteristics: gender, race/ethnicity (combined variable), region of the country (Northeast, Midwest, South, West),

urban or rural, and presence of one or more chronic conditions (based on whether the patient's diagnoses correspond to a list of chronic and severe pediatric conditions [Kuhlthau, Beal, Ferris, & Perrin, 2002]). Visit covariates included expected payment source (categorized as private insurance, Medicaid, self-pay, or other), number of visits in the past 12 months (0, 1–2, 3 or more), whether the patient was referred for the visit (yes or no), whether the physician shared care for the problem with another provider (yes or no), and number of prescriptions given at the visit (1, 2, or 3-6; 't Jong et al., 2003). Physician covariates included type of office setting and whether or not the physician was the patient's primary care physician ('t Jong et al., 2003). We excluded variables from our final model if the bivariate analyses revealed *P*-values >.1, unless theoretical concerns justified their inclusion.

Statistical Analysis

We derived national estimates from this probability survey by using sampling weights provided in NAMCS. These weights reflected the probability of selecting the primary sampling unit (geographic area), the probability of selecting a physician within the area, and the probability of selecting a patient visit within the physician's practice. Sampling weights compensate for overrepresentation and underrepresentation in the sampling design. By correcting for unequal probabilities of selection, they enable unbiased national estimates regarding the approximately 880 million outpatient visits in the U.S. each year. Our analyses also took into account stratification and clustering of visits within geographic area and within physician by using the masked design variables that NAMCS supplies to estimate standard errors via Taylor linearization. By correcting for clustering, we accounted for the non-independence of visits within an area or physician, which otherwise could have artificially decreased standard errors in regression analyses.

Multivariate logistic regression modeling was used to determine whether patient age and physician specialty were associated with off-label prescribing for age or indication. These analyses were performed at the visit level. We calculated odds ratios and 95% confidence intervals (CI) for all independent variables in our multivariate regression models. Then, to describe the independent probability that each variable was associated with off-label prescribing with all other variables held constant, we determined multivariate adjusted differences in probabilities with bootstrapped CIs. All analyses were performed using Intercooled Stata 9.0 (StataCorp LP, College Station, TX). Statistical significance was predetermined as $P<.05$.

Results

Characteristics of the estimated 312 million visits by children during 2001 to 2004 in which at least one medication was prescribed (prescription visits) are presented in Table 1. Forty-eight percent of visits were by females; 71% of visits were by white children, with 14% by Hispanics, and 10% by black children. Two thirds of visits were by patients with private insurance, with 23% having Medicaid. Fifty-eight percent of visits were to general pediatricians and 25% were to general practitioners or family physicians. At 62% of prescription visits (95% CI, 61%–64%), children received at least one off-label prescription for age or indication, so that children were exposed to medications outside of their FDA-approved use during 193.5 million visits (95% CI, 189–200 million) in 2001 to 2004. Over 90% of prescriptions for cardiovascular-renal medications and over 80% of prescriptions for pain and gastrointestinal were off-label for age or indication (Figure 2). Two thirds of pulmonary and dermatologic prescriptions were for off-label uses. Anti-infective medications were prescribed off-label least often (42% of anti-infective prescriptions).

Table 2 describes the top five medications most commonly prescribed off-label within each major medication category. Almost 30% of prescriptions were for anti-infective medications, and amoxicillin, azithromycin (Zithromax; Pfizer Inc, New York, NY), amoxicillin/clavulanate (Augmentin; GlaxoSmithKline plc, Brentford, Middlesex, UK), cephalexin (Keflex; MiddleBrook Pharmaceuticals Inc, Germantown, MD), and cefpodoxime (Omnicef; Abbott Laboratories, Abbott Park, Ill) were the anti-infective medications most often prescribed off-label. Upper respiratory medications composed the second largest portion of prescriptions (17% of prescriptions). The most often prescribed off-label within this category included the antihistamines, cetirizine (Zyrtec; Pfizer Inc), loratadine (Claritin; Schering-Plough Healthcare, Kenilworth, NJ), promethazine (Phenergan; Baxter Healthcare, Deerfield, Ill), and the nasal steroids mometasone (Nasonex; Schering-Plough Healthcare) and fluticasone (Flonase; GlaxoSmithKline plc). Central nervous system medications represented the third most often prescribed category (15% of prescriptions). The antidepressants paroxetine (Paxil; GlaxoSmithKline plc) and sertraline (Zoloft; Pfizer Inc), the antipsychotic risperidone (Risperdal; Ortho- McNeil-Janssen Pharmaceuticals Inc, Titusville, NJ), and the stimulants methylphenidate extended-release (Concerta; Ortho-McNeil-Janssen Pharmaceuticals Inc) and amphetamine-mixed salts (Adderall; Shire Pharmaceuticals, Wayne, Pa) comprise the central nervous system medications most commonly prescribed off-label. The pulmonary medications most commonly prescribed off-label included albuterol, montelukast sodium (Singular; Merck & Co Inc, Whitehouse Station, NJ) and levalbuterol (Xopenex; Sepracor, Marlborough, Mass). Within the cardiovascular-renal medications, physicians prescribed clonidine most often off-label. Much of the gastrointestinal off-label prescribing was due to prescriptions for polyethylene glycol (MiraLax; Schering-Plough Healthcare).

Multivariate logistic regression revealed that children aged 6 to <12 had a 59% adjusted probability of receiving at least one prescription not FDA-approved for their age or diagnosis at U.S. visits (Table 3). Compared with this group, visits by children aged <1 year had a 74% adjusted probability of involving an off-label prescription, visits by 1 to <2-year-old children had a 67% adjusted probability of off-label prescribing, and visits by 2 to <6 year olds had a 65% adjusted probability of off-label prescribing (P<.001). Children who received more than one drug were also significantly more likely to receive off-label prescriptions (26%–39% increased probability depending on number of drugs received; P<.001). Visits by children with chronic diseases were slightly less likely to result in off-label prescriptions (60% adjusted probability) than visits by children without chronic diseases (64% adjusted probability).

Children visiting general pediatricians had a 59% adjusted probability of receiving drugs prescribed off-label. Those visiting family physicians had a 63% probability of receiving off-label prescriptions. The adjusted probability of off-label prescribing was 68% for children visiting physicians of other specialties, resulting in a 5% increased probability as compared with family physicians (95% CI, 2%-8%). No other characteristics examined were significantly associated with off-label prescribing.

Discussion

Physicians prescribe medications off-label to children at the majority of physician visits in the U.S. outpatient setting. Despite evidence of an association between off-label prescribing to children and increased adverse events (including those requiring treatment or those that are potentially life threatening; Horen et al., 2002; Turner, Nunn, Fielding, & Choonara, 1999) no U.S. studies have followed children who receive off-label medications to examine outcomes longitudinally. The substantial number of children exposed to off-label prescriptions, even

several years after FDA regulations strengthening pediatric drug labeling requirements, suggests the need for such studies.

Some of the medications most commonly prescribed off-label in the current study are widely used medications for which little evidence exists of harm to children. For example, the off-label use of albuterol was quite common. The long history of albuterol use without indications of serious adverse events may serve as a rationale for pediatric off-label use. However, several drugs like albuterol, which were once commonly used off-label in children, later were found to be ineffective or have serious side effects when systematically studied. For example, physicians used cisapride off-label for gastric motility in neonates and infants before links to life-threatening arrhythmias resulted in its voluntary withdrawal (Henney, 2000). Similarly, promethazine, one of the medications most commonly prescribed off-label in our study, more recently received a black box warning in 2005 for children aged under two years due to respiratory depression and death (Starke, Weaver, & Chowdhury, 2005). Other drugs used widely off-label for children, the antidepressants paroxetine (Paxil; Glaxo-SmithKline plc) and citalopram (Celexa; Forest Pharmaceuticals Inc, New York, NY), as of 2005 have black box warnings for suicide in children (CDER, FDA, 2004). The dermatologic medication pimecrolimus (Elidel; Novartis Pharmaceuticals, Basel, Switzerland) received black box warning in 2006, stating that it is not indicated in children aged under two years (Novartis Pharmaceuticals Corp., 2007). Finally, 27 years after approval of albuterol (Ventolin HFA), in March 2008 the FDA reported that safety and effectiveness of albuterol with or without a spacer device has not been established for children aged younger than four years, based on three randomized, double-blind placebo controlled studies with 250 children aged younger than four years with dosing from 90 mcg to 360 mcg HFA in which efficacy was not demonstrated (U.S.

Food and Drug Administration [FDA], n.d.). These examples highlight potential adverse outcomes of off-label prescribing and emphasize the need for systematically evaluating safety and efficacy, even when drugs have been widely used off-label for some time. Though all medications deserve a second look for safety and efficacy after long-term and widespread use, medications used off-label extensively in children should be prioritized because they have not received even initial FDA scrutiny.

We found substantial variation in off-label prescribing by drug category, which was driven by several key medications and conditions. Much of the off-label prescribing of anti-infectives and upper respiratory medications was for the common cold and unspecified upper respiratory infections (URI). Many physicians describe antibiotic prescribing for a diagnosis of URI as "overuse." At the same time, off-label use applies because antibiotics are not FDA-approved for viral infections. Previous literature has documented such use (Nyquist, Gonzales, Steiner, & Sande, 1998) and lack of evidence for its effectiveness (Arroll, & Kenealy, 2005). Given recent safety concerns regarding use of over-the-counter cough and cold preparations in young children (Centers for Disease Control and Prevention [CDC], 2007), the frequency of off-label use of prescription upper respiratory medications implies that scrutiny of these medications is also warranted.

Physicians commonly prescribed several psychoactive medications off-label, including antidepressants and atypical antipsychotics, a result consistent with other studies showing a high prevalence and increasing use of off-label psychotropic medications in children (Cooper et al., 2006; Zito et al., 2000). Such use is known to be out of proportion with the evidence base for psychotropic medications in children (Bhatara, Feil, Hoagwood, Vitiello, & Zima, 2004; Findling, Steiner, & Weller, 2005). The long-term effects of many off-label central nervous

system medications in children have not been evaluated, and some studies suggest that more adverse drug reactions occur in pediatrics (King, Zwi, Nunn, Longworth, & Dossetor, 2003; Sikich, Hamer, Bashford, Sheitman, & Lieberman, 2004). Given the limited evidence for safety and effectiveness of these medications, further evaluation of these drugs in children and efforts to examine the circumstances in which this prescribing occurs are needed.

Nearly all cardiovascular-renal medication prescriptions were off-label. This result was due primarily to use of clonidine both for children younger than the FDA-approved age and for children with non-cardiac diagnoses, for example, possibly for behavioral conditions or insomnia. Much of the gastrointestinal off-label prescribing was accounted for by use of polyethylene glycol (MiraLax), which is not approved for children, for constipation. Thus, the relatively small number of medications and conditions that account for a significant portion of off-label prescribing suggest focused targets for research.

Many of the medications most often prescribed off-label in our study (21 of 50) have undergone testing in children and/or had labeling changes from 2000 to 2007 under efforts of the FDA to improve pediatric drug information (FDA, n.d.). Our results, which take these labeling changes into account, indicate that pediatric practice urgently needs wider dissemination of the pediatric studies completed under the FDA authority and of these labeling changes. Some labels have not undergone changes although studies indicate effectiveness. For example, studies suggest that montelukast, which was frequently prescribed off-label, is effective for perennial allergic rhinitis, though this is not a labeled indication (Chen, Lu, & Sun, 2006). Additionally, five medications from the most common (azithromycin, hydrocortisone, methylphenidate [Concerta], clonidine, and furosemide [Lasix]) were included on the FDA/National Institute of Child Health and Human Development priority list of drugs for which pediatric studies are

needed, but all remained incomplete (National Institute of Child Health and Human Development, 2007). The frequency of off-label use of these and other off-patent medications may provide information to further guide efforts at prioritization of pediatric studies and labeling changes.

Younger children in our study were more likely to receive off-label medications, especially children aged less than two years. Few medications are tested or approved in this age group (Giacoia, Birenbaum, Sachs, & Mattison, 2006), giving physicians limited choices for medications approved for young children. Given the difficulties in enrolling young children in studies, this group likely will continue to be understudied by pharmaceutical manufacturers. The results of the upcoming National Institutes of Health Neonatal Drug Initiative (Giacoia & Mattison, 2005), as well as improving post-marketing data, may help to bridge this evidence gap.

Off-label prescribing varied by physician specialty; non-general pediatricians were more likely to prescribe off-label than general pediatricians, a result consistent with a prior study (Radley, Finkelstein, & Stafford, 2006; Schirm et al., 2003). When treating adults, physicians frequently prescribe medications off-label (Radley et al., 2006). Additionally, non-pediatric physicians sometimes lack familiarity with FDA approval ages or indications of certain drugs (Li, Jaffe, Li, & Haynes, 1998). Common sources of pediatric prescribing information, such as the Harriet Lane Handbook (Robertson & Shilkofski, 2005), do not always distinguish the FDA-approved age and indications from dosing for children younger than the approved age. This suggests that an information gap may hinder physicians caring for children, and provision of more accessible and comprehensive pediatric prescribing resources may ameliorate some off-label prescribing.

Limitations

The use of the NAMCS database for this study presented several limitations. Some variables that may explain off-label prescribing, such as physician and family attitudes, previously used medications, and the context of the visit, are not included in NAMCS. Without these variables and other further scrutiny, we cannot determine appropriateness of specific instances of off-label use. NAMCS data rely on International Classification of Disease, 9th Revision, Clinical Modification coding of physicians' diagnoses, which may be imprecise. For example, with "unspecified URI," a physician could have intended "sinusitis," for which antibiotics may be indicated. Though we coded indications broadly, we cannot be sure that every indicated diagnosis was included. Additionally, for 3% of medications in our sample, different approval ages exist for different indications. For example, fluoxetine is approved for age eight years for obsessive compulsive disorder, but age 18 years for depression. We used the lowest age for FDA approval because NAMCS data did not allow determination of which particular indication a particular drug was prescribed. Thus, we used age eight years for any child prescribed fluoxetine. As a result, we may have somewhat underestimated the frequency of off-label prescribing for age, particularly for central nervous system drugs, which most commonly had two approval ages. NAMCS data provided visit-based rather than patient-based estimates and do not account for potential repeat visits. Thus, these data are not intended for extrapolation to the patient level. Additionally, labeling of medications is a dynamic process, and our data do not reflect changes after September 2007. Nonetheless, this study may provide baseline data for monitoring trends in off-label prescribing to children. Despite these limitations, NAMCS is well known as a reliable database that has been frequently used by previous studies to estimate prescribing (Thomas, Conrad, Casler, & Goodman, 2006).

Conclusions

This study demonstrates a large extent of off-label prescribing to children. In view of legislation intended to strengthen pediatric labeling and therefore decrease off-label use, the high incidence of off-label prescribing across multiple drug categories leads us to propose that dissemination of up-to-date pediatric prescribing information should be a national priority. Research efforts should target the unstudied medications and conditions that account for some off-label prescribing. Further research should also focus on determining the circumstances of off-label prescribing and its appropriateness. Development of guidelines for appropriate off-label prescribing may help to inform clinical practitioners.

Table 1. Characteristics of U.S. Outpatient Pediatric Prescription Visits from 2001-2004*

Characteristic	Visits, %*	95% CI*
Patient gender		
Female	48	46-49
Patient race/ethnicity		
White	71	68-75
Hispanic	14	11-18
Black	10	8-11
Other	5	4-6
Patient age		
0 - <1 year	10	9-11
1 - <2 years	10	9-11
2 - <6 years	23	22-25
6 - <12 years	28	27-30
12 - <18 years	29	27-31
Any chronic diseases		
Yes	25	23-27
Payment source		
Private insurance	67	65-70
Medicaid	23	21-26
Self-pay	4	3-5
Other (Medicare, military, etc.)	6	5-7
Number of prescription medications		
1	63	62-65
2	24	23-25
3-6	13	11-14
Physician specialty		
General pediatrics	58	54-61
General or family practice	25	22-28
Other specialties	17	15-20

**Based on weighted sample from National Ambulatory Medical Care Survey. Unweighted *n*=7901, weighted *n*=312,079,000.
†CI indicates confidence interval.

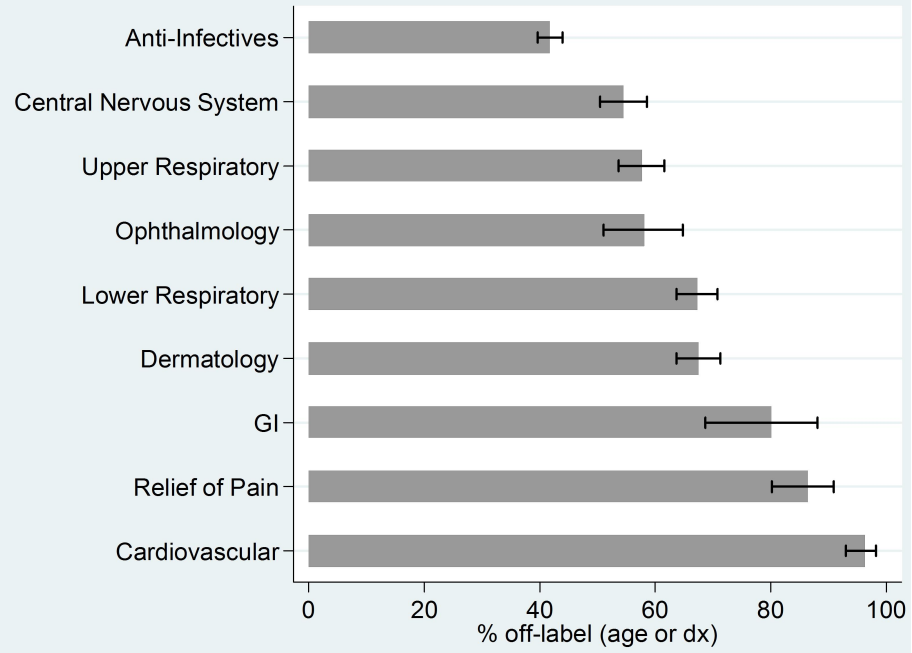

Figure 2. Proportion of prescriptions that are off-label by common drug categories (estimated prescriptions, N=484,010,000).
GI indicates gastrointestinal; dx indicates diagnosis.

Table 2. 2001-2004 NAMCS Top Five Medications Most Often Prescribed Off-Label within Each Major Drug Category*

Drug Category (% of Rx[a]§)	Rank within Category	Rank Overall	Generic Medication Name (Proprietary†)	FDA Approval Age (yrs)‖	Number of Off-Label Rx[†]	Unweighted *n* of Off-Label Rx
Anti-infectives (28%)	1	1	Amoxicillin	0.25	15,580,000	346
	2	3	Azithromycin (Zithromax)	0.5	13,160,000	270
	3	5	Amoxicillin/clavulanate (Augmentin)	0	9,240,000	208
	4	14	Cephalexin	1	3,260,000	78
	5	16	cefpodoxime (Omnicef)	0.5	2,790,000	61
Upper respiratory (17%)	1	6	Cetirizine (Zyrtec)	0.5	9,090,000	224
	2	7	Loratadine (Claritin)	2	5,370,000	133
	3	10	Promethazine (Phenergan)	2	4,500,000	76
	4	12	Mometasone (Nasonex)	2	4,220,000	108
	5	15	Fluticasone nasal (Flonase)	4	2,870,000	78
CNS (15%)	1	28	Sertraline (Zoloft)	6	1,760,000	82
	2	27	Fluoxetine (Paxil)	18	1,750,000	67
	3	31	Risperidone (Risperdal)	5	1,650,000	79
	4	34	Methylphenidate (Concerta)	6	1,600,000	39
	5	37	amphetamine/ dextroamphetamine (Adderall)		1,530,000	45
Dermatologics (topicals) (12%)	1	11	Hydrocortisone	0	4,240,000	95
	2	17	Nystatin (Mycostatin)	0	2,780,000	55
	3	19	Mupirocin (Bactroban)	0.17	2,360,000	64
	4	24	Pimecrolimus (Elidel)	2	1,850,000	42
	5	26	Triamcinolone	0	1,800,000	58
Pulmonary (11%)	1	2	Albuterol	4	14,140,000	268
	2	4	Montelukast (Singulair)	1	11,030,000	222
	3	8	Levalbuterol (Xopenex)	6	5,090,000	96
	4	9	Fluticasone (Flovent)	4	5,010,000	105
	5	32	Budesonide, inhaled (Pulmicort Respules)	1	1,640,000	31
Neurologics (4%)	1	41	Divalproex sodium (Depakote)	2	1,350,000	69
	2	¶	Topiramate (Topamax)	2	460,000‡	27
	3	¶	Oxcarbazepine (Trileptal)	4	430,000‡	25
	4	¶	Sumatriptan (Imitrex)	18	300,000‡	14
	5	¶	Gabapentin (Neurontin)	3	250,000‡	14
Ophthalmologic (ophthalmics) (3%)	1	33	Olopatadine (Patanol)	3	1,630,000	31
	2	48	Ciprofloxacin (Cipro HC)	1	1,230,000	48
	3	¶	Tobramycin/dexamethasone (Tobradex)	2	500,000‡	20
	4	¶	Neomycin/polymyxin B/dexamethasone (Maxitrol)	18	420,000‡	8
	5	¶	Tobramycin (Tobrex)	2	420,000‡	12

(table continues)

Table 2. (continued)

Drug Category (% of Rx[a]§)	Rank within Category	Rank Overall	Generic Medication Name (Proprietary†)	FDA Approval Age (yrs)‖	Number of Off-Label Rx[†]	Unweighted n of Off-Label Rx
GI (2%)	1	13	Polyethylene glycol (Miralax)	17	3,320,000	64
	2	38	Ranitidine (Zantac)	0.083	1,510,000	33
	3	53	Lansoprazole (Prevacid)	1	1,060,000‡	23
	4	68	Lactulose	18	870,000‡	19
	5	¶	Esomeprazole (Nexium)	12	440,000‡	8
Cardiovascular-renal (2%)	1	23	Clonidine	12	1,870,000	69
	2	71	Guanfacine (Tenex)	12	790,000	36
	3	¶	Epinephrine (Epipen)	0	580,000‡	20
	4	¶	Metoprolol (Toprol XL)	6	390,000‡	10
	5	¶	Furosemide (Lasix)	18	340,000‡	9
Relief of pain (2%)	1	74	Acetaminophen/codeine (Tylenol with Codeine)	3	710,000	36
	2	¶	Acetaminophen/ hydrocodone (Lortab or Vicodin)	18	650,000‡	16
	3	¶	Propoxyphene/ acetaminophen (Darvocet)	18	510,000‡	16
	4	¶	Cyclobezaprine (Flexeril)	15	420,000‡	10
	5	¶	Celecoxib (Celebrex)	2	390,000‡	10

*N=484,010,000 estimated prescriptions, rounded to nearest 10,000; unweighted n=12,432 prescriptions); NAMCS indicates National Ambulatory Medical Care Survey.
†Proprietary names, which are all trademarked, are provided for reference only and do not indicate an endorsement of the product.
‡National Ambulatory Medical Care Survey advises that estimates based on unweighted samples of <30 may be unreliable.
§Rx indicates prescription. Percentages do not add up to 100% because categories with <2% of prescriptions are not included.
**CNS indicates central nervous system.
‖Late information as of September 2007. Changes in approval ages may have occurred since 2007.
¶Not ranked in the top 100 drugs.

Table 3. Adjusted Patient Probability of Having a Visit With Off-Label Prescribing†

Characteristics‡	AOR§ of Visit With Off-Label Prescribing (95% CI)‖	Adjusted Probability of Visit With Off-Label Prescribing	Difference In Adjusted Probabilities (95% CI)
Gender			
Male	Referent	62%	referent
Female	1.04 (0.95, 1.15)	63%	1% (-1, 3)
Race/Ethnicity			
White	Referent	62%	referent
Black	1.13 (0.94, 1.35)	64%	2% (-1, 6)
Hispanic	1.08 (0.92, 1.26)	63%	1% (-2, 5)
Other	1.44 (1.1, 1.85)*	69%	7% (3, 12)
Age			
0 - <1 year	2.2 (1.8, 2.67)***	74%	15% (12, 19)
1 - <2 years	1.52 (1.25,1.84)***	67%	8% (4, 13)
2 - <6 years	1.36 (1.18, 1.57)***	65%	6% (4, 9)
6 - <12 years	Referent	59%	referent
12 - <18 years	1.02 (0.89, 1.16)	59%	0% (-2, 3)
Chronic diseases			
Yes	0.85 (0.75, 0.96)*	60%	-4% (-6, 0.2)
No	Referent	64%	referent
Payment source			
Private insurance	Referent	62%	referent
Medicaid	1.13 (0.99, 1.29)	65%	3% (-0.1, 5)
Self-pay	1.1 (0.85, 1.4)	64%	2% (-4, 7)
Other	0.89 (0.73, 1.1)	60%	-2% (-7, 2)
Number of Rx medications			
1	Referent	51%	referent
2	3.36 (2.97, 3.8)***	77%	26% (24, 29)
3-6	9.3 (7.41, 11.67)***	90%	39% (37, 42)
Physician specialty			
General pediatrics	0.85 (0.74, 0.97)*	59%	4% (-7, 0.3)
General/family practice	Referent	63%	referent
Other specialty	1.3 (1.12, 1.51)**	68%	5% (2, 8)

†Based on patient, visit, and physician characteristics. Unweighted *n*=7901, weighted *N*=312,000,000.
‡All variables included in the model are described in the table.
§AOR indicates adjusted odds ratio.
‖CI indicates confidence interval.
{Rx indicates prescription.
**P*<.05.
***P*<.01.
****P*<.001

References

Arroll, B., & Kenealy, T. (2005). Antibiotics for the common cold and acute purulent rhinitis. *Cochrane Database of Systematic Reviews, 3,* CD000247.

Bajcetic, M., Jelisavcic, M., Mitrovic, J., Divac, N., Simeunovic, S., Samardzic, R., & Gorodischer, R. (2005). Off-label and unlicensed drugs use in paediatric cardiology. *European Journal of Clinical Pharmacology, 61,* 775-779.

Best Pharmaceuticals for Children Act. (2002). Pub L No. 107 109, 115 Stat 1408.

Bhatara, V., Feil, M., Hoagwood, K., Vitiello, B., & Zima, B. (2004). National trends in concomitant psychotropic medications with stimulants in pediatric visits: Practice versus knowledge. *Journal of Attention Disorders, 7*, 217-226.

Carrin, G. (1987). Drug prescribing: A discussion of its variability and (ir)rationality. *Health Policy, 7*, 73-94.

Centers for Disease Control and Prevention (CDC). (2007). Infant deaths associated with cough and cold medications--two states, 2005. *Morbidity and Mortality Weekly Report, 56*, 1-4.

Chalumeau, M., Treluyer, J., Salanave, B., Assathiany, R., Cheron, G., & Crocheton, N. (2000). Off-label and unlicensed drug use among French office based paediatricians. *Archives of Disease in Childhood, 83,* 502-505.

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

Chen, S., Lu, K., & Sun, H. (2006). Randomized placebo-controlled trial comparing montelukast and cetirizine for treating perennial allergic rhinitis in children aged 2-6 yr. *Pediatric Allergy and Immunology, 17*, 49-54.

Cherry, D. K., Burt, C. W., & Woodwell, D. (2003). National ambulatory medical care survey: 2001 summary. *Advanced Data, 337*, 1-44.

Cooper, W. O., Arbogast, P. G., Ding, H., Hickson, G. B., Fuchs, D. C., & Ray, W. A. (2006). Trends in prescribing of antipsychotic medications for U.S. children. *Ambulatory Pediatrics, 6*, 79-83.

Eiland, L., & Knight, P. (2006). Evaluating the off-label use of medications in children. *American Journal of Health-System Pharmacy, 63,* 1062-1065.

Ekins-Daukes, S., Helms, P. J., Simpson, C. R., Taylor, M. W., McLay, J. S. (2004). Off-label prescribing to children in primary care: Retrospective observational study. *European Journal of Clinical Pharmacology, 60*(5), 349-533.

Findling, R., Steiner, H., & Weller, E. B. (2005). Use of antipsychotics in children and adolescents. *Journal of Clinical Psychiatry, 66*, 29-40.

Giacoia, G., & Mattison, D. (2005). Newborns and drug studies: The NICHD/FDA newborn drug development initiative. *Clinical Therapeutics, 27,* 796-813.

Giacoia, G., Birenbaum, D., Sachs, H., & Mattison, D. (2006). The newborn drug development initiative. *Pediatrics, 117*, S1-S8.

Henney, J. (2000). Withdrawal of troglitazone and cisapride. *Journal of the American Medical Association, 283*, 2228.

Horen, B., Montastruc, J., & Lapeyre-Mestre, M. (2002). Adverse drug reactions and off-label drug use in paediatric outpatients. *British Journal of Clinical Pharmacology, 54*, 665-670.

King, B., Zwi, K., Nunn, K., Longworth, J., & Dossetor, D. (2003). Use of risperidone in a paediatric population: An observational study. *Journal of Paediatrics and Child Health, 39,* 523-527.

Kuhlthau, K., Beal, A., Ferris, T., & Perrin, J. (2002). Comparing a diagnosis list with a survey method to identify children with chronic conditions in an urban health center. *Ambulatory Pediatrics, 2,* 58-62.

Li, V. W., Jaffe, M. P., Li, W. W., & Haynes, H. A. (1998). Off-label dermatologic therapies: Usage, risks, and mechanisms. *Archives of Dermatology, 134*(11), 1449-1454.

McIntyre, J., Conroy, S., Avery, A., Corns, H., & Choonara, I. (2000). Unlicensed and off-label prescribing of drugs in general practice. *Archives of Disease in Childhood, 83*, 498-501.

McKinzie, J. P., Wright, S. W., & Wrenn, K. D. (1997). Pediatric drug therapy in the emergency department: Does it meet FDA-approved prescribing guidelines? *American Journal of Emergency Medicine, 15,* 118-121.

Micromedex. (2004). *Volume I USP DI: Drug information for the health care professional.* Greenwood Village, CO: Thompson.

National Center for Health Statistics (NCHS). (n.d.). *Ambulatory care drug database system*. Retrieved from http://www.cdc.gov/nchs/about/major/ahcd/ambulatory.htm

National Institute of Child Health and Human Development. (2007). *Table 1: Current status of drugs that have been listed by NIH (NICHD) for BPCA.* Retrieved from http://bpca.nichd.nih.gov/about/process/upload/Drug_Table_2007.pdf

Novartis Pharmaceuticals Corp. (2007). *Elidel full prescribing information*. East Hanover, NJ: Author.

Nyquist, A. C., Gonzales, R., Steiner, J. F., & Sande, M. A. (1998). Antibiotic prescribing for children with colds, upper respiratory tract infections, and bronchitis. *Journal of the American Medical Association, 279*, 875-877.

Pediatric Research Equity Act of 2003. Pub L No. 108 155, 117 Stat 1936.

Physician's Desk Reference. (n.d.). *Physician's desk reference*. Montvale, NJ: Medical Economics Co.

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

Roberts, R., Rodriguez, W., Murphy, D., & Crescenzi, T. (2003). Pediatric drug labeling: Improving the safety and efficacy of pediatric therapies. *Journal of the American Medical Association, 290*, 905-911.

Robertson, J., & Shilkofski, N. (2005). *The Harriet Lane handbook: A manual for pediatric house officers*. Philadelphia, PA: Mosby.

Schirm, E., Tobi, H., & de Jong-van den Berg, T. (2003). Risk factors for unlicensed and off-label drug use in children outside the hospital. *Pediatrics, 111,* 291-295.

Shah, S. S., Hall, M., Goodman, D. M., Feuer, P., Sharma, V., Fargason, C. Jr., . . . Slonim, A. D. (2007). Off-label drug use in hospitalized children. *Archives of Pediatrics & Adolescent Medicine, 161*(3), 282-290.

Sikich, L., Hamer, R. M., Bashford, R. A., Sheitman, B. B., & Lieberman, J. A. (2004). A pilot study of risperidone, olanzapine, and haloperidol in psychotic youth: A double-blind, randomized, 8-week trial. *Neuropsychopharmacology, 29*, 133-145.

Starke, P. R., Weaver, J., & Chowdhury, B. A. (2005). Boxed warning added to promethazine labeling for pediatric use. *New England Journal of Medicine, 352*, 2653.

't Jong, G. W., Eland, I. A., Sturkenboem, M. C., van der Anker, J. N., & Stricker, B. H. (2003). Determinants for drug prescribing to children below the minimum licensed age. *European Journal of Clinical Pharmacology, 58*, 701-705.

Thomas, C., Conrad, P., Casler, R., & Goodman, E. (2006). Trends in the use of psychotropic medications among adolescents, 1994 to 2001. *Psychiatric Services, 57,* 63-69.

Turner, S., Nunn, A. J., Fielding, K., & Choonara, I. (1999). Adverse drug reactions to unlicensed and off-label drugs on paediatric wards: A prospective study. *Acta Paediatrica, 88,* 965-968.

U.S. Center for Drug Evaluation and Research, Food and Drug Administration (CDER, FDA). (n.d.). *Drugs@FDA.* Retrieved from http://www.accessdata.fda.gov/scripts/cder/drugsatfda/

U.S. Center for Drug Evaluation and Research, Food and Drug Administration (CDER, FDA). (2004). *Suicidality in children and adolescents being treated with antidepressant medications.* Retrieved from http://www.fda.gov/cder/drug/antidepressants/ssripha200410.htm

U.S. Food and Drug Administration (FDA). (n.d.). *Pediatric exclusivity labeling changes.* Retrieved from http://www.fda.gov/cder/pediatric/labelchange.htm

Ufer, M., Kimland, E., & Bergman, M. (2004). Adverse drug reactions and off-label prescribing for paediatric outpatients: A one-year survey of spontaneous reports in Sweden. *Pharmacoepidemiology and Drug Safety, 13*, 147-152.

Ufer, M., Rane, A., Karlsoon, A, Kimland, E., & Bergman, U. (2003). Widespread off-label prescribing of topical but not systemic drugs for 350,000 paediatric patients in Stockholm. *European Journal of Clinical Pharmacology, 58*, 779-783.

World Health Organization (WHO). (2006). *International classification of disease, 9th Revision, clinical modification.* Los Angeles, CA: Practice Management Information.

Yoon, E. Y., Dombkowski, K. J., Rocchini, A., Lin, J.-J., & Davis, M. M. (2007). Off-label utilization of antihypertensive medications in children. *Ambulatory Pediatrics, 7*, 299-303.

Zito, J. M., Safer, D. J., dos Reis, S., Gardner, J. F., Boles, M., & Lynch, F. (2000). Trends in the prescribing of psychotropic medications to preschoolers. *Journal of the American Medical Association, 283*, 1025-1030.

CHAPTER 3: OFF-LABEL PRESCRIBING TO U.S. INFANTS AND TODDLERS AND ASSOCIATED FACTORS

Abstract

Objective. To determine frequencies of off-label prescribing to children younger than the FDA-approved age and for unapproved indications in U.S. children <3 years (yrs) old in the outpatient setting and to determine factors associated with off-label prescribing.

Design/Setting/Participants. The 2001-2004 National Ambulatory Medical Care Survey, a national probability sample survey of outpatient physician visits, was used to derive population estimates of visits where children <3 yrs got prescriptions (81 million). FDA-approved age and indications were compared to the child 's age and diagnoses.

Main Outcome Measures. Population-level visit-based frequencies of off-label prescribing for age and indication; patient, visit and physician factors associated with receiving at least one off-label prescription for age or indication.

Results. Off-label prescribing occurred in 65% of prescription visits **(**52.7 million). At 42% of visits (33.6 million), children <3 yrs received at least one off-label prescription for age and at 53% of visits (42.9 million), at least one prescription was off-label for indication. At 30% of visits (23.8 million), prescriptions were off-label for both age and indication. Children prescribed multiple drugs and those seeing subspecialists had increased odds of receiving off-label prescriptions for age or indication compared to children prescribed one drug or seeing a pediatrician respectively (p <0.01 for both comparisons).

Conclusions. About two-thirds of children <3 yrs receive off-label prescriptions for age and/or indication at U.S. outpatient prescription visits. Many off-label prescriptions are for medications with unproven benefit or safety concerns. Physician and consumer education and population-based surveillance of off-label prescribing outcomes are warranted.

Introduction

Prescribing drugs to patients who are younger than the U.S. Food and Drug Administration (FDA) approved age for the drug or for unapproved medical indications is referred to as off-label prescribing. Studies have indicated that off-label prescribing to children may increase the risk of adverse drug events (Horen, Montastruc, & Lapeyre-Mestre, 2002; Turner et al., 1999). However, the literature on off-label prescribing to children in the U.S. is limited. To date, most studies of off-label prescribing have examined single drug classes (Aparasu, & Bhatara, 2007; Cooper et al., 2006; Olfson, Blanco, Lui, Moreno, & Laje, 2006) or regional samples (Chen et al., 2006), or have focused exclusively on the inpatient setting (Eiland & Knight, 2006; Shah et al., 2007; Thompson, & Heflin, 1987). Shah and colleagues reported that in U.S. tertiary care children's hospitals, 79% of inpatients received off-label medications (Shah et al., 2007). In the general pediatric inpatient setting, Eiland and Knight found that 31% of children hospitalized during one-half of the year received off-label medications (Eiland & Knight, 2006). We previously reported that 62% of outpatient visits by U.S. children 0-18 years of age include off-label prescribing. These studies indicate that children frequently receive off-label medications without sufficient evidence to support their use.

Infants and toddler may be more affected by off-label prescribing than other children. Over half of U.S. children are taking prescription or over-the-counter medications during a given week and medication use in children is most prevalent among 0-2 year olds (Vernacchio, Kelly, Kaufman, & Mitchell, 2009). Incongruously, infants and toddlers are least included in drug development studies (Giacoia, & Mattison, 2005), yet examples suggest a high potential for adverse events that are unique to these young children, such as reactions to cough and cold medications (Centers for Disease Control and Prevention [CDC], 2007) and gray baby syndrome

with chloramphenicol (Lischner, Seligman, Krammer, & Parmelee, 1961). Pharmacokinetics (the body's absorption, distribution, metabolism and elimination of drugs) in infants and toddlers also vary dramatically from those in older children and adults due to differences in body surface area, immature intestinal transport, changes in intestinal microflora and conjugation, and delayed enzymatic maturation among other factors (Steinbrook, 2002). In addition, pharmacodynamics (the physiological effects of a drug on the body) also significantly differ from those in older children, resulting in dose/response variability. Finally, children younger than three years old also represent perhaps the most neuro-developmentally vulnerable group, with dynamic developmental phenotypic changes that coincide with rapid cerebral metabolism and synaptic density growth (Rice, & Barone, 2000). Taken together, these differences indicate that infants and toddlers could be disproportionately vulnerable to the adverse effects of off-label medication use. A clearer understanding of which drugs are most frequently prescribed off-label to infants and toddlers at outpatient visits and under what circumstances could help to guide drug development and clinical care of young children. The objectives of this study were to determine the frequency of off-label prescribing to infants and toddlers at office visits in the U.S. and to characterize patient, visit and physician factors that are predictive of this off-label prescribing.

Methods

Data Sources

We used data from the 2001-2004 National Ambulatory Medical Care Survey, a national probability sample survey performed by the Centers for Disease Control of the content of outpatient physician visits (Cherry, Burt, & Woodwell, 2003). This study was designed to focus on visits in which children <3 years old received prescriptions (Rx) within NAMCS. Previously, we had reported on a more general analysis of NAMCS off-label prescribing for age to all

children less than 18 years old (Bazzano, Mangione-Smith, Schonlau, Suttorp, & Brook, 2009). NAMCS uses a multi-stage probability sampling method designed to produce national estimates of visit data. During 2001 through 2004, 5501 physician offices (64-70% of those eligible) participated in NAMCS by completing a one-page encounter form on a systematic random sample of patient visits. This encounter form included data on patient demographics, reason for the visit, diagnostic work up, diagnoses (up to three), medications (up to six), and follow-up. We analyzed only visits in NAMCS by children <3 years old during which one or more medications available by prescription were given and excluded vaccines, vitamins, over-the-counter medications, nutritional products, nonspecific treatments (e.g., "antibacterial agent"), non-medications (e.g. infant oil, soap), and rarely prescribed medications (e.g. domperidone). The total number of included unweighted prescription visits was 1811. We reviewed all NAMCS drug names for accuracy, combining brand name and generic drugs (e.g. albuterol and Proventil™) that had been missed by NAMCS to ensure precise drug counts. We reclassified some NAMCS drug categories due to small sample sizes and drug similarities. Specifically, anti-parasitics were combined with antimicrobials, neurologics were added to central nervous system drugs, and upper respiratory drugs were separated from pulmonary drugs.

Dependent Variable: Off-Label

We identified all medications available by prescription at visits for children <3 years, and found 2,534 eligible prescriptions in total. A prescription was considered off-label for indication when none of the child's diagnoses corresponded to an FDA-approved indication. FDA-approved indications were converted to International Classification of Disease 9th edition (ICD9-CM) codes, which were cross-matched with the NAMCS ICD9 variable to ensure inclusion of all plausible diagnoses. A prescription was off-label for age when the child's age

was less than the youngest FDA-approval age for the drug regardless of indication, as determined by the medication prescribing information (label), obtained from the *Physician's Desk Reference* (Physician's Desk Reference, 2001), FDA or manufacturer's website, or other compendia (Micromedex, 2004). A prescription visit was considered off-label for age or indication if at least one prescription at the visit was off-label for age or indication respectively. For consistency across data years, we used the latest available prescribing information as of September 1, 2007. For generic equivalents for which children's prescribing information was unavailable, branded drug data were substituted.

Independent Variables

Independent variables were derived from existing empiric literature (Denig, Witteman, & Schouten, 2002; Schirm, Tobi, & de Jong van den Berg, 2003) and theory on physician prescribing behavior (Carrin, 1987; Clark, Potter, & McKinlay, 1991; Walker, Grimshaw, & Armstrong, 2001). Variables included patient age, gender, race/ethnicity (combined variable), and region of the country. Patient age categories included <3 months, 3 to <6 months, 6 months to <1 year, 1 year to <2 years, and 2 years to <3 years. We also included expected payment source (private insurance, Medicaid, self-pay, or other), whether the physician shared care for the problem with another provider (yes or no), and number of prescriptions given at the visit (1, 2, 3 or more), physician specialty, solo practice versus other, and whether or not the physician was the patient's primary care physician. Due to sample size limitations, we categorized physician specialty as follows: family practice and generalists, general pediatricians, and other specialists.

Statistical Analysis

Visits were weighted to reflect the national population of visits (80 million visits with prescriptions by children <3 years) and all of our estimates took sampling design into account:

sampling weights to address unequal probability of selection, stratification, and clustering within geographic area and within physician.

Descriptive analyses were used to characterize visit characteristics and off-label prescribing frequencies. The frequency of off-label prescriptions was defined as the number of prescriptions given where the child's age was lower than the lowest FDA-approved age. The proportion of off-label prescriptions was derived by dividing the number of off-label prescriptions by the total number of prescriptions in the sample. The frequency of off-label prescribing at visits was defined as the number of visits in which at least one off-label medication was prescribed. The proportion of visits with at least one off-label prescription was determined by taking the visits in which an off-label prescription was provided and dividing by the total number of visits in the sample. Frequencies and proportions for specific indications and drug categories were derived using the same general method.

Multivariate logistic regression modeling at the visit level was used to determine which patient, visit and physician characteristics were associated with off-label prescribing for age or indication. For the logistic regression, we chose several variables that were entered into the model *a priori* to ensure an adequate description of our population. These included the following independent variables: age, gender, ethnicity, and region of the country. The other potential predictors were chosen on the basis of statistical significance in simple logistical regressions using the dependent variable of off-label prescribing. We excluded independent variables with *p*-values larger than 0.10 in the simple logistic regression from the final model. We calculated odds ratios and 95% confidence intervals for all variables in our multivariate regression models. Then, to describe the magnitude of off-label prescribing under various conditions, we used recycled predictions to determine the adjusted probability of off-label prescribing for each

variable with all other variables held constant. The differences in these adjusted probabilities and 95% confidence intervals were calculated. Analyses were based on variables with counts of ≥30 records to ensure reliability, as recommended by NAMCS documentation. All analyses were performed using Intercooled STATA 9.0© (StataCorp LP, College Station, TX). Statistical significance was predetermined to be at the $p < 0.05$ level.

Results

Sample characteristics of infants and toddlers included in the study are presented in Table 4. Sixty-five percent of prescription visits involved off-label prescribing for age or indication, so that children were exposed to medications not FDA-approved for their age or indication at 52.7 million visits. Somewhat more children received prescriptions that were off-label for indication than were off-label for age (53% vs. 42% of visits). More than one-fourth of prescription visits (23.8 million) included off-label prescribing for both age and indication (Table 5). Among the nine medication categories, only anti-infectives were prescribed in an FDA approved manner more than 50% of the time. Proportionately, almost all (98%) cardiovascular/renal drugs were prescribed off-label for age or for indication. Similarly, more than 90% of medications affecting the central nervous system, pain medications, and dermatologics were prescribed off-label (Figure 3). However, a larger number of prescriptions were off-label among anti-infectives and pulmonary medications, accounting for almost 30 million off-label prescriptions.

Albuterol sulfate was the medication most often prescribed to children younger than the FDA-approved age, with 6.5 million off-label prescriptions, followed by levoalbuterol (Xopenex™) with 2.3 million prescriptions. The topical immunomodulator, (Elidel™), was prescribed off-label over one million times to children younger than three years of age. The

inhaled corticosteroid, budesonide (Pulmicort™), was prescribed off-label for age approximately one million times as well. The phenothiazine, promethazine (Phenergan™), was prescribed off-label for age 875,000 times. Several cold and cough combination medications were also among the most frequently off-label prescribed to children younger than the approved age. Of the top 10 medications, only five had an FDA approval for any children <4 years of age (Table 6).

The antibiotics, amoxicillin and azithromycin, were mostly frequently prescribed off-label for indication, at almost five million and three million times, respectively. The diagnoses for which these antibiotics were most often prescribed off-label were upper respiratory infection (e.g., the common cold) and bronchitis. Albuterol sulfate and levalbuterol ranked second and fourth among medications most commonly prescribed off-label for indication, with 4.5 and 2.3 million off-label prescriptions, respectively. These medications, both inhaled beta agonists with an FDA approved indication for asthma, were most commonly prescribed for the diagnoses of upper respiratory infection and bronchitis. Nystatin, the topical anti-Candidal agent, was also among the top five medications, and was prescribed off-label for indication almost 2.5 million times (Table 7). Off-label prescriptions were most commonly given to infants and toddlers with the following diagnoses: acute upper respiratory infection, otitis media, and bronchitis.

Multivariate logistic regression analysis revealed three significant predictors of visits with off-label prescribing: child's age, number of medications prescribed and physician specialty (Table 8). Children younger than six months and particularly younger than three months had a significantly higher probability of receiving at least one off-label prescription than older children (15% and 26% higher, respectively). Compared to children receiving one prescription, children

prescribed two medications had a 30% higher adjusted probability of receiving at least one off-label prescription (95% CI: 26%, 35%). When prescribed three or more medications, the adjusted probability of receiving at least one prescription off-label was 38% higher than if prescribed one medication (95% CI: 33%, 43%). When children visited subspecialists, the probability of off-label prescribing was 18% higher (95% CI: 11%, 24%) than when visiting general pediatricians. Gender, race/ethnicity, region of the country, payment source, number of visits, and solo practice were not predictive of off-label prescribing at visits in which children received prescriptions.

Discussion

About two-thirds of infants and toddlers in the current study received off-label prescriptions at outpatient visits in the U.S. Off-label prescribing for an unapproved indication was more common than prescribing to children younger than the FDA-approved age, however more than one-fourth of children younger than three years of age received prescriptions that were off-label for both age and indication. These results were consistent regardless of payment source, gender of the child, or region of the country, indicating that off-label prescribing to infants and toddlers is a practice that is pervasive in pediatrics. The level of exposure in infants and toddlers to off-label medications in this study demonstrates the urgent need for further research to determine the magnitude of potential adverse effects of off-label prescribing to this vulnerable group.

This study addresses a gap in the literature by specifically analyzing off-label prescribing to infants and young children in the U.S. outpatient setting. We, and others, have previously reported on off-label prescribing for age to children 0-17 years of age but we could find no studies specific to 0-3 year olds. Neonatal studies indicate an extremely high rate of off-label

prescribing in the intensive care setting (92%; Conroy, McIntyre, & Choonara, 1999). In addition, one analysis has recently characterized off-label prescribing in tertiary care children's hospitals in the U.S. (Shah et al., 2007). In contrast, the current study addresses care in the medical setting where infants and toddlers have most contact--outpatient office visits. Prior studies in the pediatric outpatient setting have exclusively been conducted outside the U.S. where lower rates of off-label prescribing have been reported ranging from 26-41% (Bucheler et al., 2002; Chalumeau et al., 2000; Ekins-Daukes, Helms, Simpson, Taylor, McLay, 2004; McIntyre, Conroy, Avery, Corns, & Choonara, 2000; Schirm et al., 2003, 't Jong, Eland, Sturkenboem, van der Anker, & Stricker, 2003; Ufer, Rane, Karlsoon, Kimland, & Bergman, 2003). However, these studies all varied in their definitions of off-label prescribing, often not including indications. Restricted formularies in several European health systems may also account for differences from our results. Additionally, European children are mainly seen by general practice physicians and pediatricians are considered secondary subspecialty providers. In contrast, our study reflects the U.S. population in which the majority of children are seen by pediatricians.

The almost universal prescription of cardiovascular, renal, CNS and pain medications in an off-label manner, as demonstrated in our study, points to these drugs as primary targets for intervention. Case examples, such as lamotrigine-associated Stevens-Johnson syndrome (GlaxoSmithKline, 2010), provide historical precedents for severe adverse events within these medication categories. Further, anithypertensives and antiepileptics, for example, are medications that are usually used for a relatively small population of children with more severe disease and for longer time periods. Traditional clinical trials of efficacy and safety studies reflect short-term use. To augment clinical trials for these medications, an approach may be a

medication registry, which could actively monitor these populations of children over time for side effects, safety issues and efficacy.

It is not surprising that among the medications most commonly prescribed off-label were albuterol and budesonide, given the frequency of pulmonary disease in infants and toddlers. Long experience with these medications in children with few reports of serious adverse events or deaths may be reassuring; however, a recent Cochrane collaboration systematic review analyzed albuterol use for recurrent wheeze in infants (as opposed to older children) and showed no clear benefit (Chavasse, Seddon, Bara, & McKean, 2002). On the other hand, in our study, albuterol was most frequently prescribed for infants with the off-label diagnoses of bronchitis and upper respiratory infection rather than wheeze or asthma. The effectiveness of albuterol in infants and toddlers for these indications has also been unsupported by literature or guidelines and the FDA denied a labeled indication for albuterol in children under four years. Similarly, newer randomized controlled trials question the benefit of inhaled corticosteroids, such as fluticasone, in infants and toddlers with wheeze (Bisgaard, Hermansen, Loland, Halkjaer, & Buchvald, 2006) and risks of growth suppression are well-established in older children (Easton et al., 1981; Lipworth, 1999; Randell et al., 2003).

A large number of off-label prescriptions were for upper respiratory infections, including antihistamines, decongestants, cough suppressants and combinations in our study. The use of cough and cold preparations in children has recently come under increased scrutiny. In 1997, the American Academy of Pediatrics issued a policy statement advising that physicians should educate parents on the lack of efficacy, risk for adverse events, and potential for overdose in young children taking cough suppressant medications (American Academy of Pediatrics Committee on Drugs, 1997). In 2000, phenylpropanolamine (PPA), a commonly used

over-the-counter decongestant that had been marketed for many years, was withdrawn from the market after studies indicated that it could cause hemorrhagic stroke (Center for Drug Evaluation and Research, Food and Drug Administration [CDER, FDA], 2000). More recently, the CDC issued a warning following its report of 1,500 serious adverse events and six deaths in children younger than two years of age due to cough and cold preparations in 2004-2005 (CDC, 2007). A growing literature has shown that these medications are no more effective than placebo (De Sutter, Lemiengre, Campbell, & Mackinnon, 2003; Smith, & Feldman, 1993; Taverner, & Latte, 2007). In our study, the widespread off-label use of promethazine in infants and toddlers was particularly concerning due to reports of fatal respiratory depression, prompting a black box warning in 2005 (Starke, Weaver, & Chowdhury, 2005). Despite warnings, a 2011 European study indicated that prescribing patterns of these cough and cold preparations had hardly changed (Sen et al., 2011). Further research should document whether U.S. physicians reduced their prescription of promethazine and other cough and cold medications. Given the available evidence, the extensive use of these agents is of concern and may indicate the need for further tools focused on physicians, pharmacists, and consumers to reduce this inappropriate medication use.

Antibiotics accounted for the largest number of off-label prescriptions to infants and toddlers for non-FDA approved indications. Prescribing of antibiotics to children for upper respiratory infections and other viral illnesses is known to be ineffective and to produce bacterial resistance (Arason et al., 1996; Arroll, & Kenealy, 2005). Our study confirms that inappropriate antibiotic prescribing among infants and toddlers is prevalent and additional interventions and public health campaigns aimed at physicians and consumers to address this issue are needed.

For infants younger than six months old, more than 75% of visits included off-label prescriptions. Although perhaps not surprising, this is particularly concerning because compared to older infants and children, these young infants experience the highest medication adverse events rates (Moore, Weiss, Kaplan, & Blaisdell, 2002). Medications for neonates and infants are the least likely to be studied and the FDA has stated that scant information is available on neonates and young infants for drugs in any class (Rodriguez, Roberts, & Murphy, 2001). The existing research on the effects of off-label medications in infants, such as previously described for albuterol and promethazine, indicates multiple reasons for caution in using them. In another frequently used medication in our study, pimecrolimus cream, an immuno-suppressant used for eczema, higher blood levels were detected in infants and young children than adults, and it is associated with higher risk of respiratory infections and cancer (Novartis Pharmaceuticals Corp, 2007). Recently, the FDA has gained the ability to issue written requests to manufacturers for study of specific pediatric populations and indications. Of the over 300 drugs that have been studied since the new legislation, the vast majority state "study waived for 0-2 month olds" and less than 10 have received labeling changes due to study of infants (CDER, FDA, 2011). The disproportionate burden of off-label prescribing in 0-6 month old infants indicates the strong need to put resources into study of drugs in this group and FDA should consider increasing requirements for manufacturers to study 0-2 month olds rather than granting waivers.

Children who were seen by subspecialists were more likely to be prescribed off-label medications. These cases may reflect children with more complex disease. Such complexity is known to be associated with higher rates of off-label prescribing (Shah et al., 2007). Alternatively, subspecialists, in particular those without neonatal and pediatric training, may not

be as familiar with the FDA-approved ages and indications for pediatrics, indicating the potential need for continued education on prescribing to young children.

Limitations

Several limitations of this study must be acknowledged. Drug formulation and dosage were not included in the NAMCS data set. Prior studies indicate that dosing outside the label recommendation accounts for a significant portion of off-label prescribing to children (Ekins-Daukes et al., 2004). Thus, we may have underestimated the extent of off-label prescribing to infants and toddlers. It is also possible that off-label prescribing has changed over time. However, though some medications have undergone recent labeling changes (Roberts, Rodriguez, Murphy, & Crescenzi, 2003), many of the medications most frequently prescribed off-label in our analysis are still not labeled for young children or for the most frequently prescribed indications. Additionally, this study may serve as a baseline for monitoring trends in off-label prescribing as the practice continues. Finally, we were unable to comment on appropriateness of prescribing at individual visits, as NAMCS was not intended for this specific research question and details of the patient circumstances were not available.

Implications

At least two-thirds of infants and toddlers are exposed to off-label medications at U.S. outpatient prescription visits. The youngest infants are most likely to receive these medications. Many off-label prescriptions are for medications with serious safety concerns or are intended to treat self-limited disease. These findings indicate the need for review of prescribing practices to infants as a profession as well as continuing physician and consumer education regarding efficacy and risks in using off-label medications in infants and toddlers. Furthermore,

population-based surveillance of the outcomes of off-label prescribing to infants and young children, particularly for certain medication categories, is warranted.

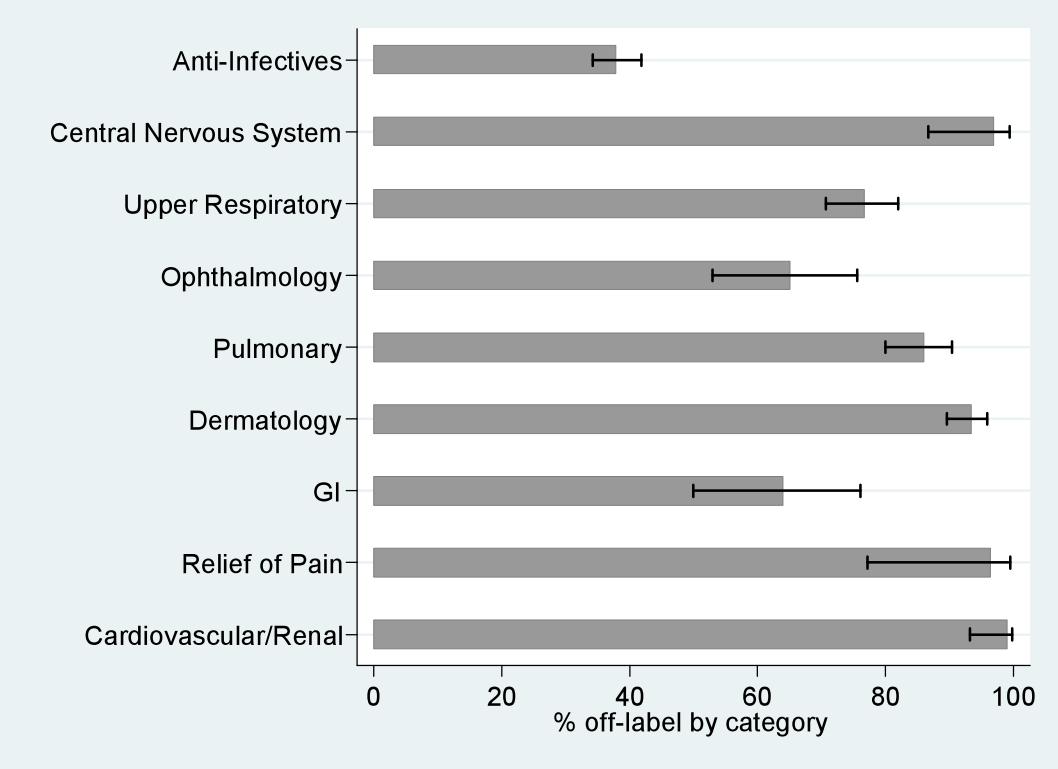

Figure 3. Percentage of prescriptions to 0≤3 year olds that are off-label for age or for indication (diagnosis) by drug categories.[1]

[1] With 95% confidence intervals.

Table 4. Characteristics of Pediatric Prescription Visits (*N*=80,630,000 Visits)*

Characteristic	% of Visits *	95% CI
Patient		
Gender		
Female	48	44,53
Male	52	47,56
Race/Ethnicity		
White	67	58,75
Hispanic	18	11,26
Black	9	7,12
Other	6	3,9
Age		
<3 months	9	7,12
3 - <6 months	9	6,13
6 - <12 months	20	18,23
1 year - <2 years	36	33,40
2 years - <3 years	25	21,29
Region of the Country		
Northeast	21	5,59
Midwest	18	6,45
South	38	19,62
West	22	5,58
Visit		
Payment Source		
Private insurance	65	59,71
Medicaid	26	20,32
Self-pay	2	1,4
Other/unknown	7	4,10
Number of Prescription Medications Given		
1	69	65,73
2	23	21,26
≥3	7	5,10
Physician		
Specialty		
General Pediatrics	77	72,82
General or family practice	18	13,24
Other subspecialties	5	4,7
Solo practice		
Yes	23	70,82
No	77	18,30
Patient's primary care physician		
Yes	86	82,88
No	14	12,18

*Visits at the population level; unweighted *n*=1,811.

Table 5. Frequency and Proportion of Visits* with Off-Label Prescribing

Type of Off-Label Rx	No. of Off-Label Prescription Visits	Proportion of Total Prescription Visits (95% CI)
Off-label for age	33.6 million	42 (39,44)
Off-label for indication	42.9 million	53 (50,56)
Off-label for both age and indication	23.8 million	30 (27,32)
Off-label for either age or indication	52.7 million	65 (63-68)

*Visits at the population level (*N*=80,630,000); unweighted *n*=1,811 visits.

Table 6. Top 10 Medications with Most Prescriptions (Rx) Off-Label for Indication

Drug Name (Proprietary)	Drug Category	# of Off-Label Rx*	% of Off-Label Rx
1. amoxicillin	anti-infectives	4,966,000	9
2. albuterol	pulmonary	4,535,000	8
3. azithromycin (Zithromax™)	anti-infectives	2,975,000	5
4. nystatin (Mycostatin™)	dermatologics	2,436,000	4
5. levalbuterol (Xopenex™)	pulmonary	2,263,000	4
6. amoxicillin-clavulinate (Augmentin™)	anti-infectives	2,184,000	4
7. cetirizine (Zyrtec™)	upper respiratory tract	1,844,000	3
8. promethazine (Phenergan™)	upper respiratory tract	1,200,000	2
9. montelukast (SIngulair™)	pulmonary	1,174,000	2
10. hydrocortisone	dermatologics	1,133,000	2

*Rounded to the nearest thousand.

Table 7. Top 10 Medications with Most Prescriptions (Rx) Off-Label for Age

Drug name (Proprietary)	Drug Category	FDA-Approval Age*	# of Off-Label Rx^	% of Off-Label Rx
1. albuterol	pulmonary	4	6,547,000	15
2. levalbuterol (Xopenex™)	pulmonary	6	2,263,000	5
3. Pimecrolimus (Elidel™)	dermatologics	2	1,023,000	2
4. budensonide inhalational powder (Pulmicort™ turbuhaler)	pulmonary	6	1,003,000	2
5. amoxicillin	anti-infective	0.25	992,000	2
6. hydroxyzine (Atarax™)	upper respiratory tract	6	984,000	2
7. promethazine (Phenergan™)	upper respiratory tract	2	874,000	2
8. fluticasone oral inhalation (Flovent™)	pulmonary	4	839,000	2
9. montelukast sodium (Singulair™)	pulmonary	1	745,000	2
10. mometasone nasal (Nasonex™)	upper respiratory tract	2	716,000	2

*As of September 2007. Since 2007, Singulair has obtained FDA approval for six months and older.
^Rounded to the nearest thousand.

Table 8. Results of Logistic Regression Model Predicting Visit with Off-Label for Age or for Indication

Characteristic	Adjusted or for Visit with Off-Label Rx (95% CI^)	Adjusted Probability for Visit with Off-Label Rx	Difference in Adjusted Probabilities (95% CI^)
Gender			
Female	0.92 (0.73, 1.16)	65%	-2% (-6%, 3%)
Male	referent	67%	referent
Age			
0≤3 mo	**5.38 (2.93, 9.86)**	**88%**	**26% (19%, 33%)**
3≤6 mo	**2.27 (1.4, 3.67)**	**77%**	**15% (7%, 23%)**
6≤12 mo	0.96 (0.69, 1.33)	61%	-1% (-7%, 6%)
1≤2 yrs	1.08 (0.77, 1.5)	64%	2% (-5%, 8%)
2≤3 yrs	referent	62%	referent
Race/Ethnicity			
White/Non-Hispanic	referent	65%	referent
Hispanic	1.24 (0.85, 1.83)	69%	4% (-3%, 12%)
Black/African-American	1.28 (0.81, 2.01)	69%	4% (-3%, 13%)
Other	1.66 (0.99, 2.78)	74%	9% (0, 18%)
Region of the country			
Midwest	0.97 (0.61, 1.56)	69%	0% (-9%, 18%)
South	0.79 (0.55, 1.14)	65%	-4% (-11%, 2%)
Northeast	referent	69%	referent
West	0.79 (0.56, 1.1)	65%	-4% (-10%, 2%)
Payment source			
Private insurance	referent	66%	referent
Medicaid	1.16 (0.84, 1.62)	69%	3% (-4%, 9%)
Self-pay	0.98 (0.44, 2.17)	65%	-1% (-16%, 14%)
Other/unknown	0.88 (0.5, 1.54)	63%	-3% (-13%, 8%)
Number of Rx medications			
1	referent	57%	referent
2	**5.57 (4.012, 7.75)**	**87%**	**30% (26%, 35%)**
3 or more	**15.56 (6.03, 40.16)**	**95%**	**38% (33%, 43%)**
Solo practice			
No	referent	66%	referent
Yes	1.09 (0.78, 1.54)	67%	1% (-4%, 8%)
Other physicians share care			
No	referent	66%	referent
Yes	1.05 (0.76, 1.45)	67%	1% (-5%, 7%))
Physician specialty			
General pediatrics	referent	63%	referent
General or family practice	1.18 (0.78, 1.81)	67%	4% (-5%, 11%)
Subspecialties	**2.87 (1.85, 4.45)**	**82%**	**19% (11%, 24%)**

^CI=confidence interval.

References

American Academy of Pediatrics Committee on Drugs (AAP). (1997). Use of codeine- and dextromethorphan-containing cough remedies in children. *Pediatrics, 99*(6), 918-920.

Aparasu, R., & Bhatara, V. (2007). Patterns and determinants of antipsychotic prescribing in children and adolescents, 2003-2004. *Current Medical Research and Opinion, 23*, 49-56.

Arason, A., Kristinsson, K., Sigurdsson, J., Stefansdottir, G., Molstad, S., & Gundmundsson, S. (1996). Do antimicrobials increase the carriage rate of penicillin resistant pneumococci in children? Cross sectional prevalence study. *British Medical Journal, 313,* 387-391.

Arroll, B., & Kenealy, T. (2005). Antibiotics for the common cold and acute purulent rhinitis. *Cochrane Database of Systematic Reviews, 3,* CD000247.

Bazzano, A. T., Mangione-Smith, R., Schonlau, M., Suttorp, M. J., & Brook, R. H. (2009). Off-label prescribing to children in the United States outpatient setting. *American Academy of Pediatrics, 9*(2), 81-88.

Bisgaard, H., Hermansen, M. N., Loland, L., Halkjaer, L. B., & Buchvald, F. (2006). Intermittent inhaled corticosteroids in infants with episodic wheezing. *New England Journal of Medicine, 354*(19), 1998-2005.

Bucheler, R., Schwab, M., Morike, M., Kalchthaler, B., Mohr, H., Schroder, H., . . . Gleiter, C. H. (2002). Off-label prescribing to children in primary care in Germany: Retrospective cohort study. *British Medical Journal, 324*(7349), 1311-1312.

Carrin, G. (1987). Drug prescribing: A discussion of its variability and (ir)rationality. *Health Policy, 7*, 73-94.

Centers for Disease Control and Prevention (CDC). (2007). Infant deaths associated with cough and cold medications--two states, 2005. *Morbidity and Mortality Weekly Report, 56*, 1-4.

Chalumeau, M., Treluyer, J., Salanave, B., Assathiany, R., Cheron, G., & Crocheton, N. (2000). Off-label and unlicensed drug use among French office based paediatricians. *Archives of Disease in Childhood, 83,* 502-505.

Chavasse, R., Seddon, P., Bara, A., & McKean, M. (2002). Short acting beta2-agonists for recurrent wheeze in children under two years of age. *Cochrane Database of Systematic Reviews, 3*(2), CD002873.

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

Cherry, D. K., Burt, C. W., & Woodwell, D. (2003). National ambulatory medical care survey: 2001 summary. *Advanced Data, 337*, 1-44.

Clark, J. A., Potter, D. A., & McKinlay, J. B. (1991). Bringing social structure back into clinical decision making. *Social Science and Medicine, 32*(8), 853-866.

Conroy, S., McIntyre, J., & Choonara, I. (1999). Unlicensed and off-label drug use in neonates. *Archives of Disease in Childhood. Fetal and Neonatal Edition, 80*(2), 142-145.

Cooper, W. O., Arbogast, P. G., Ding, H., Hickson, G. B., Fuchs, D. C., & Ray, W. A. (2006). Trends in prescribing of antipsychotic medications for U.S. children. *Ambulatory Pediatrics, 6*, 79-83.

De Sutter, A., Lemiengre, M., Campbell, H., & Mackinnon, H. (2003). Antihistamines for the common cold. *Cochrane Database of Systematic Reviews, 3*, CD001267.

Denig, P., Witteman, C. L., & Schouten, H. W. (2002). Scope and nature of prescribing decisions made by general practitioners. *Quality and Safety in Health Care, 11*(2), 137-143.

Easton, J., Hilman, B., Shapiro, G., Weinberger, M., Anderson, J., Buckley, J., . . . Bierman, C. W. (1981). Management of asthma. *Pediatrics, 68*(6), 874-879.

Eiland, L., & Knight, P. (2006). Evaluating the off-label use of medications in children. *American Journal of Health-System Pharmacy, 63,* 1062-1065.

Ekins-Daukes, S., Helms, P. J., Simpson, C. R., Taylor, M. W., McLay, J. S. (2004). Off-label prescribing to children in primary care: Retrospective observational study. *European Journal of Clinical Pharmacology, 60*(5), 349-533.

Giacoia, G., & Mattison, D. (2005). Newborns and drug studies: The NICHD/FDA newborn drug development initiative. *Clinical Therapeutics, 27,* 796-813.

GlaxoSmithKline. (2010). *Lamictal* [package insert]. Research Triangle Park, NC: Author.

Horen, B., Montastruc, J., & Lapeyre-Mestre, M. (2002). Adverse drug reactions and off-label drug use in paediatric outpatients. *British Journal of Clinical Pharmacology, 54*, 665-670.

Lipworth, B. J. (1999). Systemic adverse effects of inhaled corticosteroid therapy: A systematic review and meta-analysis. *Archives of Internal Medicine, 159*(9), 941-955.

Lischner, H., Seligman, S. J., Krammer, A., & Parmelee, A. H., Jr. (1961). An outbreak of neonatal deaths among term infants associated with administration of chloramphenicol. *Journal of Pediatrics, 59*, 21-34.

McIntyre, J., Conroy, S., Avery, A., Corns, H., & Choonara, I. (2000). Unlicensed and off-label prescribing of drugs in general practice. *Archives of Disease in Childhood, 83*, 498-501.

Micromedex. (2004). *Volume I USP DI: Drug information for the health care professional.* Greenwood Village, CO: Thompson.

Moore, T. J., Weiss, S. R., Kaplan, S., & Blaisdell, C. J. (2002). Reported adverse drug events in infants and children under two years of age. *Pediatrics*, *110*(5), e53.

Novartis Pharmaceuticals Corp. (2007). *Elidel full prescribing information*. East Hanover, NJ: Author.

Olfson, M., Blanco, C., Lui, L., Moreno, C., & Laje, G. (2006). National trends in the outpatient treatment of children and adolescents with antipsychotic drugs. *Archives of General Psychiatry, 63*(6), 679-685.

Physician's Desk Reference. (2007). *Physician's desk reference*. Montvale, NJ: Medical Economics Co.

Randell, T. L., Donaghue, K. C., Ambler, G. R., Cowell, C. T., Fitzgerald, D. A., & van Asperen, P. P. (2003). Safety of the newer inhaled corticosteroids in childhood asthma. *Paediatric Drugs, 5*(7), 481-504.

Rice, D., & Barone, S., Jr. (2000). Critical periods of vulnerability for the developing nervous system: Evidence from humans and animal models. *Environmental Health Perspectives, 108*, 511-533.

Roberts, R., Rodriguez, W., Murphy, D., & Crescenzi, T. (2003). Pediatric drug labeling: Improving the safety and efficacy of pediatric therapies. *Journal of the American Medical Association, 290*, 905-911.

Robertson, J., & Shilkofski, N. (2005). *The Harriet Lane handbook: A manual for pediatric house officers*. Philadelphia, PA: Mosby.

Schirm, E., Tobi, H., & de Jong-van den Berg, T. (2003). Risk factors for unlicensed and off-label drug use in children outside the hospital. *Pediatrics, 111,* 291-295.

Sen, E., Verhamme, K., Felisi, M., 'tJong, G., Giaquinto, C., Picelli, G., . . . Sturkenboom, M. C. (2011). Effects of safety warnings on prescription rates of cough and cold medicines in children below two years of age. *British Journal of Clinical Pharmacology, 71*(6), 943-950.

Shah, S. S., Hall, M., Goodman, D. M., Feuer, P., Sharma, V., Fargason, C. Jr., . . . Slonim, A. D. (2007). Off-label drug use in hospitalized children. *Archives of Pediatrics & Adolescent Medicine, 161*(3), 282-290.

Smith, M., & Feldman, W. (1993). Over-the-counter cold medications. A critical review of clinical trials between 1950 and 1991. *Journal of the American Medical Association, 269*(17), 2258-2263.

Starke, P. R., Weaver, J., & Chowdhury, B. A. (2005). Boxed warning added to promethazine labeling for pediatric use. *New England Journal of Medicine, 352*, 2653.

Steinbrook, R. (2002). Testing medications in children. *New England Journal of Medicine, 347*(18), 1462-1470.

't Jong, G. W., Eland, I. A., Sturkenboem, M. C., van der Anker, J. N., & Stricker, B. H. (2003). Determinants for drug prescribing to children below the minimum licensed age. *European Journal of Clinical Pharmacology, 58*, 701-705.

Taverner, D., & Latte, J. (2007). Nasal decongestants for the common cold. *Cochrane Database of Systematic Reviews, 1,* CD001953.

Thompson, D., & Heflin, N. R. (1987). Frequency and appropriateness of drug prescribing for unlabeled uses in pediatric patients. *American Journal of Hospital Pharmacy, 44,* 792-794.

Turner, S., Nunn, A. J., Fielding, K., & Choonara, I. (1999). Adverse drug reactions to unlicensed and off-label drugs on paediatric wards: A prospective study. *Acta Paediatrica, 88,* 965-968.

U.S. Center for Drug Evaluation and Research, Food and Drug Administration (CDER, FDA). (2011). *Pediatric studies characteristics.* Retrieved from http://www.accessdata.fda.gov/scripts/SDA/sdNavigation.cfm?filter=&sortColum*n*=6a&sd=fdaaadescriptorssortablewebdatabase&page=1

U.S. Center for Drug Evaluation and Research, Food and Drug Administration (CDER, FDA). (2000). *Public health advisory: Safety of phenylpropanolamine.* Washington, DC: Author.

Ufer, M., Rane, A., Karlsoon, A, Kimland, E., & Bergman, U. (2003). Widespread off-label prescribing of topical but not systemic drugs for 350,000 paediatric patients in Stockholm. *European Journal of Clinical Pharmacology, 58*, 779-783.

Vernacchio, L., Kelly, J. P., Kaufman, D. W., & Mitchell, A. A. (2009). Medication use among children <12 years of age in the United States: Results from the Slone survey. *Pediatrics, 124*(2), 446-454.

Walker, A. E., Grimshaw, J. M., & Armstrong, E. M. (2001). Salient beliefs and intentions to prescribe antibiotics for patients with a sore throat. *British Journal of Health Psychology, 6*(4), 347-360.

CHAPTER 4: DIFFERENCES IN OFF-LABEL PRESCRIBING TO CHILDREN FOR AGE VERSUS FOR INDICATION

Abstract

Background. Previous studies have determined that off-label prescribing to children is pervasive. However, few studies have compared off-label prescribing for age, in which drug safety has not been scrutinized by the U.S. Food and Drug Administration (FDA), with off-label prescribing for indication, in which drug efficacy has not been reviewed by the FDA. Differences in prescribing frequencies, medications, patient and physician characteristics could warrant different approaches to interventions.

Objective. The first objective of this study was to determine the frequencies of off-label prescribing for age and off-label prescribing for indication to U.S. children at outpatient visits. The second objective was to compare off-label prescribing for age to off-label prescribing for indication in terms of most commonly used medications and classes, patient characteristics and physician specialty.

Methods. We analyzed data from the National Ambulatory Medical Care Survey over a four year period (2001-2004). This probability sample survey of outpatient visits was used to derive nationally representative estimates of numbers and proportions of visits that included off-label prescribing for age or for indication. We used two multivariate logistic regression models to determine which patient, visit and physician characteristics were associated with off-label prescribing for age and for indication.

Results. Of the estimated 312 million children's visits (unweighted *n*=7901 visits), 25% (95% CI: 23%, 27%) included off-label prescribing for age and 53% (95% CI: 50%, 56%) included off-label prescribing for indication. Whereas no age-related differences were found with off-label prescribing for indication, visits by children aged 0-2 years involved more off-label

prescribing for age (46%, 95% CI: 42%,50%) than did other age groups. Anti-infectives, upper respiratory medications, and pulmonary medications were much more commonly prescribed off-label for indication (41%, 52%, and 61%) than for age (6%, 16%, and 24%). Physician specialists were 14% (95% CI: 7%, 20%) more likely to prescribe off-label for age than general pediatricians or family physicians.

Conclusions. We found striking differences between the epidemiologic profiles of off-label prescribing for indication and for age. Children are consistently exposed to medications that are off-label for indication and this exposure is disproportionate in comparison to adults. Medications used off-label for age, though used relatively less frequently, require special prioritization for study due to safety concerns. FDA policies should be strengthened to increase such study, mandate patient registries to assess off-label prescribing over time, and provide more accessible prescribing information. Physician prescribing education, especially for subspecialists, should be targeted at the most commonly prescribed drugs within each type of off-label prescribing.

Introduction

Medications are scrutinized and approved by the U.S. Food and Drug Administration (FDA) for a specific indication and population. Once the medication receives a license, physicians may legally prescribe the medication for an unapproved indication, in an unapproved age group, in an unapproved formulation, or at an unapproved dose. The FDA considers this part of the "practice of medicine" and does not interfere with this prescribing (Stafford, 2008). Though children are vulnerable to all of the types of off-label prescribing, most often off-label prescribing for indication and for age have been studied and addressed by policymakers.

Off-label prescribing for indication occurs when a physician prescribes a medication for an indication or diagnosis that is different from that which the drug is approved by the FDA. In this case, the drug has been approved as safe for the patient's age, but the medication has not undergone FDA scrutiny with regard to efficacy for treating the diagnosis. This prescribing is very common across all physicians and patient groups (Radley, Finkelstein, & Stafford, 2006). One notorious example of this type of off-label prescribing is gabapentin. This medication was originally approved as an anti-epileptic and was quickly promoted and used off-label for diagnoses ranging from neuropathic pain to headaches (Steinman, Bero, Chren, & Landefeld, 2006). In the largest settlement of its kind until 2004, the manufacturer was fined $430 million for promotion of off-label use.

Off-label prescribing for age occurs when a physician prescribes a medication to a child who is younger than the FDA-approved age. The drug manufacturer has not obtained FDA-approval indicating that the drug is safe or effective for the patient's age group. In general, the youngest children appear most at risk for off-label prescribing for age (Bazzano, Mangione Smith, Schonlau, Suttorp, & Brook, 2009; Shah et al., 2007). One study indicated that 50% of cardiovascular medications were prescribed to children younger than the FDA-approved age (Yoon, Dombkowski, Rocchini, Lin, & Davis, 2007).

Historically, the FDA has regulated drug safety and drug efficacy differently, in large part as a result of pediatric drug prescribing. In 1937, a liquid preparation of the antibiotic sulfanilamide, which contained diethylene glycol (a.k.a. "antifreeze"), killed 107 people, primarily children. This tragedy led to the 1938 Federal Food, Drug and Cosmetics Act (serving as the basis for today's FDA), which required that safety be proven before marketing a drug. In 1962, thalidomide caused phocomelia (limb defects) in thousands of babies, prompting the

Kefauver-Harris Drug Amendment, which required establishment of efficacy prior to marketing drugs. When studying drugs in humans for FDA approval, safety trials are completed first (phase I) and are followed by efficacy trials (phase II and III). Nonetheless, despite historical precedents, most drugs have not been studied on children and their labels have carried the statement "Safety and effectiveness have not been examined in children." Recently, growing concerns about lack of pediatric prescribing information in the face of increased pediatric prescribing have prompted legislation encouraging and in some cases mandating safety and efficacy studies of pediatric populations for FDA review (Best Pharmaceuticals for Children Act, 2002). Since 1997, these policies have resulted in a number of medications receiving FDA scrutiny and labeling for children of different ages and for pediatric indications (Roberts, Rodriguez, Murphy, & Crescenzi, 2003).

We have previously reported on off-label prescribing to U.S. children in general, combining off-label for age and for indication (Bazzano et al., 2009). Others have described off-label prescribing to children for age only (Shah et al., 2007) or indication only (Radley et al., 2006). In a small study in a single teaching hospital, Eiland and Knight found significant differences in rates of off-label prescribing for age (10%) versus indication (21%) as well as in which medications were prescribed off-label for age or indication (Eiland & Knight, 2006). To our knowledge, studies have not compared off-label prescribing for indication with off-label prescribing for age in U.S. children in the outpatient setting.

Determining which medications are most frequently prescribed off-label for indication and off-label for age can assist with prioritization of efficacy and safety studies. Understanding whether factors such as drug category, child's age and physician specialty differ among off-label prescribing for age and off-label prescribing for indication could help policymakers and

clinicians understand the breadth of the practice in order to better target solutions appropriate to each type of off-label prescribing. Thus, the objectives of this study were to determine the frequency of off-label prescribing for age and off-label prescribing for indication as well as to compare them in terms of medication categories, most common medications, children's ages and physician specialties.

Methods

This study used National Ambulatory Medical Care Survey (NAMCS) data from a four-year period (2001-2004) to examine off-label prescribing for age and indication to children. The NAMCS is a nationally representative probability sample survey of outpatient medical visits conducted by the National Center for Health Statistics intended for use to describe the national population of visits.

Office-based, non-federally employed physicians engaged in direct patient care, not including anesthesiology, pathology and radiology, and their office staff completed the survey regarding approximately 30 visits randomly selected during a 1-week period. The 1-page written survey included questions on patient demographics, reason for the visit, diagnoses (up to three), diagnostic testing, medications (up to six), and follow-up. In addition, data are collected on physician demographics and type of practice. During 2001-2004, 5501 physician offices participated (64-70% of eligible).

Our sample consisted of all visits by children less than 18 years old during which a medication available by prescription was given (prescription visits). We excluded vitamins, oxygen, vaccines, over-the-counter medications, nutritional products, nonspecific treatments (e.g., "antibacterial agent"), non-medications (e.g., infant oil, soap), and rarely prescribed medications (e.g., chloramphenicol, domperidone) in our definition of prescription medications.

We reviewed all NAMCS drug names for accuracy, and combined brand name and generic drugs (e.g. albuterol and Proventil™) to ensure precise drug counts.

Dependent Variables: Off-Label Prescribing for Age and Off-Label Prescribing for Indication

We considered a prescription to be "off-label for age" if the child's age was younger than the FDA-approval age. A prescription was considered "off-label for indication" if none of the given diagnoses corresponded to an FDA-approved indication. FDA-approved age and indications were obtained from the package insert (label), the Physician's Desk Reference (Physician's Desk Reference, 2007), FDA website (Center for Drug Evaluation and Research, Food and Drug Administration [CDER, FDA], n.d.) or other compendia. These indications were converted into *International Classification of Disease, 9th Revision, Clinical Modification* (World Health Organization [WHO], 2006) codes to correspond with the NAMCS diagnosis variable. For consistency across data years, we used the latest available prescription information as of September 1, 2007. For generic equivalents for which children's prescribing information was unavailable, we substituted brand-name medication information. A prescription visit was considered off-label if at least one prescription from that visit was off-label.

Independent Variables of Interest

Drug Category

We used NAMCS drug categories, based on National Drug Code (NDC) Directory classifications, which broadly categorize drugs by their uses. We did not change drug category based on potential off-label uses of a medication.

We reclassified categories with small sample sizes and drug similarities. For example, we combined anti-parasitics with antimicrobials, and we added neurological medications to central

nervous system medications, which included psychiatric medications. The respiratory tract category was divided into upper respiratory drugs and pulmonary drugs.

Child's Age

Age was categorized as 0 to <2 years, 2 to <6 years, 6 to <12 years, and 12 to <18 years. These categories translate roughly to infants and toddlers, preschoolers, school age and adolescents and reflect standard pediatric groupings.

Physician Specialty

NAMCS classifications of physician specialties were combined into larger categories than originally in NAMCS due to sample size limitations. Our categories included generalists and family physicians, general pediatricians, and other specialists.

Covariates

We included relevant patient demographic variables, such as gender, race/ethnicity, region of the country, and urban vs. rural as model covariates. In addition, we measured presence of chronic disease based on whether the patient had one of any diagnoses on a list of chronic and severe pediatric conditions previously used in the literature (Kuhlthau, Beal, Ferris, & Perrin, 2002). Expected payment source (private insurance, Medicaid, self-pay or other), number of visits in the past 12 months, number of medications prescribed at the visit (1, 2, 3-6) and whether the physician shared care for the diagnosis with another provider (yes or no) were included as visit characteristics.

Statistical Analysis

Our analyses used weighted national estimates of visits. In order to construct unbiased national population estimates, NAMCS used a multistage stratified sampling design in which visits are sampled within physicians who are sampled within geographic areas of the country.

These visits are weighted to reflect under or over-representation within the sample. In addition, we corrected for clustering, or similarities of visits by the same provider or region of the country. More detailed descriptions of sampling and weighting procedures of NAMCS are available online (Centers for Disease Control and Prevention [CDC], n.d.).

We used descriptive analyses that were weighted to reflect population estimates of off-label prescribing for age and off-label prescribing for indication and the same techniques were used for each type of off-label prescribing. The frequency of off-label prescribing at visits was defined as the number of visits in which at least one off-label medication was prescribed. The proportion of visits with at least one off-label prescription was determined by dividing the visits in which an off-label prescription was provided by the total number of visits in the sample. We compared frequencies and proportions of off-label prescribing for indication and for age among various age groups and drug categories at the visit level. The most frequently prescribed medications were tabulated from weighted estimates as well.

We analyzed factors that could be associated with off-label prescribing by utilizing two multiple logistic regression models with the dependent variables of off-label prescribing for age and off-label prescribing for indication. The unit of analysis was patient visit. We derived bivariate analyses and then incorporated into our final model those variables which showed significance at the $p < 0.1$ level. We also included demographics in our final models regardless of bivariate significance. We determined multivariate adjusted probabilities for each variable using the recycled predictions technique to illustrate the independent probability that each variable was associated with off-label prescribing with all other variables held constant. We also calculated differences in adjusted probabilities and their confidence intervals. To ensure accuracy of confidence intervals while avoiding parametric assumptions of our estimation sample (Carpenter,

& Bithell, 2000), we bootstrapped the confidence intervals using the bias-corrected method. All analyses were performed using Intercooled Stata 9.0 (StataCorp LP, College Station, TX). Statistical significance was predetermined as $p < 0.05$.

Results

An estimated 312 million visits in which at least one medication was prescribed (prescription visits) were included in the analysis. Sample characteristics have been reported elsewhere (Bazzano et al., 2009). In brief, visits involved slightly more male children (52%) and about two-thirds of children were white (71%), about one-sixth were Hispanic (14%) and one-tenth were black (10%). Almost a third of visits involved adolescents (29%), or school aged children (28%), with almost one-quarter involving preschoolers (23%) and the remainder infants (20%). One fourth of children had chronic diseases.

During prescription visits overall, off-label prescribing was twice as common for indication than for age, with 53% (95% CI, 50%-56%) of visits including off-label prescribing for indication and 25% (95% CI, 23%-27%) including off-label prescribing for age (Table 9). Younger children more often received medications that are off-label for age; 46% of those less than two years old received medications approved only for older children whereas for those over two years old, about 20% of visits included off-label prescribing for age. There was no association between age and off-label prescribing for indication and 50-56% of visits by children in each age group included this off-label prescribing.

Vast differences were found between rates of the two types of off-label prescribing by drug categories. Off-label prescribing for age was rare for anti-infectives (6%), and increased in frequency for upper respiratory medications (16%), pulmonary drugs (24%), ophthalmologics

(30%), drugs affecting the central nervous system (32%), and dermatologics (39%). Over half of cardiovascular-renal medications (70%), gastrointestinal drugs (61%) and pain medications (55%) were prescribed off-label for age (Figure 4). Anti-infectives, upper respiratory medications, and pulmonary medications were much more commonly prescribed off-label for indication (41%, 52%, and 61% respectively) than for age. Almost half of dermatological (42%) and central nervous system (47%) prescriptions were off-label for indication. Most prescriptions for pain medications (70%), gastrointestinal drugs (68%) and cardiovascular-renal medications (80%) were off-label for indication (Figure 5).

The medications most commonly prescribed off-label for age spanned across medication categories. The top-ranked were the two related pulmonary medications, albuterol and levalbuterol, which together accounted for about 10 million prescriptions (Table 10). Polyethylene glycol, a gastrointestinal medication used for constipation, ranked third. Four medications affecting the central nervous system were among the top 20 prescribed off-label for age. These included the antidepressants, paroxetine, buproprion and escitalopram as well as the second generation anti-psychotic, quetiapine. Several upper respiratory medications were among the top medications, including triamcinolone actetonide, a nasal steroid, and two products containing first generation antihistamines, chlorpheniramine/phenylephrine and hydroxyzine. Medications most commonly prescribed off-label to infants (0≤2 years) included pulmonary, dermatologics, upper respiratory and antibiotics. In adolescents, 8 of the 10 most commonly prescribed off-label were medications affecting the central nervous system and two were pain medications.

In contrast, the medications that were most commonly prescribed off-label for indication cluster around fewer drug categories. Several of the medications prescribed for a non-approved

indication were anti-infectives. Top overall and among the anti-infectives were amoxicillin and azithromycin, accounting for 28 million prescriptions, with amoxicillin-clavulanate prescriptions accounting for over nine million of those off-label for indication (Table 10). The pulmonary medications, albuterol and montelukast sodium, accounted for more than 11 million off-label uses each. Others among the top 20 from the pulmonary medications included levalbuterol and fluticasone oral inhalation, and each was prescribed off-label for indication about five million times. The other group of medications that ranked highly in terms of use for unapproved indications was the upper respiratory medications, such as cetirizine, promethazine, fluticasone and fexofenadine. The medications most commonly prescribed off-label for indication were similar across age groups.

In multiple logistic regression analysis, we found significant differences among factors associated with off-label prescribing for age compared to off-label prescribing for indication. Child's age was significantly associated with rates of off-label prescribing for age (Table 11). Those children who were 6-12 years old had a 23% adjusted probability of receiving an off-label medication not approved for their age group; in contrast, the adjusted probability for infants less than a year of age was 61% and for those between 1 and 2 years of age, it was 50%. Payment source also was associated with differences in off-label prescribing for age. Those with private insurance had the lowest adjusted probability of off-label prescribing for age (26%), whereas those who had Medicaid or self-pay were more likely to receive at least one prescription that was off-label for age (31% and 41% adjusted probabilities respectively). The number of medications also predicted a visit that included receipt of a prescription that was off-label for age--those visits that included three or more prescriptions had the highest risk, with 49% adjusted probability of at least one of those medications being off-label for age. Finally, visiting general pediatricians

conferred lower predicted probability of off-label prescribing for age (21%) than visiting other specialties (39%) or general/family medicine practitioners (25%).

In contrast, only two factors were significantly associated with off-label prescribing for indication in multiple logistic regression modeling. Having a chronic disease reduced the adjusted probability of off-label prescribing for indication by 6% compared to those who did not have chronic diseases (Table 11). Increasing number of medications was also associated with increased probability of off-label prescribing for indication, with those receiving one prescription having a 41% adjusted probability, whereas receipt of three or more prescriptions conferred an additional 44% chance of off-label prescribing (for a total of 85% adjusted probability).

Discussion

Our findings suggest that there are striking differences in national patterns of off-label prescribing to children, with off-label prescribing for indication twice as common as off-label prescribing for age. To our knowledge, this is the first study to compare off-label prescribing for age and for indication in a nationally representative sample of U.S. children. These findings have important clinical and public health implications. Half of visits during these four years involved off-label prescribing for indication. In comparison, a recent national study revealed that 21% of prescriptions to adults were off-label for indication (Radley et al., 2006). Children are receiving prescriptions without evidence that they will be effective as assured through FDA-approval at an alarming rate. The disparity of this exposure in comparison to adults necessitates further study to determine the underlying mechanisms and consequences of this prescribing behavior to children. In particular, research should focus on understanding differences in factors surrounding pediatric visits that contribute to off-label prescribing for non-approved indications in children.

Furthermore, the large degree of off-label prescribing for indication to children supports maintenance and strengthening of FDA regulation of advertising of off-label uses.

Given the large reliance on the practice, it appears that off-label prescribing to children for unapproved indications is unlikely to be eliminated. In fact, in evaluating off-label prescribing for an indication that is not labeled, an argument can be made in select cases for clinical appropriateness if there is good quality evidence of effectiveness in the medical literature. In some cases, substantial literature exists to support the use of the medication for the off-label diagnosis and this information has not been incorporated into the label. For example, ondansetron has FDA approval for the indications of chemotherapy-related, radiation therapy-related and post-operative vomiting. It has been found effective in clinical trials and is often used for vomiting related to gastroenteritis (Freedman, Adler, Seshadri, & Powell, 2006). In these cases, the physician may have a foundation for prescribing for an off-label indication. With FDA surveillance of this literature, the agency could make an argument of substantial off-label use of medications and potentially require pharmaceutical manufacturers to put forth the product for FDA approval.

On the other hand, previous studies on children and adults have shown that off-label prescribing typically occurs in the absence of evidence of effectiveness (Radley et al., 2006). One study demonstrated that 79% of off-label prescribing for indication in adults did not have a body of supporting evidence for efficacy (Eguale et al., 2012). Likewise, children often receive off-label prescriptions for indications that are non-evidence based and do not follow practice guidelines (Pandolfini, Campi, Clavenna, Cazzato, & Bonati, 2005). Pediatric studies also point to increased rates of adverse events and serious harm with off-label prescribing for indication (Horen, Montastruc, & Lapeyre-Mestre, 2002). In the absence of evidence, physicians and

patients may benefit from a standardized approach to determining and documenting whether off-label prescribing for unapproved indications is appropriate (Gazarian et al., 2006).

Whereas the majority of prescribing was off-label for indication, off-label prescribing for age involved a smaller portion of children and disproportionately affected younger children (0-2 year olds). Fewer medications are tested or approved in this age group. The FDA considers medications that are off-label for indication differently from those which are used off-label for age in terms of requirements for study. In order to gain FDA approval, these drugs require studies indicating safety in younger age groups, including pharmacokinetic and pharmacodynamic profiles. Some newer medications fall under recent regulations that require or give incentives for studying children if the drug is expected to treat children (Best Pharmaceuticals for Children Act, 2002; Pediatric Research Equity Act, 2003). Other, especially older, medications are less likely to be studied, with a few exceptions such as albuterol (which was denied FDA approval for children <4 years old). Some have argued for high-cost, high-risk older drugs to be prioritized for study (Walton et al., 2008). We agree with that recommendation and would like to see it expanded to highly utilized drugs as well and those in certain high-risk populations (e.g., infants and toddlers).

One of the major barriers to decreasing off-label prescribing for age is thought to be difficulty in studying children. While this may be true for classic randomized controlled trials, alternatives that provide data on large numbers of children at lower cost do exist. In particular, given the national mandate for use of electronic medical records, patient registries are becoming an accessible, low cost option to follow cohorts of children over time. For example, the FDA mandated a strict registry for oral tretinoin (Accutane) prescribers and users (Martin, 2006), pregnancy registries follow women taking anti-convulsants (Holmes, Wyszynski, & Lieberman,

2004), and the Centers for Disease Control administers a national network of cancer registries that Congress authorized in 1992 (CDC, 2012). While we believe the major goal should be to reduce off-label prescribing for age, children currently taking medications off-label would benefit from similar registries.

Medications most commonly used off-label for indication closely mirrored the medications most commonly prescribed overall to children (Vernacchio, Kelly, Kaufman, & Mitchell, 2009) and included those drug categories in which the most prescribing occurred (antibiotics, pulmonary, upper respiratory). In contrast, the medications most commonly prescribed off-label for age followed more typical patterns of adult prescribing (Vernacchio et al., 2009). This finding is concerning especially for the central nervous system medications, and newer antipsychotics in particular, which have a poor evidence base and significant safety concerns in children (Correll, 2008; Egger, 2010). On a policy level, this finding indicates that the FDA's incentives and requirements for study of pediatric drugs may not be sufficient even for newer medications. Furthermore, especially for children, FDA should continue to uphold its high standards with regard to studies required for labeling.

Factors associated with off-label prescribing for indication differed from those associated with off-label prescribing for age. Children with chronic diseases were prescribed medications that were off-label for indication less often than children without chronic diseases. This is consistent with adult literature in which patients with higher co-morbidities had lower off-label use (Eguale et al., 2012). Indications on labels tend to correspond to diagnoses, such as diabetes, rather than symptoms, such as fever and cough. Thus, children with some chronic diagnoses may already benefit from increased study and labeling of medications. Additionally, children with co-morbidities may not receive off-label medications due to higher risks of adverse drug

interactions (Levi, Levy, Andersen, & Truloff, 2010). With regard to insurance, children with Medicaid or who were self-pay were exposed to off-label prescribing for age more frequently, a result that is consistent with previous studies (Leslie & Rosenheck, 2012); this may be due to formulary restrictions by private insurers or perhaps that children with Medicaid may receive older, generic drugs that have not been approved and have little incentive for study. Finally, subspecialists were more apt to prescribe medications that were off-label for age than general pediatricians. Subspecialists, especially those not trained in pediatrics, may not have as much familiarity with medications for children (Li, Jaffe, Li, & Haynes, 1998) or approved ages and safety concerns regarding differences between children of different ages and adults. Continuing education and prescribing incentives, using techniques with proven effectiveness, regarding prescribing for different age groups may be helpful in reducing off-label prescribing for age by subspecialists.

Limitations

This study was a secondary analysis of a national database of outpatient visits. It was not originally specifically intended to analyze off-label prescribing and as such, several variables that may better characterize differences between off-label prescribing for age and for indication are not present. Though the NAMCS database is frequently used for prescribing data and has been used for other off-label prescribing studies, a more specific prospective data set could help guide interventions. The NAMCS data measure a specific four-year period. Prescribing is a physician behavior that changes over time and specific frequencies may have changed as new drugs are marketed since the study began. Already marketed medications are also undergoing label revisions in response to pediatric study so that some medications previously considered off-label for age might now be labeled. Nonetheless, as one of the first national studies of

off-label prescribing at children's office visits, this may serve as a reference with which to compare future research.

Conclusions

This study indicates that children are prescribed medications off-label for indication much more frequently than off-label for age. In comparison to adults, children are disproportionately exposed to medications that are off-label for indication. Medications prescribed off-label for age, though used less frequently, require special prioritization for study due to safety concerns. FDA policies should be strengthened to require such study, mandate registries, and provide more accessible prescribing digests. Physician education and prescribing incentives should be targeted at these most commonly prescribed drugs within each type of off-label prescribing.

Table 9. Off-Label Prescribing for Age and for Indication by Age Group (*N*=312 Million Based on Unweighted *n*=7901 Visits)

Age Group	Proportion of Visits with Off-Label Prescribing for age (95% CI)	Proportion of Visits with Off-Label Prescribing for Indication
0 to <2 years	46% (42, 50)	50% (45, 55)
2 to <6 years	21% (17, 26)	56% (52, 60)
6 to <12 years	19% (16, 23)	52% (46, 57)
12 to <18 years	20% (17, 23)	56% (52, 59)
Total	25% (23, 27)	53% (50, 56)

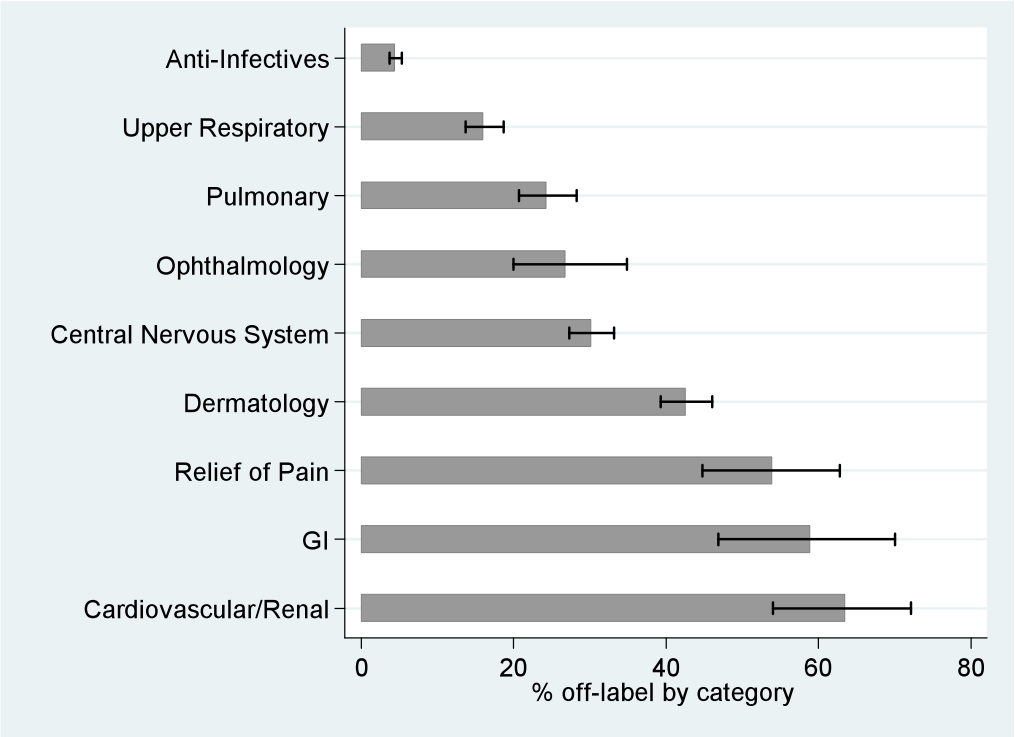

Figure 4. Percentage of off-label prescriptions for age in each drug category (N=484,010,000 estimated prescriptions).

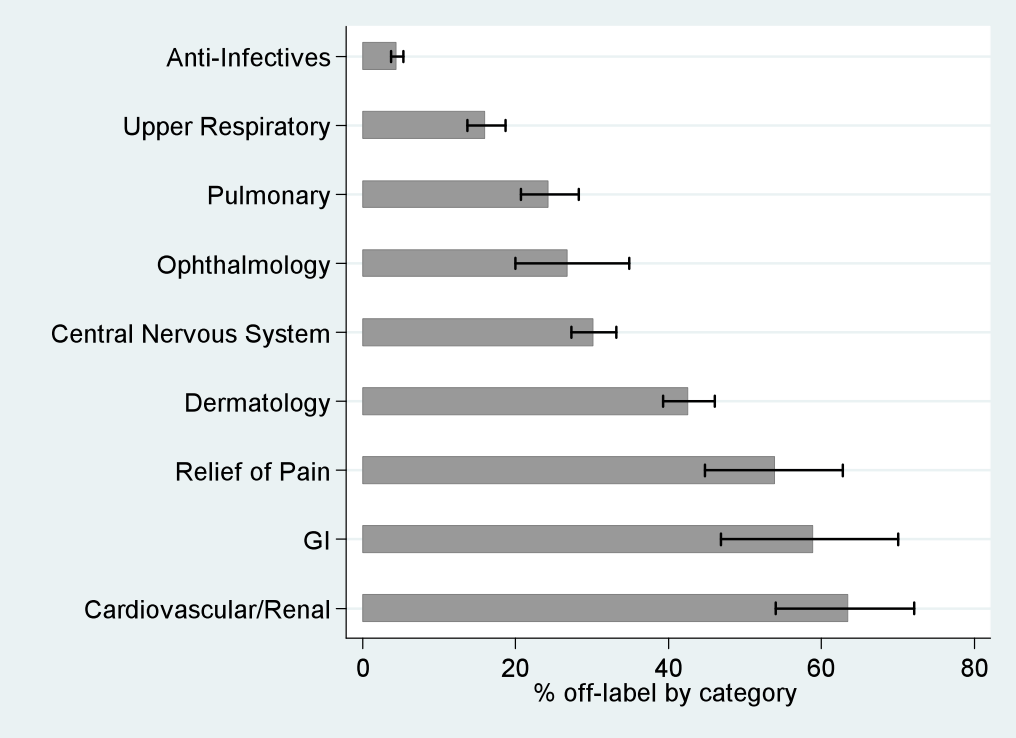

Figure 5. Percentage of off-label prescriptions for indication in each drug category (N=484,010,000 estimated prescriptions).

Table 10. A Comparison of the Top 20 Most Common Medications Off-Label for Age vs. Off-Label for Indication (*N*=484,010,000 Estimated Prescriptions; Unweighted *n*=12,432 Prescriptions)

Rank	Off-Label for Age				Off-Label for Indication		
	Medication (Proprietary Name)	**Drug Category**	**No. of Rx Off-Label for Age**	**FDA Approval Age (Yrs)**	**Medication (Proprietary Name)**	**Drug Category**	**No. of Rx Off-Label for Indication**
1	Albuterol	Pulmonary	6,550,000	4	Amoxicillin	Anti-infectives	14,980,000
2	Levalbuterol (Xopenex)	Pulmonary	3,480,000	6	Azithromycin	Anti-infectives	13,090,000
3	Polyethylene glycol (MiraLax)[#]	Gastrointestinals	3,320,000	17	Albuterol	Pulmonary	11,240,000
4	Mometasone (Nasocort)	Upper respiratory	1,800,000	2	Montelukast sodium (Singulair)	Pulmonary	11,030,000
5	Paroxetine (Paxil)	CNS	1,750,000	18	Amoxicillin-clavulanate (Augmentin)	Anti-infectives	9,240,000
6	Chlorpheniramine /phenylephrine (Ryantan)	Upper respiratory	1,600,000	18	Cetirizine (Zyrtec)	Upper respiratory	9,040,000
7	hydroxyzine	Upper respiratory	1,430,000	6	Loratadine (Claritin)	Upper respiratory	5,160,000
8	Budesonide inhalation powder (Pulmocort turbuhaler)	Pulmonary	1,330,000	6	Levalbuterol (Xopenex)	Pulmonary	5,080,000
9	Buproprion (Wellbutrin)	CNS	1,280,000	6	Fluticasone oral inhalation (Flovent)	Pulmonary	5,000,000
10	Hydrocortisone valerate (Westcort)	Dermatologics (topicals)	1,240,000	18	Promethazine (Phenergan)	Upper respiratory	4,450,000
11	Clotrimazole (Lotrimin)	Dermatologics (topicals)	1,210,000	2	Mometasone (Nasonex)	Upper respiratory	3,810,000
12	escitalopram (Lexapro)	CNS	1,170,000	12	Cephalexin	Anti-infectives	3,060,000
13	clonidine	Cardiovascular-renal	1,130,000	12	Fluticasone nasal spray (Flonase)	Upper respiratory	2,820,000
14	Fluticasone oral inhalation (Flovent)	Pulmonary	1,090,000	4	Nystatin	Dernatologics (topicals)	2,780,000
15	Lansoprasole (Prevacid)	Gastrointestinal	1,060,000	1	Hydrocortisone topical	Dermatologics (topicals)	2,770,000
16	Pimecrolimus topical (Elidel)	Dermatologics (topicals)	1,020,000	2	Polyethylene glycol (MiraLax)	Gastrointestinal	2,590,000

(table continues)

Table 10. (continued)

Rank	Off-Label for Age				Off-Label for Indication		
	Medication (Proprietary Name)	**Drug Category**	**No. of Rx Off-Label for Age**	**FDA Approval Age (Yrs)**	**Medication (Proprietary Name)**	**Drug Category**	**No. of Rx Off-Label for Indication**
17	Citalopram (Celexa)	CNS	1,010,000	18	Cefdinir (Omnicef)	Anti-infectives	2,530,000
18	amoxicillin	Anti-infectives	990,000	0.25	Mupirocin (Bactroban)	Dermatologics (topicals)	2,360,000
19	Quetiapine (Seroquel)	CNS	970,000	18	Cefprozil (Ceftin)	Anti-infectives	2,360,000
20	Ciprofloxacin (Cipro)[$]	Anti-infectives	880,000	18	Fexofenadine (Allegra)	Upper respiratory	2,250,000

[#] Miralax™ has since become over-the-counter, but does not have an indication for pediatric use under 17 years of age.
[$] Ciprofloxacin is now approved for use as second-line therapy in complicated urinary tract infections and pyelonephritis for children aged 1-17 years. Labeling reflects it is not a drug of first choice due to increased adverse events compared to controls including events related to joints and/or surrounding tissues. No visits in our study in which ciprofloxacin was prescribed included the diagnosis of pyelonephritis or urinary tract infection.

Table 11. Adjusted Probability of Having a Visit with Off-Label Prescribing for Age vs. Off-Label Prescribing for Indication (*N*=312 Million Estimated Visits Based on Unweighted *n*=7901 Visits)

Characteristic	Adjusted Probability of Visit With Off-Label Prescribing for Indication	Difference In Adjusted Probability of Visit With Off-Label Prescribing for Indication (95% Confidence Interval)	Adjusted Probability of Visit With Off-Label Prescribing for Age	Difference In Adjusted Probability of Visit With Off-Label Prescribing for Age (95% Confidence Interval)
Gender				
Male	54%	referent	27%	referent
Female	52%	-2% (-6%, 1%)	28%	1% (-2%, 4%)
Race/Ethnicity				
White	52%	referent	28%	referent
Black	58%	6% (-0.1%, 11%)	30%	2% (-3%, 8%)
Hispanic	55%	3% (-5%, 10%)	27%	-1% (-5%, 3%)
Other	58%	6% (-2%, 14%)	28%	0% (-7%, 7%)
Age				
0 - <1 year	55%	2% (-4%, 8%)	**61%**	**38% (32%, 43%)*** **
1 - <2 years	49%	-4% (-13%, 4%)	**50%**	**27% (21%, 33%)*** **
2 - <6 years	55%	2% (-3%, 7%)	**28%**	**5% (0%, 9%)****
6 - <12 years	53%	referent	**23%**	referent
12 - <18 years	53%	0% (-5%, 5%)	**19%**	**-4% (-8%, -1%)***
Chronic diseases				
Yes	**49%**	**-6% (-11%, -1%)***	30%	3% (-2%, 8%)
No	**55%**	**referent**	27%	referent
Payment source				
Private insurance	53%	referent	**26%**	referent
Medicaid	54%	1% (-3%, 5%)	**31%**	**5% (1%, 9%)***
Self-pay	56%	3% (-12%, 15%)	**41%**	**15% (4%, 26%)***
Other	48%	-5% (-12%,2%)	27%	1% (-7%, 9%)
Number of Rx medications				
1	**41%**	referent	**19%**	referent
2	**69%**	**28% (24%, 34%)*** **	**39%**	**20% (16%, 24%)*** **
3-6	**85%**	**44% (39%, 49%)*** **	**49%**	**30% (24%, 37%)****
Physician specialty				
General pediatrics	52%	-6% (-12%, 1%)	**21%**	**-4% (-8%, -1%)***
General/family practice	58%	referent	**25%**	referent
Other specialty	53%	-5% (-13%, 2%)	**39%**	**14% (7%, 20%)***

*p <0.05; **p <0.01; ***p <0.001

References

Bazzano, A. T., Mangione-Smith, R., Schonlau, M., Suttorp, M. J., & Brook, R. H. (2009). Off-label prescribing to children in the United States outpatient setting. *American Academy of Pediatrics, 9*(2), 81-88.

Best Pharmaceuticals for Children Act. (2002). Pub L No. 107 109, 115 Stat 1408.

Carpenter, J., & Bithell, J. (2000). Bootstrap confidence intervals: When, which, what? A practical guide for medical statisticians. *Statistics in Medicine, 19*(9), 1141-1164.

Centers for Disease Control and Prevention (CDC). (n.d.). *Ambulatory health care data: Questionnaires, datasets and related documentation.* Retrieved from http://www.cdc.gov/nchs/ahcd/ahcd_questionnaires.htm.

Centers for Disease Control and Prevention (CDC). (2012). National program of cancer registries: About. Retrieved from http://www.cdc.gov/cancer/npcr/about.htm

Correll, C. U. (2008). Antipsychotic use in children and adolescents: Minimizing adverse effects to maximize outcomes. *Journal of the American Academy of Child and Adolescent Psychiatry, 47,* 9-20.

Demonaco, H. J., Ali, A., & Hippel, E. (2006). The major role of clinicians in the discovery of off-label drug therapies. *Pharmacotherapy, 26,* 323-332.

Dubin, A., Kikkert, M., Mirmiran, M., & Ariagno, R. (2001). Cisapride associated with QTc prolongation in very low birth weight preterm infants. *Pediatrics, 107*(6), 1313-1316.

Egger, H. (2010). A perilous disconnect: Antipsychotic drug use in very young children. *Journal of the American Academy of Child and Adolescent Psychiatry, 49,* 3-6.

Freedman, S. B., Adler, M., Seshadri, R., & Powell, E. C. (2006). Oral ondansetron for gastroenteritis in a pediatric emergency department. *New England Journal of Medicine, 354*(16), 1698-1705.

Gazarian, M., Kelly, M., McPhee, J. R., Graudins, L. V., Ward, R. L., & Campbell, T. J. (2006). Off-label use of medicines: Consensus recommendations for evaluating appropriateness. *Medical Journal of Australia, 185*(10), 544 548.

Henney, J. (2000). Withdrawal of troglitazone and cisapride. *Journal of the American Medical Association, 283*, 2228.

Holmes, L. B., Wyszynski, D. F., & Lieberman, E. S. (2004). The AED (antiepileptic drug) pregnancy registry: A six year experience. *Archives of Neurology, 61*, 673-678.

Horen, B., Montastruc, J., & Lapeyre-Mestre, M. (2002). Adverse drug reactions and off-label drug use in paediatric outpatients. *British Journal of Clinical Pharmacology, 54*, 665-670.

Kuhlthau, K., Beal, A., Ferris, T., & Perrin, J. (2002). Comparing a diagnosis list with a survey method to identify children with chronic conditions in an urban health center. *Ambulatory Pediatrics, 2,* 58-62.

Leslie, D. L., & Rosenheck, R. (2012). Off-label use of antipsychotic medications in Medicaid. *American Journal of Managed Care, 18*(3), e109-117.

Levi, M., Levy, J. H., Andersen, H. F., & Truloff, D. (2010). Safety of recombinant activated factor VII in randomized clinical trials. *The New England Journal of Medicine, 363*, 1791-800.

Li, V. W., Jaffe, M. P., Li, W. W., & Haynes, H. A. (1998). Off-label dermatologic therapies: Usage, risks, and mechanisms. *Archives of Dermatology, 134*(11), 1449-1454.

Lischner, H., Seligman, S. J., Krammer, A., & Parmelee, A. H., Jr. (1961). An outbreak of neonatal deaths among term infants associated with administration of chloramphenicol. *Journal of Pediatrics, 59*, 21-34.

Martin, J. (2006, March 6). "FDA launches Accutane registry." *Medical News Today.* Retrieved from http://www.medicalnewstoday.com/releases/38787.php

Pandolfini, C., Campi, R., Clavenna, A., Cazzato, T., & Bonati, M. (2005). Italian paediatricians and off-label prescriptions: Loyal to regulatory or guideline standards? *Acta Paediatrica, 94*(6), 753-757.

Pediatric Research Equity Act of 2003. Pub L No. 108 155, 117 Stat 1936.

Physician's Desk Reference. (2007). *Physician's desk reference*. Montvale, NJ: Medical Economics Co.

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

Roberts, R., Rodriguez, W., Murphy, D., & Crescenzi, T. (2003). Pediatric drug labeling: Improving the safety and efficacy of pediatric therapies. *Journal of the American Medical Association, 290*, 905-911.

Saarto, T., & Wiffen, P. J. (2007). Antidepressants for neuropathic pain. *Cochrane Database of Systematic Reviews, 4,* CD005454.

Shah, S. S., Hall, M., Goodman, D. M., Feuer, P., Sharma, V., Fargason, C. Jr., . . . Slonim, A. D. (2007). Off-label drug use in hospitalized children. *Archives of Pediatrics & Adolescent Medicine, 161*(3), 282-290.

Stafford, R. S. (2008). Regulating off-label drug use-rethinking the role of the FDA. *New England Journal of Medicine, 358,* 1427-1429.

Steinman, M. A., Bero, L. A., Chren, M. M., & Landefeld, C. S. (2006). Narrative review: The promotion of gabapentin: An analysis of internal industry documents. *Annals of Internal Medicine, 145,* 284-293.

U.S. Center for Drug Evaluation and Research, Food and Drug Administration (CDER, FDA). (n.d.). *Drugs@FDA.* Retrieved from http://www.accessdata.fda.gov/scripts/cder/drugsatfda/

Vernacchio, L., Kelly, J. P., Kaufman, D. W., & Mitchell, A. A. (2009). Medication use among children <12 years of age in the United States: Results from the Slone survey. *Pediatrics, 124*(2), 446-454.

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

World Health Organization (WHO). (2006). *International classification of disease, 9th Revision, clinical modification.* Los Angeles, CA: Practice Management Information.

Yoon, E. Y., Dombkowski, K. J., Rocchini, A., Lin, J.-J., & Davis, M. M. (2007). Off-label utilization of antihypertensive medications in children. *Ambulatory Pediatrics, 7*, 299-303.

CHAPTER 5: DISCUSSION AND CONCLUSIONS

The intent of this dissertation was to determine the magnitude of off-label prescribing to children. Part of the goal was to achieve an understanding of what is involved--what drugs, what children's and what physicians' characteristics are predictive of whether off-label prescribing occurs.

Summary of the Three Papers

The first paper, "Off-Label Prescribing to Children in the U.S. Outpatient Setting" found that off-label prescribing to children at office visits was pervasive and over half of U.S. children were exposed. Cardiovascular-renal, pain and central nervous system medications were almost exclusively prescribed off-label. Younger children, those seeing subspecialist physicians and those receiving higher numbers of drugs all were associated with a higher probability of off-label prescribing. Many of the medications had insufficient evidence to support their off-label use in children.

The second paper, "Rates and Predictors of Off-Label Prescribing to U.S. Infants and Toddlers," considered a specific subpopulation: 0-3 year olds. Due to their developmental immaturity (Rice & Barone, 2000) and evidence of increased risk of adverse events (Moore, Weiss, Kaplan, & Blaisdell, 2002), this group represented a particularly vulnerable population. This study found that 65% of infants and toddlers were exposed to off-label prescribing and, in children younger than six months, a 77-88% adjusted probability of off-label prescribing was found. Both off-label prescribing for indication and off-label prescribing for age were common. Many of the 20 most common off-label medications were associated with safety concerns or unproven benefit and were for self-limited disease.

The third paper found considerable differences between off-label prescribing for age and off-label prescribing for indication, with off-label prescribing for indication more than twice as common as off-label prescribing for age and in disproportion as compared to adult off-label prescribing for indication. Anti-infectives, upper respiratory medications, and pulmonary medications were much more commonly prescribed off-label for indication than for age, whereas no differences were noted for pain medications, gastrointestinal medications and cardiovascular-renal medications, which were mostly prescribed off-label for both age and indication. Off-label prescribing for age was associated with younger children and subspecialist physicians.

Placing the Papers in the Context of the Literature

This body of work adds to the literature on off-label prescribing to children as it is the first and to date only examination of the pharmacoepidemiology of pediatric off-label prescribing that used a large database to establish national population rates. This new contribution goes beyond single site or drug class studies in determining that off-label prescribing to U.S. children is extensive and varied. This dissertation also adds to the data available to prioritize the study and regulation of off-label use of medications that are used most commonly in various pediatric populations.

Throughout these analyses, medications for pain, gastrointestinal medications and cardiovascular-renal medications were prescribed off-label in the greatest proportion--up to 90+% of prescriptions for each of these categories were off-label. Few pain medications are studied for use in children resulting in high proportions of off-label use (Conroy, & Peden, 2001). These findings are echoed in a study of off-label prescribing of cardiovascular medications in pediatric inpatients, in which 60% of medications were never used on label

(Pasquali et al., 2008). Antihypertensive medications are also frequently prescribed off-label even when less expensive on-label alternatives from the same medication class are available (Yoon, Dombkowski, Rocchini, Lin, & Davis, 2007). Previous studies have similarly indicated that these categories have many medication uses with little or no scientific support (Radley, Finkelstein, & Stafford, 2006). More concerning, of the top 15 drugs most often named in fatal events reported to the FDA MedWatch adverse reporting system, seven were medications for pain (Moore et al., 2002). Even though collectively these medications only accounted for 6% of all exposure to off-label prescribing to children, their ramifications in terms of safety underscores the need to prioritize the study of these medications in children.

CNS medication use was often found to be off-label for age, indication and both age and indication, accounting for 15% of off-label prescribing. Many studies document CNS medication use in children is out of proportion to the evidence base (Zito et al., 2008). When prescribed to adults off-label, in 83-94% of the instances, CNS medications had little or no evidence of efficacy (Radley et al., 2006). Moreover, when several CNS medications have been studied for children, they have been found to be ineffective or unsafe (e.g. anti-depressants). Four of the top 15 drugs most often reported to FDA MedWatch for serious adverse events or deaths were psychiatric medications (Moore et al., 2002). Data indicating long-term safety are even scarcer. For example, in the Treatment of Adolescents with Depression Study, at 36 weeks, suicidal events were more common in patients receiving fluoxetine therapy (15%) than in patients receiving cognitive behavioral therapy (i.e., talk therapy; 6%; March et al., 2007). Unlike in adults (Doresey, Rabbani, Gallagher, Conti, & Alexander, 2010), despite black box warnings for use in children, antipsychotic use in pediatrics has increased precipitously over the past 10 years without any indication of slowing (Comer, Olfson, & Mojtabai, 2010). Given the long-term

potential consequences, these drugs require special treatment in children. In particular, patient registries to collect long-term data, improved unbiased education on study results for physicians, and appropriate prescribing tools (e.g. formulary restrictions) may be useful strategies to decrease inappropriate off-label prescribing of CNS medications.

Younger children were clearly most affected by and most vulnerable to off-label prescribing. Most often, children 0-3 years of age received prescriptions that were off-label for age rather than indication. Prescribing in the neonatal intensive care unit almost entirely involves off-label prescribing, with 90% of infants in one study exposed (Conroy, McIntyre, & Choonara, 1999). Similarly, hospitalized infants and young children are at higher risk of off-label prescribing (‘t Jong, Eland, Sturkenboem, van der Anker, & Stricker, 2003). The current study compliments previous work by assessing infants and young children in the U.S. outpatient setting and corroborates the findings that off-label prescribing is ubiquitous in this population. Frequently, off-label medications were prescribed for self-limited disease, such as upper respiratory infection, or even in the face of labeling indicating that use is not recommended (e.g., promethazine). These findings engender serious doubt as to the safety and advisability of the current state of prescribing to infants and young children.

The findings of this dissertation also call into question the effectiveness of the current FDA regulations promoting study of off-label medications. Very few medications prescribed off-label in this body of work had either been studied and had significant labeling changes or were targeted for study on the list of pediatric drugs most urgently needing study. In a 2009 study of off-label prescribing for pediatric cardiovascular disease, medications that had been studied under recent federal legislation were prescribed to only 20% of patients, and were still used in an off-label manner 62% of the time (Pasquali et al., 2008).

These results imply that the existing system of studying pediatric medications is not adequately protecting children and continues to be in need of revision and strengthening. At the same time, the variation in off-label prescribing, with some categories having very low prescribing off-label for age, suggests that it is possible to reduce off-label prescribing in all categories. For example, very little off-label prescribing for age or indication was found for pediatric oncology medications because the clinical model is to routinely place children on clinical trials (Shah et al., 2007). Perhaps other children could receive similar protections and benefits using cancer therapy as a model.

This Study in Relation to the Conceptual Model

Although not intended to test all of the concepts in a theory-based conceptual model, this dissertation does indicate that some variables tested are predictive of off-label prescribing to children. Specifically, patient age as a characteristic was found to play a significant role in off-label prescribing for age, with physicians prescribing off-label for age more often to younger children. While one explanation is simply that fewer labeled medications are available, physicians' attitudes towards younger children and the belief that younger children may be more vulnerable to disease may also have influenced prescribing off-label. Additionally, physician characteristics, and in particular, physician specialty played a significant part in differential rates of off-label prescribing. The social norms associated with certain specialties, such as the expectation for subspecialists who are not pediatric trained to care for children and be familiar with pediatric medications, may also have led to increased off-label prescribing. While further study is needed, this body of work supports partial validation of the proposed explanatory conceptual model of off-label prescribing.

Limitations

The body of work presented here should be viewed in light of several limitations. Prescribing is a dynamic process as medications are moving through the FDA approval process and being tested daily. Likewise, physicians may change their prescribing habits based on new information or beliefs. This study addressed a four year time period of U.S. office visits from January 2001 through December 2004. Many new medications have entered the pediatric market and been labeled for use in children. Additionally, it is possible that physicians have become more aware of off-label prescribing to children since the legislation has been in place.

On the other hand, no subsequent U.S. studies similar to this work have been performed. In addition, most drugs included have not undergone labeling changes that would have significantly altered these results. Of the labeling changes of the 20 medications most commonly prescribed off-label for age, only three could have affected study results (Table 12). The paucity of study and labeling change is particularly true of older and generic medications, which have been associated in other studies with higher off-label use (Eguale et al., 2012). In fact, some medications listed as most urgently needing study have remained unstudied since the list's inception in 2002 (U.S. Food and Drug Administration [FDA], 2009). Furthermore, no large-scale physician interventions have been directed at reducing off-label prescribing. Finally, even if some prescribing has changed, this dissertation may serve as a baseline from which to consider off-label prescribing trends.

In developing a conceptual model of off-label prescribing based on the Theory of Planned Behavior, physician prescribing was assumed to be a rational behavior and with the intention to prescribe a medication resulting in a prescription. There is reason to doubt this interpretation and instead to recognize that prescribing may take on the characteristics of a habit

(Sbarbaro, 2001). Additionally, even though the Theory of Planned Behavior has widely been used as a model for prescribing, some studies question the effectiveness of its higher-level constructs (e.g., subjective norms) in predicting some behavior (Rashidian & Russell, 2011). As a result, interventions using some of the factors thought to predict off-label prescribing may not result in improved prescribing behaviors. Though the factors in this dissertation generally relate to demographics and describe pharmacoepidemiology, future intervention studies should carefully consider which constructs have evidence of affecting prescribing behavior change.

In a related issue, as a secondary analysis, not all variables were present in NAMCS that would have more fully evaluated the relationship between children, physicians and medications. In particular, several physician factors such as sources of prescribing information and formulary use could not be gleaned using such a large dataset. One newer study using an electronic health record database of the primary care research network in Canada found that formulary-restricted drugs had lower off-label use. The same study reported that for physicians caring for adults, those who practiced more evidence-based medicine were less likely to prescribe for an off-label indication (Eguale et al., 2012). Large databases capable of generating national population-level statistics invariably are restricted in the number of factors they include and our weighing of the options favored use of such a data set over clearer elucidation of associated factors. Future studies in the U.S. using datasets similar to the Canadian research network data may be useful in further elucidating omitted factors.

Additionally, in NAMCS up to three diagnoses were included and up to six medications. However, a direct link describing the specific diagnosis for which the medication was prescribed was not provided. Thus, while our methodology allowed us to determine that none of the listed diagnoses was an approved indication for the drug, we could not always determine which

specific diagnosis was the impetus for the off-label use when more than one diagnosis was listed. If we had, we could have identified indication-drug pairs with the highest prevalence of off-label prescribing, even more directly targeting new studies. For example, several studies have described the most common off-label indications for specific psychiatric medications, such as oxazepam and insomnia (Eguale et al., 2012; Radley et al., 2006; Zito et al., 2008). Nonetheless, we were able to provide direction for study in describing which medications to prioritize.

Conclusions

In sum, this dissertation provides evidence of pervasive off-label prescribing to U.S. children and demonstrates disproportionate off-label prescribing to the particularly vulnerable group of infants and toddlers. Furthermore, vast differences in off-label prescribing for indication and off-label prescribing for age were found. As new legislation is debated, these findings suggest that strengthening requirements to study all medications commonly prescribed off-label to children is urgently needed. Improved, proactive FDA dissemination of study results and labeling are essential, as are patient registries to follow children exposed to off-label medications. Concomitant physician prescribing incentives and supports as well as educational campaigns have the potential to reduce the ubiquitous, long-standing, and potentially dangerous practice of off-label prescribing to children.

Table 12. Changes to Medication Labeling of the Top 20 Off-Label Medications and Potential Effects on Off-Label Prescribing*

Medication	Drug Category	Labeling Change	Potential Effects on Off-Label Prescribing
Amoxicillin (Moxatag™)	Anti-infective	For children ≥12 years, once daily dosing for pharyngitis or tonsillitis.	No effect.
Clonidine (Kapvay™)	CNS	New proprietary formulation, Kapvay™, extended release tablets. Approved for ADHD in children ≥6 years.	Reduces off-label prescribing as approval age changed from 12 years to 6 years.
Fluticasone oral inhalation (Flovent™)	Pulmonary	Safety and efficacy in >4 years (no change). Studies in children 6 months - ≤4 years added to label.	No change or possible increase in off-label prescribing given new PK data described in ≥6 months old.
Quetiapine (Seroquel™)	CNS	Approved in children ≥10 years with bipolar mania. Approved in children ≥13 years with schizophrenia.	Reduces off-label prescribing as approval age changed to 10 years.

*Since 2007.

References

Comer, J. S., Olfson, M., & Mojtabai, R. (2010). National trends in child and adolescent psychotropic polypharmacy in office-based practice, 1996-2007. *Journal of the American Academy of Child and Adolescent Psychiatry*, *49*(10), 1001-1010.

Conroy, S., & Peden, V. (2001). Unlicensed and off-label analgesic use in paediatric pain management. *Paediatric Anaesthesia, 11*(4), 431-436.

Conroy, S., McIntyre, J., & Choonara, I. (1999). Unlicensed and off-label drug use in neonates. *Archives of Disease in Childhood. Fetal and Neonatal Edition, 80*(2), 142-145.

Doresey, E. R., Rabbani, A., Gallagher, S. A., Conti, R. M., & Alexander, G. C. (2010). Impact of FDA black box advisory on antipsychotic medication use. *Archives of Internal Medicine, 170,* 96-103.

Eguale, T., Buckeridge, D. L., Winslade, N. E., Benedetti, A., Hanley, J. A., & Tamblyn, R. (2012). Drug, patient, and physician characteristics associated with off-label prescribing in primary care. *Archives of Internal Medicine, 16,* 1538-3679.

March, J. S., Silva, S., Petrycki, S., Curry, J., Wells, K., Fairbank, J., . . . Severe J. (2007). The treatment for adolescents with depression study (TADS): Long-term effectiveness and safety outcomes. *Archives of General Psychiatry, 64*(10), 1132-1143.

Moore, T. J., Weiss, S. R., Kaplan, S., & Blaisdell, C. J. (2002). Reported adverse drug events in infants and children under two years of age. *Pediatrics*, *110*(5), e53.

Pasquali, S. K., Hall, M., Slonim, A. D., Jenkins, K. J., Marino, B. S., Cohen, M. S., & Shah, S. S. (2008). Off-label use of cardiovascular medications in children hospitalized with congenital and acquired heart disease. *Circulation: Cardiovascular Quality and Outcomes, 1*(2), 74-83.

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

Rashidian, A., & Russell, I. (2011). Intentions and statins prescribing: Can the theory of planned behaviour explain physician behaviour in following guideline recommendations? *Journal of Evaluation in Clinical Practice, 17,* 749-757.

Rice, D., & Barone, S., Jr. (2000). Critical periods of vulnerability for the developing nervous system: Evidence from humans and animal models. *Environmental Health Perspectives, 108*, 511-533.

Sbarbaro, J. A. (2001). Can we influence prescribing patterns? *Clinical Infectious Diseases, 15*, 240-244.

Shah, S. S., Hall, M., Goodman, D. M., Feuer, P., Sharma, V., Fargason, C. Jr., . . . Slonim, A. D. (2007). Off-label drug use in hospitalized children. *Archives of Pediatrics & Adolescent Medicine, 161*(3), 282-290.

't Jong, G. W., Eland, I. A., Sturkenboem, M. C., van der Anker, J. N., & Stricker, B. H. (2003). Determinants for drug prescribing to children below the minimum licensed age. *European Journal of Clinical Pharmacology, 58*, 701-705.

U.S. Food and Drug Administration (FDA). (2009). *List of drugs for which pediatric studies are needed.* Retrieved from http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm077695.htm

Yoon, E. Y., Dombkowski, K. J., Rocchini, A., Lin, J.-J., & Davis, M. M. (2007). Off-label utilization of antihypertensive medications in children. *Ambulatory Pediatrics, 7*, 299-303.

Zito, J. M., Safer, D. J., dos Reis, S., Gardner, J. F., Boles, M., & Lynch, F. (2000). Trends in the prescribing of psychotropic medications to preschoolers. *Journal of the American Medical Association, 283*, 1025-1030.