Off-Label Prescribing to Children in the United States Outpatient Setting

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Objective.—The aim of this study was to determine the frequency of off-label prescribing to children at United States 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.

KEY WORDS: children; medication safety; off-label; prescribing

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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 (eg, dosing, interactions). Furthermore, off-label prescribing has been associated with adverse drug events.[1,2] Recent legislation gave FDA authority to require evaluation of certain new drugs for children and to encourage evaluation of others through patent extensions.[3,4] As a result, the FDA has reported an increase in the number of medications approved for use in children.[5] 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%.[6–9] One recent US study reported that 79% of children admitted to tertiary care children's hospitals received off-label prescriptions.[7] 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[1] and others concluding that topical preparations are most often prescribed off label.[10] Studies also differ with regard to age of children receiving off-label medications.[9,11] Some studies indicate that physician specialists prescribe off label to children more frequently.[11] Prior investigations have been limited by small sample size,[12] single US or international geographic location,[13,14] examination of prescribing for a single or limited set of conditions,[15,16] exclusive focus on the inpatient setting,[7,14] and lack of control for other potential explanatory variables.[16]

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 US children in the outpatient setting? 2) what is the

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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),[17] 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 United States. 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 US nonfederally 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 1-page encounter form on a systematic random sample of approximately 30 patient visits during a randomly assigned 1-week period.[17] This form included data on patient demographics, reason for the visit, diagnostic workup, diagnoses (up to 3), medications (up to 6), and follow-up. Nonresponse 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 (eg, "antibacterial agent"), nonmedications (eg, infant oil, soap), and rarely prescribed medications (eg, 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 1 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,[18] which were crossmatched 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*,[19] FDA Web site,[20] or other compendia[21] 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 1 off-label medication was prescribed. The proportion of visits with at least 1 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 (eg, 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 Web site.[22] 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 antiparasitics with antimicrobials, and from the respiratory tract category, we separated upper respiratory drugs (ie, otic, cough, cold, and allergy preparations) from pulmonary drugs (eg, 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[11,23] and theory on physician prescribing behavior,[24] 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 1 or more chronic conditions (based on whether the patient's diagnoses correspond to a list of