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Structured Abstract

Purpose: I studied non--FDA-approved (“off-label”) uses of widely available prescription drugs and the scientific, market, and regulatory/legal events that might affect the frequency, characteristics, and costs of off-label uses in drugs for hematology/oncology, neuropsychiatry, and rare diseases.

Scope: Off-label prescription of drugs is routine among physicians. Sometimes, such prescribing is based on rigorous randomized trial data that has not (yet) led to formal FDA approval for a given indication; other off-label use is based on less well-established evidence. Few studies have detailed the extent to which newly approved drugs are prescribed for off-label uses; the evidence supporting such utilization; or the impact of marketing or other legal, regulatory, or financial forces on the practice of off-label drug use.

Methods: I developed a comprehensive typology of off-label use and its clinical, economic, and policy implications. I then evaluated the frequency and patterns of off-label drug use among hematology/oncology, neuropsychiatry, and rare disease drugs for Medicaid patients, Medicare patients, and patients covered by a large health insurer. Multivariable regression determined predictors of off-label use and identified characteristics of patients, physicians, and medications. Finally, time-trend analysis determined the impact of changes in legal, regulatory, or financial factors on off-label use.

Results: I found varying effects of the various interventions studied on off-label drug use. For example, initiation of government investigations into illegal off-label marketing had little impact on off-label prescribing, whereas aspects of the drug/disease being studied, heightened consent requirements, and local restrictions on pharmaceutical/physician interactions had statistically significant effects.

Key Words: Off-label, drug promotion, FDA

Purpose

My K-08 award research addressed the phenomenon of off-label drug use and medical, social, legal, and economic factors that influence off-label drug use. Off-label prescription of drugs is a routine practice among physicians. The Food and Drug Administration (FDA) approves new drugs based on their effectiveness for a particular indication, but once a drug enters the market, physicians can prescribe drugs for other indications that they deem appropriate. Sometimes, such prescribing is based on rigorous randomized trial data that has not (yet) led to formal FDA approval for a given indication; other off-label use is based on less well-established evidence. Because of concerns about cost and/or quality of care, payors in both the private and public sectors have sought to prohibit off-label use, limit its coverage, and/or require patients to assume an increasing fraction of its cost.

Off-label drug use thus involves prescriptions that may or may not be sound therapy, that may involve unnecessary risk to patients, and that may be cost-effective or cost-ineffective—or a mix of all three. Though off-label use has been estimated to account for nearly three quarters of the use of some drugs, the practice remains poorly understood. Few studies have detailed the extent to which newly approved drugs are prescribed for off-label uses or the evidence supporting such utilization. In addition, scant data exist regarding the patient or physician or drug characteristics that predict when an off-label use is more likely to occur. Though promotion of drugs for off-label uses is strictly regulated, there have been several recent high-profile instances of violations of these regulations. No studies have systematically evaluated the impact of marketing or other legal, regulatory, or financial forces on the practice of off-label drug use.

I therefore sought to accomplish three specific aims related to off-label drug use. First, I sought to develop a comprehensive scheme for studying off-label drug use to categorize the different types of off-label use and their clinical, economic, and policy implications. Second, I sought to apply this typology to evaluate the frequency and patterns of off-label drug use in three important categories: hematologic/oncologic drugs, neuropsychiatric drugs, and drugs for other rare diseases. Within this aim, I sought to evaluate the characteristics of off-label drug use in large population databases of prescriptions and diagnoses—including Medicaid patients, Medicare patients, and patients covered by private health insurers—and to use multivariable regression to determine predictors of use of off-label drugs and identify characteristics of patients, physicians, and medications that are associated with off-label use. Third, I sought to use time-trend analysis to determine the changes in legal, regulatory, or financial factors that impact off-label use.

Overall, the purpose of this project was to better understand the properties and predictors of off-label use, which can inform evidence-based prescribing of these products. Studying the benefit-risk-cost relationships associated with such uses can lead to more enlightened approaches to prescribing and policy decisions in this increasingly contentious area.

Scope

Off-label use is the prescription of a pharmaceutical product at a dose and/or for a condition that the FDA has not reviewed. The frequency of off-label use is substantial and may be increasing. In 1985, Strom et al. studied the 1,000 most common uses of prescription drugs and found that 31 were for non--FDA-approved indications.¹ In 2003, using physician-reported prescribing data, the reasons for use of 45 drugs (the three top drugs in each of the 15 leading drug classes) were analyzed for 1988-89 and 2002-03. Off-label use rates were 22%.² A more recent study by Stafford et al. used 2001 data to define prescribing patterns for 160 drugs,

¹ Strom B, Melmon K, Miettinen O. Post-marketing studies of drug efficacy: why? *Am J Med* 1985;78:475-480.

² Adams C, Young A. Risky Rx: A Knight Ridder investigation. 2003.

http://www.realcities.com/mld/krrwashington/special_packages/riskyrx.

including the top 100 most-prescribed office-based drugs, for a total of over 6,000 drug-diagnosis pairs.³ That study found a 21% off-label prescription rate generally and concluded that “73% of off-label drug mentions had little or no scientific support.”

The practice of off-label drug use raises important public health concerns. Once a drug is approved, the FDA does not prevent physicians from prescribing it for off-label uses outside the specific approved indication. When based on reasonable scientific evidence, off-label drug use can be extremely valuable. Some off-label uses may have substantial support from post-approval clinical trials, but FDA approval for this subsequent indication may be pending or the manufacturer may choose to forego official review. Other off-label use may be appropriate despite scant evidence of efficacy. For example, narrowly defined populations, including children,⁴ pregnant women,⁵ and patients with extremely rare diseases,⁶ are not usually included in drug clinical trials, because the numbers of patients might be too small, the patients may be unable or unwilling to provide informed consent, or the situation may be too risky. These patients depend on off-label prescriptions for their care.

However, off-label drug use can also impose unnecessary risk and cost without proven benefit. A drug’s safety may not be known in off-label contexts, and its risk-benefit relationship is not clearly established. This concern has increased as dangers have emerged surrounding common off-label uses of drugs such as antipsychotics in elderly patients with dementia and non-fluoxetine antidepressants for depression in children. Antipsychotic medications are disproportionately used off-label in elderly patients for conditions such as dementia and affective disorders.⁷ A study of anticonvulsants found that off-label use in the Georgia Medicaid population has reached 71%, but only a minority of that use was supported by evidence from controlled trials.⁸ However, a doubling of the mortality risk has been seen in this population with atypical antipsychotic drugs⁹ and other drugs in the class.¹⁰ This off-label use of antipsychotics accounts for billions of dollars in annual spending by public health insurers, even though such use is of limited effectiveness and can impose important risks.^{11,12} Controversy around these off-label uses has been heightened by the recent spate of government-directed investigations in this field. The Department of Justice (DOJ) has settled illegal off-label marketing lawsuits directed against the manufacturers of gabapentin (Neurontin) and the antipsychotics olanzapine (Zyprexa) and aripiprazole (Abilify), leading to over \$15 billion in settlements.¹³

³ Radley D, Finkelstein S, Stafford R. Off-label prescribing among office-based physicians. *Arch Intern Med* 2006;166:1021-1026.

⁴ Choonara I, Conroy S. Unlicensed and off-label drug use in children: implications for safety. *Drug Safety*. 2002;25:1-5.

⁵ Rayburn W, Turnbull G. Off-label drug prescribing on a state university obstetric service. *J Reproductive Medicine* 1995;40:186-188.

⁶ Donofrio P, Busis N. Regulatory and reimbursement issues in treating patients with immune-mediated nephropathies. *Neurology*. 2002;59:498-501.

⁷ Alexopoulos G, Streim J, Carpenter D, Docherty J. Using antipsychotic agents in older patients. *J Clin Psychiatry*. 2004;65(Suppl 2):5-99.

⁸ Chen H, Deshpande AD, Jiang R, Martin BC. An epidemiological investigation of off-label anticonvulsant drug use in the Georgia Medicaid population. *Pharmacoepidemiol Drug Saf*. 2005;14(9):629-638.

⁹ Food and Drug Administration. FDA issues public health advisory for antipsychotic drugs used for treatment of behavioral disorders in elderly patients. <http://www.fda.gov/bbs/topics/ANSWERS/2005/ANS01350.html>.

¹⁰ Schneeweiss S, Avorn J. Antipsychotic agents and sudden cardiac death--how should we manage the risk? *N Engl J Med*. 2009;360(3):294-296.

¹¹ Schneider LS, Tariot PN, Dagerman KS, et al. Effectiveness of atypical antipsychotic drugs in patients with Alzheimer’s disease. *N Engl J Med*. 2006;355(15):1525-1538.

¹² Saddichha S, Manjunatha N, Ameen S, Akhtar S. Diabetes and schizophrenia--effect of disease or drug? Results from a randomized, double-blind, controlled prospective study in first-episode schizophrenia. *Acta Psychiatr Scand*. 2008;117(5):342-347.

¹³ Almashat S et al. Rapidly increasing criminal and civil monetary penalties against the pharmaceutical industry: 1991-2010. Public Citizen. Dec 16, 2010. Available at: <http://www.citizen.org/documents/rapidlyincreasingcriminalandcivilpenalties.pdf>

In the case of the selective serotonin reuptake inhibitor (SSRI) antidepressants, government investigations led GlaxoSmithKline and other manufacturers to release data from previously undisclosed clinical trials of SSRIs.¹⁴

Apart from psychiatric conditions and patients with extremely rare diseases, off-label use is also common in hematology/oncology patients. Investigators found that nearly 75% of a new oncologic drug's use was off label, leading to over \$1 million in costs compared with less than \$400,000 for on-label use.¹⁵

Many intersections between the regulatory and legal systems and prescribing practices may influence the frequency and characteristics of off-label use. First, the FDA requires that communications by pharmaceutical companies about their products relate only to on-label uses.¹⁶ Regulation of manufacturers' promotional statements incentivizes manufacturers to subject their claims to rigorous scientific study and subsequent FDA evaluation. In recent years, drug manufacturers and some activists have objected to this rule.¹⁷ Some have argued that such restrictions unfairly limit the ability of manufacturers to disseminate truthful information about their products,¹⁸ with advocates presenting their objections as defense of the manufacturers' free speech.¹⁹

Methods

This study used three primary methods. First, I conducted a qualitative analysis of reports from physicians and participants in the private-sector drug industry about off-label prescribing, including its prevalence, predictors, clinical and public health impact, and the role of external factors such as promotion and reimbursement. The goal was to develop a comprehensive typology of off-label drug use that categorizes the different ways prescription drugs are used beyond the specific indications approved by the FDA. This involved both an analysis of complaints filed in lawsuits describing programs implemented at pharmaceutical manufacturers to encourage off-label prescribing as well as a direct qualitative analysis of whistleblowers who brought these cases to light. For the latter analysis, using the unsealed complaints and settlement agreements, as well as direct approaches to attorneys involved in the litigation, 42 whistleblowers involved in these cases were identified and individual, semi-structured interviews were conducted with 26 (62%) of them. The interview transcripts were analyzed using the constant comparative method of qualitative analysis. The results of this work helped lay the groundwork for a typology of off-label drug use, including the subcategories clinical and policy characteristics.

I also organized a focus group of patients with rare diseases to talk, in part, about off-label prescribing. Participants were recruited via recruitment letters sent through the National Organization for Rare Disorders—an umbrella organization that helps organize individual disease-specific rare disease patient and professional groups—to its member organizations. Participants were accepted on a first-come, first-served basis, with concessions made to provide diversity in disease type on the panels. The in-person focus groups of patients advocates (n=9 participants), caregivers (n=8 participants), and patients (n=9 participants) lasted 90 minutes in

¹⁴ Spitzer v GlaxoSmithKline. Civ Action 04-CV-5304 (SD NY 2004). 2004; http://www.oag.state.ny.us/press/2004/aug/aug26a_04_attach1.pdf

¹⁵ Kocs D, Fendrick A. Effect of off-label use of oncology drugs on pharmaceutical costs: the rituximab experience. *Am J Manag Care* 2003;9:393-400.

¹⁶ Kefauver-Harris Drug Amendments of 1962. Public Law 87-781, 76 Stat. 780. 10 October 1962 (codified as amended at 21 U.S.C. § 352 (n)).

¹⁷ Klein DB, Tabbarok A. Who certifies off-label?: FDA efficacy requirements may do more harm than good. *Regulation*. 2004;27(2):60-64.

¹⁸ Seferian SC, Clarke D, O'Brien P. Johnson & Johnson comment on First Amendment issues. <http://www.fda.gov/ohrms/dockets/dailys/02/Sep02/09160/80027d25.pdf>.

¹⁹ Troy DE, Gottlieb S. Pharmaceutical promotion and First Amendment rights. *N Engl J Med*. Jul 31 2008;359(5):536; author reply 536-537.

length and were conducted outside Washington, DC. The focus groups followed semi-structured discussion guides in which participants were asked to describe their experiences as a patient with a rare disease, what they would want to know about a new drug they might consider using for their own treatment, what outcomes should be assessed in drug testing, off-label drug use, participation in clinical trials, the role of the FDA, and recommendations for researchers testing a potential new drug or device.

Second, I identified selected drugs in three target categories—neuropsychiatric drugs, oncologic drugs, and drugs for other rare diseases. In various studies, I defined the current range of off-label uses, assessed the association between the quality of the evidence base and the prevalence of off-label prescribing for drug-diagnosis pairs, and determined predictors of non-evidence-based off-label drug uses. The neuropsychiatric drugs of interest were the antiepileptic drug gabapentin (Neurontin) and selective serotonin-reuptake inhibitors (SSRIs). The hematologic/oncologic drugs of interest included imatinib (Gleevec) for chronic myelogenous leukemia (CML) and romiplostim (Nplate) and eltrombopag (Promacta), two drugs for primary immune thrombocytopenia (ITP). The rare disease drugs included topical lidocaine (Lidoderm patch) for postherpetic neuralgia, modafinil (Provigil) for narcolepsy, and cinacalcet (Sensipar) for hypercalcemia of parathyroid carcinoma.

A diverse set of large secondary databases was used to identify patterns of on- and off-label use of selected drugs within three target drug classes. These datasets included:

(1) Participants in the Pennsylvania Pharmaceutical Assistance Contract for the Elderly (PACE) program and the New Jersey Pharmaceutical Assistance for the Aged and Disabled (PAAD) and Medicaid programs. PACE was established in 1984 to assist state residents ≥ 65 years old who may be unable to pay for their prescription medications. Beneficiaries have to demonstrate limited income resources; for example, the annual income criteria is $< \$14,500$ if single and $< \$17,700$ if married. PACE provides complete pharmacy benefits for all drugs. Virtually all prescription medications are covered by PACE without restrictions, with a small copayment. PAAD was established in 1975 and also is aimed at the lower-income elderly. There is no payment deductible, and a small copayment ($\$5$ per prescription) is required. As in PACE, all marketed prescription drugs are covered.

(2) The Optum Research Database, which contains individual-level, linked, and anonymized medical and pharmacy data on insurance claims for more than 13 million current beneficiaries of the commercially insured UnitedHealth population. The source population reflects the nationwide geographic distribution of the health insurer, which has a greater market presence in the South and Midwest and which has demographics similar to the US census for gender and age below 65 years.

(3) IMS Health, which provided counts of prescriptions for all study drugs that were written by pediatricians and child and adolescent psychiatrists who were affiliated with certain hospitals filled at any retail pharmacy for the period January 2006–June 2009. IMS Health populated its database with physician prescribing information that it purchased from retail pharmacies.

Finally, I conducted time-series analyses to identify trends in off-label use for the study drugs in these selected datasets, assessing the effect of various scientific, market, and regulatory/legal events on the frequency, characteristics, and costs of off-label drug use, including changes in regulations or local policies affecting physicians' interactions with pharmaceutical companies, FDA approval of a new indication of a previous off-label use, initiation of government investigation into a manufacturer's off-label marketing program, conclusion/settlement of that investigation, and publication of clinical data documenting lack of efficacy and/or safety concerns concerning the off-label use.

The approach to interrupted time-trend regression analysis was to divide the observation period into meaningful segments (i.e., periods between external events and interventions) and compare changes in level and slope of the time-series of utilization rates with changes during a

previous period. Generalized linear models were used to estimate changes in levels and slopes of the rate of target drug use. The unit of analysis was the patient. Count data of drug use were modeled with a log link function assuming Poisson distributed errors, and starting (or stopping) a particular drug was modeled with a logistic link function and a binomial error distribution. Regression models included constant terms, terms for linear baseline time trend before the first event, and binary terms and linear time trends for each of the studied events or interventions. For drugs with more than one qualifying event, the level and slope functions were repeated. Covariates included age, gender, self-identified race, chronic disease score, indicator terms for income status (when appropriate), cost of drug or copayment level (when available), and type/ evidence basis for the off-label use.

Limitations exist for each analysis. For the qualitative analyses, limitations include the small sample size and related lack of generalizability. For the determination of predictors for off-label use, claims data may not accurately reflect all the underlying diagnoses due to coding incompleteness or errors. The validity of the time-series analysis depends on the accurate extrapolation of baseline trends to reflect hypothetical results had the external event not occurred. Potential confounders that vary over time, including age and comorbidity, will be controlled to the extent that they can be measured accurately, although these factors will not cause “interruptions” in the time-series that a) occur suddenly shortly after the qualifying event and b) are large enough to be clinically significant.

Results

The qualitative components of this study produced a number of important findings. A series of qualitative data-collecting interviews with whistleblowers in pharmaceutical fraud cases regarding illegal promotion of off-label drug use provided perspectives on a number of different types of off-label drug uses, such as costly but ineffective off-label drug use, potentially dangerous off-label drug use, and off-label uses encouraged by the manufacturer to enhance competition with other drugs in the field (see List of Publications and Products #5). Analyses of these results and other qualitative studies of whistleblower complaints helped generate a typology of the origins of off-label use: expansion of use to different disease entities, to variations on the approved indication, and to alternatives to the approved dosing schedule (see List of Publications and Products #17, 28).

In the qualitative study of rare disease patients, I found that off-label uses were commonly considered but that patients carefully considered the sort of off-label uses that they were undertaking (see List of Publications and Products #47). Some said that their physicians experimented with off-label use, occasionally with dangerous effects. When available treatments were limited, patients or their caregivers felt that they had to take whatever they could get, even if the treatment was not FDA approved, was an off-label use of the medication, was only available outside the US, or was a treatment that might be considered to be an alternative therapy.

These data allowed me to generate a full typology of off-label drug use, describing the clinical and policy implications of the different types of uses (see List of Publications and Products #19). In general, I found that there are multiple different types of off-label uses, with varying implications for clinical care. These different varieties need to be managed with a nuanced approach to regulation and professional oversight.

This work has particular significance because of recent cases that challenge the government’s ability to restrict off-label promotion, which my qualitative studies show strongly influences off-label prescribing. The FDA’s regulation of off-label promotion protects the public from companies inundating physicians with study findings that may not be completely false but that are unreliable because they are based on flawed study design or lack proper context. Removing restrictions on off-label promotion would reduce manufacturers’ incentives to conduct well-controlled trials of potential off-label uses that could satisfy the FDA. Instead, it

could lead to a proliferation of poorly documented claims about the efficacy and safety of products for off-label indications—claims not adequately substantiated by rigorous data. Because costly products would carry the highest incentive for such activity, evidence-poor prescribing would result in runaway costs. Thus, in a post-*Caronia* medical world, once a drug was approved for any indication, its manufacturer could conduct “studies” of variable quality showing its utility for unapproved indications that would not meet the current FDA standards for scientific rigor. Many studies would predictably appear to support claims of efficacy, and those that best met marketing aims could be selected for emphasis in promotional campaigns, with the others ignored. As I describe in other publications (see List of Publications and Products #37, 43), policymakers may need to revisit the legal basis for FDA oversight of off-label drug promotion, a process that will hopefully be informed by the off-label drug use typology and the resulting policy analyses.

My process of identifying off-label prescribing in neuropsychiatric, oncologic, and rare disease drugs has also led to a number of conclusions. Among neuropsychiatric drugs, my focus on the evidence behind gabapentin (Neurontin) use in epilepsy (see List of Publications and Products #3) and off-label indications led to a publication in Health Affairs in which I described upward trends in the number of new prescriptions for gabapentin and spending on them that continued unchecked during all phases of the Department of Justice’s investigation and were greatest for off-label uses. Not until after the settlement did growth trends in gabapentin use become negative, but this occurred for both on- and off-label uses. I concluded that the government should re-examine the goals of enforcement and consider additional administrative responses to off-label promotion (see List of Publications and Products #23).

Other results among neuropsychiatric drugs include a study my co-authors and I published looking at off-label use of SSRI antidepressants in children (see List of Publications and Products #41). We found that the introduction of strict policies limiting interactions between physicians and pharmaceutical manufacturers reduced prescribing among physicians serving pediatric patients of drugs marketed to doctors in detailing visits. Decreases in the market share of detailed drugs were greater among drugs approved for any use in children but were also significant for off-label use. One interpretation of these results is that illegal off-label marketing of the study drugs to pediatricians was prevalent during the study period. If so, strict hospital detailing policies effectively reduced the consequences of illegal off-label marketing activity, in contrast to the lack of effect observed with alternative approaches, such as federal fraud prosecutions.

In the context of drugs for rare diseases, I described patterns of off-label use of four top-selling orphan drugs and found that off-label uses predominate in orphan drugs used for popular “symptoms” (e.g., pain and fatigue) or laboratory abnormalities (hypercalcemia) that are commonly observed in other conditions as well. By contrast, the orphan drug in the sample approved for specific disease conditions (imatinib [Gleevec] for chronic myelogenous leukemia) did not experience substantial uptake of off-label uses (see List of Publications and Products #25). A related publication examining the policy implications of these findings in the context of off-label use of the orphan drug recombinant factor VIIa (NovoSeven)—approved for use in hemophilia patients but used widely in surgery and in patients with cerebrovascular accidents—was published last year but required further examination this year to respond to a letter to the editor (see List of Publications and Products #19, 20). My co-author and I commented on rapidly increasing use of a costly treatment that does not benefit patients and increases the risk for dangerous thrombotic events. We concluded that allowing physician autonomy to choose medications is appealing, but not when it results in unhelpful, dangerous, and expensive decisions. We suggested that hospitals should be providing more organizational oversight to protect patients as well as the institutions’ own pharmacy budgets.

Finally, in looking at two drugs for ITP, we specifically considered how an FDA program seeking to limit their prescribing to only approved uses—called a Risk Evaluation and Mitigation Strategy (REMS)—affected prescribing (see List of Publications and Products #45). We found that implementation of the REMS for these drugs was associated with nearly absent off-label initiation of the drugs in the years following approval. Removal of these restrictive components was followed by a substantial increase in eltrombopag initiation in patients with HCV but did not change off-label initiation of romiplostim. Off-label initiation of romiplostim was extremely low throughout the study. Eltrombopag presented a different story. In the REMS period, off-label prescriptions of eltrombopag were rare. However, following removal of the REMS requirements, there was an increase in initiation of eltrombopag in off-label patients co-diagnosed with HCV as well as a decrease in initiation of eltrombopag for its on-label indication over time. The most likely explanation for elevated off-label initiation of eltrombopag in the post-REMS period is that, by December 2011, support for eltrombopag in treating HCV-associated thrombocytopenia was growing in the medical literature, ultimately leading to FDA approval for this indication in November 2012.

These empirical studies were supplemented by numerous policy analyses considering the clinical, ethical, and legal implications of off-label drug prescribing and promotion (see List of Publications and Products #s 6, 9, 10, 31, 47, among others). Many of these analyses were published in leading peer-reviewed medical and health policy journals, and I was called to testify before Congress on topics related to evidence-based drug and device prescribing and the role of the FDA in overseeing the pharmaceutical market (see List of Publications and Products #27, 48, among others). All these efforts have helped disseminate the essential lessons uncovered in empirical analyses and have contributed to an ongoing understanding of the proper role of off-label prescribing and promotion in the US, for the benefit of physicians and, most importantly, patients.

List of Publications and Products

1. Engelberg AB, **Kesselheim AS**, Avorn J. Balancing innovation, access, and profits—market exclusivity for biologics. *New England Journal of Medicine* 2009;361:1917-1919.
2. **Kesselheim AS**. The Supreme Court, process patents, and medical innovation. *New England Journal of Medicine* 2009;361:2303-2306.
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