Off-Label Use of Pharmaceuticals: Trends and Drivers[1]

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Abstract

We identify the rate of off-label use of prescription drugs in the United States during 1993-2008. We apply Detection Controlled Estimation to a comprehensive cross-section of prescriptions and find that rates of off-label use rise from 30.2% to 39.1% during this period. This coincides with a surge in settlements of Department of Justice lawsuits for off-label marketing. Additionally, physicians are more likely to prescribe off-label when there are fewer FDA-approved alternatives and when a patient's insurance has less restrictive formularies and lower copayments. These substitution patterns are consistent with off-label prescribing by physicians that enhances the welfare of patients.

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1 Introduction

Since 1962, the US Food and Drug Administration (FDA) has restricted the marketing of a drug to just the set of "on label" indications for which the drug is approved. However, physicians may prescribe any approved drug for any indication.[2] In the market for pharmaceuticals, which accounted for $321.3 billion in sales in the United States in 2010 (2.2% of US GDP),[3] "off label" use is common and potentially desirable. On one hand, the best treatment for a patient's particular indication may require using a drug off-label. In addition, applying FDA-approved drugs to new uses may be a particularly cost-effective type of innovation because these drugs have already passed safety benchmarks in clinical trials. On the other hand, ineffective off-label use is socially wasteful. In a few cases, off-label use has also led to patients being physically harmed.

Not surprisingly, off-label use is enormously controversial in the clinical and policy communities and among federal regulators (Salbu 1999; Klein and Tabarrok 2004; Stafford 2008). And yet, no prior research supports broad, systematic, and trend-based analysis of off-label use. Indeed, no economics papers analyze it empirically, and virtually nothing is known about its welfare consequences. In this paper, we start to fill these gaps.

We apply Detection Controlled Estimation (Feinstein 1990) to a comprehensive data set of patient prescriptions from the National Ambulatory Medical Care Survey (NAMCS) during 1993-2008 to identify the incidence of off-label use and to test for what drives it. We find that in the most recent years, more than one in three prescriptions are written for off-label uses. This rate is lowest in the earliest years, and rises from 30.2% in 1993 to 39.1% in 2008, a 29.6% increase. The three years with the highest frequency are 2006, 2007, and 2008. Coincidentally, this is also a period in which off-label use has been part of the national policy conversation due to settlements between pharmaceutical manufacturers and the U.S. Department of Justice (DOJ) on cases involving off-label use claims (Kesselheim,

[2]For clarity, we use the term "indication" instead of "diagnosis," "condition," "disease," etc., throughout the paper.

[3]Source: 2010 IMS National Sales Perspectives.

Mello and Studdert 2011).[4]

Perhaps most importantly, our estimates show patterns of off-label use that are consistent with choices we expect rational, fully-informed patients to make. For example, after controlling for a host of drug and patient characteristics, we show that a ten percent increase in the number of drugs that have been approved to treat a patient's set of diagnoses leads to a 4.7% reduction in the probability that a physician prescribes off-label. We also find that when patients face lower out-of-pocket costs, physicians tend to prescribe off-label more often. Relative to patients with no insurance, patients with insurance (of any type) are more likely to be prescribed off-label. Of those with insurance, those with Medicaid are the most likely to be prescribed off-label. Specifically, relative to those with private insurance, the probability of a physician prescribing off-label is about 2.2% higher when a patient is insured through Medicaid. This may be in response to the relatively weak prior authorization programs at the state level for Medicaid since 1990 (Dranove, 1989; Huskamp, 2003) or the very low copayments (relative to privately insured patients) that Medicaid recipients pay. Those on Medicare are prescribed off-label at a similar rate to those on private insurance, which is consistent with the privatized nature of "Medigap" policies that were in place over much of our sample time period (Oliver, Lee and Lipton, 2004; Rowland, 2001). Together, these substitution patterns are consistent with the hypothesis that off-label prescribing by physicians enhances patient welfare. To our knowledge, this is the first research to shed light on how off-label use affects welfare.

Studying off-label use retrospectively using prescription data presents two significant challenges. First, we must classify uses as on-label and off-label. Unfortunately, no existing archive tracks a drug's FDA-approved uses across time. We use annual issues of the Physician's Desk Reference (PDR) to build yearly matches between drugs and their approved (on-label) indications. To match the non-standardized indications in the PDR to the list of International Classification of Disease - 9th Revision (ICD-9) codes from NAMCS pre-

[4]Combining cases from our own search with those from Kesselheim et al. (2011), we identify 33 DOJ settlements during 2004-12.

scription records, we rely on a professional Clinical Documentation Specialist employed at a major academic medical center hospital. We treat a drug as being on-label for an indication if it has the same active ingredient as one of the drugs identified in the PDR as being on-label for that indication.

Second, the way that NAMCS prescription data (and data in nearly every other survey or retrospective data set) are recorded almost guarantee false detection of off-label use. For one thing, indications recorded on survey forms are limited by the number of available fields. For another, physicians often base their reports on administrative claims on which indications will maximize reimbursement.[5] Perhaps most importantly, patients frequently visit their physicians about one indication and receive a prescription for another. For example, suppose a person with chronic hypertension visits the physician because he has the flu. If the physician does not record hypertension as an indication on the NAMCS form, but does record a (convenience-driven) re-fill prescription for an ACE inhibitor, then naïve inspection of the prescription record would classify the use of the ACE inhibitor as off-label. This issue is problematic in nearly every other clinical, administrative or retrospective data source.

To overcome these problems, we appeal to Detection Controlled Estimation (DCE), first used by Feinstein (1989; 1990; 1991) to study tax evasion and regulation of U.S. nuclear power plants. Intuitively, this procedure constructs a model that separately predicts the probability of on-label use and the probability of whether it is detected, with estimation done via maximum likelihood. Crucially, identification requires a subset of variables that affect only the probability of on-label use and a subset of variables that affect only the probability of detection. For the latter category, we rely on the plausible assumption that changes to the NAMCS survey form affect detection but do not affect a physician's decision to prescribe on-label. The form permits up to five prescriptions during 1993-94, up to six from 1995-2002 and up to eight from 2003-2008. Since the maximum number of prescriptions

[5]In a study providing advice to physicians on how to increase revenue through careful attention to reimbursement intricacies, Heidelbaugh et al. (2008) states "Be sure to list active and acute medical indications discussed during the visit... rather than those that are stable...". Again, this could cause a prescription to appear off-label in claims data, even if it were actually prescribed for an approved use.

and indications is often binding, and an increase in the number of prescriptions relative to the number of indications tends to increase the likelihood that on-label use is not detected, these changes vary the rate of detection exogenously.

More work is required to fully understand the efficiency and welfare properties of off-label prescribing. For example, our paper does not identify either the dollar costs or treatment gains of off-label uses relative to on-label alternatives. We view our results, which identify the overall rate with which the practice occurs and identify some determinants of physicians' decisions to prescribe off-label, as an important first step in understanding the phenomenon of off-label prescribing.

The remainder of the paper is as follows. Section 2 provides some background on the practice of off-label use in the pharmaceutical industry, including a literature review. We discuss our data and model in Sections 3 and 4, respectively. Section 5 discusses our results and Section 6 concludes.

2 FDA Oversight and the Nature of Off-Label Use

The Food and Drug Administration Act of 1906 created the FDA, initially just to set manufacturing standards. In the wake of the Elixir Sulfanilamide episode, Congress passed the Federal Food, Drug and Cosmetic Act of 1938.[6] This prevents a new drug's introduction without FDA certification that the drug is safe. The law also led to the modern arrangement where many drugs are available only with a physician's prescription (Temin 1979).[7]

In 1962, Congress passed the Kefauver-Harris Amendments to the Food, Drug and Cosmetic Act. This grants the FDA the authority to certify a drug's efficacy, in addition to safety, before a firm can sell it. Initially, supporters of this law argued the law would prevent

[6] In the 1930s, the S.E. Massengill Company sold the antibiotic sulfanilamide first as tablets and capsules. They then developed a liquid version by dissolving sulfanilamide in diethylene glycol. In September 1937, Massengill marketed this liquid as "Elixir Sulfanilamide." Unbeknownst to their chemists, diethylene glycol is toxic. Over 100 people died. See Temin (1979).

[7] As Temin (1979) discusses, the new law did not directly implement the prescription system, but the FDA moved quickly to use the law to establish this system.

firms from aggressively marketing drug products, with dubious effectiveness, to physicians who would then write prescriptions for their patients. However, the Thalidomide episode of 1961-62 created a sense of urgency that also helped facilitate passage of the law (Harris, 1964). While the 1938 law kept Thalidomide off the US market, some physicians had already received the drug for experimental purposes. The FDA did not heavily regulate this type of distribution. Reports of birth defects in babies born to European mothers who had taken Thalidomide raised concerns that pharmaceutical firms might harm patients by moving their products to market too quickly (Peltzman 1973). This series of events contributed significantly to the emergence of the current regulatory environment, which has important implications for the incentives for firms to gain approval for particular indications.

2.1 Drug Development

Drug development begins with the isolation of a new molecule. A researcher then tests to determine whether the molecule is biologically active and to identify the nature of that action. Once action is determined, usually in animal models, the researcher (typically backed by a pharmaceutical manufacturer) files an investigational new drug application (IND) to begin human trials. These clinical trials follow a strict three-phase process in which the applicant must prove safety and efficacy.[8] If successful in these trials, the applicant submits a New Drug Application (NDA) to the FDA; if it is approved, the NDA allows the applicant to sell the drug in the U.S. and specifies a list of approved indications. Firms may market their product for the approved (i.e., on-label) indications only.

The process from IND to NDA is long, risky and costly. Typically, it takes a decade or more (DiMasi et al., 2003), and only around 9% of drugs for which an IND is filed achieve an NDA (DiMasi 2001). Because firms typically seek molecule patents at the moment of initial discovery, the process often consumes half or more of the life of the core patent covering the

[8]In Phase I, healthy humans are given the compound to establish safety. Phase II tests involve a small number of volunteers with the disease for which the manufacturer is ultimately seeking approval. Phase II aims to establish some measurable treatment effect. Once a minimal efficacy standard is met, the study proceeds to Phase III, which requires much larger pools of volunteers with the disease be tested to identify the treatment effect more precisely. All three phases are generally double blind.

molecule. Given failure rates, direct costs of drug discovery and testing, and the opportunity cost of capital that must be devoted to the effort, estimated average costs of achieving an NDA range from $800 million to $1 billion (DiMasi et al. 2003; Adams and Brantner 2006).

Because of the incentives in the clinical-trials process, firms do not typically include a broad list of approved indications on their drugs' labels. Part of the reason is that clinical trials center on demonstrating efficacy for a given indication, and the results of one approval (NDA) are often not transferable to another. To add a new indication for an existing drug, a manufacturer must go through the same tedious, costly clinical-trials process needed to achieve the original marketing approval.[9] In addition, physicians may prescribe a drug off-label anyway, in which case obtaining a new indication is unnecessary.

The FDA grants a variety of marketing exclusivities, some of which affect strongly the incentives to pursue NDAs and new indications. First, a drug approved with a new molecule may earn a new chemical entity (NCE) exclusivity. For five years, the FDA prevents any other firm from marketing the drug, regardless of patent protection.

More importantly, the FDA also grants a three-year marketing exclusivity for a label change that recognizes a new indication (NI). In principle, the NI exclusivity grants a significant incentive to endure clinical trials to modify a drug's label. However, this benefit depends crucially on generic competition. If one or more generic manufacturers have gained approval to sell a drug, then the benefits of obtaining an NI may spill over to generic manufacturers. Intuitively, a firm that obtains an NI receives only a three-year exclusive right to *advertise* its product for the new use. But since a physician can prescribe a drug for any reason, if one version of a drug is advertised for a use, physicians may prescribe all other versions at nearly the same rate.

Prior to 1984, generic competition was less of a concern. Because generic applicants had

[9] As the USGAO has described it: "If, after FDA has approved a drug, evidence arises of its safety and effectiveness in treating conditions or patient groups other than those named in the label, then the drug's manufacturer (or any other interested party) can submit a new application to have the label changed. This application, known as an 'efficacy supplement,' is similar to the original application in that it must contain evidence demonstrating to FDA's satisfaction that the product is both safe and effective for the treatment of the new condition" (USGAO, 1996: page 2).

to go through clinical trials to sell drugs bioequivalent to approved drugs, and because there was tremendous uncertainty about whether testing a drug infringed on patents, generic products were a relatively small part of the approved drug portfolio in the US. In 1984, however, Congress passed the Hatch-Waxman Act to clarify the rules for, and increase the rate of, generic entry.[10] Now, a generic applicant may receive an Abbreviated New Drug Application (ANDA), permitting entry, by demonstrating that its product is bioequivalent to the branded product. The cost of an ANDA is a small fraction of that of an NDA. Generic entry has expanded so rapidly, that generics now account for nearly two-thirds of all prescriptions written in the U.S. (Aitken et al. 2009).

Practically speaking, obtaining a new indication for a drug (and getting the three-year NI marketing exclusivity) has high economic value when the drug is covered by an NCE, moderate economic value after the NCE expires but patents still partially block generic entry,[11] and low economic value upon generic entry. Since some new uses emerge late during a drug's life cycle, manufacturers may often find it optimal not to pursue an NI exclusivity.

As an alternative, a manufacturer may pursue approval for a new drug. For example, Glaxo-Wellcome gained FDA approval for buproprion hydrochloride in 1985, called it Wellbutrin (IR formulation) and marketed it as an antidepressant.[12] Some time after, Dr. Linda Ferry, a family practitioner in California, noticed that many of her patients taking Wellbutrin (for depression) showed decreased interest in smoking. She then convinced Glaxo to pursue clinical trials. After successful trials, Glaxo got approval in 1997 for an on-label indication for buproprion as a treatment for smoking cessation. However, Glaxo did not add smoking cessation to the label for Wellbutrin (and they never have). Rather, they got

[10] Innovating firms can also earn (up to five years) patent life lost during the clinical-trials process.

[11] Under the Hatch-Waxman Act, a generic may file for an ANDA once four of the five NCE years have expired. It must then show the pioneering firm's patents are invalid or would not be infringed by the generic product.

[12] Initially, there were a significant number of seizures at the recommended dosage of 400-600 mg. Glaxo removed Wellbutrin from the market in 1986. After subsequently discovering that reducing the dose by about half sharply reduced the risk of seizures, Glaxo reintroduced Wellbutrin to the market in 1989 with a maximum dose of 450 mg/day. See http://www.emedexpert.com/facts/bupropion-facts.shtml.

smoking cessation on the label for a new drug, Zyban (Perkins et al. 2008, pp. 113-114). Obfuscating the relationship between Wellbutrin and Zyban may mitigate the advertising spillover effect.

2.2 Literature Review

Given the FDA's regulatory architecture, there are a variety of reasons that drugs' labels do not cover all uses. Numerous papers discuss anecdotes of off-label use. Collectively, these anecdotes illustrate that the desirability of off-label use varies widely.

For example, beta-blockers, such as metaprolol and propranolol, have been used for decades to treat hypertension, cardiac dysrhythmias, and other diseases. Clinicians have noted that beta-blockers also control physical sensations associated with anxiety (such as rapid heartbeat, tightness in the chest, and trembling), and that when patients do not feel these sensations, their psychological experience of anxiety is significantly reduced. As a result, these drugs are widely prescribed for situational and other forms of anxiety, to apparent great effect. Lin et al. (2006) estimate that 52% of prescriptions for beta-blockers were off-label from 1999-2002. Anxiety is not, however, an approved use of any beta-blocker. Such examples of effective re-purposing are not rare and off-label use is not a new phenomenon. In a 1991 survey, roughly one-third of cancer drugs were prescribed off-label and about one-half of patients were prescribed at least one drug off-label (USGAO 1991).[13]

On the other hand, off-label use has led to clear cases of patients being harmed. During the 1990s, after Dr. Michael Weintraub showed that a group of 121 patients using a combination of the weight-loss drugs fenfluramine and phentermine lost an average of 30 pounds, this "Fen-Phen" combination surged in popularity. Because neither drug's label discussed using the drugs in combination, this was an off-label use. Dr. Weintraub looked for side effects, but he assumed the drugs were safe (Kolata 1997). Unfortunately, numerous patients suffered heart-valve damage (O'Reilly and Dalal 2003).

[13]Salbu (1999) and Klein and Tabarrok (2004) discuss a number of other examples of beneficial off-label use.

There are also many cases, especially among the drugs involved in the DOJ settlements, where pharmaceutical firms are alleged to have marketed their drugs for off-label uses with uncertain clinical support (Stafford 2008). In perhaps the best-known case, Warner-Lambert's drug Neurontin was initially approved for "adjunctive therapy in the treatment of partial seizures...in patients above the age of 12 years," and was later approved for patients 3-12 years old (2000) and for "postherpetic neuralgia" (2004). Physicians have prescribed Neurontin for a number of off-label indications, such as bipolar disorder and neuropathic pain, for which the evidence for effect is at best equivocal (Mack, 2003). In 2004, Pfizer (which merged with Warner-Lambert in 2000) pled guilty to two felony counts of marketing a drug for unapproved uses, and paid $430 million in civil and criminal fines. Some $26.6 million went to whistleblower David Franklin, who started working for Warner-Lambert in 1996 (Evans, 2009).

Numerous clinical papers study rates of off-label prescribing. Nearly all are narrowly focused, and their results vary widely and are virtually impossible to compare to each other. For example, in a survey of papers studying off-label use in pediatrics, Cuzzolin et al. (2003) identify 16 studies published during 1995-2001. Of these, 13 are prospective studies, 2 are retrospective, and 1 is prescription-event monitoring (a much longer study, 10 years). The number of patients varies from 40 to 24,337, while the number of prescriptions varies from 257 to 4,455.[14] The percentage of off-label use varies from a low of 10.8% (McIntyre et al. 2000, "pediatric ambulatory") to a high of 72% (Avenel et al. 2000, NICU). In the most comprehensive work, Radley et al. (2006) study off-label use during 2001 of 160 drugs. Studying data from the *National Disease and Therapeutic Index* (NDTI), a survey of physicians from IMS,[15] they find off-label use at about 21% of overall use. This is near the 32.5% rate we estimate for 2001, even though we examine a more comprehensive set of drugs and use different (non-proprietary) data on prescriptions. Finally, USGAO (1991) and Molitor (2012) examine some drivers of off-label drug use by cancer patients. USGAO

[14]Some studies did not indicate numbers for both categories.

[15]These data are "nationally representative diagnostic and treatment data similar to that contained in the National Ambulatory Medical Care Surveys (NAMCS)" (Radley et al. 2006)

(1991) shows, for example, no pattern of off-label use by age group and gender, while Molitor (2012) finds that over 20% of new cancer drug use within the Medicare population during 1998-2008 was off-label.

3 Data

Our data are drawn from two sources. The *National Ambulatory Medical Care Survey* (NAMCS) provides information on the prescriptions written for a representative set of US physician office visits. NAMCS data are collected for 1993-2008. The *Supplement* to the *Physicians' Desk Reference* (PDR) is titled either the *PDR Companion Guide* or *PDR Guide to Drug Interactions, Side Effects, Indications, Contraindications*, depending on the year. This serves as physicians' primary reference on FDA-approved indications for each drug, for 1993-2008 as well.

No existing research combines these two sources.[16] Moreover, because of the incentives facing firms to get indications on drug labels, the usually unanticipated timing of discoveries of useful ways to repurpose drugs, and the ways physicians' manuals (like the PDR) list sets of approved indications, there are multiple ways of classifying on-label and off-label use. To clarify, we first define two types of on-label use:

- *A **drug-label use** occurs whenever a drug is used for an indication on the drug's FDA-approved label.*
- *An **active-ingredient-label use** occurs whenever a drug is used for an indication on any label of any drug with the same active ingredient.*

For any drug, the set of drug-label uses is a subset of the set of active-ingredient-label uses.

Next, we define two types of off-label use.

- *An **anticipated off-label use** is any active-ingredient-label use that is not a drug-label use.*

[16] Radley et al. (2006) use the PDR to classify off-label use.

- *An **unanticipated off-label use** is any use that is not an active ingredient use.*

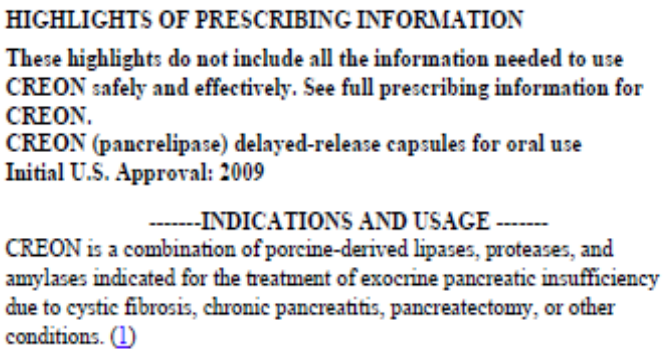
Legally, active-ingredient uses that are not drug-label uses are off-label uses. However, these off-label uses are natural candidates for prescribing physicians given that the use has been approved for some other drug with the same active ingredient. Hence, we say such off-label uses (e.g., Wellbutrin used for smoking cessation) are anticipated. For the purpose of our analysis, we define off-label use as *unanticipated off-label use*. All other uses of a drug will be defined as on-label.

3.1 NAMCS

The NAMCS is an annual survey, conducted by the Center for Disease Control and Prevention (CDC). The multi-state design generates a representative sample of patient visits to community-based (non-institutional, non-clinic) physician offices. The data include variables capturing office visits, indications, characteristics of patients, insurance coverage, medical procedures, tests conducted, and medications prescribed. The survey has been conducted annually from 1973 to 1981, in 1985, and then again annually since 1989. Each year approximately 1,500 physicians participate in the survey. Each physician is randomly assigned a one-week participation window and uses an abstraction form to characterize approximately 30 office visits. This results in detailed quantitative descriptions of around 35,000 office visits each year. Visit weights are assigned so that national estimates can be produced.[17]

We extract data on all visits from 1993 to 2008. After we keep those visits with at least one prescription, the resulting data set contains information on 547,977 prescriptions from the 141,523 office visits during 1993 to 2008. For each visit, the physician may record up to

[17]This use of the NAMCS weights to estimate prescribing volume has been validated in the literature; see Pincus et al. (1998), Thomas et al. (2006), and Iizuka (2004). Note that the NAMCS visit weights are calculated to impute prescriptions to the national and annual level. Given the weight construction we could allocate annual prescription estimates to the month by dividing the weighted estimate by 12; allocating prescriptions to the region could be accomplished by re-weighting on the basis of the region's proportion of the national population. In either case, any biases from not explicitly adjusting our prescription counts will be isolated in the intercept term, and will not affect the marginal effects of interest.



HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use CREON safely and effectively. See full prescribing information for CREON.

CREON (pancrelipase) delayed-release capsules for oral use

Initial U.S. Approval: 2009

-------INDICATIONS AND USAGE -------

CREON is a combination of porcine-derived lipases, proteases, and amylases indicated for the treatment of exocrine pancreatic insufficiency due to cystic fibrosis, chronic pancreatitis, pancreatectomy, or other conditions. (1)

Figure 1: *The Current FDA Label for Creon (Pancrelipase)*

3 indications. The NAMCS data code indications according to the ICD-9 classification. In addition to prescriptions and indications, we extract information on visit payment source, patient age and gender, physician specialty, and Census region.

3.2 PDR

Each prescription drug available for sale in the U.S. has an FDA-mandated label, which lists (among many other things) the indications for which the FDA has approved use. Figure 1 is an extract from the first part of the Creon label. Its label shows the drug-label use (treatment of exocrine pancreatic insufficiency due to cystic fibrosis, chronic pancreatitis, pancreatectomy, or other conditions) in specific populations. Identifying the history of FDA-approved indications for a drug is surprisingly difficult. Although the FDA maintains the current FDA-approved indications for a drug in the Orange Book, these listings do not include the history of how the label reached its current state.

The annual *Supplement* to the PDR fills this void. In particular, the "Indications" section lists FDA-approved drugs for each indication, giving physicians up-to-date information on a drug's approved uses, interactions, side effects, and contraindications. We obtain each edition of the PDR from 1993 to 2008 and capture all drug-indication combinations.[18] Fig-

[18]To extract this information from over 1000 pages formatted in this way, we remove the *Supplement*'s binding and use a high resolution scanner to create images of each page. We use Able2Extract Professional, software that uses Optical Character Recognition (OCR) technology, to extract the information to a raw text format to parse into a useable form. Following the extraction and parsing processes, we search for and remove

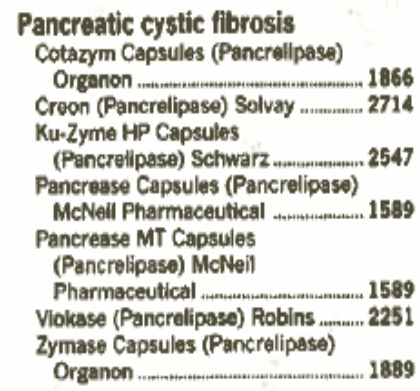


Figure 2: An Example of an Indication in the PDR

ure 2 provides an example of the *Supplement*'s formatting from 1997. For the indication "Pancreatic cystic fibrosis," there are seven associated FDA-approved drugs: Cotazym Capsules, Creon, KuZyme HP Capsules, Pancrease Capsules, Pancrease MT Capsules, Viokase, and Zymase Capsules. PDR records also include the active ingredient for each drug—in this case, Pancrelipase for all drugs—and the manufacturers.

Note that this list represents anticipated off-label uses as being on-label. For example, Creon is approved for "treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions," i.e., pancreatic cystic fibrosis. But Viokace is approved just for "treatment of exocrine pancreatic insufficiency in adults due to chronic pancreatitis or pancreatectomy," i.e., not pancreatic cystic fibrosis. Use of Viokace for pancreatic cystic fibrosis, like Wellbutrin for smoking cessation, is an active-ingredient use that is an anticipated off-label use.

Clearly, anticipated off-label use is qualitatively distinct from unanticipated off-label use. Often, manufacturers wish to market drugs with the same active ingredient differently, so a drug's labels do not include all safe and effective uses. As mentioned above, to most closely

the (surprisingly small) number of errors in the resulting files. The consistency in the *Supplement*'s format and few changes in the text descriptors for indications and drug names make this feasible. For example, to catch errors in the text describing an indication, we sort the entire panel (all years) by indication and flag subtle changes to the text descriptor. We then compare the flags to the original image files. We use a similar cleaning process for drug names.

match the actual list of all safe and effective uses, we define any active-ingredient-label use as on-label. Hence, *we treat anticipated off-label use as on-label use.* This provides a liberal definition of on-label use and a conservative definition of off-label use.

We format the data so that the unit of observation is an indication-year-ingredient (IYI) combination. For the text from Figure 2, the IYI is "pancreatic cystic fibrosis - 1997 - pancrelipase." There are 178,823 total IYIs, composed of 3,587 unique indication descriptors and 3,342 unique active ingredients.

3.3 Matching NAMCS to PDR

Drugs and indications are each defined differently in the NAMCS and the PDR. Hence, matching drugs to indications for the purposes of identifying off-label use requires careful interpretation of language from both definitions. For drugs, we use a word-based matching algorithm to match the text for each active ingredient in the PDR to the NCHS Multum codes used by the NAMCS to identify active ingredients. This corrects for abbreviations and is virtually one-to-one.[19]

Matching indications in the PDR to indications in the NAMCS is far more complicated. The PDR uses terms for indications that do not map directly to the ICD-9 codes used on NAMCS prescription records. In fact, processing the language in these descriptors and matching them to ICD-9 codes is sufficiently complicated that we rely on a Clinical Documentation Specialist, or *coder*, from a large academic medical center.[20] The coder manually matches each PDR indication to the appropriate ICD-9 code(s).[21]

This process is often not straightforward. Some of the language in the PDR indications requires further research for additional information to establish an appropriate match. In other situations where the PDR indication is not specific enough to map to a single 5-digit

[19]The few instances where the match is not one-to-one is due to combinations.

[20]This person's primary role at the medical center is to look for missing, vague, or incomplete physician documentation and to query the physician for the specificity needed to ensure that the coders can capture the most accurate indication, indication or symptoms for the patient.

[21]Our coder was provided a spreadsheet with the 3,587 unique text descriptors from the PDR for 1993-2008, as well as the ICD-9-CM Manual Volumes 1, 2, 3 published by HCPro, Inc (2011).

ICD-9 code, we match to a less-specific (four- or three-digit) code corresponding to a broader range of indications. For example, "Pneumonia, Community Acquired" and "Pneumonia Nosocomial" are listed as separate indications in the PDR. "Pneumonia Nosocomial" is a more complex pneumonia with an easily identified ICD-9 code for Gram Negative Pneumonia, 482.83. "Pneumonia, Community Acquired" is less specific and is coded as a Pneumonia, NOS (not otherwise specified), 486. In other situations, a descriptor requires more than one ICD-9 code to adequately describe the indication. In these situations, the coder lists all relevant codes.

Hence, matching PDR indications to NAMCS indications is a many-to-many match. Our conservative matching approach also leads us to under count off-label use. Alternatively, we could make subjective decisions regarding the closest matching indication. We regard a conservative approach as most sensible here.

Having matched PDR indications to NAMCS indications and PDR active ingredients to NAMCS active ingredients, we reformat our data so that the unit of observation is a prescription. For each observation, we then list the characteristics of the patient, the date of the visit and the complete list of indications assigned for the visit. For each prescription, we cycle through the indications to determine whether the set of approved active ingredients for those indications includes the prescribed drug. To be conservative in our estimates of off-label use, we convert the NAMCS indications to the three-digit ICD-9 level before querying the set of approved drugs. For example, 410.01 would be matched to any 410 code.

We set the *on-label indicator* to 1 if the prescribed drug's active ingredient is among the set of approved active ingredients for at least one of the indications listed for the visit. This serves as the dependent variable in our analysis. As we discuss in more detail in section 4, this variable cannot be used to directly measure the amount of on-label use because of imperfect detection.

3.4 Descriptive Statistics

Table 1 shows the demographic composition of the individuals and physician specialties associated with prescriptions written in our sample from the NAMCS. Just over 58% of prescriptions are written for female patients, 8.9% are for African-Americans, and 7.5% are for Hispanics. The average prescription is written for a patient who is 51.8 years of age. Over 93% of prescriptions are written for patients who have some form of insurance—47.5% with private insurance, 31.3% with Medicare, 10.2% with Medicaid, and 4.1% with some other form of insurance. The physician specialties with the greatest frequency are internal medicine (13.2%) and cardiology (11.2%). The Midwest Census region accounts for the largest proportion of prescriptions at 34.4%, while the East Census region (omitted region) accounts for the lowest, only 20.3%.

Table 2 shows that the most commonly prescribed drugs are central nervous system agents (20.2%), cardiovascular agents (18.5%), and anti-infective agents (10.5%). The most common indications are associated with circulatory disorders (25.4%) and respiratory disorders (17.7%). The frequencies of the indications do not sum to one, because all indications from a visit are listed for each prescription from the same visit.

On average, a patient is prescribed 3.9 prescriptions per visit. However, the standard deviation is quite large. Across all visits, a physician has an average of 71.5 FDA-approved alternatives for the entire set of (up to three) visit-specific indications, defined at the three-digit ICD-9 level, reported in NAMCS. The median number of approved prescription alternatives (i.e., unique Multum codes) per indication is 27.7. We expect that when the on-label alternatives for treating a patient are limited (i.e., a small number of approved drugs for the complete set of observed indications), a physician will be more likely to prescribe off-label.

The NAMCS survey form changes significantly over our sample. From 1995 to 2002 (40.1% of our sample), the form allows six prescriptions to be reported, up from only five in 1993 and 1994. From 2003 onward, the form allowed a total of eight prescriptions to be listed. The form never increases the maximum allowable number of indications, three, during our

period of study. Over 61.7% of prescriptions appear on a form with two indications listed and 33.5% appear on a form with three indications.

Table 3 highlights how the NAMCS form limitations affect detection. The numbers in the table are conditional means of the on-label indicator, by numbers of prescriptions and indications. If the form limitations have identifying power, then our ability to detect on-label use should be highest for those visits with a low number of prescriptions and a high number of indications (top right corner of the table), and lowest for those visits with a high number of prescriptions but a low number of indications (lower left corner of the table). These are precisely the patterns we observe. The conditional means of this indicator rise virtually monotonically up the columns and across the rows, and plateau in the top-right corner of Table 3. Thus there is a group of observations for which the NAMCS form limitations appear to have significantly less impact on our ability to detect on-label use.

Hence, time-varying form limitations are very useful for identification purposes. Each of the exogenous increases in the maximum number of prescriptions that can be recorded was not accompanied by a similar increase in the maximum number of recorded indications during a visit. These form limitations result in only 33.5% of all prescriptions in our data appearing to be written for an FDA-approved use, or 66.5% off-label use. [22] In the next section, we discuss how we correct for detection error and identify the rate of on-label use.

4 The Model

We cannot use our naïve indicator of on-label use directly because of *false negatives*. When a prescription is on-label but the indication is not listed on the NAMCS survey form, true on-label use is unobserved. To identify the rate of on-label use, we adopt the DCE methodology

[22] The most comprehensive of these studies, Radley, et al. (2006), estimates a rate of off-label use of 21% for over 160 drugs in 2001; we estimate an off-label use rate of around 26.5% for that same year. However, Radley and coauthors are only able to conduct the study for one year and had to rely upon an expensive proprietary data set (the National Disease and Therapeutic Index (NDTI) from IMS Health) and a hand-generated indicator for on-label use. Consequently, their findings and methodology are both limited and dated.

introduced by Feinstein (1990).[23]

Let a physician's decision, of whether to write prescription i for a drug that is on-label, be summarized by a stochastic latent variable,

$$Y_{1i}^* = x_{1i}\beta_1 + \varepsilon_{1i}, \tag{1}$$

where ε_{i1} is independently and identically distributed $N(0,1)$. The binary outcome of this decision-making process, which is not observed, is then

$$Y_{1i} = \begin{cases} 1 & \text{if } Y_{1i}^* > 0 \\ 0 & \text{otherwise .} \end{cases} \tag{2}$$

With the normality assumption, the probability that the physician prescribes on-label, conditional on x_{1i}, is

$$Pr(Y_{1i} = 1) = \Phi(x_{1i}\beta_1), \tag{3}$$

where $\Phi(x_{1i}\beta_1)$ is the standard normal cumulative distribution function (CDF). The variables in the linear index, $x_{1i}\beta_1$, alter the likelihood of a physician writing a prescription for an approved indication.

The difficulty is that we do not observe this binary outcome and cannot infer our outcome of interest (i.e., $\Phi(x_{1i}\beta_1)$) by estimating a Probit model. Instead, we observe an indicator that takes on a value of one when a prescription is both on-label and we can detect it in the data. Conversely, the indicator takes on a value of zero when the prescription is actually off-label or when we have a false negative. By specifying a model for detection, along with the equation characterizing the physician's choice to prescribe on-label, DCE allows us to distinguish between these two cases.

Consider cases when on-label prescribing actually occurs and let

$$Y_{2i} = \begin{cases} 1 & \text{if on-label use is detected} \\ 0 & \text{otherwise .} \end{cases} \tag{4}$$

[23]DCE has been applied previously in a health context by Kleit et al. (2003) and Bradford et al. (2001), and a non-health context by Helland (1998), Feinstein (1989), and Feinstein (1991).

Thus, when $Y_{2i} = 1$, on-label use occurs (i.e., $Y_{1i} = 1$) and is detected. This is precisely the naïve on-label indicator we construct. Further, assume the distribution of the underlying latent variable for the Y_{2i} indicator is given by

$$Y_{2i}^* = x_{2i}\beta_2 + \varepsilon_{2i}.$$

We assume ε_{2i} is distributed standard normal and the linear index, $x_{2i}\beta_2$, includes those variables that alter the probability of detecting off-label use.

The probability of detecting true on-label use is

$$Pr(Y_{2i} = 1) \quad = Pr(Y_{2i} = 1|Y_{1i} = 1) * P(Y_{1i} = 1) + Pr(Y_{2i} = 1|Y_{1i} = 0) * P(Y_{1i} = 0).$$

Assuming there are no *false positives*, i.e., all detected on-label use is truly on-label, then $Pr(Y_{2i} = 1|Y_{1i} = 0) = 0$ and $Pr(Y_{2i} = 1|Y_{1i} = 1) = Pr(Y_{2i} = 1)$.[24] With the normality assumption,

$$Pr(Y_{2i} = 1) = \Phi(x_{1i}\beta_1)\Phi(x_{2i}\beta_2).$$

The likelihood function is then

$$\mathcal{L} = \prod_i \quad [\Phi(x_{1i}\beta_1)\Phi(x_{2i}\beta_2)]^{Y_{2i}} [1 - \Phi(x_{1i}\beta_1)\Phi(x_{2i}\beta_2)]^{1-Y_{2i}}.$$

As Feinstein (1990) points out, certain conditions must be satisfied to identify the parameters of the model via maximum likelihood. In particular, note that when $\Phi(x_{1i}\beta_1)\Phi(x_{2i}\beta_2)$ is high, it is unclear whether this is due to a high rate of on-label prescribing, or a high rate of detection. For example, if x_{1i} and x_{2i} include all the same variables, then nothing differentially shifts the probability of on-label prescribing and the probability of detection,

[24] We assume that there are no false positives in our measure of on-label prescribing. Given the presence of false negatives, this assumption is required for the detection model to be identified. In our application, false positives can arise if there are errors in matching NAMCS indications to the PDR data. We hire a professional medical records coder to do the matching to minimize this possibility. The other source of false positives arises when a patient is actually prescribed a drug off-label for one observed indication but the drug is approved for another of the patient's observed indications. We believe the frequency of such events is rare, and would lead to a conservative estimate of off-label use.

so β_1 and β_2 are not separately identified. But if there are some variables in the group determining on-label prescribing but not in the group determining detection (and vice-versa), then each probability will vary significantly conditional on a fixed value for the other probability and the model is identified. Ideally, we would include a variable in x_{2i} that pushes the probability of detection to one, and identify the rate of on-label prescribing in a simple discrete choice model. Without this variable, the parametric assumptions (i.e., normality and linear indices) are required for identification. In Section 5, we discuss how close we get to this ideal setting.

The common elements in x_{1i} and x_{2i} move both the probability of on-label use and the probability of detection. For this group of elements, we include patient characteristics such as age, gender, and race. For example, a patient's age may lead physicians to take a more cautious or aggressive approach in prescribing off-label. Also, certain types of patients may be more likely to have a chronic indication (e.g., African-Americans have a higher incidence of diabetes), which decreases the probability of observing the relevant indication for the visit, lowering the probability of detection. Those variables only in x_{1i} move the probability of on-label use but do not affect the probability of detection. These include the number of FDA-approved drugs for the visit-specific indications, plus indicators for physician specialty, categories of indications (e.g., mental disorders), the patient's insurance status and census region and year. Those variables only in x_{2i} move the probability of detection but do not affect the probability of prescribing off-label. These include the number of prescriptions written on the visit, plus indicators for whether there were two or three indications and for the maximum number of prescriptions recordable on the NAMCS survey form.

Thus our strategy for separately identifying β_1 and β_2 relies largely on exploiting the limitations, and changes in those limitations, of the NAMCS form during our sample period, along with some visit-specific information. Recalling Table 3, we expect an increase in the maximum allowable number of prescriptions to decrease our chances of detecting on-label use, but not to affect the physician's actual decision to prescribe off-label.

With estimates of the $\hat{\beta}_1$ and $\hat{\beta}_2$ parameters, we recover the rate of off-label prescribing as the complement of the rate of on-label prescribing, $1 - \Phi(x_{1i}\hat{\beta}_1)$. This can be calculated at the individual prescription or population level. However, as noted by Feinstein (1990), even when valid exclusion restrictions give consistent estimates of $\Phi(x_{1i}\hat{\beta}_1)$, the coefficient estimates on those variables common to x_{1i} and x_{2i} may not be precisely estimated, as identification relies largely on parametric assumptions. In general, we interpret these coefficients with caution.

5 Results

It is simplest to discuss our estimates as two separate models, one describing detection and the other physician behavior. Table 4 and 5 present the coefficient estimates for selected variables in the model of detection and physician behavior, respectively. The top half of each table contains the estimates for variables that are exclusive to each model, while the bottom half of the respective tables presents estimates for variables common to both models. Because identification of the coefficients for variables common to both models is driven largely by the parametric structure of the model, we are hesitant to draw strong conclusions about them. Tables 4 and 5 also have two columns. Column 1 presents the results from a parsimonious specification, restricting temporal trends to be the same for all physician specialties in the model of physician behavior. Column 2 presents estimates from a more general model of physician behavior that allows for differential trends by including a full set of interactions of year and physician specialty indicators. We emphasize the results from Column 2.

It is useful to first consider the results for the detection model. The coefficient estimates in Table 4 for the detection model are consistent with our expectations. Both the number of prescriptions for a visit and the form changes to the NAMCS decrease the probability of detecting on-label use, and each coefficient is statistically significant at the 1% level. Further, the indicators for whether there are two or three indications for a visit are positive

and statistically significant, such that for a fixed number of prescriptions an increase in the number of indications increases our rate of detection. The results in Table 4 are similar in both columns. Collectively, the intuitive results in Table 5 give us confidence that we successfully identify the rate of detection.

NEED TO MENTION THAT INCLUSION OF DUMMIES OR TIME TREND DOES NOT CHANGE THE RESULTS, WHICH SHOWS THAT THE EXCLUSION RESTRICTION IS CORRECT AND WE'RE WELL IDENTIFIED.

NEED TO MENTION HOW THE PROBABILITY OF DETECTION CHANGES WITH FORM CHANGES FROM COLUMN (2). Prob[detection — form1=0, form2=0] = .545104 Prob[detection — form1=1, form2=0] = .5169105 Prob[detection — form1=1, form2=1] = .4895006

NEED TO MENTION HOW WE CAN INCLUDE PHYSICIAN SPECIALTY INDICATORS IN THE DETECTION MODEL AND NOTHING CHANGES FROM COLUMN (3). ALSO MENTION THAT WE CAN ADD THE INSURANCE INDICATORS TO THE DETECTION EQUATION AND ESTIMATES ARE STILL VIRTUALLY UNCHANGED IN EITHER DETECTION OR ON-LABEL MODEL.

NEED TO SAY THE ESTIMATES ARE NEARLY IDENTICAL REGARDLESS OF THE ROBUSTNESS CHECKS, SO WE FOCUS ON COLUMN (2).

Moving to the model of physician behavior, Table 5 reports how the rate of actual on-label prescribing varies with the number of FDA-approved alternatives for the physician to treat a patient. We find that an increase in available alternatives significantly increases the probability that a physician prescribes on-label. The effect is also economically significant. Increasing the observed number of on-label alternatives by 10% (about 7.2) decreases the probability of prescribing off-label by 1.6 percentage points, from 34.0% to 32.4%. This corresponds to a 4.7% reduction in the probability of off-label prescribing. This is, at a minimum, consistent with welfare-enhancing behavior on the part of physicians. In going beyond FDA-approved alternatives to find a good match between a patient and a drug,

physicians are more likely to prescribe off-label when their choices are more limited.

Table 5 also reports the estimates of the effect of insurance status on the physician's decision to prescribe on-label. Relative to the base case of a patient with no insurance (the omitted dummy variable), patients with any type of insurance are significantly more likely to be prescribed a drug off-label. We estimate marginal effects for insurance status by assuming a particular insurance status for every patient, calculating the probability of on-label prescribing, and comparing that to the probability of on-label prescribing when all patients have a different insurance status. If no patient has insurance, our estimates predict the proportion of prescriptions written off-label as 32.8%. If all patients have Medicaid, we estimate the proportion as 34.8%. This corresponds to a 5.9% increase in the probability that a prescription is written off-label for patients on Medicaid. In comparing patients with Medicaid to those with private insurance, those on Medicaid are 2.2% more likely to be prescribed a drug off-label. Results are similar when comparing to patients with Medicare.

These results are consistent with at least two behavioral hypotheses. First, physicians may account for the insurance status of their patients when deciding whether to prescribe a drug off-label (which may run counter to a patient's insurance formulary or prior authorization program). Thus, consistent with the decision to go off-label when the portfolio of approved choices is limited, the physician appears to have patients' pecuniary welfare in mind when writing prescriptions. Second, the difference in the effect of other forms of insurance and Medicaid suggests either that reimbursement for off-label prescriptions through Medicaid is less constrained or that physicians respond to the very low (or no) patient copayments for prescription drugs in Medicaid compared to other insurance by more frequently providing off-label prescriptions.[25]

Using the estimates of β_1 and β_2 from Column 2 of Tables 4 and 5, we construct implied estimates of the probability of detection and off-label use. Table 6 gives the mean of the

[25]Due to space considerations, we omit the remainder of coefficient estimates for the model of physician behavior: indicators for physician specialty, indication codes, and census region and year. These estimates are available from the authors upon request.

predicted probability of detection, $\Phi(x_{2i}\beta_2)$, for the taxonomy of prescription-indication combinations from Table 3. Over all observations, we estimate that the naive indicator is correct 50.6% of the time. The rate of detection falls significantly as the number of prescriptions increases, given any fixed number of indications. For example, on average, for visits with three indications and only one prescription, we detect on-label use 66.3% of the time. Yet this probability falls to only 29.7% when the maximum number of eight prescriptions is listed for a visit, along with three indications. This pattern holds across all 3 columns of Table 6. These probabilities provide the average adjustment applied to observations with certain combinations of number of prescriptions and indications.

NEED TO RE-ITERATE THAT WE GET A BIG BUMP FROM THE FORM INDICATORS ALONE HERE.

For some prescriptions, the detection rate is over 80%, which means that we have a group of prescriptions detected to be on-label with a very high probability. The limiting case where the probability of detection is one is accomplished through the model's parametric assumptions. The limiting case where the linear index equals infinity does not exist in real-world retrospective data, but observing very high detection rates for a subset of prescriptions in our data gives us confidence in the DCE approach. A very cautious interpretation of results would treat our estimates of off-label use as tight upper bounds on the true rate since we get close to the limiting case in our data. Feinstein (1990) argues that this is how DCE models should be interpreted.[26]

Figure 3 plots yearly rates of off-label use, along with a fitted polynomial. The rate of off-label prescribing fluctuates between around 30% and 35% between 1993 and 2002, and then rises consistently from 2003 to 2008. Overall, off-label use rises by nearly a third, from 30.2% in 1993 to 39.1% in 2008. Interestingly, this detected trend in off-label use also leads, by just a few years, the trend in off-label settlements, which accelerated from 2008 to 2011. Since our results cover essentially all drugs listed in the PDR, this gives us further

[26]For example, in Feinstein's (1991) study of tax evasion, it is necessary to assume that there is at least one auditor in the data that detects evasion with probability 1 in the absence of parametric assumptions.

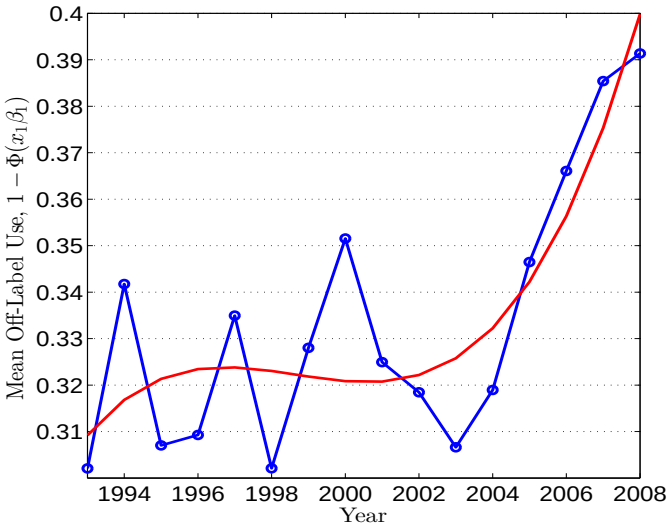


Figure 3: *Trend in Off-label Use*

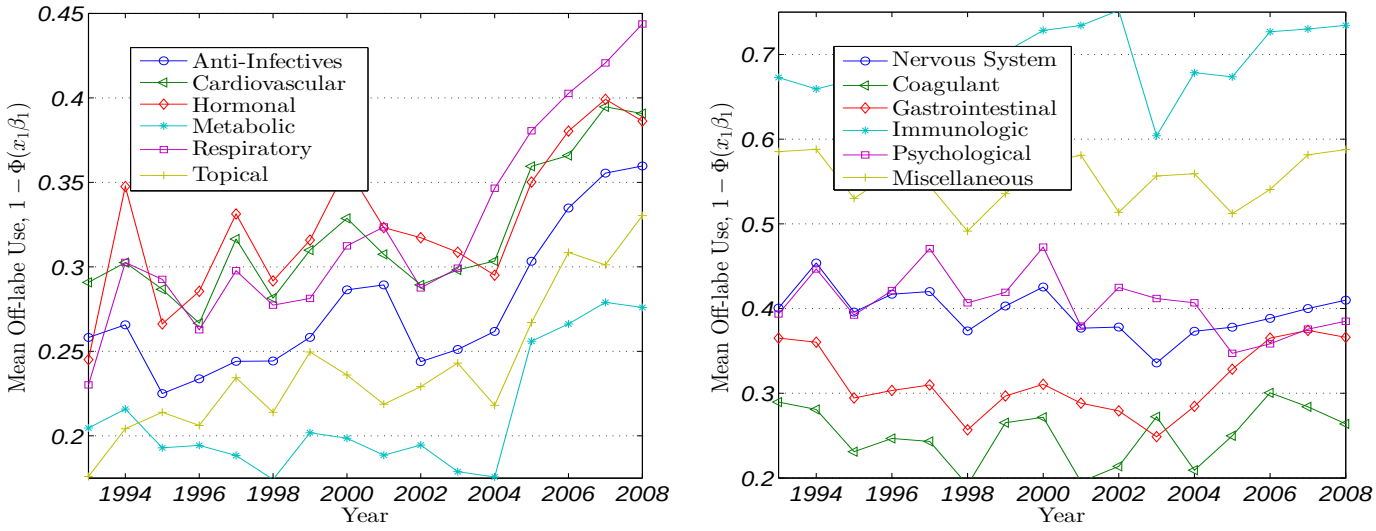
confidence in our results over the 15-year period we study.

NEED TO PLOT THE ESTIMATES FROM EACH COLUMN TO SHOW THAT THEY ARE VIRTUALLY IDENTICAL.

NEED TO SAY WE FOCUS ON ESTIMATES FROM COLUMN (2).

Figures 4(a) and 4(b) summarize the trends in off-label use by drug class; drug classes with the highest percentage increase in off-label use are in Figure 4(a), while drug classes with the lowest percentage increase in off-label use are in Figure 4(b). With the exception of a few drug classes (coagulant, gastrointestinal, and psychological), each ends our sample period with a higher rate of off-label use than it begins. Additionally, it is uniformly true that those classes with the lowest rates of off-label use in 1993 had higher percentage increase in off-label use. Thus the practice appears to be growing most quickly in drug classes where it had been less common.[27]

[27]Radley et al. (2006) is the only other study, to our knowledge, that makes any attempt to estimate off-label use by drug class; however, we do not know the identify of the few drugs they study within each class, making the estimates impossible to compare.



(a) Largest % Increase in Off-Label Use

(b) Smallest % Increase in Off-Label Use

Figure 4: Off-label Use by Drug Class

6 Conclusion

Off-label use is prevalent, controversial and under-studied. In this paper, we take the important step of identifying the incidence of off-label use from 1993 to 2008 and important factors that drive it. We are optimistic that our approach and these results will lead to further insights about this controversial subject and, hopefully, recommendations for policy.

For example, our finding that Medicaid patients are more likely to be prescribed off-label is important in light of recent policy developments. As of 2008, Medicaid expenditures on prescription drugs for certain low-income adults and children total $15.2 billion dollars (USGAO, 2010: page 1); however, this program will be expanded significantly under the Patient Protection and Affordable Care Act of 2010. While our findings suggest that off-label prescribing patterns are consistent with the enhancement of patient welfare, additional economic analysis is required to ensure that the practice is desirable from a societal perspective and that tax dollars are spent efficiently. For instance, research that builds on our findings might study whether treatment outcomes from using drugs off-label justify potential costs (realized by any entity) in excess of on-label alternatives.

In addition, the DOJ continues to enforce FDA guidelines that ban promotion of off-label uses for drugs, but it does not know the extent to which this promotion induces physicians to prescribe off-label or the effect that strict enforcement has on patient welfare. Our finding that physicians tend to prescribe off-label when it is in the best interest of the patient suggests that an out-right ban on off-label use, and possibly even the current ban on promotion of off-label uses, has the *potential* to harm welfare. However, much more research is needed for clear and effective policy to be developed.

For example, little is known about how the current FDA regulatory architecture affects incentives for firms to invest in identifying new uses for existing drugs. The FDA provides three-year exclusivities to incentivize firms to incur the costs associated with seeking new indications for existing drugs, but this incentive may be negligible if the drug is already generic. Currently, firms face a difficult decision of whether to rely on clinicians to discover and promote these new uses, or incur the costs associated with adding the indication to a drug's label that will likely soon be, or already is, generic. Data from the FDA Orange Book on new chemical entities, associated patents and associated exclusivities exist can shed light on these questions. We look forward to further progress.

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Table 1: Patient and Physician Variables

	mean	sd
Patient age	51.780	23.220
Patient is female	0.582	0.493
Patient is Hispanic	0.075	0.263
Patient is African-American	0.089	0.284
Patient is other (non-Caucasian) race	0.093	0.290
Patient has Medicare	0.313	0.464
Patient has Medicaid	0.102	0.303
Patient has private insurance	0.475	0.499
Patient has other insurance	0.041	0.198
Physician specialty is internal medicine	0.132	0.339
Physician specialty is pediatrics	0.064	0.245
Physician specialty is OB/GYN	0.023	0.149
Physician specialty is cardiology	0.112	0.316
Physician specialty is psychiatry	0.072	0.258
Physician specialty is neurology	0.062	0.242
Physician has other specialty	0.304	0.460
Southern Census region	0.228	0.419
Mid-West Census region	0.344	0.475
West Census region	0.225	0.418
Observations	547,977	

Note: These statistics reflect the demographic composition and insurance status of patients in our NAMCS sample of prescriptions during 1993-2008, as well as the specialty and location of the physician treating them.

Table 2: Prescription and Indication Variables

	mean	sd
Prescription observed to be on-label	0.335	0.472
Number of drugs approved to treat indications	71.490	69.290
Number of prescriptions written during visit	3.872	2.244
Two indications recorded on the NAMCS form	0.617	0.486
Three indications recorded on the NAMCS form	0.335	0.472
NAMCS form allows six prescriptions	0.887	0.316
NAMCS form allows eight prescriptions	0.485	0.500
Anti-infectives	0.105	0.306
Cardiovascular agents	0.185	0.388
Central nervous system agents	0.202	0.402
Coagulant modifiers	0.018	0.134
Gastrointestinal agents	0.044	0.205
Hormonal agents	0.063	0.242
Miscellaneous agents	0.017	0.130
Respiratory agents	0.083	0.276
Topical agents	0.094	0.292
Psychological agents	0.081	0.272
Immunologic agents	0.028	0.166
Metabolic agents	0.079	0.270
ICD9 code for infectious and parasitic disease	0.035	0.185
ICD9 code for neoplasm	0.039	0.192
ICD9 code for endocrine disorders	0.154	0.361
ICD9 code for mental disorders	0.130	0.337
ICD9 code for nervous system disorders	0.137	0.344
ICD9 code for circulatory system disorders	0.254	0.435
ICD9 code for respiratory system disorders	0.177	0.382
ICD9 code for digestive system disorders	0.058	0.234
ICD9 code for genitourinary system disorders	0.066	0.247
ICD9 code for skin disorders	0.074	0.261
ICD9 code for musculoskeletal system disorders	0.123	0.329
ICD9 code for ill-defined disorders	0.137	0.344
ICD9 code for injury and poisoning	0.046	0.209
Observations	547,977	

Note: These statistics reflect information on the prescriptions and indications in our NAMCS sample during 1993-2008. The top portion of the table provides information on the number of prescriptions and indications, while the middle and bottom portions provide information on the types of drugs and indications, respectively.

Table 3: Form Limitations and Detection, Mean Y_{2i}

	(1) One Indications	(2) Two Indications	(3) Three Indications	(4) Average
One Prescription	0.379	0.448	0.461	0.408
Two Prescriptions	0.318	0.454	0.469	0.392
Three Prescriptions	0.271	0.413	0.464	0.370
Four Prescriptions	0.207	0.365	0.428	0.334
Five Prescriptions	0.164	0.308	0.390	0.302
Six Prescriptions	0.114	0.256	0.361	0.278
Seven Prescriptions	0.086	0.202	0.318	0.234
Eight Prescriptions	0.069	0.151	0.277	0.205
Average	0.267	0.364	0.388	0.335
Observations	209,733	154,843	183,401	547,977

Note: These statistics reflect the mean of Y_{2i}, the indicator for whether on-label use both occurred and is detected, by number of prescriptions and indications recorded by the physician on the NAMCS survey form.

Table 4: DCE Model for Detection of On-Label Prescribing

	(1)	(2)	(3)
Exclusive to Detection Model			
Number of prescriptions written during visit	-0.120***	-0.123***	-0.128***
	(-98.69)	(-99.13)	(-99.86)
Two indications recorded on the NAMCS form	0.011*	0.010*	0.020***
	(1.71)	(1.64)	(3.15)
Three indications recorded on the NAMCS form	0.067***	0.067***	0.045***
	(12.12)	(12.03)	(8.01)
NAMCS form allows six prescriptions	-0.077***	-0.073***	-0.067***
	(-9.59)	(12.03)	(-8.06)
NAMCS form allows eight prescriptions	-0.069***	-0.061***	-0.039***
	(-11.94)	(-10.97)	(-6.72)
Common to Both Models			
Patient age	-0.003***	-0.003***	-0.003***
	(-24.72)	(-24.62)	(-23.89)
Patient is female	-0.048***	-0.048***	-0.027***
	(-9.53)	(-9.47)	(-5.20)
Patient is Hispanic	0.027***	0.026***	0.002
	(2.85)	(2.72)	(0.24)
Patient is African-American	0.130***	0.127***	0.101***
	(15.20)	(15.07)	(11.76)
Patient is other (non-Caucasian) race	-0.050***	-0.053***	-0.053***
	(-5.40)	(-5.75)	(-5.62)
Other Controls			
Indicators for Year	On-Label	—	—
Quadratic Time Trend	—	On-Label	—
Indicators for Physician-Specialty	On-Label	On-Label	Detection
Interacted Indicators for Year and Physician Specialty	—	—	On-Label
Observations	547,977	547,977	547,977

Note: These coefficient estimates are for the model of detection. The top portion of the table reports estimates for those variables that are exclusive to the model of detection, while the middle portion reports those variables that are also in the model of physician on-label prescribing. The bottom portion of the table indicates whether each of the various controls is included in the specification of the on-label and detection models. Numbers in parentheses are t-statistics. $^{*}p < 0.10$, $^{**}p < 0.05$, $^{***}p < 0.01$.

Table 5: DCE Model for On-Label Prescribing

	(1)	(2)	(3)
Exclusive to Model of On-Label Prescribing			
Number of drugs approved to treat indications	0.044***	0.043***	0.033***
	(64.45)	(67.24)	(84.07)
Patient has Medicare	-0.087***	-0.088***	-0.086***
	(-5.06)	(-5.10)	(-5.05)
Patient has Medicaid	-0.140***	-0.140***	-0.126***
	(-7.02)	(-7.06)	(-6.32)
Patient has private insurance	-0.079***	-0.084***	-0.078***
	(-5.69)	(-6.02)	(-5.61)
Patient has other insurance	-0.087***	-0.110***	-0.070***
	(-3.37)	(-4.08)	(-2.69)
Common to Both Models			
Patient age	-0.003***	-0.003***	-0.002***
	(-9.07)	(-9.43)	(-5.29)
Patient is female	-0.076***	-0.072***	-0.044***
	(-6.73)	(-6.39)	(-4.01)
Patient is Hispanic	-0.035*	-0.021	-0.000
	(-1.72)	(-1.02)	(-0.01)
Patient is African-American	-0.110***	-0.100***	-0.079***
	(-5.75)	(-5.28)	(-4.21)
Patient is other (non-Caucasian) race	-0.016	0.017	0.026
	(-0.76)	(0.79)	(1.28)
Other Controls			
Indicators for Year	On-Label	—	—
Quadratic Time Trend	—	On-Label	—
Indicators for Physician-Specialty	On-Label	On-Label	Detection
Interacted Indicators for Year and Physician Specialty	—	—	On-Label
Observations	547,977	547,977	547,977

Note: These coefficient estimates are for the model of physician on-label prescribing. The top portion of the table reports estimates for those variables that are exclusive to the model of physician behavior, while the middle portion reports those variables that are also in the model of detection. Patients without insurance are the excluded dummy variable. The bottom portion of the table indicates whether each of the various controls is included in the specification of the on-label and detection models. Numbers in parentheses are t-statistics. $^{*}p < 0.10$, $^{**}p < 0.05$, $^{***}p < 0.01$

Table 6: Form Limitations and Detection, Mean of $\Phi(x_{2i}\hat{\beta}_2)$

	(1) One Indication	(2) Two Indications	(3) Three Indications	(4) Average
One Prescription	0.652	0.649	0.663	0.653
Two Prescriptions	0.602	0.602	0.618	0.605
Three Prescriptions	0.549	0.549	0.568	0.555
Four Prescriptions	0.495	0.495	0.514	0.502
Five Prescriptions	0.440	0.442	0.464	0.451
Six Prescriptions	0.379	0.383	0.408	0.395
Seven Prescriptions	0.317	0.322	0.344	0.332
Eight Prescriptions	0.269	0.273	0.297	0.286
Average	0.539	0.509	0.465	0.506
Observations	209,733	154,843	183,401	547,977

Note: These estimates reflect the mean probability of detection, $\Phi(x_{2i}\hat{\beta}_2)$, by number of prescriptions and indications recorded by the physician on the NAMCS survey form.