Off-Label Use of Pharmaceuticals: A Detection-Controlled Estimation Approach

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Off-Label Use

- ▶ Drugs are approved by the FDA for certain indications. Physicians can prescribe a drug for any indication.
 - ▶ “Off-label” use occurs when a physician prescribes a drug for an indication for which it is not FDA approved.
- ▶ Current FDA policy restricts pharmaceutical companies from marketing “off-label” uses for drugs.
- ▶ This creates tension in the market for pharmaceuticals, a market with sales of \$321.3 billion in 2010 (2.2% of GDP).
 - ▶ Controversial in the clinical and policy communities and among federal regulators. Many instances of successful repurposing but also instances of harm.
 - ▶ Off-label use has been part of the national policy conversation due to settlements between pharmaceutical manufacturers and the DOJ (approximately 33 suits were settled between 2004 and 2012).

Off-Label Use: The Lucentis/Avastin Controversy

- ▶ Macular degeneration occurs when a person's retina is damaged and the person loses vision in the center of the visual field.
 - ▶ It is quite common—approximately 10% of people 66-74 years old have findings of macular degeneration.
- ▶ Lucentis is FDA approved to treat macular degeneration. It sells for \$2,000 a dose. A typical regimen is monthly injections for 12-24 months.
- ▶ Avastin is FDA approved to treat metastatic colon cancer (and some other cancers) but has been shown to be effective in treating macular degeneration. In treating macular degeneration, it sells for \$50 a dose because the dosage is far smaller for this than for treating cancer. Again, a typical treatment regimen is monthly injections for 12-24 months.
 - ▶ For this use, Avastin must also be “compounded” by pharmacies. There have been cases of bad batches of Avastin, and these have caused ocular infections and blindness.

Off-Label Use: The Lucentis/Avastin Controversy

- ▶ This creates a dilemma for ophthalmologists.
 - ▶ Prescribe a \$2,000 med which is indicated but which many patients can't or won't pay?
 - ▶ Prescribe an off-label med which costs \$50 a dose but carries a risk of infection?
- ▶ Note that for a typical Medicare reimbursement of 80%, then that still leaves \$400 per dose of Lucentis uncovered.
- ▶ Straightforward consumer choice theory predicts the following:
 - ▶ No Insurance → Avastin.
 - ▶ Partial Insurance → Tough Choice.
 - ▶ Full Insurance → Lucentis.

Off-Label Use: Research Questions

- ▶ What is the frequency of off-label prescribing?
- ▶ What drives off-label prescribing?
- ▶ Does insurance coverage matter?

Our Approach

- ▶ For intuition, develop a simple model of random drug match quality showing how patients without insurance may choose inferior but cheaper drugs.
 - ▶ This predicts that insurance leads patients to substitute away from inferior alternatives.
 - ▶ Hence, if insurance leads to more off-label use, the implication is that off-label use as a cheap-but-inferior option is relatively uncommon (for patients without insurance).
- ▶ Capture prescription data from NAMCS office-visit records, indication data from the Physician's Desk Reference (PDR).
- ▶ For each prescribed drug, construct an indicator for observed on-label use.
- ▶ Estimate an empirical model relating covariates to this indicator.
 - ▶ We use Detection Control Estimation (DCE) to control for cases where our indicator is falsely negative.

Main Results

- ▶ During 1993-2008, the frequency of off-label use increases from 30.35% to 38.9%, an increase of 28.2%.
- ▶ Physicians are more likely to prescribe off-label when approved options are limited.
 - ▶ A 10% increase in the number of drugs approved for a patient's set of diagnoses leads to a 4.7% reduction in the probability a physician prescribes off label.
- ▶ Physicians are more likely to prescribe off-label when patients have insurance, particularly Medicaid.
 - ▶ Compared to the case of no insurance, the frequency of off-label prescribing when all patients have private insurance rises by 3.7%. This frequency rises by 2.2% more when all patients have Medicaid.
 - ▶ It appears physicians are more likely to prescribe off-label when patients have insurance with less-restrictive formularies.
 - ▶ These results suggest off-label use as a cheap-but-inferior option is relatively uncommon.

Prescription Data

- ▶ National Ambulatory Medical Care Survey (NAMCS)
 - ▶ Annual physician survey of patient visits to community-based physician offices conducted by CDC.
 - ▶ Physicians randomly selected to characterize 30 office visits.
 - ▶ Includes indications, characteristics of patients and physicians, type of insurance, and medications prescribed.
 - ▶ Extract all visits from 1993 to 2008, keeping visits with at least one prescription. 144,279 total visits. 547,977 total prescriptions.
 - ▶ Diagnoses are captured by ICD-9 codes, form limit of 3 codes.
 - ▶ Unit of observation: prescription with associated visit/patient characteristics.

PDR Indications Data

- ▶ Physicians Desk Reference (PDR)
 - ▶ Total of 3,587 unique text descriptors for diagnoses from 1993 to 2008.
 - ▶ MUSC medical records coder assigns ICD-9 codes to all descriptors.
 - ▶ Not one to one—some descriptors require multiple ICD-9 codes to accurately capture diagnosis (e.g., indication X with complications due to indication Y).
 - ▶ Unit of observation: ICD-9 code-year-drug after reshaping.

Defining On-Label Use

- ▶ We classify a use as “on label” if at least one drug with the same active ingredient is on-label for the given indication.
- ▶ For example, we consider Wellbutrin to be on label for smoking cessation because Zyban is approved for smoking cessation and has the same active ingredient (bupropion).
 - ▶ Specifically, we call such uses *anticipated* off-label use.
 - ▶ In our paper, we classify off-label use as purely the *unanticipated* kind.

On-Label Indicator Variables

- ▶ The unit of observation is the prescription.
- ▶ We merge PDR information to NAMCS by 3-digit ICD-9 code and year for each visit.
- ▶ We use the 3-digit code to provide conservative measure of off-label use (4-digit results are very similar).
- ▶ Create two variables:
 1. On-label indicator for prescription: Identify if the prescription is an approved drug for at least one diagnosis listed for visit. Naïve approach would use mean of this indicator to infer frequency of on-label use.
 2. Number of approved drugs for diagnoses: Identify the number of approved active ingredients to treat visit-specific diagnoses.

Descriptive Statistics

- ▶ Patient Characteristics and Insurance Status
 - ▶ Age (51.78), Female (0.58), Hispanic (0.074), African-American (0.09).
 - ▶ Medicare (0.31), Medicaid (0.10), Private Insurance (0.48), Other Insurance (0.04).
- ▶ Prescription and Indication Variables
 - ▶ Naïve On-label Indicator (0.33), Number of Drugs Approved for Diagnoses (71.49), Number of prescriptions per visit (3.87).
 - ▶ Two ICD-9 Codes (0.62), Three ICD-9 Codes (0.33).

Difficulty Inferring The Rate Of On-Label Use

- ▶ The *true* rate of on-label prescribing is hidden from the researcher.
- ▶ Four possible outcomes we need to think about:
 1. Physician prescribed on-label and we code on-label.
 2. Physician prescribed on-label and we code off-label.
 3. Physician prescribed off-label and we code off-label.
 4. Physician prescribed off-label and we code on-label.
- ▶ If no detection problem (indication reported for each prescription), only 1 and 3 will be present in our data and naïve on-label descriptives are sufficient.
- ▶ Frequency of 2 (*false negatives*) is unknown and 4 (*false positives*) should arise only if data is not accurate.
- ▶ We assume frequency of 4 is negligible but must address 2.

Detection Controlled Estimation (DCE)

- ▶ Feinstein (1990) introduced DCE as a means to infer the true frequency of some event in the presence of false negatives.
- ▶ Essentially two separate econometric models
 1. Behavioral model: relates covariates (e.g., insurance status of patient, on-label options, etc) to physician's decision to truly prescribe on-label.
 2. Detection model: relates covariates (e.g., NAMCS survey form limitations, patient characteristics, etc) to the probability we detect true on-label use.
- ▶ Once probability of detection is estimated, the naïve on-label probability can be “adjusted” to account for false negatives.

Physician On-Label Prescribing Decision

- ▶ Physician's decision to *truly* prescribe on-label in instance i is summarized by a stochastic latent variable,

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

where x_{1i} are covariates altering physician's decision.

- ▶ Binary outcome (1 if on-label) which we do not perfectly observe

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

- ▶ If ε_{i1} is iid $N(0, 1)$, probability of prescribing on-label

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

Detection of False Negatives

- ▶ Need to identify rate at which we do not detect true on-label use.
- ▶ Our naïve indicator is imperfect due to false negatives

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

- ▶ Assume binary outcome has underlying latent structure

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

where x_{2i} are covariates altering rate of detection.

Detection of False Negatives

- ▶ The probability of *detecting* true on-label use

$$Pr(Y_{2i} = 1) = Pr(Y_{2i} = 1|Y_{1i} = 1) * P(Y_{1i} = 1)$$

since $Pr(Y_{2i} = 1|Y_{1i} = 0) = 0$.

- ▶ If ε_{1i} and ε_{2i} are independent, the probability of detection is

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

where x_{2i} are covariates altering rate of detection.

Likelihood Function

- ▶ Each observation's likelihood contribution in terms of the probability of those events we observe

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

- ▶ Requires indicator for detected on-label prescriptions, Y_{2i} , the naïve indicator, and covariates altering probability a physician writes a prescription on-label (x_{1i}) and we detect it (x_{2i}).
- ▶ Our estimate of the probability of off-label use in instance i is

$$Pr(\text{Prescription } i \text{ is off-label} \mid x_{1i}) = 1 - \Phi(x_{1i}\hat{\beta}_1)$$

Identification Requirements

- ▶ Two probabilities enter likelihood multiplicatively as $\Phi(x_{2i}\beta_2)\Phi(x_{1i}\beta_1)$.
- ▶ When product is high (low), unclear whether due to high (low) rate of true on-label prescribing, or high (low) rate of detection.
- ▶ Ideally one would have covariates in x_{2i} pushing rate of detection to 1, allowing on-label use to be directly observed in those cases (e.g., perfect tax auditor in Feinstein 1991).

Identification: Exclusion Restrictions

- ▶ Common elements in x_{1i} and x_{2i}
 - ▶ Patient covariates may be related to incidence of chronic disease and probability that physician prescribes off-label.
- ▶ Only in x_{1i}
 - ▶ Number of FDA-approved drugs for diagnoses, and indicators for physician specialty, type of ICD-9 codes, insurance status, census region, and year.
- ▶ Only in x_{2i}
 - ▶ NAMCS form limitations: Detection becomes more difficult with higher ratio of prescriptions to diagnoses. NAMCS increased number of allowable prescriptions from 5 to 6 in 1995 and then 6 to 8 in 2003.
 - ▶ CDC exogenously making it harder to detect on-label use is actually very helpful. Would be similar to IRS suddenly deciding to hire worse tax auditors in Feinstein (1991).

Detection: Descriptive Evidence

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

	(1)	(2)	(3)	(4)
	One Indications	Two Indications	Three Indications	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

Detection of On-Label Use: Results

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

	(1)	(2)	(3)	(4)
Exclusive to Detection Model				
Number of prescriptions written during visit	-0.123*** (-98.69)	-0.123*** (-99.13)	-0.122*** (-97.37)	-0.128*** (-99.86)
Two indications recorded on the NAMCS form	0.011* (1.71)	0.010* (1.64)	0.012* (1.85)	0.020*** (3.15)
Three indications recorded on the NAMCS form	0.067*** (12.12)	0.067*** (12.03)	0.067*** (12.06)	0.045*** (8.01)
NAMCS form allows six prescriptions	-0.077*** (-9.59)	-0.073*** (12.03)	-0.072*** (-9.14)	-0.067*** (-8.06)
NAMCS form allows eight prescriptions	-0.069*** (-11.94)	-0.061*** (-10.97)	-0.072*** (-12.37)	-0.039*** (-6.72)

► * $p < 0.10$; ** $p < 0.05$; *** $p < 0.01$

Drivers of On-Label Use: Results

Table 5: DCE Model for On-Label Prescribing

	(1)	(2)	(3)	(4)
Exclusive to Model of On-Label Prescribing				
Number of drugs approved to treat indications	0.044*** (64.45)	0.044*** (64.42)	0.043*** (67.24)	0.033*** (84.07)
Patient has Medicare	-0.087*** (-5.06)	-0.080*** (-4.37)	-0.088*** (-5.10)	-0.086*** (-5.05)
Patient has Medicaid	-0.140*** (-7.02)	-0.128*** (-6.67)	-0.140*** (-7.06)	-0.126*** (-6.32)
Patient has private insurance	-0.079*** (-5.69)	-0.074*** (-5.40)	-0.084*** (-6.02)	-0.078*** (-5.61)
Patient has other insurance	-0.087*** (-3.37)	-0.066*** (-2.55)	-0.110*** (-4.08)	-0.070*** (-2.69)

► * $p < 0.10$; ** $p < 0.05$; *** $p < 0.01$

Overall Trend

Figure: Trend in Off-label Use

Conclusions

- ▶ Our results suggest that physicians' off-label prescribing patterns are consistent with enhancement of patient welfare.
 - ▶ Limited on-label options increase frequency of off-label prescribing.
 - ▶ Better insurance and less-restrictive formularies (i.e., lower out-of-pocket costs) increase off-label prescribing.
- ▶ Future Research
 - ▶ Patient welfare:
 1. Clinical outcomes and costs?
 2. Ban on off-label prescribing and patient welfare?
 - ▶ Innovation:
 1. Does off-label use induce more clinical trials and indications?
 2. Off-label use induce generic entry and NMEs?
 3. Does regulatory environment induce firms to not seek new indications?

Detection: Estimated Probabilities

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

	(1)	(2)	(3)	(4)
	One ICD9 Code Listed	Two ICD9 Codes Listed	Three ICD9 Codes Listed	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	209733	154843	183401	547977

Indications - A Raw Label

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)

Raw PDR Indications Data

Pancreatic cystic fibrosis
Cotazym Capsules (Pancrelipase)
Organon 1866
Creon (Pancrelipase) Solvay 2714
Ku-Zyme HP Capsules
(Pancrelipase) Schwarz 2547
Pancrease Capsules (Pancrelipase)
McNeil Pharmaceutical 1589
Pancrease MT Capsules
(Pancrelipase) McNeil
Pharmaceutical 1589
Viokase (Pancrelipase) Robins 2251
Zymase Capsules (Pancrelipase)
Organon 1889

- ▶ Consistent structure, text descriptor of diagnosis followed by list of approved drugs.
- ▶ Brand name (Generic name) Manufacturer.