The Heterogeneity of Concentrated Prescribing Behavior: Theory and Evidence from Antipsychotics

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Scenario: Physician Sees Patient…

- Patient has confirmed diagnosis for which
  several pharmaceutical treatments are available

- Patient response (efficacy, side effects) is
  idiosyncratic and unpredictable;
  little evidentiary support favoring one treatment vs. another

- What treatment algorithms might the physician employ
  to learn about the efficacy and side effects of
  the variety of possible treatments for this and future patients?

- Concentrate or diversify on drug treatment across patients?

Tradeoff btwn Exploiting and Exploring

Concentrate on one drug (exploiting):

- By observing patients' responses to that drug,
  physician learns by doing how to advice patients on:
  - Efficacy, side-effects, dosage, time, other drugs

Diversify across several drugs (exploring):

- Physician tries to find the best match between different drugs and current and future similar patients based on:
  - Patients' history, scientific and clinical literature,
    interactions with fellow physicians and sales representatives

Issues We Address

- How different physicians locate along this concentration-diversification continuum?
  - volume of patients treated
  - physician's specialty, training, and age

- Will physicians with concentrated prescriptions converge or diverge?
  - Path-dependence in learning leads to divergence

Related Literature

- Concentrated prescribing behavior by physicians:
  - Coscelli (2000), Coscelli and Shum (2004), and Frank and Zeckhauser (2007)
- Evolution of patients' treatment over time:
  - Crawford and Shum (2005) and Dickstein (2012)
- Patient-specific data is relatively unimportant:
  - Hellerstein (1998) and Zhang, Baicker, and Newhouse (2010)
  - Solomon et. al (2003), Schneeweis et. al (2005)

Schizophrenia

- Incurable mental illness
- Positive (hallucinations, delusions, voices) and negative (depression, lack of emotion) symptoms
- 1-2% prevalence
- Strikes males around 20, females slightly later
- Unknown origins (genetics?)
- Patients experience unemployment, lose family contact, become homeless, experience periods of incarceration
- In 2010 US spending on antipsychotics was over $16B

Available Treatments for Schizophrenia

- From 1955 thru early 1990s, pharmacological treatments called ***typical****, conventional,* and/or *neuroleptic antipsychotics*
  - Better for positive than negative symptoms
  - Some patients have lasting side effects (e.g., involuntary movement disorder) for which there's no treatment

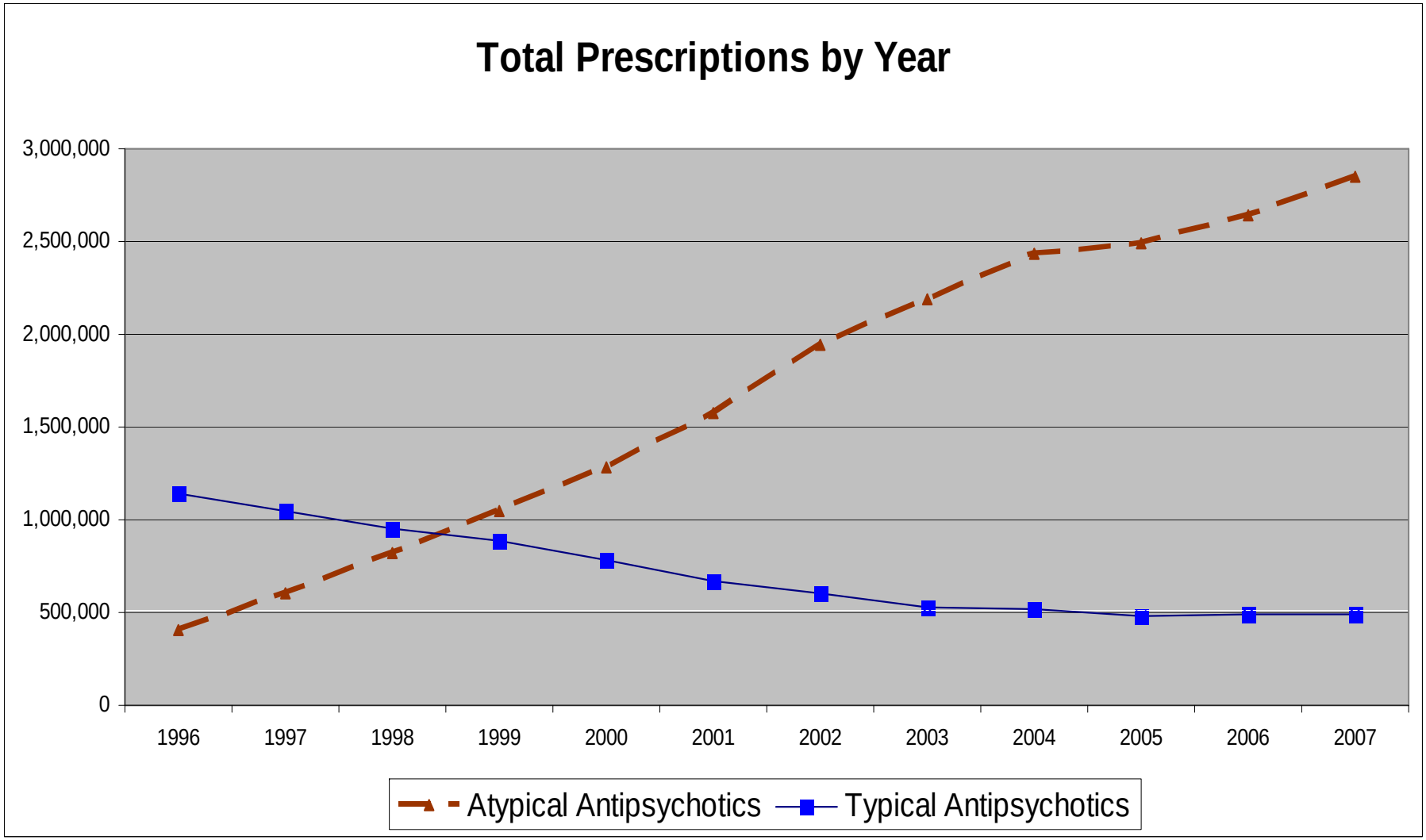
- Clozaril (clozapine) approved in 1989,
  - For 1-2%, side effect of agranulocytosis (can be lethal), so use requires frequent white blood cell count monitoring
- Clozaril called *first generation* ***atypical*** drug – "FGA"

Second Generation Atypicals (SGAs)

- Five SGAs introduced in US 1993-2002
  - Risperdal (risperidone) – 1993
  - Zyprexa (olanzapine) – 1996
  - Seroquel (quetiapine) – 1997
  - Geodon (ziprasidone) – 2001
  - Abillify (aripiprazole) – 2002

- Initially SGAs perceived as similar to typicals for positive but better for negative symptoms, without typicals' side effects
- Since 2001-02 concern grew over SGA side effects (e.g. weight gain)
- In 2007: typicals and clozapine are off patent, but SGAs are very costly

Typical and Atypical Prescriptions
Annually 1996-2007



Preliminary Evidence on Concentration

- In 2007, five years after launch of the last SGA, among those writing at least twelve antipsychotic prescriptions:
  - Mean share of prescriber's favorite drug was 59%
- But concentration is very diverse for concentrated prescribers
  - Those who wrote > 75% of all scripts for their favorite atypical

Drug	Concentrated Prescribers	Market Shares
Seroquel	54%	36%
Risperdal	28%	27%
Zyprexa	13%	13%
Abilify	2.5%	14%
Geodon	1.5%	7.3%
Clozapine	0.4%	2.4%

Geographic Variation?

- Our measure of concentration is HHI = $\Sigma_d s_d^2$
  - s_d is a share of prescriptions for drug d ($0 \leq s_d \leq 1$)
  - HHI ranges from 1/D – equal shares on all D drugs
  - HHI ranges up to 1 -- concentration on one drug

- Calculate HHI at various geographic levels
  - Prescribing behavior is highly variable at the individual level, but is not variable at larger regional aggregates
  - 95% of the difference in mean HHI between individual prescriber and national market shares disappears at the HRR level, and 99% disappears at the state level

- We focus on factors affecting behavior of individual prescribers

Why physicians treat differently similar patients?

- Perception
  - We don't know we are behaving differently
  - Example: Physicians read different articles arriving at different conclusions
- Motivation
  - We know we are behaving differently, but we don't want to change it
  - Example: Detailing by pharmaceutical sales representatives to physicians
- Administration
  - We know we are behaving differently and we want to change it

    But we can't make the desired change happen
  - Example: Best treatment is drug A but only drug B is covered
- Inspiration
  - We know we're behaving differently, but we don't know what else to do
  - Example: Physicians learn about drugs from patients' responses

Physician Learning by Doing

• Patients	$t = 1, 2, \ldots$	arrive sequentially
• Symptoms	$s \in \{s_1, \ldots, s_S\}$	randomly drawn
• Prob. of symptom	$p_1, \ldots, p_S$	indep. across patients
• Drugs	$d \in \{d_1, \ldots, d_D\}$	$d^*(s)$
• Time btwn patients	w	Arrival at time 0, w, 2w, …
• Discount rate	r	Continuous time

- Maximum potential benefit of drug d for symptom s is B_{sd} (known)
  - $B_{sd*(s)} > B_{sd}$ for all $d \neq d^*(s)$
- Therapy = drug (d) and unobserved complementary actions (a)
- Ideal effectiveness requires ideal complementary actions (uncertain)
- Realized effectiveness = $b_{sdt} = B_{sd} - (a - x_{dt})^2$
  - $x_{dt} = \theta_d + \varepsilon_{dt}$ where θ_d and ε_{dt} are independently normal for all d,t
- Physician observes x_{dt} and therefore learns something about θ_d

Intuition

- The physician learns by combining different complementary actions a when prescribing drug d, and observing how patients respond (x_{dt})
- The best action that the physician can potentially learn to make, θ_d, depends on the drug prescribed
- Symptoms determine which drug has the highest potential for giving a patient the best outcome, d*(s), if ideal complementary actions are taken
- Uncertainty associated with drug d depends on how many times the physician prescribed drug d in the past

Prescriber Learning by Doing

- To maximize discounted patient well-being, the physician's dynamic strategy is to
  - Choose a drug $d_t(s, h_t)$
  - And complementary actions $a_t(d, h_t)$

    - For each patient t with symptom s and each history h_t,
    - where history is determined by what the physician prescribed for patients in the past and their response

Comparative Statics wrt Volume

- Suppose first that w is large (low-volume physician):
  - The physician will concentrate on only a subset of drugs.
  - Number and identity of these drugs depend on the initial history of symptom presentation to the physician -- idiosyncratic.
- As w is decreased (medium-volume physician):
  - Physicians have a larger incentive to invest in learning how to use new or different drugs effectively, future patients will benefit.
  - The set of drugs a physician uses will still depend on the initial history of symptoms the physician has seen; but this dependence is weaker.
- As w decreases to zero (very high-volume physician):
  - The physician will eventually learn a lot about optimal complementary actions θ_d for each drug d and will prescribe d*(s) for every s.

Model Predictions

- High-volume physicians prescribe a wider variety of drugs
  - Concentration decreases with volume
- High-volume physicians prescribing behavior will have smaller dependence on random initial history
  - Deviation from national norms decreases with volume
- Physicians with more specialist training use a wider variety of drugs and are less dependent on random initial history
  - Concentration and deviation decreases with training

Physician Prescribing Data

- IMS Health Xponent™ monthly
  - Tracks prescriptions dispensed at retail and mail order by NDC code,
  - Links to prescriber ID
  - Links to American Medical Association directory of physicians
- We take 10% random sample of all prescribers who wrote at least one antipsychotic prescription in 1996
  - Refresh each year with 10% random sample of “new” prescribers
- Here we only utilize 2007 data – five years after introduction of last new antipsychotic
- We restrict our attention to those prescribers who wrote at least 12 antipsychotic prescriptions in 2007
- ***Only data on prescribers, no data on patients***

Five Prescriber Groups

- Psychiatrists (PSY)
  - General, child-adolescent and geriatric psychiatry
- Neurologists (NEU)
  - General, geriatric and child neurologists
- Primary care physicians (PCP)
  - Internal medicine, family medicine and practice, pediatrics, and general practice prescribers
- Other (OTH)
  - All other prescribers
- Non-physicians (NP)
  - Primarily nurse practitioners and physician assistants

Mean Values of Characteristics of 2007 Prescriber Sample, by Prescriber Specialty

Specialty Group	No. of Prescribers	Annual Prescriptions	Antipsy HHI	% Prescriptions for Atypicals
PSY	3,431	611.03	0.33	91.37
NEU	688	97.53	0.61	85.3
PCP	8,536	66.49	0.5	86.85
OTH	2,382	54.42	0.62	88.35
NP	1,376	200.11	0.5	92.19

Concentration and Deviation Measures

- Physician i prescribing drug d in region r
- Share of prescriptions for d is s_{idr},
  whereas regional share for d is m_{dr}
- Our measure of concentration is $C_{ir} = HHI = \Sigma_d s_{idr}^2$
- Our measure of deviation is $D_{ir} = \Sigma_d (s_{idr} - m_{dr})^2$

Regression Specification

- General form of the regression equation

$$Y_i = \beta\left(1/Volume_i\right) + \varphi X_i + \varepsilon_i$$

- Dependent Variables:
  - Concentration and corrected concentration
  - Deviation and corrected deviation

Correction for Mechanical Dependence on Volume

- Corrected HHI

$$\hat{C}_i = \frac{Volume_i}{Volume_i - 1}\left(C_i - \frac{1}{Volume_i}\right).$$

- Corrected Deviation (Ellison-Glaeser 1997)

$$\hat{D}_{ir} = \frac{Volume_i}{Volume_i - 1}\left(D_i - (1 - HHI_r)\frac{1}{Volume_i}\right).$$

Common Set of Explanatory Variables in Regression Equations

- Various dependent variables are function of (where **bold** denotes reference case)
  - 1/Volume interacted with specialty (OTH, PCP, PSY and NEU)
  - Age quartiles (**< 43**, 43-50, 51-58, 59+)
  - Specialty (**OTH**, PCP, PSY and NEU)
  - County population **(< 150K**, 150K-500K, 500K-1M, and > 1m)
  - **Male**/Female,
  - **Group**/Solo practice,
  - **Office**/Hospital base,
  - **MD**/DO degree
  - **Physician Prescriptions Data Can Be Used**/Opt Out

Variable	Obs	Mean	Std. Dev.	Min	Max
Number of Different Antipsychotics Prescribed	15,037	4.41	2.64	1	15
HHI of Individual Physician's Antipsychotic Prescribing	15,037	0.48	0.23	0.12	1
Corrected HHI of Individual Physician's Antipsychotic Prescribing	15,037	0.47	0.23	0.12	1
Dev Physician's Antipsy prescribing from Nat. Mkt. Shares	15,037	0.22	0.19	0.00	1
Corr, Dev. of Physician's Antipsy prescribing from Nat. Mkt. Shr	15,037	0.20	0.19	-0.05	1
Number of Different Atypicals Prescribed	15,037	3.21	1.48	0	6
HHI of Individual Physician's Atypical Prescribing	14,865	0.55	0.24	0.17	1
% of Prescriptions for Antipsychotics that were for Atypicals	15,037	88.05	20.01	0	100
Total Yearly Antipsychotic Prescriptions	15,037	190	464	12	7,186
Total Yearly Atypical Antipsychotic Prescriptions	15,037	172	417	0	6,780
Prescriber Age	15,037	50.60	10.89	26	92
PCP	15,037	0.57	0.50	0	1
PSY	15,037	0.23	0.42	0	1
NEU	15,037	0.05	0.21	0	1
OTH	15,037	0.16	0.42	0	1
Solo Practice	15,037	0.20	0.40	0	1
Population (county)	15,037	1,022,341	1,752,971	1,299	9,734,701
Female	15,037	0.27	0.44	0	1
Hospital Based Physician	15,037	0.08	0.27	0	1
DO Flag	15,037	0.09	0.28	0	1
Physician Opt Out	15,037	0.04	0.19	0	1

Results 1: Concentration of Prescribing

- HHI and Corrected HHI
  - Concentration decreases with Volume for all specialties
  - Given volume, PSY<PCP<OTH<NEU;
  - Oldest physicians (59+) have significantly more concentrated prescribing, else zero;
  - Female and Solo positive
  - DO, Population, Hospital Based and MD opt out insignificant

Concentration of Physician's Antipsychotic Prescribing Shares

	HHI		Corrected HHI	
	Linear	Tobit	Linear	Tobit
OTH*(1/Total Yearly Antipsychotic Prescriptions)	3.620***	4.192***	3.365***	3.943***
PCP*(1/Total Yearly Antipsychotic Prescriptions)	3.940***	4.218***	3.584***	3.866***
PSY*(1/Total Yearly Antipsychotic Prescriptions)	6.236***	6.526***	5.832***	6.125***
NEU*(1/Total Yearly Antipsychotic Prescriptions)	3.322***	3.780***	3.047***	3.512***
Age Quartile 43-50^	0.004	0.005	0.005	0.006
Age Quartile 51-58^	0.004	0.005	0.005	0.006
Age Quartile 59+^	0.011**	0.014***	0.012**	0.015***
PCP^	-0.095***	-0.094***	-0.094***	-0.093***
PSY^	-0.216***	-0.213***	-0.213***	-0.210***
NEU^	0.040***	0.044***	0.041***	0.045***
Female^	0.030***	0.031***	0.030***	0.032***
Population 150,000-500,000 (county)^	-0.004	-0.005	-0.004	-0.005
Population 500,000-1,000,000 (county)^	0.001	-0.001	0.000	-0.002
Population more than 1,000,000 (county)^	-0.005	-0.007	-0.006	-0.008*
Solo Practice^	0.009**	0.009**	0.009**	0.009**
Hospital Based Physician^	-0.009	-0.009	-0.009	-0.009
DO Flag^	-0.008	-0.009	-0.008	-0.009
Physician Opt Out^	-0.002	-0.003	-0.002	-0.002
Cons	0.462***	0.457***	0.458***	0.453***
Number of Observations	15,037	15,037	15,037	15,037
R^2	0.332		0.292	
Num Observations Rt. Censored		1,146		1146
^ indicates dummy variable				

*** p<0.01, ** p<0.05, * p<0.1

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Results 2: Deviation from National Market Share Norms

- Similar results for national and HRR shares – only show national share results
  - Deviation decreases with Volume for all specialties
  - Given volume, deviation of PSY<PCP<OTH<NEU
  - Deviation increases with Age
  - Deviation smaller in large counties
  - Female effect and Solo positive
  - Other variables not significant

Deviation of Physician's Antipsychotic Prescribing Shares

	Deviation	Corrected Deviation
OTH*(1/Total Yearly Antipsychotic Prescriptions)	2.957***	2.573***
PCP*(1/Total Yearly Antipsychotic Prescriptions)	3.263***	2.796***
PSY*(1/Total Yearly Antipsychotic Prescriptions)	5.009***	4.534***
NEU*(1/Total Yearly Antipsychotic Prescriptions)	2.872***	2.464***
Age Quartile 43-50^	0.009**	0.009**
Age Quartile 51-58^	0.019***	0.020***
Age Quartile 59+^	0.032***	0.034***
PCP^	-0.076***	-0.076***
PSY^	-0.144***	-0.142***
NEU^	0.005	0.006
Female^	0.013***	0.013***
Population 150,000-500,000 (county)^	-0.013***	-0.014***
Population 500,000-1,000,000 (county)^	-0.007*	-0.008**
Population more than 1,000,000 (county)^	-0.016***	-0.017***
Solo Practice^	0.011***	0.011***
Hospital Based Physician^	-0.005	-0.006
DO Flag^	-0.006	-0.007
Physician Opt Out^	-0.002	-0.002
Cons	0.191***	0.188***
Number of Observations	15,037	15,037
R^2	0.279	0.226
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NEU^	0.005	0.006
Female^	0.013***	0.013***
Population 150,000-500,000 (county)^	-0.013***	-0.014***
Population 500,000-1,000,000 (county)^	-0.007*	-0.008**
Population more than 1,000,000 (county)^	-0.016***	-0.017***
Solo Practice^	0.011***	0.011***
Hospital Based Physician^	-0.005	-0.006
DO Flag^	-0.006	-0.007
Physician Opt Out^	-0.002	-0.002
Cons	0.191***	0.188***
Number of Observations	15,037	15,037
R^2	0.279	0.226
^ indicates dummy variable		

*** p<0.01, ** p<0.05, * p<0.1

Deviation of Physician's Antipsychotic Prescribing Shares

	Deviation	Corrected Deviation
OTH*(1/Total Yearly Antipsychotic Prescriptions)	2.957***	2.573***
PCP*(1/Total Yearly Antipsychotic Prescriptions)	3.263***	2.796***
PSY*(1/Total Yearly Antipsychotic Prescriptions)	5.009***	4.534***
NEU*(1/Total Yearly Antipsychotic Prescriptions)	2.872***	2.464***
Age Quartile 43-50^	0.009**	0.009**
Age Quartile 51-58^	0.019***	0.020***
Age Quartile 59+^	0.032***	0.034***
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Robustness Checks

- Results essentially unchanged when we allow volume to enter in linearly or log linearly
- Results essentially unchanged when we restrict our sample to physicians who prescribe greater than 50 scripts in a year
- If we restrict sample to 3K+ Psychiatrists, still get same volume, age and gender results, but not as significant, and other variables not as significant

Competing Hypothesis: Physician Detailing

- Suppose high-volume prescribers are exposed to detailing by a greater number of different pharmaceutical manufacturers and that is why they prescribe a wider variety of drugs
  - Drugs having lost market exclusivity many years ago unlikely to have been detailed to young doctors practicing in 2007
  - Older physicians in 2007 were likely detailed on older drugs years ago

Predictions of Detailing Hypothesis

- Young physicians prescribe very few of the older drugs
- High-volume young physicians prescribe the old drugs less frequently (they are exposed to the most detailing on the new drugs)
- Oldest physicians prescribe both old and new drugs because they were detailed on both

Predictions of our model

- Young physicians prescribe more new drugs
- High-volume young physicians prescribe “old drugs” more frequently (larger incentive to explore, i.e. match patients to drugs)
- Old physicians prescribe more of the old drugs because they knew about how to use them when the new drugs were introduced
- High-volume vs low-volume old physicians ambiguous
  - High volume have an increased incentive to explore the new drugs
  - High volume have the most knowledge about the old drugs
  - High volume have shortened time horizon

Empirical Test

- Separate antipsychotic drugs into “old drugs” and “new drugs”
  - Approved before 1990 and had generic entry by 1996
  - Approved after 1993 and no generic available in 2007
- Compare the behavior of the
  - Oldest (59+) cohort - detailed on many of the old drugs and had an established prescribing routine before the first “new drug” was approved
  - Youngest (26-42) cohort - never detailed on the old drugs
- Focus on Psychiatrists as they were the group that was likely exposed to the most detailing

Tobit regression: Percentage of prescriptions filled that are for new antipsychotics (SGA atypical antipsychotics)

	% Rxs for New Drugs
Physician Age 59+^	-4.552***
1/Total Yearly Antipsychotic Prescriptions	215.403***
(Physician Age 59+)^(1/Total Yearly Antipsychotic Prescriptions)	-136.807**
Female^	3.730***
Population 150,000-500,000 (county)^	1.637
Population 500,000-1,000,000 (county)^	1.053
Population more than 1,000,000 (county)^	0.771
Solo Practice^	0.486
Hospital Based Physician^	-2.439*
DO Flag^	0.97
Physician Opt Out^	-5.314**
Constant	90.754***
Number of Observations= 1,843	
Pseudo R^2= 0.0089	
Left Censored = 0 Right Censored = 440	
Mean of dependent variable	*88.29*
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215.403-136.807=78.596

Conclusions

- Tractable model of Bayesian learning by doing
  - Technical innovation – complimentary action
  - Path dependence in learning by doing
  - What factors of the physician determine concentration and deviation?

- Empirical analysis
  - Unique dataset on antypsychotics
  - New correction for the mechanical bias present in HHI
  - Empirical regularities consistent with the model
  - Test against a competing hypothesis of detailing by sales reps

Limitations

- Major limitation is that we don't observe patient data
  - Finding of dominant role of physician over patient is frequent (Frank-Zeckhauser [2007], Hellerstein [1997], Zhang, Baicker and Newhouse [2010], Schneeweis, Glynn, Avorn and Solomon [2005])
- How generalizable to other medication classes? Non-physician prescribers?
- Our 2007 analysis is a single cross-section