HEALTH CARE SYSTEM, PROVIDER AND PATIENT PREDICTORS OF PRESCRIBING QUALITY AND EFFICIENCY

by

Yan Tang

BA in Business Management, China Pharmaceutical University, China, 2005

MS in Management, China Pharmaceutical University, China, 2008

Submitted to the Graduate Faculty of

Graduate School of Public Health in partial fulfillment

of the requirements for the degree of

Doctor of Philosophy

University of Pittsburgh

2015

UNIVERSITY OF PITTSBURGH

GRADUATE SCHOOL OF PUBLIC HEALTH

This dissertation was presented

by

Yan Tang

It was defended on

January 20, 2015

and approved by

Dissertation Advisor:
Julie M. Donohue, PhD
Associate Professor
Department of Health Policy and Management
Graduate School of Public Health
University of Pittsburgh

Judith R. Lave, PhD
Professor
Department of Health Policy and Management
Graduate School of Public Health,
University of Pittsburgh

(Joyce) Chung-Chou H. Chang, PhD
Professor
Department of Biostatistics
Graduate School of Public Health
University of Pittsburgh

Walid F. Gellad, MD, MPH
Assistant Professor
VA Pittsburgh Health Care System, RAND, and University of Pittsburgh

HEALTH CARE SYSTEM, PROVIDER AND PATIENT PREDICTORS OF PRESCRIBING QUALITY AND EFFICIENCY

Yan Tang, PhD

University of Pittsburgh, 2015

ABSTRACT

Understanding factors influencing medication utilization and provider prescribing behavior has important implications for the quality improvement and cost containment in health care. This dissertation seeks to shed light on the quality and efficiency of medication prescribing.

Chapter one examines the association between Medicare Part D plan features and choice of generic antidepressants, antidiabetics, and statins using Medicare claims data. Low cost-sharing for generics, large differentials in cost-sharing for generic vs. brand drugs, and tools such as prior authorization and step therapy are associated with higher generic drug use. Modifying the benefit design and utilization management of Medicare prescription drug plans might increase generic use, which could generate substantial savings for the Medicare program and for beneficiaries.

Chapter two examines physician antipsychotic prescribing behavior in a large Medicaid program. By linking multiple data sources and using the multiple membership modeling approach, we examine the degree to which psychiatrists are diversified vs. concentrated in their choice of antipsychotic medication and identify factors associated with the concentration of prescribing. Antipsychotic prescribing behavior is relatively concentrated and varies substantially across psychiatrists regularly prescribing antipsychotics. Several characteristics of the treated patient population and physicians are significantly associated with antipsychotic

prescribing. The few characteristics of organizations examined have little influence over psychiatrist prescribing behavior.

Chapter three assesses provider-level clozapine and antipsychotic polypharmacy practices – one with strong evidence base and the other with little support. Using multiple years' claims data in a large Medicaid program, we find provider-level underuse of clozapine and use of non-evidence supported practice of non-clozapine antipsychotic polypharmacy. However, these prescribing practices vary tremendously across providers. In particular, a sizable portion of providers use more antipsychotic polypharmacy than clozapine to their patients. Quality initiatives may take actions to improve evidence-based practice and to decrease unsupported practices in the management of antipsychotic drug use.

This dissertation has important implications for public health because appropriate prescribing can alleviate tremendous health and economic burdens while inappropriate prescribing can generate substantial costs and increase risk of undesirable consequences. Understanding how providers make prescribing decisions points to potential opportunities for improving the quality of care and reducing cost through altering providers' prescribing behavior.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ACKNOWLEDGEMENTS

I would like to express my deepest gratitude to my dissertation committee members: Julie Donohue, Judith Lave, Joyce Chang, and Walid Gellad. I am indebted to my committee chair and advisor, Julie Donohue, for her tremendous guidance, endless patience, great support and encouragement throughout my dissertation and my graduate career at the University of Pittsburgh. Julie is a role model in every sense of the word. I consider myself truly fortunate to have been working with Julie in the past several years, as her student and as a research assistant. No matter how busy her schedule is, Julie has always kept an open door to discuss and provide me with valuable advice from small method issues to the big picture. Julie's guidance, motivation, insight, and encouragement throughout the process has been crucial for my completion of this dissertation. I am endlessly grateful for Julie's mentorship and want to pay it forward in future. I am greatly thankful to Judith Lave for providing me with insightful advice and comments which are invaluable in improving my dissertation work and in helping me think through my research. Judith's breadth of knowledge and dedication to health services research as an outstanding health economist has given me constant inspiration. I will also always remember the time that Judith spent on helping me go over the whole Handbook of Health Economics years ago. I thank Joyce Chang for enormous help and advice on my dissertation. Whenever I had any statistical-related questions or issues that I needed help, Joyce always made time for me. Her expertise and support made my completing the dissertation much easier. I could not have asked

for a better statistician on my committee. I am extremely thankful to Walid Gellad for his continued guidance and invaluable help and support on my dissertation. Walid's vast knowledge and sharp insights was crucial to this dissertation.

I am grateful to my coauthors, Marcela Horvitz-Lennon, Haiden Huskamp, and Sharon-Lise Normand, who have provided me helpful advice throughout the dissertation process. My special thanks are to Aiju Men, for her expert advice in programming and her constant encouragement.

I want to thank faculty members from the Department of Health Policy and Management including Mark Roberts, Nicholas Castle, Howard Degenholtz, Beaufort Longest, Gerald Barron, Julia Driessen, Marian Jarlenski, and others who have provided me with help during my study at the University of Pittsburgh. I also want to thank my colleagues and friends for their support and advice. In particular, I would like to thank Ana Progovac, Yomei Shaw, Manik Razdan, Carroline Lobo, Johanna Bellon, Tri Le, Inma Delso, Mina Kabiri, Jenny Lo, Yu Xiao, Yun Wang, and Yue Li.

I thank my parents for a lifetime of love, support, inspiration, and encouragement. Thanks to my husband, Jeff Du, for being on my side to support and encourage me, for being so patient with me, and for experiencing both hard and good moments with me. I am also grateful to the big family for their support in my life, particular thanks to my grandma, my uncles and aunts, my parents-in-law, my cousins, and my niece and nephews.

To my parents and husband

1.0 IMPACT OF MEDICARE PART D PLAN FEATURES ON USE OF GENERIC DRUGS

Yan Tang, Walid F. Gellad, Aiju Men, Julie M. Donohue

Published Manuscript (Medical Care 2014; 52(6): 541-548)

ABSTRACT

Background: Little is known about how Medicare Part D plan features influence choice of generic vs. brand drugs.

Objectives: Examine association between Part D plan features and generic medication use.

Methods: Data from a 2009 random sample of 1.6 million fee-for-service, Part D enrollees ≥65 years, who were not dually eligible or receiving low-income subsidies, was used to examine the association between plan features (generic cost-sharing, difference in brand and generic copay, prior authorization, step therapy) and choice of generic antidepressants, antidiabetics, and statins. Logistic regression models accounting for plan-level clustering were adjusted for sociodemographic and health status**.**

Results: Generic cost-sharing ranged from $0 to $9 for antidepressants and statins, and from $0 to $8 for antidiabetics (across 5^{th}-95^{th} percentiles). Brand-generic cost-sharing differences were smallest for statins (5^{th}-95^{th} percentiles: $16-$37) and largest for antidepressants ($16-$64) across plans. Beneficiaries with higher generic cost-sharing had lower generic use (adjusted odds

ratio [OR] = 0.97, 95% confidence interval [CI] =0.95-0.98 for antidepressants; OR = 0.97, CI =0.96-0.98 for antidiabetics; OR = 0.94, CI =0.92-0.95 for statins). Larger brand-generic cost-sharing differences and prior authorization were significantly associated with greater generic use in all categories. Plans could increase generic use by 5-12 percentage points by reducing generic cost-sharing from the 75th ($7) to 25th percentiles ($4-$5), increasing brand-generic cost-sharing differences from the 25th ($25-$26) to 75th ($32-$33) percentiles and using prior authorization and step therapy.

Conclusions: Cost-sharing features and utilization management tools were significantly associated with generic use in three commonly-used medication categories.

Key Words: Medicare Part D, cost-sharing, prior authorization, step therapy, generic drugs

1.1 INTRODUCTION

Increasing generic drug use has the potential to reduce prescription drug costs without harming quality, because generic equivalents are typically as effective as their brand counterparts[1,2] and are available at a quarter of the cost.[3] In fact, aggressive generic substitution has been a key driver of the lower than expected growth in prescription drug spending in Medicare Part D.[4] However, studies point to opportunities for substantial additional savings in Medicare from greater *therapeutic* substitution (switching from a brand drug to the generic version of another drug in the same class).[5,6] Because consumers face much lower cost-sharing for generics, increasing their use may reduce cost-related non-adherence,[7] and lead to substantial welfare gains to beneficiaries.[8]

Choice of generic drugs is shaped by patient characteristics[9-12] and provider preferences.[13,14] In Medicare, differences in Part D plan features may also be an important determinant of drug choice. In 2009, there were 1,689 Medicare Part D stand-alone prescription drug plans (PDP) which differed in premiums, formularies, cost-sharing, use of utilization management tools, and other features.[15] There was 4-fold variation across Part D plans in cost-sharing for the top ten brand drugs in 2009. For example, cost-sharing for Lipitor ranged from $21 to $77 across plans.[16]

There is strong evidence that demand for drugs is sensitive to cost-sharing and utilization management tools (e.g., prior authorization).[17-26] Yet, few studies have examined the association between Part D plan features and choice of generic vs. brand drugs. Hoadley and colleagues,

using 2008 Medicare data, found low or zero cost-sharing for generic statins could increase their use from 51% to 88% and could result in substantial savings.[27] It is not clear whether these findings generalize to other medications. We used 2009 Medicare data to examine whether cost-sharing for generic and brand drugs and use of utilization management tools (prior authorization or step therapy) were associated with choice of generic antidepressants, oral antidiabetics, and statins [3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors]. We focused on these categories because they are widely used by older adults, account for a large share of drug spending,[28,29] and include multiple brand and generic options with different levels of generic penetration. We hypothesized that lower cost-sharing for generic drugs, larger cost-sharing differences between brand and generic drugs, and use of prior authorization and step therapy for brand drugs would lead to greater generic use.

1.2 METHODS

1.2.1 Data sources

We analyzed data from the Centers for Medicare and Medicaid Services (CMS) for a 10% sample of 2009 Medicare beneficiaries (N = 4,891,885) who were continuously enrolled in fee-for-service Parts A and B and a stand-alone Part D plan (N = 1,529,825) that year. We did not request data on Medicare Advantage enrollees because complete medical claims are not available for those enrollees. The Prescription Drug Event (PDE) file contains information for each prescription on date of fill, National Drug Code (NDC), days supply, total cost, amount paid by the PDP and beneficiary (i.e., cost-sharing), benefit phase in which the claim occurred (e.g.,

initial coverage limit, coverage gap, or catastrophic phase), whether the plan required prior authorization/step therapy for the drug, and encrypted identifiers for the prescriber, pharmacy, and plan. We used the Plan Characteristics file to obtain the plan's monthly premium, deductible, and whether the plan covered generics in the gap. We obtained the primary dispenser type (e.g., retail, mail order) from the Pharmacy Characteristics file. We obtained the specialty of the provider prescribing the medication from the Prescriber Characteristics file. The Medi-Span® database was used to determine the drug name, category, dose, brand or generic status, and active ingredient by NDC.[30] From the Medicare Denominator file we obtained beneficiaries' demographics, ZIP code, Part D dual eligible status, and low-income subsidy (LIS) status. We obtained information on beneficiaries' diagnoses and health care utilization from the claims files. We used 2010 Census data to get ZIP code-level information on education (proportion with high school education) and median household income.[31]

We assigned beneficiaries to one of 306 Dartmouth Atlas of Health Care hospital-referral regions (HRRs) based on ZIP code[32] to adjust for additional regional factors that might affect.

1.2.2 Study sample

We excluded low-income subsidy recipients and dual eligibles who faced low or no cost-sharing and beneficiaries under 65 years eligible for Medicare based on disability whose drug utilization patterns may differ substantially from those of older adults (N = 761,070). We further excluded beneficiaries who switched plans during the year (N = 20,825), or were residents of US territories (N = 3,468). We limited analyses to individuals with at least one prescription drug event for antidepressants, oral antidiabetics, or statins during the year (see **Table A.1** for list of drugs). We eliminated a small number of enrollees (<1% of users in each category) who were in

PDPs with low enrollment due to difficulty in estimating cost-sharing for generic and brand drugs.

1.2.3 Dependent variable

Our primary outcome was whether a beneficiary's first prescription within a specific category in 2009 was for a generic. Most of the study sample used only generics or only brand drugs throughout the year (90.7% of antidepressant users, 79.9% of antidiabetic users, and 93.8% of statin users). In sensitivity analyses described in the statistical analysis section we used alternate specifications.

1.2.4 Key independent variables

The main predictors of interest were calculated at the plan-level for each therapeutic category separately. All prescriptions were standardized to a 30-day supply (i.e., a 90-day supply equaled three prescriptions). First, we calculated median cost-sharing for a generic prescription in the plan by therapeutic category in 2009. We used only prescription drug events from the initial coverage phase since cost-sharing is 100% in the coverage gap and uniform across plans after catastrophic coverage is in effect. Median instead of mean cost-sharing was used because of the skewed distribution. Overall, 89% of the claims had flat copayment and 11% had coinsurance. Our second key independent variable was the difference between the plan's median cost-sharing for a brand drug and the plan's median cost-sharing for a generic drug in the same category. We did not classify brand drugs into multiple categories (e.g., preferred vs. non-preferred brand drugs) because plans frequently assigned more than one drug type to a tier. Thus, it was not

feasible to distinguish between preferred or non-preferred brands if a tier contains more than one type. Finally, we included separate indicators of whether the plan required prior authorization or step therapy for at least one brand drug in the category.

1.2.5 Covariates

Covariates included other plan features (indicators of deductible, gap coverage, and premium level) and beneficiaries' demographic and socioeconomic characteristics (sex, age, race/ethnicity, and ZIP code-level education and income). We adjusted for a number of indicators of health status including person-level prescription-drug Hierarchical Condition Category (RxHCC) scores based on patients' claims (inpatient, outpatient, carrier, home health agency, and hospice claims),[33] which is a measure of health status and predictive of drug spending and is used to adjust PDP payments.[34] In addition, we included a variable for end-stage renal disease (ESRD) eligibility and a set of disease-specific comorbidities for each drug category to adjust for clinical severity (see **Table 1.1**). We included separate indicators for whether the beneficiary had at least one hospitalization or emergency department visit in the year. To adjust for differences in drug choice by provider specialty we included a variable indicating whether the beneficiary received at least one prescription from a specialist (e.g., geriatric psychiatry, psychiatry, advanced practice psychiatric nurses for antidepressant users; endocrinology for antidiabetic users; cardiology for statins). HRR indicator variables were added to address additional regional factors affecting use of generic vs. brand drugs.[35]

1.2.6 Statistical analysis

We used logistic regression models with robust standard errors clustered at the plan-level to estimate the association between plan features and whether a beneficiary's first prescription was for a generic drug. Regressions were performed at the person-level, adjusting for all covariates discussed above. Correlations among plan features were tested using variance inflation factor (VIF) diagnostics.[36] All VIFs were smaller than 2.7 indicating that the plan features were not too highly correlated to be included in the models.

We conducted sensitivity analyses altering the specification of the dependent variable, and the analytic sample. First, we used the last prescription filled in the year instead of the first as the dependent variable for generic use, an outcome variable used in previous studies.[27] Second, we conducted an analysis restricting the sample to beneficiaries who did not switch drugs between generic and brand medications throughout the year. Third, multiple concurrent medication use is common among antidepressant (13.1%) and antidiabetic (36.0%) users. Therefore, we conducted an analysis in which the dependent variable was 'generic drug use only' in the category. The results for all of these analyses were similar to the main analysis and thus are not reported. We considered a sensitivity analysis for one of our key independent variables where instead of the difference in brand vs. generic cost-sharing in the category, we used the ratio; however, the ratio of brand to generic was too highly correlated with cost-sharing for generic drugs to be included in the same model.

To ease interpretation of the findings, we calculated marginal effects of plan features on the use of generic drugs for 16 hypothetical scenarios with different plan features for each drug category, adjusting for all other covariates. To predict rates of generic use, we chose different

combinations of the 25th and 75th percentiles of the cost-sharing for generic drugs, the 25th and 75th percentiles of the brand-generic cost-sharing differential, and whether or not prior authorization or step therapy was used for brand drugs.

Analyses were performed using SAS (Version 9.3, SAS Institute, Cary, NC) and STATA (Version 12.0, Stata Corporation, College Station, TX). The study was deemed exempt from Human Subject Review by our Institutional Review Board.

1.3 RESULTS

1.3.1 Sample characteristics and plan features

Our study sample included 142,767 beneficiaries using antidepressants, 101,841 using antidiabetics, and 318,934 using statins in 2009 (**Table 1.1**). More than one-quarter (27.5%) of the antidepressant users had at least one hospitalization as did 22.1% of antidiabetic and 19.7% of statin users.

The mean absolute cost-sharing for generics was similar across the three therapeutic categories [$6 for antidepressants (5th-95th percentiles: $0-$9), $5 for antidiabetics (5th-95th percentiles: $0-$8), and $6 for statins (5th-95th percentiles: $0-$9)] (**Table 1.2)**. Mean cost-sharing differences between brand and generic drugs were also similar across the three drug categories ($32 for antidepressants, $31 for antidiabetics, $28 for statins) but varied substantially across plans (5th-95th percentiles: $16-$64 for antidepressants, $16-$49 for antidiabetics, and $16-$37 for statins).

Table 1.1: Characteristics of the study sample*

Characteristic	Antidepressants (N=142,767)	Antidiabetics (N=101,841)	Statins (N=318,934)
Demographic and socioeconomic characteristics			
Mean age (SD)	76.6 (7.9)	75.4 (7.0)	75.6 (7.1)
Female sex (%)	73.8	53.7	58.4
White race (%)	97.0	91.8	94.9
Proportion of population in ZIP code who are high school graduate or higher (%)	87.3 (7.9)	86.1 (8.3)	87.3 (8.0)
Median household income in $ (SD) †	57,298 (22,974)	55,067 (21,546)	58,115 (23,581)
Health services utilization in 2009			
At least one hospitalization (%)	27.5	22.1	19.7
At least one emergency department visit (%)	38.4	30.2	27.7
At least one prescription by mail order (%)	10.0	13.1	14.7
At least one specialist visit (%)	7.6	6.7	14.7
Health status			
RxHCC score (SD)‡	1.13 (0.42)	1.17 (0.35)	1.02 (0.35)
End-stage renal disease (ESRD) (%)	0.55	0.52	0.48
Disease-specific comorbidities			
Delirium, dementia, and amnestic and other cognitive disorders (%)	17.2		
Anxiety disorders (%)	20.2		
Bipolar disorders (%)	2.9		
Depressive disorders (%)	38.0		
Schizophrenia and other psychotic disorders (%)	5.0		
Diabetic neuropathy (%)		15.0	
Diabetic nephropathy (%)		5.8	
Diabetic retinopathy (%)		15.4	
Diabetes with peripheral vascular disease (%)		8.4	
Insulin use during the year (%)		15.0	
Hyperlipidemia (%)		84.2	92.2
Type 2 diabetes (%)		97.4	34.6
Coronary heart disease (%)			39.9
Stroke/TIA (%)			8.3
Medication use in the year (%)			
Only generic drugs	73.4	70.4	58.7
Only brand drugs	17.3	9.5	35.1
Both generic and brand drugs	9.3	20.1	6.2

* Figures with parentheses are means and SDs.

† Household income is based on the median income of the patient's geographic area according to ZIP code and 2010 U.S. Census data.

‡ Prescription-drug Hierarchical Condition Category (RxHCC) scores are based on diagnoses from 2009 inpatient, outpatient, carrier, hospice, and home health agencies claims and are normalized to equal 1.00 on average for all Medicare Part D enrollees, with a range in the study sample of 0.37 to 5.90. Higher scores indicate an increase likelihood of higher drug spending and poorer health status.

Table 1.2: Plan features for the study sample*

Variables		Antidepressants	Antidiabetics	Statins
Cost-sharing for a generic drug ($)				
	5th percentile	0	0	0
	25th percentile	5	4	5
	Mean	6	5	6
	Median	7	7	7
	75th percentile	7	7	7
	95th percentile	9	8	9
Cost-sharing difference between brand and generic drugs ($)				
	5th percentile	16	16	16
	25th percentile	26	26	25
	Mean	32	31	28
	Median	31	31	31
	75th percentile	33	33	32
	95th percentile	64	49	37
Prior authorization (%)		6.2	41.9	6.7
Step therapy (%)		44.8	53.2	40.1
Deductible (%)†		21.5	21.8	21.5
Gap coverage (%)‡		17.2	17.6	14.6
Premium per month ($)				
	5th percentile	24	24	24
	25th percentile	33	33	35
	Mean	43	43	42
	Median	38	38	38
	75th percentile	44	45	43
	95th percentile	81	81	78

* Plan features are described at person level.

† In Medicare Part D program, the deductible is a specific amount of money that beneficiaries have to pay for their prescriptions before their Part D plans start to pay their share of enrollees' prescription drug claims. The deductible varies across plans, some plans may have a deductible while others do not; besides, plans can have different amounts for their deductibles.

‡ The Medicare Part D standard benefit design requires beneficiaries (except those with low-income-subsidies) to pay for 100% of total prescription costs after their expenditures exceed the initial coverage phase and before reaching the catastrophic coverage limit. This benefit phase is usually called "coverage gap" or "doughnut hole". However, plans can offer alternative benefit designs with gap coverage that covers some drug costs in the gap.

The proportion of beneficiaries in plans requiring prior authorization varied across the categories, with 41.9% in plans using prior authorization for at least one antidiabetic agent vs. only 6.2% in plans requiring prior authorization for antidepressants and 6.7% for statins. A large proportion of beneficiaries were in plans with step therapy requirements (53.2% for antidiabetics, 44.8% for antidepressants, and 40.1% for statins). More than one fifth of beneficiaries enrolled in plans with a deductible. The proportion of users enrolled in plans with any gap coverage was 17.2% for antidepressants and 17.6% for antidiabetics vs. 14.6% for statins. The monthly premium varied substantially across plans (5^{th}-95^{th} percentiles: $24-$81 for antidepressant users and antidiabetic users, $24-$78 for statin users).

1.3.2 Effects of plan features

Effects of Part D plan features on generic use were similar across the three drug categories in 2009 (**Table 1.3**). After adjustment for demographic, socioeconomic, and health status and comorbidities, beneficiaries in plans with higher average generic cost-sharing were less likely to use generics than those in plans with lower cost-sharing for antidepressants (odds ratio [OR] per $1 increase= 0.97, 95% confidence interval [CI] = 0.95-0.98, $p<0.05$), antidiabetics (OR = 0.97, CI = 0.96-0.98, $p<0.05$), and statins (OR = 0.94, CI = 0.92-0.95, $p<0.05$). Beneficiaries in plans with larger within-category cost-sharing differences between brand and generic drugs were more likely to use generic drugs than those in plans with smaller differences (antidepressants: OR per $1 increase= 1.01, CI = 1.01-1.02; antidiabetics: OR = 1.01, CI = 1.01-1.02; statins: OR = 1.02, CI = 1.01-1.02; $p<0.05$ for all). Enrollees in plans with use of prior authorization had significantly higher odds of using generics for antidepressants (OR = 1.29, CI = 1.15-1.44, $p<0.05$), antidiabetics (OR = 1.14, CI = 1.09-1.20, $p<0.05$), and statins (OR = 1.12, CI = 1.00-

1.27, p<0.05) compared to their counterparts in plans without prior authorization requirement. Beneficiaries in plans using step therapy were more likely to use generic antidepressants (OR = 1.07, CI = 1.02-1.13, p<0.05) and generic statins (OR = 1.13, CI = 1.08 – 1.19, p<0.05), but these policies were not significantly associated with use of generic antidiabetics (OR = 1.04, CI = 0.99 – 1.09, p = 0.15).

Other plan features also had a significant impact on the use of generic drugs (**Table 1.3**). Beneficiaries in plans with no deductible were more likely to use generics than those in plans with deductibles across all three categories. Beneficiaries in plans that covered some drugs in the coverage gap had increased odds of using generic statins (OR = 1.24, CI = 1.04-1.47, p<0.05), but were no more likely to use generic antidepressants (OR = 1.09, CI = 0.90-1.30, p=0.38) or antidiabetic drugs (OR = 1.03, CI = 0.86-1.24, p = 0.74). Beneficiaries enrolled in plans with higher premiums using antidepressants or statins were less likely to use generics than those in plans with lower premiums, possibly because beneficiaries able to pay premiums at $50+/month might be less sensitive to out-of-pocket spending. However, plan premium was not associated with generic vs. brand use for antidiabetics.

1.3.3 Prediction of generic use associated with plan features

Table 1.4 shows the predicted rates of generic use in the three studied drug categories in several hypothetical Part D plans that vary by the key features of interest (cost sharing and utilization management tools). Plans could potentially increase generic use from 75.3% to 83.3% for antidepressants, from 79.0% to 84.2% for antidiabetics, and from 55.9% to 67.4% for statin drugs by reducing generic cost-sharing from the 75th ($7) to 25th percentiles ($4-$5), increasing brand-generic cost-sharing differences from the 25th ($25-$26) to 75th ($32-$33) percentiles and

using prior authorization and step therapy requirements. (**Table A.2** contains predictions for all hypothetical plans).

Table 1.3: Estimated effects of plan features on the use of generic drugs*

Variables	Adjusted Odds Ratios (95% CI)		
	Antidepressants	**Antidiabetics**	**Statins**
Plan cost-sharing features			
Cost-sharing for a generic drug ($)	0.97 (0.95-0.98)†	0.97 (0.96-0.98)†	0.94 (0.92-0.95)†
Cost-sharing difference between brand and generic drugs ($)	1.01 (1.01-1.02)†	1.01 (1.01-1.02)†	1.02 (1.01-1.02)†
Utilization management tools			
Prior authorization (ref=no)			
Yes	1.29 (1.15-1.44)†	1.14 (1.09-1.20)†	1.12 (1.00-1.27)†
Step therapy (ref=no)			
Yes	1.07 (1.02-1.13)†	1.04 (0.99-1.09)	1.13 (1.08-1.19)†
Other plan features			
Deductible (ref=yes)			
No	1.10 (1.01-1.19)†	1.09 (1.01-1.19)†	1.45 (1.33-1.58)†
Gap coverage (ref=no)			
Yes	1.09 (0.90-1.30)	1.03 (0.86-1.24)	1.24 (1.04-1.47)†
Premium ($, ref=$1-<30)			
$30-50/month	0.90 (0.84-0.96)†	1.08 (1.00-1.17)	0.75 (0.69-0.81)†
$50+/month	0.79 (0.66-0.95)†	0.84 (0.69-1.02)	0.56 (0.46-0.67)†
Demographic and socioeconomic characteristics			
Sex (ref=male)			
Female	0.94 (0.91-0.97)†	1.14 (1.10-1.18)†	1.08 (1.06-1.10)†
Race/ethnicity (ref=other)			
Non-Hispanic white	0.81 (0.75-0.88)†	1.00 (0.94-1.06)	0.95 (0.91-0.98)†
Age group (year, ref=65-74)			
75-84	1.05 (1.02-1.09)†	0.99 (0.95-1.03)	1.01 (1.00-1.03)
85+	1.04 (1.00-1.09)†	0.94 (0.89-1.00)	1.10 (1.07-1.13)†
Education (%, ref=other)			
High school graduate or higher	0.99 (0.99-0.99)†	1.00 (0.99-1.00)†	1 .00(0.99-1.00)†
Median household income ($)	1.00 (1.00-1.00)†	1.00 (1.00-1.00)†	1.00 (1.00-1.00)†
Health services utilization			
At least one hospitalization (ref=no)			
Yes	1.06 (1.02-1.10)†	1.04 (0.99-1.09)	1.09 (1.07-1.12)†

Table 1.3 (Continued)

Variables	Adjusted Odds Ratios (95% CI)		
	Antidepressants	**Antidiabetics**	**Statins**
At least one emergency department visit (ref=no)			
Yes	1.02 (0.99-1.06)	1.03 (0.98-1.07)	1.05 (1.03-1.07)†
At least one prescription by mail order (ref=no)			
Yes	1.15 (1.08-1.22)†	0.94 (0.88-1.01)	1.15 (1.07-1.24)†
At least one prescription by specialist prescribers (ref=no)			
Yes	0.81 (0.76-0.85)†	0.60 (0.57-0.64)†	0.82 (0.81-0.84)†
Health status			
RxHCC score	0.89 (0.86-0.93)†	1.05 (1.00-1.11)	1.27 (1.23-1.31)†
ESRD (ref=no)			
Yes	1.19 (0.98-1.43)	0.65 (0.54-0.79)†	0.99 (0.88-1.10)
Disease-specific comorbidities			
Antidepression specific predictors			
Delirium, dementia, and amnestic and other cognitive disorders (ref=no)			
Yes	0.88 (0.85-0.91)†		
Anxiety disorders (ref=no)			
Yes	1.00 (0.96-1.03)		
Bipolar disorders (ref=no)			
Yes	0.97 (0.90-1.04)		
Depressive disorders (ref=no)			
Yes	0.72 (0.70-0.74)†		
Schizophrenia and other psychotic disorders (ref=no)			
Yes	1.07 (1.01-1.13)†		
Antidiabetes specific predictors			
Diabetic neuropathy (ref=no)			
Yes		0.96 (0.92-1.01)	
Diabetic nephropathy (ref=no)			
Yes		0.76 (0.71-0.81)†	
Diabetic retinopathy (ref=no)			
Yes		0.83 (0.79-0.86)†	
Diabetes with peripheral vascular disease (ref=no)			
Yes		0.99 (0.93-1.05)	
Insulin use during the year (ref=no)			
Yes		0.85 (0.81-0.89)†	

Table 1.3 (Continued)

Variables	Adjusted Odds Ratios (95% CI)		
	Antidepressants	**Antidiabetics**	**Statins**
Hyperlipidemia (ref=no)			
Yes		0.89 (0.85-0.94)†	
Type 2 diabetes (ref=no)			
Yes		0.68 (0.61-0.77)†	
Statins specific predictors			
Coronary heart disease (ref=no)			
Yes			0.76 (0.75-0.78)†
Stroke/TIA (ref=no)			
Yes			1.03 (1.00-1.06)†
Hyperlipidemia (ref=no)			
Yes			0.87 (0.84-0.90)†
Type 2 diabetes (ref=no)			
Yes			1.00 (0.99-1.03)

*Regression results were adjusted for HRR indicators.
†Statistically significant odds ratios, $p<0.05$.

Table 1.4: Prediction of generic use*

Benefit design scenario	Cost-sharing for a generic drug ($)	Cost-sharing difference ($)	Prior authorization	Step therapy	Predicted generic use
		Antidepressants			
I	7	26	N	N	75.3%
II	7	33	N	N	77.1%
III	5	26	Y	Y	81.9%
IV	5	33	Y	Y	83.3%
		Antidiabetics			
I	7	26	N	N	79.0%
II	7	33	N	N	80.4%
III	4	26	Y	Y	83.0%
IV	4	33	Y	Y	84.2%
		Statins			
I	7	25	N	N	55.9%
II	7	32	N	N	58.9%
III	5	25	Y	Y	64.6%
IV	5	32	Y	Y	67.4%

*For each drug category, we calculated marginal effects of plan features on the use of generic drugs (Appendix displays predicted generic use for all 16 scenarios in each drug category). We chose different combinations of the 25th and 75th percentiles of the cost-sharing for generic drugs, the 25th and 75th percentiles of the cost-sharing difference between brand and generic drugs, and whether or not prior authorization or step therapy was used. All covariates were adjusted for the predictions.

1.4 DISCUSSION

We found that rates of generic drug use for common chronic conditions are closely related to Part D plan features in Medicare. Specifically, low cost-sharing for generics, large differentials in cost-sharing for generic vs. brand drugs, and tools such as prior authorization and step therapy were associated with higher generic drug use. Our analysis points to potential opportunities for savings[5] through altering benefit design in Part D plans.

Previous studies have reported positive associations between brand-generic cost-sharing differentials and use of generics in employment-based insurance.[37] Our findings are similar to those reported by Hoadley.[27] Using more recent data (2009), two additional drug categories, and adjusting for a richer set of health and socioeconomic status measures, our study confirms the association between benefit design in Part D plans and use of generic drugs. It is notable that our findings were quite consistent across the three drug categories in spite of differences in the formulary requirements for these categories, the potential for within-category polypharmacy, and differing generic availability. Specifically, when the Part D program was established in 2006, antidepressants were designated as a "protected class" requiring Part D plan formularies to cover all or substantially all drugs in the category[38] to ensure access, although CMS is considering eliminating protected status for antidepressants.[39] While antidepressants have similar comparative effectiveness, on average, these agents are not equally effective at the individual-level and patients with depression may try multiple antidepressants before finding one that works.[40,41] As a result, physicians may be reluctant to engage in therapeutic substitution in this category. It is possible that beneficiaries with poorly controlled diabetes would be prescribed

multiple oral antidiabetic agents, some of which have no generic equivalents. If choice of plan is correlated with diabetes severity our estimates of the effect of plan features may be biased. We addressed this issue by adjusting for a rich set of diabetes severity indicators (including several complications, overall comorbidity, and receiving antidiabetic prescriptions from an endocrinologist). Finally, while the overall rate of generic drug use was slightly lower in the statin class due to fewer available generic equivalents during our study period, the magnitude of the effects of our key plan features was similar to the other two categories.

The Medicare Prescription Drug and Modernization Act (MMA) created a market for prescription drug coverage that was meant to provide multiple plan choices to beneficiaries so they could find a plan that best met their needs. Our findings point to relatively small variation in some plan features (e.g., plans' cost-sharing for generic antidepressants ranged only from $5 to $7 in the 25th and 75th percentiles, respectively) and more variation in others (e.g., the cost-sharing difference between brand and generic drugs ranged from $26 to $33 for antidepressants in the 25th and 75th percentiles). It is possible that our findings on the relationship between plan features and generic use could be partly due to selection bias if beneficiaries who are more likely to use generics chose plans with lower generic cost-sharing. However, the evidence on factors driving plan choice points to this bias being minimal. Research suggests that Part D plan choice is driven largely by plan premiums and that beneficiaries actually fail to pay sufficient attention to cost-sharing and utilization management tools when selecting plans.[42,43] The typical beneficiary, who faces a choice of 40 plans on average, seldom chooses the optimal plan (i.e., the one with the lowest out-of-pocket spending for someone with their drug utilization).[43,44] Furthermore, beneficiaries are reluctant to switch plans in response to changes in their medication needs or plan options over time.[45,46] We are, therefore, reasonably confident that

potential selection bias should be minimal after adjusting for the many plan- and beneficiary-level covariates in our analyses.

It is possible that some standardization of pharmacy benefit designs under Part D (e.g., requiring all plans to have very low cost-sharing for generics) may save money for the Medicare program and beneficiaries. However, Medicare policy has consistently favored a more market-based approach to plan benefit design. Alternatively, CMS could add efficiency measures to its performance measurement for Part D plans: the Star Rating system, information available to consumers on the Medicare Drug Plan Finder website and used by CMS to terminate contracts with poorly performing Part D plans. The Star Rating system, which has been found to be associated with beneficiaries' enrollment decisions,[47] has 4 domains for quality measurement: 1) drug plan customer service; 2) member complaints, problems getting services, and improvement in the drug plan's performance; 3) member experience with the drug plan; and 4) patient safety and accuracy of drug pricing.[48] The rating system does not currently evaluate generic vs. brand drug use, which could be a potential measure of efficiency. If Part D plans are rewarded for more generic use, they might change their cost-sharing to drive greater use of generic drugs by their enrollees.

Our study has important limitations. First, while we adjusted for patients' socio-demographic characteristics and health status, provider-level factors, which also influence prescribing decisions,[49] were limited to specialty of the prescriber. Second, we restricted the sample to those with 12 months continuous enrollment whose medication use patterns may differ from other Medicare beneficiaries. Third, we measured plan's utilization management for at least one brand drug in the drug category using the PDE file. If no enrollees in a particular plan filled the drug requiring prior authorization or step therapy by the plan we would not observe the

utilization management requirement for that drug and may thus underestimate use of and effects of these tools. Fourth, use of specific utilization management tools (e.g., prior authorization) vary from year to year so our findings may not generalize to other years. Fifth, it is difficult to predict beneficiaries' behavioral responses in drug categories where polypharmacy is common (e.g., antidiabetics). If beneficiaries respond to reductions in generic drug copays by combining a generic with a brand drug to treat the same condition instead of substituting the generic for the brand, changes in cost-sharing features may not result in savings. Finally, if beneficiaries purchased generic drugs at discounted prices without using the plan (e.g., $4 generic programs), use of generic drugs would be underestimated. Since use of these programs was relatively limited among elderly beneficiaries at the time,[50] their impact on our findings should be minimal.

In conclusion, lower cost-sharing for generic drugs, larger brand-generic cost-sharing differences, and use of prior authorization and step therapy requirements were associated with greater use of generic drugs in three widely used drug categories in Part D. Modifying the benefit design and utilization management of Medicare prescription drug plans might increase generic use, which could generate substantial savings for the Medicare program and for beneficiaries.

2.0 PATIENT, PHYSICIAN AND ORGANIZATIONAL INFLUENCES ON THE CONCENTRATION OF ANTIPSYCHOTIC PRESCRIBING IN MEDICAID

Yan Tang, Chung-Chou H. Chang, Judith R. Lave, Walid F. Gellad, Haiden A. Huskamp, Julie M. Donohue

ABSTRACT

Objectives: Antipsychotics have been approved to treat several serious mental disorders. Given considerable variability in treatment response and medication side effects across individual patients using antipsychotic drugs, customizing treatment to the needs of each individual is key to improving patient outcomes. This study examined the degree to which psychiatrists were diversified vs. concentrated in their choice of antipsychotic medication and identified patient, physician, and organization-level factors associated with the concentration of antipsychotic prescribing.

Methods: Using 2011 data from Pennsylvania's Medicaid program we identified all psychiatrists who regularly prescribed antipsychotics (defined as 10 or more unique patients in that year). Using prescriber ID we linked claims data, from which we obtained information on patient characteristics and psychiatrist prescribing behavior, to demographic information on psychiatrists from the AMA Masterfile, and to IMS Health's HCOS ^{TM} database from which we obtained information on psychiatrists' organizational affiliations. We used three measures of antipsychotic prescribing concentration: the number of ingredients ever prescribed in the year,

the share of prescriptions for the most preferred ingredient, and the Herfindahl index (HHI). We used descriptive analyses and multiple membership linear mixed models with restricted maximum likelihood estimation to evaluate the degree of physician-level concentration for antipsychotic prescribing. Predictors included patient characteristics (e.g., diagnoses, disability status, demographics), physician characteristics (e.g., sex, age, educational background, practice location), and features of affiliated health care organizations (e.g., inpatient vs. clinic, behavioral health specialty).

Results: The analytic cohort included 764 psychiatrists treating 65,256 patients. Psychiatrists prescribed several unique ingredients (mean number: 9); however, prescribing behavior was relatively concentrated (share of most preferred ingredient: 37.8%; mean HHI: 2,603), with wide variation across psychiatrists in all measures (range number of ingredients: 2-17; share of most preferred ingredient: 16.4%-84.7%; HHI: 1,088-7,270). About 15% of psychiatrists had a HHI higher than 3,333, which suggests that these psychiatrists only prescribed 3 ingredients equally to their patients (each 33.3%), or prescribed more ingredients but relied heavily on only 1 or at most 2 ingredients. Having a higher share of SSI-eligible patients and patients with serious mental illnesses was associated with less concentrated (more diversified) prescribing although effects were relatively small ($p<.01$ or $p<.05$). Female psychiatrists prescribed 0.29 fewer unique antipsychotic ingredients than did males ($p<.10$) and had a HHI that was 97.5 units higher ($p<.10$). Psychiatrists affiliated with behavioral health organizations had more diversified antipsychotic prescribing in terms of number of ingredients ($p<.10$). By increasing psychiatrist's share of patients with serious mental illnesses from 20% to 100%, the degree of concentration would decrease (e.g., from 3,102 to 2,382 for HHI). Similar patterns were also found by share of SSI-eligible patients.

Conclusions: Antipsychotic prescribing behavior in a large state Medicaid program was relatively concentrated and varied substantially across psychiatrists regularly prescribing antipsychotics. Some psychiatrists treating Medicaid enrollees with antipsychotics may be limited in their ability to tailor treatment to individual patient needs and preferences. Psychiatrists treating more disabled patients with a higher prevalence of severe mental illnesses had slightly more diversified prescribing although the effects were small. Health systems may consider exploring strategies for educating providers or guiding patients to providers with greater ability to tailor treatment decisions.

Key Words: physician prescribing, customization, concentration, variation, antipsychotics

2.1 INTRODUCTION

Physicians often face many choices when prescribing drugs in a therapeutic class. In some drug classes a most effective drug may exist for the treatment of certain diseases. For example, when treating patients with diabetes and other heart risk factors, ramipril in the drug class of antiotension-converting enzyme (ACE) inhibitors has been proven to be the most effective drug in that class to reduce the risk of heart attack, stroke, and premature deaths.[51] However, in most drug classes there is no "best drug" for all patients; but there is "best drug" for a particular patient. Accordingly, appropriate prescribing is the result of a matching process that results in identifying the medication that best fits the patient's clinical characteristics and preferences. Although personalizing prescribing choices to each individual could potentially lead to better clinical outcomes –sometimes by improving medication adherence, which is evidenced in antidepressant treatment,[52,53] many physicians tend to prescribe the same drug (or only a limited subset of drugs) to all patients.[54]

There are now more than 20 molecules and their reformulations in the class of antipsychotic drugs.[55] As a top-selling drug class,[56] antipsychotics have been approved by the US Food and Drug Administration (FDA) to treat several serious psychiatric conditions including schizophrenia, bipolar disorder, major depressive disorder, and autism. Off-label use of antipsychotics for other conditions is also common.[57,58] The widespread substitution of atypical (new) for conventional (old) antipsychotics in the past two decades resulted in high expenditures for antipsychotics, which are mainly financed by Medicare and state Medicaid programs.[59] Although atypicals were introduced with the promise of greater effectiveness and safety than

their conventional counterparts, comparative effectiveness research found that non-clozapine atypicals are no more effective than conventional antipsychotics.[60,61] Because there is considerable variability in treatment response and medication side effects across individual patients using antipsychotic drugs,[62,63] tailoring treatment to the needs and preferences of patients is essential to achieving good clinical outcomes. In fact, a major focus of the National Institute of Mental Health (NIMH) in recent years has been fostering personalized medicine to improve health outcomes.[64]

Despite a wide variety of choices in antipsychotic products, two studies have found antipsychotic prescribing to be relatively concentrated although they differed in their sampling frame and study period.[55,65] These findings are similar to results reported from studies examining prescribing concentration in multiple disease conditions (acute vs. chronic diseases)[54] and the drug class of antidepressants.[52] The studies examining antipsychotic prescribing concentration adjusted for physician characteristics but did not have information on the patient case mix or on the setting in which the physicians practiced. In addition to physicians' own characteristics[66,67] (e.g., education and training background, practicing experience, age), characteristics of the treated patient population (e.g., demographic factors, health status and clinical needs) may also influence prescribing decision because physician is expected to act in patient's best interests and to personalize treatment as her agent.[68] Furthermore, physician prescribing practices may be shaped by the organizations within which they practice through multiple mechanisms (e.g., guideline dissemination, quality improvement initiatives, normative influences, financial incentives).[49,69]

This study examined physician antipsychotic prescribing behavior in the Medicaid program because of the important role Medicaid plays in financing antipsychotic drugs. Using

2011 Pennsylvania's Medicaid dataset and information from IMS Health databases and the American Medical Association (AMA) Masterfile, we assessed psychiatrists' prescribing of antipsychotics and the influence of patient characteristics, physician characteristics, and organizational features.

2.2 METHODS

2.2.1 Overview

By linking 2011 data from Pennsylvania's Medicaid program, AMA Masterfile, and IMS Health's HCOS ^{TM} dataset, we identified psychiatrists who regularly prescribed antipsychotics (defined as psychiatrists who treated 10 or more unique Medicaid patients in that year). We constructed 3 measures to quantify the degree of concentration for psychiatrist antipsychotic prescribing. A number of continuous and categorical variables were constructed to describe the characteristics of treated patient population, physician characteristics, and features of the health care organizations with which psychiatrists were affiliated. Using descriptive analyses and multiple membership linear mixed models, we examined the degree of physician-level concentration for antipsychotic prescribing in this large Medicaid program and the three types of factors associated with psychiatrists' prescribing behavior.

2.2.2 Data sources

Medicaid data

We obtained data on patient characteristics, physician and practice setting information for calendar year 2011. Pennsylvania's Medicaid dataset from the Department of Public Welfare (DPW) contains enrollment information, medical claims (inpatient, outpatient, and professional), pharmacy claims for the 2.2 million individuals who were enrolled in either fee-for-service or managed care programs. It also contains a provider file for providers who bill for visits with Medicaid patients. This file includes prescribing provider's information such as National Provider Identifier (NPI), name, and ZIP code information for practice location. From the enrollment file we obtained beneficiaries' demographic information (age, sex, race/ethnicity), dual eligible status, eligibility type [SSI (Supplemental Security Incomes), TANF (temporary assistance for needy families), GA (general assistance), waiver], and insurance type (fee-for-service vs. individual managed care programs). The eligibility type of general assistance is a Pennsylvania-specific program for nonelderly adults with a temporary disability, limited income or special circumstances. We obtained information on patients' diagnoses using the outpatient, professional, and inpatient claims files. As indicated below, we used these data to describe the psychiatrists' patient population. The pharmacy claims file includes prescription information such as the National Drug Code (NDC), date of fill, dose, form, days supply, and prescribing provider identifier. We used the Medi-Span® database to acquire antipsychotic drugs' information including drug name, dose, and active ingredient by NDC.[70]

Physician characteristics

Using the NPI, we linked prescribers with at least one antipsychotic prescription in Pennsylvania's Medicaid database to physician characteristics from the AMA Masterfile and to information on organizational characteristics from the 2011 IMS Health's Healthcare Organizational Services™ (HCOS) database. The AMA Masterfile, which includes data on all physicians (both domestic and foreign graduates) practicing in the US, contains information on physician demographic, specialty, medical education, and other information.[71]

Organizational affiliation and characteristics

We obtained information on organizational affiliation from IMS Health's HCOS™ database, on all US psychiatrists with ≥10 antipsychotic prescriptions in 2011. HCOS™ identifies physician affiliations with health care organizations (e.g., medical groups, hospitals, nursing homes), along with the type of affiliation with each organization (e.g., attending, affiliated, admitting, staff, consulting, treating). HCOS™ also contains information on the specialty of the organization, for example, whether a medical group had a primary care or behavioral health specialty, and the total number of providers from all specialties affiliated with that organization.[72] The HCOS™ database seldom captures solo or 2-person practices, but includes virtually all hospitals in Pennsylvania according to the hospital list from the Centers for Medicare and Medicaid Services (CMS) Hospital Compare database,[73] and larger medical groups, clinics or outpatient facilities.

2.2.3 Study population

We identified psychiatrists prescribing at least one antipsychotic drug to Medicaid beneficiaries who were under the age of 65 and not dually eligible for Medicare. We excluded dual eligible

beneficiaries because Medicaid data do not contain complete claims information for those beneficiaries, particularly for prescription drugs. We then limited our analyses to all psychiatrists who regularly prescribed antipsychotics to 10 or more unique Medicaid enrollees in 2011. Low volume prescribers provide little information about the diversity of antipsychotic prescribing and account for a small fraction of antipsychotic prescribing (<1% of the prescriptions by psychiatrists participating in Pennsylvania Medicaid were prescribed by prescribers with ≤9 patients using antipsychotic drugs in 2011) so they were not included in the analyses (see **Figure B.1** for physician-level concentration of antipsychotic prescribing by physician patient volume and **Figure B.2** for the sample size flow chart).

2.2.4 Outcome variables

We constructed three outcome variables to capture the degree of physician-level concentration/diversity for antipsychotic prescribing. We considered concentrated prescribing to be the opposite of diverse prescribing; *more concentrated* antipsychotic prescribing indicates *less diversified* prescribing and vice versa. The first outcome measure was the number of unique ingredients ever prescribed in the year. A recent study examining adoption of second-generation antipsychotics implies tremendous variation in the time to adoption and sizable differences in number of agents prescribed across specialties.[74] The second outcome measure was the share of prescriptions accounted by the psychiatrist's most preferred antipsychotic ingredient, a measure of prescribing concentration used in previous research.[54] Studies have documented that prescribers tended to have favorite agents when multiple drugs were available in a therapeutic class.[52-54] The third outcome measure was Herfindahl index (HHI), which is a commonly accepted measure of market concentration of firms[75-77] but has also been applied to measure the

concentration of product choice within physicians.[52,53,55,65] In economic studies, if HHI is greater than 1,800, it reflects a highly concentrated market.[78] We calculated the HHI for a psychiatrist who prescribed N unique antipsychotic ingredients in 2011, by summing up the square of each antipsychotic ingredient's prescription share. The value of the HHI index ranged from 10,000/N (if a physician prescribed each of N antipsychotic ingredients with equal share) to 10,000 (if a psychiatrist prescribed only one antipsychotic ingredient). The HHI index incorporates information on both number and share of antipsychotic ingredients prescribed by the psychiatrist, with a larger value implying more concentrated and a smaller value indicating more diversified prescribing behavior.

A larger number of ingredients indicates *less concentrated* (more diversified) prescribing of antipsychotics, while higher share of ingredients prescribed made up by the most preferred ingredient and a higher HHI imply a *more concentrated* (less diversified) prescribing behavior. Each of the three measures captures a slightly different aspect of concentration; the three variables together can comprehensively explore psychiatrists' concentrated vs. diversified prescribing behavior of antipsychotic drugs.

2.2.5 Explanatory variables

We examined three types of predictors of antipsychotic prescribing: characteristics of the treated patient population, physician characteristics, and features of the health care organizations with which psychiatrists were affiliated.

We used data on patient characteristics to adjust for differences in the psychiatrists' caseloads. For each psychiatrist we calculated the share of his or her patients in certain

sociodemographic groups (share that were female, non-Hispanic white, under 18 years old, and 50 or older). We included a variable of the share of patients eligible for Medicaid through SSI to measure disability status. To adjust for possible variability in management of antipsychotics by payers we included a variable for the share of a psychiatrist's patients in fee-for-service vs. managed care programs. The only prior authorization policies in existence were for children under 18 years old. Furthermore, antipsychotic policies in Pennsylvania Medicaid did not target a particular agent. To adjust for patients' health status and diagnosis, we included psychiatrist's share of patients with serious mental illnesses [any diagnosis of schizophrenia (ICD-9 codes: 295.xx), bipolar disorder (ICD-9 codes: 296.0, 296.1, 296.4, 296.5, 296.6, 296.7, 296.8), major depressive disorder (ICD-9 codes: 296.2, 296.3), or autism spectrum disorder (ICD-9 codes: 299.xx, excluding 299.9)]. To capture patient population's non-mental comorbidities, first, for each patient we constructed separate indicators of 25 non-mental illness Elixhauser comorbidity index (a widely used comorbidity measure)[79-81] based on patient's medical claims. Second, we created a variable for physician-level share of patients with 2 or more of these conditions based on the distribution in our patient sample.

The physician characteristics included psychiatrist's sex (female vs. male), age categories (≤40, 40–49, 50–59, ≥60), educational background (whether the psychiatrist graduated from a top 20 medical school according to 2011 *US News and World Report Rankings*, and whether he/she received a degree from US or foreign medical school), prescription volume measured by total number of antipsychotic prescriptions in the year, and whether the psychiatrist only practiced in an urban area based on the ZIP code of practice settings. We measured each psychiatrist's professional network by calculating the total number of other regular antipsychotic prescribers in all health care organizations with which the psychiatrist was affiliated. We

hypothesized that psychiatrists practicing in larger organizations may have more diversified prescribing behavior than those in smaller organizations due to greater availability of information from peers.

To measure features of affiliated health care organizations, we included dummy variables for organizational affiliation type (whether the psychiatrist practiced in outpatient only, inpatient only, or in both outpatient and inpatient organizations), and an indicator of whether the psychiatrist was affiliated with any behavioral health organization (psychiatric hospital, or medical group with specialization in behavioral health/addiction medicine). We also included a variable of number of providers from all disciplines as a proxy for organization size. Because each organization with which a psychiatrist was affiliated had its own number of providers, and the degree of membership with different organizations for each psychiatrist varied, the new variable of provider numbers for each psychiatrist was derived as the weighted average of the provider numbers across all the organizations to which the psychiatrist belonged. Weights were applied based on the weighting structure of the multiple membership modeling[82] as discussed in more detail below.

2.2.6 Statistical analysis

Descriptive analysis

We examined the distribution of the 3 outcome variables across psychiatrists in the study sample, reporting mean, standard deviation, percentiles, and calculated the coefficient of variation, a commonly used measure of variability.[65,83]

Multiple membership data structure and modeling

Traditional multilevel models are used to analyze data that have hierarchical or nested structures (i.e., each observation at a lower level is nested within a single unit at a higher level).[84-87] However, sometimes the assumption of purely hierarchical data structure does not hold in practice.[88,89] One complex type of non-hierarchical data is multiple membership structure, in which lower-level observations are not nested within only one higher-level unit; instead, they are members of multiple higher-level units simultaneously.[88,90] For example, a psychiatrist (lower-level unit) may be affiliated with more than one health care organization (higher-level unit) during the year as is the case in our sample. In analyses with multiple membership data structure, it is assumed that there are known weights which could be used to quantify the degree of membership for a lower-level unit to the different higher-level units. The sum of weights across different clusters for each lower-level unit equals to 1.

To tackle the complexity of multiple membership data structure, we used the multiple membership linear mixed models with restricted maximum likelihood estimation (REML) for the evaluation of the 3 continuous outcome measures, which were approximately normally distributed in the study sample. We used REML other than maximum likelihood estimation (ML) because REML not only provides unbiased estimates but also takes into account the loss of degrees of freedom due to the inclusion of covariates.[91] All regressions were performed at the physician-level. The regression models included fixed effects for all explanatory variables discussed above and health care organization-level random effects. The model can be expressed as:

$$y_i = \beta_0 + \beta_1 x_{i,pt} + \beta_2 x_{i,phy} + \beta_3 x_{i,org} + \beta_4 \sum_{j \in org(i)} w_{j,i}^2 size_j^2 + \sum_{j \in org(i)} w_{j,i}^2 \mu_j^2 + e_i$$

where y_i represents the outcome variable for psychiatrist i. β_0 is the intercept. $x_{i,pt}$ is a vector of variables for patient characteristics for psychiatrist i, with corresponding vector of coefficients β_1; similarly, $x_{i,phy}$ stands for a vector of variables for psychiatrist characteristics with coefficients β_2 for psychiatrist i; and $x_{i,org}$ is a vector of organizational setting factors for psychiatrist i with corresponding coefficients β_3. $w_{j,i}^2$ measures the degree of membership for psychiatrist i (level 1) to organization j (level 2), summing to 1 for psychiatrist i. $size_j^2$ represents total number of providers for organization j (level 2). $\sum_{j\in org(i)} w_{j,i}^2 size_j^2$ is the weighted average of the provider numbers across all the organizations (level 2) with which psychiatrist i was affiliated, β_4 stands for corresponding coefficient. The first 5 items on the right-hand side of the model are termed the fixed part of the model. $\sum_{j\in org(i)} w_{j,i}^2 \mu_j^2$ represents the weighted sum of organizational-level random effect, and e_i is the residual error term. The last 2 terms stand for the random part of the equation.

The affiliation type identifies the relationship a psychiatrist has with a health care organization (e.g., attending, affiliated, or admitting in a hospital; staff, consulting, or treating in a nursing home), which was used to construct the weighting structure to represent the extent of membership for a psychiatrist to each of his or her affiliated organizations. Medical group affiliations were given the same weight as the affiliation type "attending" in inpatient facilities. We categorized the degree of membership into 2 groups based on this information: 1) "*strong relationship"* if a psychiatrist was affiliated with a medical group, had an attending relationship with a hospital, practiced at an outpatient location of a hospital (affiliated provider), or was contractually on staff at a nursing home (staff); 2) "*weak relationship"* if a psychiatrist admitted patients to a hospital but was not designated as an attending or affiliated provider, consulted or treated patients at a nursing home without being on staff.

In the main analysis, we assigned the weighting ratio of "strong relationship" to "weak relationship" to be 5:1 (total weights summed to 1 for each psychiatrist), assuming affiliated organizations in the "strong relationship" group would be more influential to the psychiatrist's prescribing behavior than organizations in the "weak relationship" group. To check the robustness of the results, in sensitivity analyses we explored other weighting schemes: 1:1 (i.e., equal weights), 10:1, and 2:1.

In addition, we ran the regressions on each outcome without including any explanatory variable. Variation reductions between the null and above full models were reported. Finally, to assess the degree of concentration in response to the severity of patient illness (since prescribing customization is expected to meet patients' clinical needs), we predicted the 3 outcomes on antipsychotic prescribing by share of patients with serious mental illnesses and by share of SSI-eligible patients, respectively. All other covariates were adjusted for the predictions.

SAS (Version 9.4, SAS Institute, Cary, NC) and STATA (Version 13.0, Stata Corporation, College Station, TX) were used for the analyses.

2.3 RESULTS

2.3.1 Physician and patient characteristics

In 2011, a total of 764 psychiatrists treating 65,256 patients in the Pennsylvania Medicaid program were included in our sample (the median number of treated patients was 68 for a psychiatrist). Of the 764 psychiatrists in the study, 33.3% were female, more than half (55.9%) were 50 years of age or older, 44.0% graduated from foreign schools. At the physician-level, the

mean share of SSI-eligible patients was 69.6% and the mean share of patients with serious mental illnesses was 77.7% **(Table 2.1)**.

2.3.2 Organizational and physician affiliations

Among the study sample, about half (50.5%) of the psychiatrists were affiliated with 2 or more organizations in 2011 (mean number of organizations per physician: 1.9; range: 1–7), 38.2% had an affiliation with at least one behavioral health organization (psychiatric hospital, or medical group with specialization in behavioral health/addiction medicine) **(Table 2.1).** More than half (57.9%) were affiliated with inpatient organizations only, 15.8% were affiliated with outpatient organizations only and 26.3% with both inpatient and outpatient organizations. Of the 539 organizations with which the psychiatrists billing Pennsylvania Medicaid were affiliated, the majority of them (63.5%) were non-behavioral health organizations and most (63.6%) were inpatient organizations **(Table 2.2).** The mean number of regular antipsychotic prescribers affiliated with these organizations was 3.

Table 2.1: Descriptive characteristics of regular psychiatrist prescribers

Characteristic	Mean (SD) or percent
N	764
Characteristics of provider's treated patients	
Demographic information	
Share of female patients (%)	49.59 (15.10)
Share of SSI-eligible patients (%)	69.60 (13.94)
Share of non-Hispanic whites (%)	62.80 (27.20)
Share of patients <18 years old (%)	23.41 (31.36)
Share of patients ≥50 years old (%)	18.29 (15.00)
Health status	
Mean number of non-mental comorbidities	1.39 (0.66)
Share of patients with serious mental illnesses (%)	77.72 (16.46)
Health insurance	
Share of patients enrolled in fee-for-service program (%)	22.14 (32.51)
Physician characteristics	
Female	33.25%
Physician age	
<40	15.97%
40–49	28.14%
50–59	33.25%
≥60	22.64%
Attended medical school	
US top 20	8.77%
Ranked ≥21	47.25%
Foreign schools	43.98%
Number of antipsychotic prescriptions (#)	
1st quartile (13-99)	55.82 (23.48)
2nd quartile (100-279)	182.09 (54.92)
3rd quartile (281-742)	483.72 (141.85)
4th quartile (746-8,234)	1,572.72 (1,057.20)
Number of other antipsychotic prescribers in the same	
0	7.59%
1–9	39.92%
≥10	52.49%
Practice in urban only	86.65%

Table 2.1 (Continued)

Characteristic	Mean (SD) or percent
Organizational setting	
Number of affiliated organizations	
1	49.48%
2	28.14%
≥3	22.38%
Any affiliation with a behavioral health organization	38.22%
Organizational affiliation types	
Outpatient only	15.84%
Inpatient only	57.85%
Both inpatient and outpatient	26.31%
Organization size measured by number of providers*	
1st quartile (1-35)	12.20 (8.27)
2nd quartile (36-208)	96.79 (48.62)
3rd quartile (210-464)	314.79 (60.13)
4th quartile (466-3,392)	972.38 (603.61)

* Number of providers includes providers of all disciplines affiliated with a business.

Table 2.2: Features of affiliated organizations of the study sample

Characteristic	Number (percent)
Total number of organizations	539
Number stratified by organization specialty	
Behavioral health	197 (36.55%)
Non-behavioral health	342 (63.45%)
Number stratified by organization type	
Outpatient	196 (36.36%)
Inpatient	343 (63.64%)
Acute care hospitals	222 (41.19%)
Psychiatric hospitals	36 (6.68%)
Nursing homes	81 (15.03%)
Rehabilitation hospitals	4 (0.74%)
Mean number of providers of all disciplines/organization [mean (SD)]*	249.60 (464.55)
Mean number of regular antipsychotic prescribers/organization [mean (SD)]	3.05 (5.11)

* Number of providers includes providers of all disciplines affiliated with a business.

2.3.3 Variation in physicians' antipsychotic prescribing

Variations in unadjusted number of ingredients, share of most preferred ingredient, and HHI across psychiatrists are shown in **Table 2.3.** Psychiatrists prescribed several unique ingredients, an average of 9 in 2011. However, prescribing behavior was relatively concentrated. Psychiatrists wrote 37.8% of prescriptions for their most preferred ingredient, and the mean HHI was 2,603 (maximum value 10,000) -- which equals 3.9 ingredients used equally (each 25.5%), or ≥4 ingredients used but with a limited subset of drugs being predominantly prescribed. Of the 764 psychiatrists, 114 (14.9%) had a HHI higher than 3,333, which suggests that these psychiatrists only prescribed 3 ingredients equally to their patients (each 33.3%), or prescribed more ingredients but relied heavily on only 1 or at most 2 ingredients.

There was substantial variability in all three measures of concentration across psychiatrists, with number of ingredients ranging from 2 to 17, share of most preferred ingredient ranging from 16.4% to 84.7%, and HHI from 1,088 to 7,270. The coefficient of variation was 0.33 both for number of ingredients and for HHI, and 0.29 for share of most preferred ingredient, suggesting moderate to large variability in concentration.[83] There were 12 antipsychotic ingredients on the list of most preferred antipsychotics by psychiatrists, among which quetiapine was preferred by 42.7% of the psychiatrists, followed by risperidone (34.0%) and aripiprazole (17.2%) (see **Figure B.3** for the complete list of psychiatrists' preferred antipsychotics).

Table 2.3: Distributions of number of ingredients, share of most preferred ingredient, and HHI of the study sample

Variable	Number of ingredients	Share of most preferred ingredient (%)	HHI of ingredients
Mean (SD)	9 (3)	37.83 (11.00)	2,603 (847)
5^{th} percentile	4	22.73	1,530
25^{th} percentile	6	29.76	1,991
50^{th} percentile	9	36.06	2,483
75^{th} percentile	11	43.75	3,018
95^{th} percentile	14	58.41	4,073
Range across all providers	2-17	16.38-84.74	1,088-7,270
Ratio of 75^{th} to 25^{th} percentiles	1.83	1.47	1.52
Coefficient of variation	0.33	0.29	0.33

2.3.4 Predictors of the concentration of physicians' antipsychotic prescribing

Characteristics of treated patients

Table 2.4 reports results from the multiple membership linear mixed models. Of the 3 types of factors included in the regressions, several characteristics of the treated patients were associated with psychiatrists' antipsychotic prescribing although the effects were relatively small. After adjusting for physician characteristics and organizational features, psychiatrists with a 1 percent increase in share of SSI-eligible patients were associated with a 0.02 unit increase in number of ingredients ($p<.05$), a 0.16 percent decrease in share of the most preferred antipsychotic ingredient ($p<.01$) and a 13.2 unit decrease in HHI ($p<.01$). Similarly, a 1 percent increase in psychiatrists' share of patients with serious mental illnesses was associated with a 0.02 unit increase in number of ingredients ($p<.01$), a 0.11 percent decrease in share of antipsychotic prescriptions for most preferred ingredient ($p<.01$), and a 9.0 unit decrease in HHI ($p<.01$). Psychiatrists with a 1 percent increase in share of patients <18 years old were associated with a 0.03 unit decrease in number of ingredients, a 0.07 percent increase in most preferred ingredient, and a 8.0 unit increase in HHI (all $p<.01$). Other patient characteristics, including a larger share of older patients ($p<.05$ for share of most preferred ingredient, and $p<.1$ for HHI) and higher share of non-Hispanic whites ($p<.1$ for both share of most preferred ingredient and HHI), were also significantly associated with more diversified prescribing behavior of antipsychotics. We predicted the marginal effects on prescribing concentration by 2 patient-level variables of interest **(Figure 2.1).** By increasing psychiatrist's share of patients with serious mental illnesses from 20% to 100% (using the range observed in our study sample), the degree of concentration of antipsychotics prescribing would decrease significantly in terms of share of most preferred

ingredient (from 43.4% to 34.6%) and HHI (from 3,102 to 2,382). Similar patterns were also found by share of SSI-eligible patients.

Physician characteristics

Of the several physician characteristics examined, only physician sex and prescribing volume were significantly associated with prescribing concentration **(Table 2.4).** Controlling for all other explanatory variables, female psychiatrists prescribed 0.29 fewer antipsychotic ingredients than did male psychiatrists and had a HHI that was 97.5 units higher than that of their male counterparts although both associations were only significant at the $p<.1$ level . Older physicians appeared to be more concentrated in their antipsychotic prescribing behavior, although this association was not statistically significant at the $p = 0.1$ level.

Organizational setting

In regard to the 3 organizational factors included in the regressions, only 1 variable was significantly associated with the degree of concentration for antipsychotic prescribing **(Table 2.4).** Psychiatrists who had any affiliation with behavioral health organizations tended to prescribe 0.8 more unique antipsychotic ingredients compared to those who did not have affiliation with any behavioral health organization although this association was only significant at the $p<.1$ level. Regression results of the 3 outcome variables for all sensitivity analyses were very similar to the main analysis (see **Table B.1-B.3** for results of sensitivity analyses).

2.3.5 Variance attributable to explanatory variables

In total, our explanatory variables accounted for a 45.7% reduction of the total variance for number of ingredients, 21.1% for share of most preferred ingredient, and 28.0% for HHI **(Table**

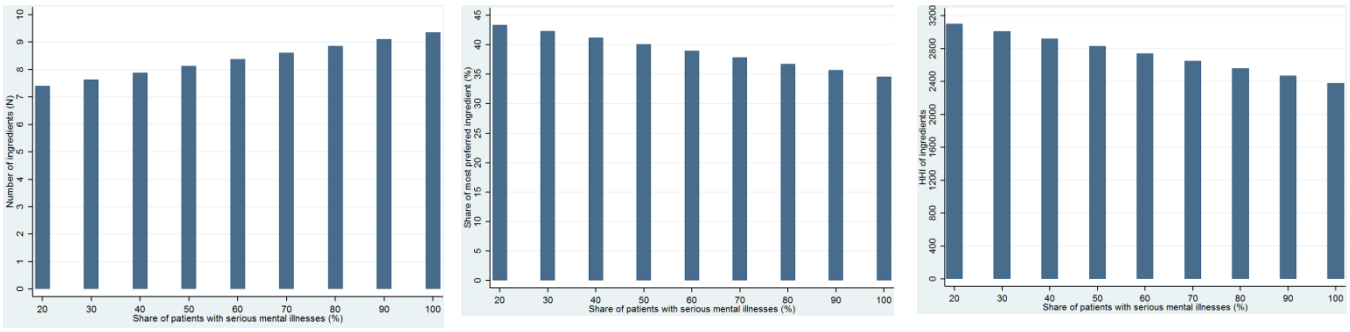
2.4). Adjusting for all explanatory variables, organizational-level influence on unexplained variation in psychiatrists' antipsychotic prescribing was very small (results not shown). This variability obtained from the multiple membership modeling is not constant; rather, it varies across psychiatrists by their weighting schemes.[82] For example, for a psychiatrist who was affiliated with only 1 organization during the study period, organizational-level influence only explained 8% of the variance in number of ingredients, 1.5% in share of most preferred antipsychotic ingredient, and 4% of the unexplained total variance in HHI. The remaining portion of the variation was attributable to physician- and patient-level impacts (which could not be disentangled because analysis unit was at the physician-level).

Table 2.4: Predictors of the concentration of psychiatrist prescribing of antipsychotics and related variance reduction

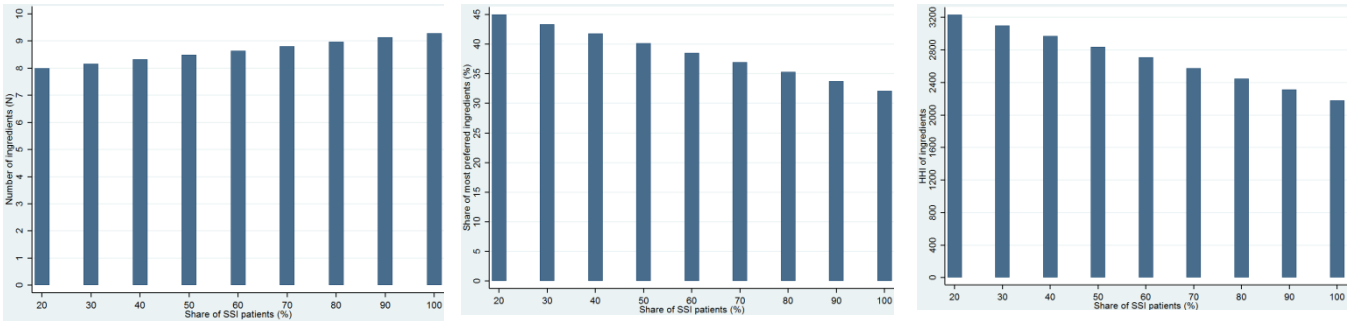
Variables	Coefficients (standard errors)		
	Number of ingredients	Share of most preferred ingredient	HHI of ingredients
Characteristics of provider's treated patients			
Share of female patients (%)	-0.01 (0.01)	0.02 (0.03)	3.80 (2.24)*
Share of SSI-eligible patients (%)	0.02 (0.01)**	-0.16 (0.03)***	-13.15 (2.32)***
Share of non-Hispanic whites (%)	0.00 (0.00)	-0.03 (0.02)*	-2.11 (1.26)*
Share of patients <18 years old (%)	-0.03 (0.00)***	0.07 (0.02)***	8.01 (1.61)***
Share of patients ≥50 years old (%)	0.00 (0.01)	-0.08 (0.04)**	-5.59 (3.03)*
Share of patients with serious mental illnesses	0.02 (0.01)***	-0.11 (0.03)***	-9.00 (2.26)***
Share of patients with 2+ non-mental	0.01 (0.01)	0.06 (0.04)	3.71 (3.08)
Share of patients enrolled in fee-for-services	0.00 (0.00)	0.02 (0.01)	1.79 (1.09)*
Physician characteristics			
Physician sex (ref = male)			
Female	-0.29 (0.18)*	1.23 (0.8)	97.53 (58.88)*
Physician age (ref = <40)			
40–49	0.17 (0.25)	1.05 (1.14)	62.46 (83.84)
50–59	-0.05 (0.25)	1.24 (1.13)	76.55 (82.87)
≥60	0.25 (0.27)	1.92 (1.22)	103.37 (89.74)
Attended medical school (ref = ranked ≥21)			
US top 20	-0.26 (0.30)	1.90 (1.33)	131.32 (97.92)
Foreign schools	0.11 (0.17)	1.41 (0.76)*	62.29 (55.98)
Total number of antipsychotic prescriptions	0.00 (0.00)***	0.00 (0.00)***	-0.22 (0.03)***
Number of other antipsychotic prescribers in the same organizations (ref = 0)			
1–9	0.18 (0.33)	0.06 (1.46)	-66.56 (107.72)
≥10	0.34 (0.34)	1.26 (1.47)	-33.44 (109.88)
Practice location (ref = otherwise)			
Urban only	-0.24 (0.27)	0.78 (1.21)	41.23 (88.81)
Organizational setting			
Organization specialty (ref = otherwise)			
Any affiliation with a behavioral health	0.79 (0.45)*	1.42 (1.96)	46.82 (145.66)
Organizational affiliation type (ref = outpatient only)			
Inpatient only	0.36 (0.49)	2.74 (2.08)	135.78 (155.89)
Both inpatient and outpatient	0.06 (0.28)	1.50 (1.22)	101.45 (90.76)
Organization size	0.00 (0.00)	0.00 (0.00)	0.05 (0.07)
Intercept	5.09 (0.96)***	50.84 (4.24)***	3751.94 (312.75)***
Variance reduction by adding above explanatory variables			
Total variation reduction	45.68%	21.05%	28.02%

*p<.1, **p<.05, ***p<.01.

A. By share of patients with serious mental illnesses



B. By share of SSI-eligible patients



*All measures were adjusted for patient population, physician, and organizational setting covariates listed in the regression.

Figure 2.1: Concentration of antipsychotics prescribing by psychiatrist's share of patients with serious mental illnesses, share of SSI-eligible patients*

2.4 DISCUSSION

Our study provides a comprehensive assessment of how the diversity of psychiatrists' antipsychotic choice is shaped by patient, physician, and organizational characteristics. We found that psychiatrist antipsychotic prescribing behavior was relatively concentrated within physicians in a large state Medicaid program. However, the degree of concentration in antipsychotic prescribing varied substantially across psychiatrists. Of the 3 types of factors examined in our study, several characteristics of the treated patient population and physicians were significantly associated with psychiatrists' diversity vs. concentration of antipsychotic prescribing. The few characteristics of organizations we were able to measure had little influence over psychiatrist prescribing behavior.

Previous studies have suggested that physicians rely heavily on preferred medications in multiple therapeutic classes.[52,54] Three studies have examined physician antipsychotic prescribing previously; all used the IMS Health's Xponent™ database which has comprehensive information on physician prescribing but limited patient information. Taub and colleagues[65] found antipsychotic prescribing was quite concentrated for physicians who wrote ≥12 antipsychotic prescription – with a mean HHI of 4,612 for primary care providers and of 3,245 for psychiatrists in 2007. Donohue and colleagues,[55] using 2002-2007 data for physicians with ≥20 antipsychotic prescriptions per year, found the concentration of antipsychotic prescribing at the physician level decreased over time and reached a mean of 2,900 in 2007. Berndt and colleagues also found a mean HHI of 2,900 for physicians with ≥50 antipsychotic prescriptions in 2007.[92] Using Medicaid data from a more recent time period (2011), measuring concentration

in three ways, and adjusting for a comprehensive set of factors, our study also finds that antipsychotic prescribing was relatively concentrated and varied substantially across psychiatrists. By focusing on psychiatrists with at least 10 antipsychotic users in the year, we were able to evaluate the degree of concentration for those who were regular antipsychotic prescribers and accounted for most of the antipsychotic prescriptions by psychiatrists.

Our finding that there was substantial variability in the degree of concentration in antipsychotic prescribing across psychiatrists suggests that patients seeing psychiatrists who only prescribe a limited number of antipsychotics may have a very different treatment experience than do patients whose doctors prescribe a wide range of antipsychotic products. Antipsychotics have been approved to treat several serious mental disorders (such as schizophrenia and major depressive disorder), which usually need multiple trials before finding the "best drug" for a particular patient. For instance, the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) found that 74 percent of patients with schizophrenia failed the first trial,[93] indicating that the majority of patients with schizophrenia would need at least 2 trials and that patients with treatment-resistant schizophrenia would need more.[94] Psychiatrists' willingness to use a wide range of choices may potentially lead to better health outcomes through customizing prescribing choices to individual patients.[52,53] Our finding that a sizable psychiatrists (15%) treating Medicaid enrollees with antipsychotics had very concentrated prescribing behavior (e.g., relied heavily on only one or two antipsychotic agents) indicates that some psychiatrists may be limited in their ability to tailor treatment to individual patient needs and preferences.

To our knowledge, this study is the first to examine the concentration of antipsychotic prescribing with all three levels of information on physicians: characteristics of the physicians, their treated patients and practice settings. Previous research found that patient clinical factors

played trivial role in medication switches.[54] Our study found a significant relationship between patients' characteristics and the diversity of physicians' prescribing of antipsychotics although effects were relatively small. Psychiatrists had more diversified prescribing using all three measures of concentration if they had a higher share of patient population with a disability or with more severe mental illnesses. Of the several physician characteristics examined, female psychiatrists tended to have slightly more concentrated prescribing behavior than their male counterparts although the association was only marginally significant. Our organization-level factors were only limited to organization type, specialty, and size. Psychiatrists who had any affiliation with a behavioral health organization (clinic or psychiatric hospital) were associated with prescribing more unique ingredients than those not affiliated with behavioral health organizations although it was only marginally significant. We did not have information on other organizational factors such as quality improvement initiatives, financial incentives, and guideline dissemination which may also play an important role The fact that the explanatory variables included in the regressions accounted for a moderate reduction of the total variance for the 3 outcome measures (28.0%-45.7%) implies that some other factors not included in our analyses also influence physicians' antipsychotic prescribing behavior.

This study has several limitations. First, our study examined prescribing behavior in the Pennsylvania Medicaid program and thus our findings may not necessarily be generalizable to other states. Second, the HCOS™ database captures every healthcare organization and provider that is part of a health system, but it seldom includes small practices with only 1-2 providers. Third, although we adjusted for 3 types of factors likely to affect prescribing, we had a limited number of organization-level characteristics. In addition, we could not adjust for other important factors, such as physician belief and pharmaceutical manufacturer promotion on specific

antipsychotic drugs, which might also shape physician prescribing behavior.[55,95] Furthermore, we were unable to measure the severity of illness using the administrative data so we included information such as disability and comorbidity status. Finally, approximately 23% of our patient sample was <18. Psychiatrists prescribing primarily to children may be more concentrated in their prescribing because fewer antipsychotics are approved for use in children. However, given that two thirds of psychiatrists in our sample treated both adults and children we addressed this issue by including a variable for the share of patients <18 in all the regressions. This variable had very small effect on prescribing concentration.

Using the multiple membership modeling approach –a new method that has been rarely applied in health services research -- to capture the real-life data structure, we found that antipsychotic prescribing behavior by individual psychiatrists in a large state Medicaid program was relatively concentrated but it varied substantially across psychiatrists. Health systems may consider exploring strategies for educating providers or guiding patients to providers with greater ability to tailor treatment decisions.

3.0 PRESCRIBING OF CLOZAPINE AND ANTIPSYCHOTIC POLYPHARMACY FOR SCHIZOPHRENIA IN A LARGE MEDICAID PROGRAM

Yan Tang, Marcela Horvitz-Lennon, Walid F. Gellad, Judith R. Lave, Sharon-Lise T. Normand, Julie M. Donohue

ABSTRACT

Objectives: Poor response to antipsychotic treatment for schizophrenia may be due in part to poor quality prescribing. In particular, there is underuse of clozapine, the only antipsychotic approved for treatment-resistant schizophrenia, and overuse of non-clozapine antipsychotic polypharmacy, a non-evidence based treatment that may result in undesirable consequences including symptom persistence/deterioration, hospitalization and unnecessary healthcare costs. Non-clozapine antipsychotic polypharmacy (hereafter, antipsychotic polypharmacy) may in fact be used by some providers as a substitute for clozapine in the management of treatment-resistant schizophrenia. However, few studies of these prescribing practices have been conducted at the provider-level. We evaluated the prevalence of and relationship between clozapine and antipsychotic polypharmacy prescribing at the provider-level in a large Medicaid program. We also examined patient- and provider-level factors associated with these prescribing practices.

Methods: Using 2010-2012 data from Pennsylvania's Medicaid we identified providers regularly prescribing antipsychotics to patients with schizophrenia (defined as 10 or more nonelderly Medicaid patients without Medicare coverage). We characterized providers' patients

and payers (managed care vs. fee-for-service) using Medicaid data, and providers' demographics using the National Provider Identifier file from the Centers for Medicare and Medicaid Services. We measured provider-level share of patients with clozapine use and antipsychotic polypharmacy use per year. Antipsychotic polypharmacy was defined as more than 90 days' concurrent use of ≥2 non-clozapine antipsychotics, allowing for gaps of up to 32 days in days' supply for the same medication. We used descriptive analyses and generalized estimating equations with a binomial distribution and a logit link to examine clozapine and antipsychotic polypharmacy practices and associated factors at the level of patients (e.g., demographics, comorbidities, fee-for-service vs. managed care plans) and providers (e.g., high vs. low prescribing volume, sex, specialty). We included year indicators to adjust for time effects.

Results: The analytic cohort included 645 prescribers in 2010, 632 in 2011, and 650 in 2012. Provider-level clozapine and antipsychotic polypharmacy practices were relatively stable over time. In 2012, provider-level mean shares of patients with clozapine and antipsychotic polypharmacy use were 6.9% (range: 0%-88.9%) and 7.0% (range: 0%-45.2%), respectively. A sizable proportion of providers prescribed antipsychotic polypharmacy but not clozapine in each study year (e.g., 15.5% in 2012). Clozapine and antipsychotic polypharmacy prescribing were not inversely correlated at the provider-level. High volume prescribers were much more likely to prescribe both clozapine (OR = 1.43, 95% CI, 1.22-1.67, $p<0.01$) and antipsychotic polypharmacy (OR = 2.65, 95% CI, 2.29-3.05, $p<0.01$) than low volume prescribers. Primary care providers, who made up 5.7% of our sample in 2012, were substantially less likely than psychiatrists to prescribe clozapine (OR = 0.55, 95% CI, 0.36-0.84, $p<0.01$) but just as likely to antipsychotic polypharmacy. We found significant associations between several patient-level characteristics and these prescribing practices.

Conclusions: Antipsychotic polypharmacy is used as much as clozapine in the care of Medicaid beneficiaries with schizophrenia, but many prescribers only use the former; prescribing volume, provider specialty, certain patient characteristics and predominant managed care plan appear to influence prescribing practices. Clinical and policy initiatives are needed to improve providers' knowledge of clozapine and increase its use while decreasing use of antipsychotic polypharmacy. Our results suggest that targeting these initiatives to antipsychotic prescribers who use more antipsychotic polypharmacy than clozapine holds particular promise.

Key words: clozapine, antipsychotic polypharmacy, prescribing, schizophrenia, Medicaid

3.1 INTRODUCTION

Schizophrenia is a serious and chronic mental disorder associated with a heavy burden on the patient and the society.[96] Antipsychotics -- a central component for the treatment of schizophrenia -- are mainly financed by Medicare and state Medicaid programs. The widespread substitution of second-generation for first-generation antipsychotics resulted in substantial growth in expenditures for antipsychotics in the 1990s.[59] According to IMS Health's analysis, $16.1 billion was spent on antipsychotic drugs in 2010, making them one of the top 5 therapeutic classes based on total spending.[97]

The growing use of second-generation antipsychotics (SGAs) has raised concerns about the quality of care. Although SGAs were perceived to be more effective with fewer adverse effects than first-generation antipsychotics (FGAs), large clinical trials including the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) found that (1) SGAs are associated with undesirable risks and (2) non-clozapine SGAs are no more effective than their first-generation counterparts.[93,98,99] Evidence also suggests high rates of failure on the first trial of antipsychotics among patients with schizophrenia. For example, CATIE found that 74 percent of patients failed the first trial,[93] indicating that the majority of patients with schizophrenia would need at least 2 trials and that patients with treatment-resistant schizophrenia would need more.[94] The prevalence of treatment-resistant schizophrenia is approximately 30%,[100] with resistance rates of up to 60% if using broader definitions to characterize patients with schizophrenia who do not respond to adequate trials of antipsychotics.[101,102] Providers may turn to higher risk therapies for treatment-resistant schizophrenia. Because clozapine has superior efficacy than other antipsychotic drugs based on results from randomized controlled trials and meta analyses,[104-108]

clinical guidelines recommend clozapine for treatment-resistant schizophrenia and recurrent suicidal behavior.[94,103] Nevertheless, physicians are reported to be reluctant to use clozapine.[109,110] However, despite a lack of supporting evidence and high cost,[111] there is a widespread practice of non-clozapine antipsychotic polypharmacy.[112,113] Previous studies found patient-level prevalence of antipsychotic polypharmacy ranging from 7%-50%,[114,115] depending on definition of antipsychotic polypharmacy. Non-clozapine antipsychotic polypharmacy (hereafter, antipsychotic polypharmacy) has been used as a substitute for clozapine for the management of treatment-resistant schizophrenia.[116] Underuse of clozapine which is evidence-based practice and overuse of antipsychotic polypharmacy which is an unsupported practice may result in undesirable consequences such as side effects, medication non-adherence, hospitalization, and unnecessary health care costs.[116,117]

Quality improvement and cost control in schizophrenia care and antipsychotic prescribing is largely dependent on the ability to alter providers' prescribing behavior. However, little is known about prescriber-level prevalence of either evidence-based or unsupported antipsychotic prescribing practices. Little is also known about which factors are associated with those practices. To shed light on these issues, we examined providers' use of clozapine and antipsychotic polypharmacy in Pennsylvania Medicaid from 2010-2012. In particular, we evaluated the prevalence of and relationship between clozapine and antipsychotic polypharmacy prescribing. We hypothesized that prescribing of clozapine and antipsychotic polypharmacy might be inversely correlated at the provider-level; that providers with little or no use of clozapine might have higher rates of antipsychotic polypharmacy and vice versa. We also examined patient- and provider-level factors associated with these prescribing practices.

3.2 METHODS

3.2.1 Data sources

We obtained data from the Pennsylvania's Department of Public Welfare (DPW) for all beneficiaries enrolled in Pennsylvania's Medicaid program for calendar years 2010 to 2012. In each year, approximately 2.2 million individuals were enrolled either in the fee-for-service (FFS) or in managed care programs. The pharmacy claims file has information for each prescription claim including date of fill, days' supply, medication dose, quantity, form, the National Drug Code (NDC), and prescribing provider Medicaid identifier. We obtained antipsychotics' information on drug name, active ingredient, dose for each NDC from the Medi-Span® database.[70] We used the medical claims files (e.g., inpatient, outpatient, professional) to identify diagnoses associated with inpatient or outpatient facility claims or provider visits. We used the enrollment file to capture beneficiary's demographic and enrollment information such as age, sex, race/ethnicity, eligibility type, dual eligible status, enrolled health insurance plan (individual managed care plans vs. FFS). We obtained prescribing provider's National Provider Identifier (NPI), name, and ZIP code for practice settings from the provider file from DPW.

Using the NPI, we linked prescribing providers in Pennsylvania's Medicaid data to the National Plan and Provider Enumeration System's (NPPES) National Provider Identifier (NPI) file from the Centers for Medicare and Medicaid Services (CMS) to obtain each provider's sex and specialty.[118]

3.2.2 Study sample

The unit of analysis was at the provider-level; however, we started with a sample of claims at the patient-level from which we identified antipsychotic prescribers treating these patients. First, we limited Medicaid beneficiaries to nonelderly adults (18-64 years old) who were not dually eligible for Medicare. We excluded dual eligible beneficiaries because Medicaid data do not contain complete claims information for those enrollees, particularly for prescription drugs. Using inpatient, outpatient, and professional claims files, we then identified patients with ≥1 inpatient or ≥2 outpatient claims with a primary or secondary diagnosis of schizophrenia (ICD-9 codes: 295.xx) during a one-year period. We further restricted the sample to those with at least one prescription fill of antipsychotic drugs that year. We then identified all provider IDs associated with this patient sample. Finally, we limited our analyses to individual providers (both psychiatrists and non-psychiatrist providers) regularly prescribing antipsychotics, defined as having at least 10 patients with a diagnosis of schizophrenia per year. We did not restrict the study sample to psychiatrists because non-psychiatrist providers (primary care providers and other) included in this analysis were regular prescribers who treated at least 10 patients with schizophrenia and prescribed a lot of antipsychotic prescriptions (mean number of annual prescriptions by primary care providers was about 100 in 2012). By including both psychiatrist and non-psychiatrist prescribers in this study, we expected to reflect the typical prescribing practices for antipsychotic drugs in the treatment of schizophrenia.

3.2.3 Dependent variables

The two dependent variables calculated at the prescriber-level were the share of patients with any clozapine use and the share of patients with antipsychotic polypharmacy in a calendar year. Antipsychotic polypharmacy was defined as more than 90 days' concurrent use of ≥2 non-clozapine antipsychotics, allowing for gaps of up to 32 days in days' supply for the same medication. Oral and depot formulations for the same drug were considered to be same medication. This definition of antipsychotic polypharmacy is a validated measure with excellent specificity and positive predictive value, compared to alternative measures of antipsychotic polypharmacy (e.g., 14, 60, or 90 days concurrent use, allowing gaps of up to 0, 14, or 32 days).[114] Based on recommended dosing intervals, we imputed days supply for long-acting injectable antipsychotic drugs as follows: risperidione injectable (Risperdal Consta) – 14 days, fluphenazine decanoate (Prolixin decanoate) – 21 days, and haloperidol decanoate (Haldol decanoate) – 28 days.

3.2.4 Explanatory variables

We examined the association between patient characteristics, payer (individual managed care plans vs. FFS), and provider characteristics and prescribing of clozapine and antipsychotic polypharmacy. Patient characteristics were first assessed at the patient-level and then aggregated to the provider-level. For example, for each antipsychotic prescriber we calculated the share of his or her patients in certain demographic and racial/ethnic groups (share that were female, share that were Hispanic, and share that were non-Hispanic black). We included a variable for the mean age of the provider's patients. We included a measure of the share of patients eligible for

Medicaid through Supplemental Security Income (SSI) to measure disability status. To adjust for patients' comorbidities and health status, we calculated each provider's share of patients with affective disorders (ICD-9 codes: 296.xx, 300.4, 301.13, 309.1, 311), share with anxiety disorders (ICD-9 codes: 300.0, 309.81, 300.2, 300.3), share with other psychiatric disorders (ICD-9 codes: 307.1, 307.50, 307.51, 314), share with substance use disorders (ICD-9 codes: 291, 292, 303, 304, 305.0, 305.2-305.7, 305.9), share with brain/cognitive impairment comorbidity (ICD-9 codes: 331, 797, 290, 294, 310, 317-319), and share with a schizophrenia-related hospitalization. To capture the patient population's non-mental health comorbidities, first, for each patient we constructed separate indicators of the 25 non-mental illnesses incorporated in the Elixhauser comorbidity index (a widely used comorbidity measure)[79-81] based on patient's medical claims. We then created a variable for the mean number of non-mental health comorbidities of the provider's patients, which had a mean of 2 at the provider-level.

Pennsylvania Medicaid runs a fee-for-service program for approximately 25%-30% of enrollees and contracts with multiple managed care organizations and managed behavioral health organizations to manage care for the remaining 70%-75%. Managed care organizations may adopt different policies with respect to coverage and utilization management tools applied to antipsychotics. We constructed two measures to capture the influence on a provider's prescribing behavior of these different policies. The first measure was the number of unique managed care organizations in which the provider's patient population was enrolled. The second measure was a series of dummy variables indicating the managed care organization with the highest enrollment among the provider's patient population with the fee-for-service serving as the reference category.

To estimate the association between provider characteristics and our prescribing outcomes we included provider's prescribing volume, sex, specialty (psychiatrist, primary care provider, other), and practice location (urban only vs. otherwise).[66,67,74] We defined prescribing volume as the number of antipsychotic prescriptions written for patients with schizophrenia per year. We classified prescribing volume into two groups: low vs. high prescription volume (split by the median value). In addition, we included year indicators to control for potential time trend.

3.2.5 Statistical analysis

For each year we reported provider-level prevalence of clozapine prescribing and antipsychotic polypharmacy prescribing, overall and stratified by prescription volume and specialty. To examine the association between clozapine and antipsychotic polypharmacy practices at the prescriber level, we created scatter plots of the two outcome variables as well as the Lowess smoothed curve of the two outcomes, which is a robust nonparametric method using localized subsets of the data to describe underlying relationship between variables.[119] A Spearman's rank correlation coefficient (rho) was calculated to examine the correlation between the two outcome variables.

To account for repeated measures made for the same antipsychotic prescriber over the 3-year study period, we used generalized estimating equations (GEE) with robust estimation of standard errors and an unstructured correlation matrix to examine provider's clozapine and antipsychotic polypharmacy practices. We used a binomial distribution with a logit link to handle the two percentage variables which had a skewed distribution and many providers with zero values. This strategy has been applied widely in economic and health services research where outcomes are a continuous percentage.[120-122] We also calculated marginal effects for provider's

antipsychotic prescribing volume which was found to be significantly associated with the outcomes of interest, adjusting for all other explanatory variables.

We performed sensitivity analyses with alternative specifications. First, we restricted the study sample to a subset cohort who appeared in all 3 years (i.e., balanced data). Second, we conducted an analysis restricting the sample to psychiatrists – the main prescribers of antipsychotic drugs in the U.S. Third, we considered a sensitivity analysis by including a categorical variable indicating the provider's practice county (Philadelphia, Allegheny, other) because about half of the providers practiced in Philadelphia and Allegheny counties – the top 2 most populous counties in Pennsylvania. In addition, to examine the impact of case mix with respect to treatment-resistant schizophrenia which we could not observe in claims data, we described variations in clozapine and antipsychotic polypharmacy prescribing stratified by share of patients with schizophrenia-related hospitalization, which we used as a proxy for treatment-resistant schizophrenia.

3.3 RESULTS

In our study sample, there were 645 antipsychotic prescribers treating 14,072 patients with schizophrenia in 2010, 632 prescribers treating 13,606 patients in 2011, and 650 prescribers treating 13,559 patients in 2012 in Pennsylvania Medicaid program. Of the 892 unique providers prescribing antipsychotics in our study sample, 426 (47.8%) appeared in all 3 years. The characteristics of sample providers and their patients were very similar across the three year period so we present only the most recent year's characteristics in **Table 3.1.** In 2012, the mean share of patients with schizophrenia-related hospitalization was 43.3%. The mean number of

managed care organizations in which a provider's schizophrenia patients were enrolled was 4.5, and the mean share of patients enrolled in the fee-for-service program was 17.5%. Of the 650 antipsychotic prescribers in 2012, 32% were female providers, and the majority (83.5%) were psychiatrists.

Table 3.1: Characteristics of antipsychotic prescribers, 2012

Characteristic	Mean (SD) or percent
N	650
Characteristics of provider's treated patients	
Demographic information	
Share of female patients (%)	44.51 (13.53)
Share of SSI-eligible patients (%)	91.75 (8.75)
Share of Hispanic patients (%)	9.12 (15.92)
Share of non-Hispanic black patients (%)	37.08 (28.61)
Mean age of patients	42.17 (5.12)
Health status and hospitalization	
Share of patients with affective disorders (%)	66.14 (19.27)
Share of patients with anxiety disorders (%)	32.46 (16.46)
Share of patients with other psychiatric disorders (%)	4.80 (6.31)
Share of patients with substance use disorders (%)	39.31 (22.64)
Share of patients with brain impairment comorbidity (%)	10.85 (10.46)
Mean number of non-mental health comorbidities	2.09 (0.71)
Share of patients with schizophrenia-related hospitalization (%)	43.26 (23.57)
Health insurance	
Number of plans for treated patients*	4.48 (1.89)
Share of patients enrolled in FFS other than MCOs (%)	17.54 (30.21)
Provider characteristics	
Number of antipsychotic prescriptions	230.58 (266.53)
Female	32.00%
Specialty	
Psychiatrist	83.54%
Primary care provider	5.69%
Other	10.77%
Practice in urban only	93.69%

*Number of plans counted unique plans across all patients treated by the provider (i.e., FFS or each managed care plan was counted as 1 plan).

Table 3.2(A) displays the provider-level clozapine and antipsychotic polypharmacy practices from 2010-2012, which were relatively stable over time. In 2012, 60.2% of antipsychotic prescribers had any clozapine prescribing and 57.9% had any antipsychotic polypharmacy. Notably, among high volume providers 90.8% of antipsychotic prescribers used polypharmacy for at least one patient while only 77.4% used clozapine in 2012. At the provider-level, the mean share of patients with clozapine use was 6.9%, with a range across providers from 0.0% to 88.9%. The mean share of patients with antipsychotic polypharmacy was 7.0% in 2012 which varied across provider from 0.0% to 45.2%. Both the share of patients with clozapine use and share with antipsychotic polypharmacy use were much lower among low volume providers than among their high volume counterparts. **Table 3.2(B)** shows the two practices by specialty. In 2012, the prevalence of any clozapine prescribing was 63.0% among psychiatrists versus 29.7% among primary care providers. In contrast, the difference in any antipsychotic polypharmacy was relatively smaller (58.8% for psychiatrists vs. 51.4% for primary care providers in 2012). Primary care providers had higher share of patients with antipsychotic polypharmacy than that for clozapine while psychiatrists had similar shares for the two practices. As shown in **Table C.1**, we also examined variation in clozapine and antipsychotic polypharmacy prescribing by quartiles of schizophrenia-related hospitalization among provider's patient population -- proxy for treatment-resistant schizophrenia. We did not find a positive correlation between schizophrenia severity and clozapine and antipsychotic polypharmacy practices. In fact, providers in the highest quartile were much less likely to use antipsychotic polypharmacy than their counterparts in lower quartiles.

Table 3.2: Provider clozapine and antipsychotic polypharmacy practices, 2010-2012

A. By antipsychotic prescribing volume*

Year	N providers	N antipsychotic prescriptions†	Any clozapine prescribing (%)	Any polypharmacy prescribing (%)	Share of patients w/ clozapine use (%)†	Share of patients w/ polypharmacy use (%)†
			Overall			
2010	645	213.33 (246.79)	56.12	56.43	5.88 (9.13)	5.85 (7.51)
2011	632	229.46 (271.90)	59.97	59.49	6.94 (10.4)	6.91 (8.56)
2012	650	230.58 (266.53)	60.15	57.85	6.85 (9.72)	7.01 (8.60)
			Low volume prescribers			
2010	322	65.28 (30.83)	37.58	28.26	3.37 (6.19)	2.78 (5.49)
2011	315	62.90 (33.98)	45.08	28.57	4.77 (7.59)	2.77 (5.27)
2012	323	62.87 (34.69)	42.72	24.46	4.64 (8.15)	2.51 (5.26)
			High volume prescribers			
2010	323	360.93 (277.66)	74.61	84.52	8.37 (10.77)	8.91 (8.00)
2011	317	394.96 (302.25)	74.76	90.22	9.09 (12.18)	11.03 (9.19)
2012	327	396.24 (291.27)	77.37	90.83	9.04 (10.63)	11.46 (8.95)

*We defined prescribing volume as the number of antipsychotic prescriptions written for provider's patient population with schizophrenia. We classified prescribing volume into two groups: low vs. high prescription volume group, split by the median value.
†Figures within parentheses are means and SDs.

B. By provider specialty*

Year	N providers	N antipsychotic prescriptions*	Any clozapine prescribing (%)	Any polypharmacy prescribing (%)	Share of patients w/ clozapine use (%)*	Share of patients w/ polypharmacy use (%)*
			Psychiatrists			
2010	515	232.16 (267.34)	61.36	58.83	6.37 (9.19)	6.14 (7.60)
2011	526	249.41 (288.50)	62.55	61.22	7.17 (10.56)	7.17 (8.72)
2012	543	245.76 (282.28)	62.98	58.75	7.15 (9.97)	7.13 (8.56)
			Primary care providers			
2010	86	122.88 (97.52)	30.23	40.70	2.58 (5.50)	3.98 (6.18)
2011	41	80.98 (68.28)	36.59	36.59	3.18 (5.21)	3.47 (5.78)
2012	37	98.59 (101.72)	29.73	51.35	2.06 (3.61)	5.78 (7.67)
			Other			
2010	44	169.80 (128.51)	45.45	59.09	6.59 (12.37)	6.13 (8.44)
2011	65	161.63 (145.51)	53.85	60.00	7.39 (10.98)	7.02 (8.31)
2012	70	182.57 (152.88)	54.29	54.29	7.08 (9.42)	6.77 (9.43)

*Figures within parentheses are means and SDs.

We did not find evidence of inverse correlations between the share of patients with clozapine prescribing and the share of patients with antipsychotic polypharmacy at the provider-level **(Figure 3.1).** Instead, the two outcome variables had a non-linear correlation based on the Lowess smoothed curve and had a correlation of 0.31 in 2012 according to Spearman's rho coefficient. Notably, there was a sizable portion of providers who practiced antipsychotic polypharmacy but did not use any clozapine during the study period **(Table 3.3).** For example, of the 650 providers in 2012, 101 (15.5%) used zero clozapine but prescribed polypharmacy for at least one patient (mean share of patients with polypharmacy use among these providers was 11.6%), and 46 (7.1%) providers (without any clozapine use) had at least 10% of their patients on polypharmacy (mean share of patients with polypharmacy was 18.5%).

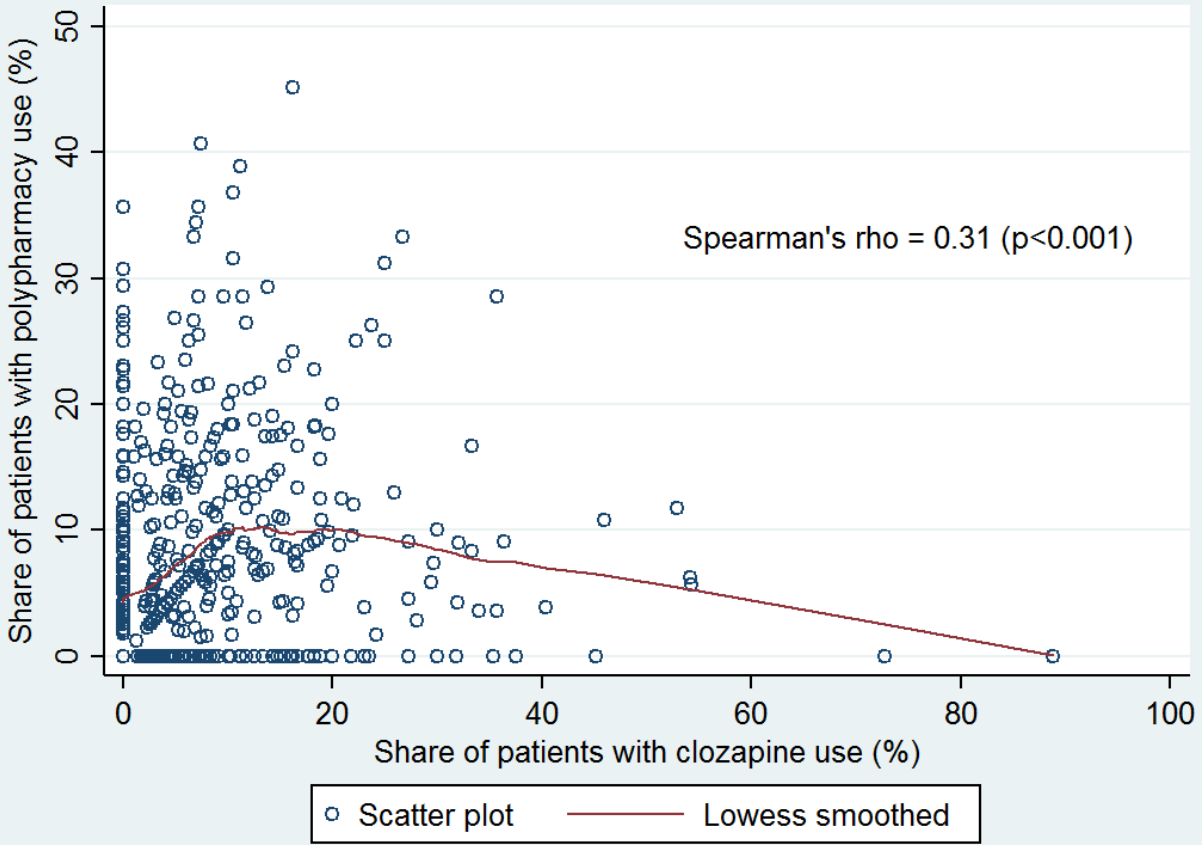


Figure 3.1: Association between clozapine and antipsychotic polypharmacy practices by antipsychotic prescribers, 2012

Table 3.3: Antipsychotic polypharmacy prescribing among providers with no clozapine use, 2010-2012*

Year	Total N providers	No clozapine prescribing			
		Any patient w/ polypharmacy use		≥10% of patients w/polypharmacy use	
		N providers (percent)	Share of patients with polypharmacy use (%)†	N providers (percent)	Share of patients with polypharmacy use (%)†
		Overall			
2010	645	116 (17.98%)	10.44 (7.21)	45 (6.98%)	17.21 (7.16)
2011	632	124 (19.62%)	11.11 (8.04)	56 (8.86%)	17.82 (7.40)
2012	650	101 (15.54%)	11.63 (7.94)	46 (7.08%)	18.46 (6.76)
		Low volume prescribers			
2010	322	55 (17.08%)	10.03 (6.32)	20 (6.21%)	16.01 (6.95)
2011	315	52 (16.51%)	10.17 (5.41)	23 (7.30%)	15.04 (4.34)
2012	323	39 (12.07%)	11.07 (6.32)	18 (5.57%)	16.41 (5.30)
		High volume prescribers			
2010	323	61 (18.89%)	10.81 (7.95)	25 (7.74%)	18.18 (7.31)
2011	317	72 (22.71%)	11.78 (9.49)	33 (10.41%)	19.76 (8.46)
2012	327	62 (18.96%)	11.98 (8.83)	28 (8.56%)	19.78 (7.34)

* We defined prescribing volume as the number of antipsychotic prescriptions written for provider's patient population with schizophrenia. We classified prescribing volume into two groups: low vs. high prescription volume group, split by the median value.
†Figures within parentheses are means and SDs.

Table 3.4 shows the regression results from the GEE models. Controlling for all other factors, when seeing a patient with schizophrenia, antipsychotic prescribers with a larger share of Hispanic patients were less likely to prescribe clozapine [odds ratio (OR) per 10% increase = 0.81, 95% confidence interval (CI), 0.75-0.88, $p<0.01$] and antipsychotic polypharmacy (OR per 10% increase = 0.89, 95% CI, 0.84-0.95, $p<0.01$) than those with a smaller share of Hispanic patients. Similar effects were found for providers with different shares of non-Hispanic black patients. Prescribers who had a larger share of patients with schizophrenia-related hospitalization had greater odds of clozapine prescribing (OR per 10% increase = 1.10, 95% CI, 1.04-1.15, $p<0.01$) and lower odds of antipsychotic polypharmacy prescribing (OR per 10% increase = 0.91, 95% CI, 0.88-0.95, $p<0.01$) to their patients than prescribers with a smaller share of patients who had a schizophrenia-related hospitalization.

There was significant variation in antipsychotic prescribing across providers based on their patients' predominant plan – 2 managed care plans were significantly different from FFS in clozapine prescribing while 5 managed care plans deviated from FFS in antipsychotic polypharmacy prescribing **(Table 3.4).** For example, prescribers with MCO plan I as the predominant plan were much more likely to prescribe clozapine when seeing a patient with schizophrenia than prescribers with FFS as the most popular plan (OR = 1.68, 95% CI, 1.00-2.80, $p<0.05$). Prescribers with MCO plan A as the predominant plan were more likely to prescribe antipsychotic polypharmacy than their counterparts with FFS (OR = 1.58, 95% CI, 1.28-1.94, $p<0.01$).

After adjustment for characteristics of treated patients and other covariates, primary care providers, who made up 5.7% of our sample in 2012, were substantially less likely than psychiatrists to prescribe clozapine to their patients (OR = 0.55, 95% CI, 0.36-0.84, $p<0.01$).

Provider specialty was not significantly associated with the prescribing of antipsychotic polypharmacy. Controlling for all other covariates, high volume prescribers were much more likely to prescribe clozapine (OR = 1.43, 95% CI, 1.22-1.67, $p<0.01$) and antipsychotic polypharmacy (OR = 2.65, 95% CI, 2.29-3.05, $p<0.01$) than their low volume counterparts. As shown in **Figure 3.2,** the predicted share of patients with clozapine use would be 4.1% for low volume prescribers and 5.8% for high volume prescribers. The predicted share of patients with antipsychotic polypharmacy would vary from 2.8% for low volume prescribers to 7.2% for their high volume counterparts. Sensitivity analyses reported very similar results as the main analysis **(Table C.2-C.4).**

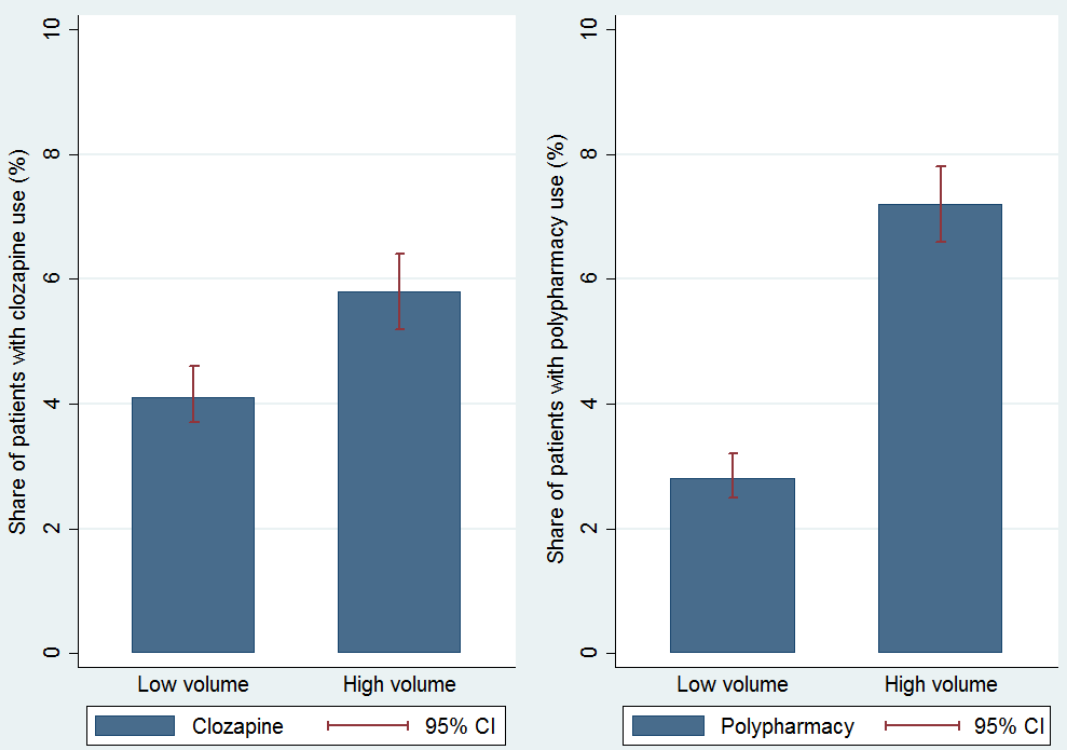
Table 3.4: GEE regression results for all antipsychotic prescribers: predictors of clozapine and antipsychotic polypharmacy prescribing

Variables	Odds Ratios (robust standard error)	
	Clozapine prescribing	**Antipsychotic polypharmacy prescribing**
Characteristics of provider's treated patients		
Demographic information		
Share of female patients (%)	1.00 (0.00)	1.00 (0.00)
Share of SSI-eligible patients (%)	1.02 (0.00)***	1.02 (0.00)***
Share of Hispanic patients (%)	0.98 (0.00)***	0.99 (0.00)***
Share of non-Hispanic black patients (%)	0.99 (0.00)***	1.00 (0.00)*
Mean age of patients	0.98 (0.01)**	0.99 (0.01)
Health status and hospitalization		
Share of patients with affective disorders (%)	0.98 (0.00)***	1.00 (0.00)
Share of patients with anxiety disorders (%)	0.99 (0.00)**	0.99 (0.00)***
Share of patients with other psychiatric disorders (%)	1.00 (0.01)	1.01 (0.01)*
Share of patients with substance use disorders (%)	0.99 (0.00)***	0.99 (0.00)***
Share of patients with brain impairment comorbidity (%)	1.00 (0.00)	1.01 (0.00)*
Mean number of non-mental health comorbidities	1.15 (0.07)**	1.11 (0.06)*
Share of patients with schizophrenia-related hospitalization (%)	1.01 (0.00)***	0.99 (0.00)***
Health insurance		
Number of plans for treated patients	1.04 (0.02)*	0.96 (0.02)**
The predominant plan among patient population (ref = FFS)		
MCO plan A	0.99 (0.15)	1.58 (0.17)***
MCO plan B	0.87 (0.16)	1.46 (0.46)
MCO plan C	1.21 (0.17)	1.38 (0.14)***
MCO plan D	2.30 (0.80)**	1.12 (0.49)
MCO plan E	0.94 (0.17)	0.75 (0.12)*
MCO plan F	1.45 (0.49)	1.11 (0.31)
MCO plan G	1.18 (0.19)	0.85 (0.11)
MCO plan H	1.19 (0.21)	1.54 (0.19)***
MCO plan I	1.68 (0.44)**	1.46 (0.24)**
MCO plan J (combined)†	1.28 (0.30)	0.8 (0.33)
Provider characteristics		
High prescription volume (ref = low prescription volume)	1.43 (0.11)***	2.65 (0.19)***
Female (ref = male)	1.07 (0.12)	1.01 (0.07)

Table 3.4 (Continued)

Variables	Odds Ratios (robust standard error)	
	Clozapine prescribing	**Antipsychotic polypharmacy prescribing**
Specialty (ref = psychiatrist)		
Primary care provider	0.55 (0.12)***	1.11 (0.20)
Other	1.01 (0.17)	0.85 (0.11)
Practice in urban only (ref=otherwise)	1.00 (0.19)	0.96 (0.13)
Year (ref = 2010)		
2011	1.02 (0.05)	1.15 (0.06)***
2012	0.98 (0.07)	1.12 (0.06)**
Intercept	0.06 (0.03)***	0.04 (0.02)***
N obs	*1,927*	*1,927*
N groups	*892*	*892*

*p<.1, **p<.05, ***p<.01.
†MCO plan J combined plans with only 1-3 observations in a year.



* All covariates included in the regression models were adjusted for the marginal effects calculation.

Figure 3.2: Marginal effects of antipsychotic prescribing volume on providers' clozapine and polypharmacy practices*

3.4 DISCUSSION

To our knowledge, this study is the first to assess provider-level clozapine and antipsychotic polypharmacy practices, using multiple years of managed care and fee-for-service program data from a large state Medicaid program. We found that providers who regularly prescribed antipsychotics to patients with schizophrenia used clozapine or antipsychotic polypharmacy in a small proportion of their patients. However, these prescribing practices varied tremendously across providers. In particular, a sizable proportion of providers (15.5% in 2012) prescribed antipsychotic polypharmacy but no clozapine.

We found that provider-level share of patients with clozapine use varied from 0% to 88.9% and share with antipsychotic polypharmacy use varied from 0% to 45.2% in 2012 (rates were relatively stable over time). When patients with schizophrenia do not respond to adequate trails of other antipsychotic agents, providers may turn to clozapine or antipsychotic polypharmacy. Although the prevalence of treatment resistance among patients with schizophrenia is approximately 30%,[100] we cannot determine the share of treatment-resistant schizophrenia for a given provider using claims data. It is possible that providers who have higher prescribing of clozapine and antipsychotic polypharmacy have a higher share of their patients with treatment-resistant schizophrenia than providers who are less likely to engage in these prescribing practices. To address this issue, we examined clozapine and antipsychotic polypharmacy practices stratified by share of patients with schizophrenia-related hospitalization--a proxy for treatment-resistant schizophrenia **(Table C.1).** We did not find that providers in the higher quartiles of schizophrenia-related hospitalization had higher clozapine or antipsychotic

polypharmacy prescribing than their counterparts in the lower quartiles, suggesting that higher clozapine or antipsychotic polypharmacy practices are not due to higher share of patients with treatment-resistant schizophrenia. Notably, providers in the highest quartile of schizophrenia-related hospitalization were much less likely to prescribe antipsychotic polypharmacy than their counterparts in the lower quartiles, indicating that providers with smaller proportion of patients with treatment-resistant schizophrenia actually were more likely to engage in antipsychotic polypharmacy prescribing than providers with higher caseloads of treatment-resistant schizophrenia.

As the only antipsychotic medication approved by the U.S. Food and Drug Administration (FDA) to manage treatment-resistant schizophrenia and recurrent suicidal behavior, clozapine is significantly under-utilized in the treatment of schizophrenia patients.[102,110,123] Our finding that providers who were regularly treating patients with schizophrenia prescribed clozapine, on average, to 6.9% of their patients points to underuse of clozapine in the Pennsylvania Medicaid program. Prescribers' reluctance to use clozapine treatment might be due to their concern about the potential risk of metabolic adverse effects associated with clozapine use (e.g., weight gain, occurrence of diabetes and dyslipidemia),[99] lack of awareness of clozapine's benefits, or lack experience.[109,110] Although it is reasonable to consider potential side effects of clozapine, previous literature indicates that providers have the tendency to overestimate the prevalence of side effects and risks associated with clozapine practices.[102,109] Clinical guidelines suggest monitoring metabolic symptoms for patients using SGAs (including clozapine) to prevent premature mortality associated with antipsychotic use.[99,124] However, the rates of monitoring are very low, ranging from 10% to 43%.[125,126] Both primary care providers and psychiatrists reported factors such as time burden and difficulty in

collaborating with other providers as major barriers to metabolic monitoring.[125,126] To increase clozapine use when appropriate and decrease associated side effects, quality initiatives may use educational interventions to improve prescribers' knowledge of clozapine and also take efforts to promote better collaboration between providers for schizophrenia patients who use antipsychotic drugs.

Compared to previous studies using various definitions of antipsychotic polypharmacy (e.g., concurrent prescribing of 2 or more antipsychotics with at least 14, 30, 60, or 90 days), we used the validated measure of antipsychotic polypharmacy with excellent specificity and positive predictive value.[114] We found that providers prescribed non-clozapine antipsychotic polypharmacy to 7% of their patients in 2012 in Pennsylvania Medicaid. Our finding that a sizable portion of providers (e.g., 15.5% in 2012) used zero clozapine but prescribed antipsychotic polypharmacy to their patients points to problematic prescribing of antipsychotics among these prescribers -- they did not try any clozapine (the evidence-based drug) before using antipsychotic polypharmacy to their patient population. Because there is little research evidence suggesting patients with schizophrenia could benefit from non-clozapine antipsychotic polypharmacy practices, those providers prescribing more polypharmacy than clozapine (especially those who use zero clozapine) should be targeted for educational interventions. Also, it may be worthwhile steering treatment-resistant schizophrenia patients to prescribers who are willing to use clozapine.

After adjustment for all other covariates, primary care providers were much less likely to prescribe clozapine than psychiatrists; however, they were just likely to practice antipsychotic polypharmacy. Compared to their psychiatrist counterparts, primary care providers treat patients with a much wider variety of conditions. Our finding of much lower clozapine use by primary

care providers than that by psychiatrists could be because primary care providers perceive clozapine to be very risky and thus they are less willing to prescribe it than their psychiatrist counterparts. Differences in clozapine prescribing could be also due to case mix by specialty -- primary care providers may treat fewer patients with treatment-resistant schizophrenia than psychiatrists. However, the second explanation is not supported by the finding of non-significant specialty difference in antipsychotic polypharmacy prescribing. In fact, primary care providers had higher share of patients with antipsychotic polypharmacy use than that for clozapine use, indicating that primary care providers appeared to perceive antipsychotic polypharmacy to be less risky than clozapine even though antipsychotic polypharmacy is a non-evidence based treatment. Given the widespread use of antipsychotic drugs in patients with schizophrenia (particularly in Medicaid because of the important role it plays in financing antipsychotics), it is important to understand the specialty differences in order to promote high quality of care in antipsychotic prescribing and schizophrenia treatment.

Our study has several limitations. First, we examined prescribers' clozapine and antipsychotic polypharmacy practices in the Pennsylvania Medicaid program and thus the findings may not necessarily be generalizable to other states. Second, to adjust for potential impact of patient case mix, we included a rich set of patients' comorbidities and health status (including SSI status, several mental illness disorders, overall non-mental health comorbidity, and schizophrenia-related hospitalization); however, we could not determine share of patients with treatment-resistant schizophrenia for a given provider using claims data. Third, we had a limited number of provider-level characteristics (specialty, sex, prescription volume, and practice location). Other factors such as provider age and education background might also play a role in prescribing behavior of clozapine and antipsychotic polypharmacy. Finally, we could not adjust

for other important factors, such as pharmaceutical manufacturer promotion on specific antipsychotic drugs, which might affect physician prescribing choice.[55]

In conclusion, we found provider-level underuse of clozapine and use of non-evidence supported practice of non-clozapine antipsychotic polypharmacy in this large Medicaid program. Quality initiatives may take actions to improve evidence-based practice and to decrease unsupported practices in the management of antipsychotic drug use. For example, educational interventions may be used to improve providers' knowledge of clozapine. Also, academic detailing may target providers who use more antipsychotic polypharmacy than clozapine, particularly those who do not try any clozapine but use a lot of polypharmacy practices. It may also be worthwhile steering treatment-resistant schizophrenia patients to prescribers who are willing to use clozapine other than antipsychotic polypharmacy.

APPENDIX A: TABLES FOR CHAPTER 1

Table A.1: List of drugs in the three drug categories, 2009*

Drug category	Drug class	Generic name	Brand name
Antidepressants		*Generic drugs:*	
	Tricyclic Agents	Amitriptyline HCL	
	Antidepressants - Misc.	Budeprion SR	
	Antidepressants - Misc.	Budeprion XL	
	Antidepressants - Misc.	Bupropion HCL	
	Antidepressants - Misc.	Bupropion HCL SR	
	Antidepressants - Misc.	Bupropion XL	
	SSRIs	Citalopram HBR	
	Tricyclic Agents	Clomipramine HCL	
	Tricyclic Agents	Desipramine HCL	
	Tricyclic Agents	Doxepin HCL	
	SSRIs	Fluoxetine HCL	
	SSRIs	Fluvoxamine Maleate	
	Tricyclic Agents	Imipramine HCL	
	Tricyclic Agents	Imipramine Pamoate	
	Tetracyclics	Mirtazapine	
	Tricyclic Agents	Nortriptyline HCl	
	SSRIs	Paroxetine HCl	
	Tricyclic Agents	Protriptyline HCL	
	SSRIs	Sertraline HCL	
	MAOIs	Tranylcypromine Sulfate	
	Modified Cyclics	Trazodone HCL	
	SNRIs	Venlafaxine HCL	
		Brand drugs:	
	Tricyclic Agents	Clomipramine HCL	Anafranil
	Antidepressants - Misc.	Bupropion HBR	Aplenzin†

Table A.1 (Continued)

Drug category	Drug class	Generic name	Brand name
	Tricyclic Agents	Amoxapine	Asendin
	SSRIs	Citalopram HCL	Celexa
	SNRIs	Duloxetine HCL	Cymbalta†
	SNRIs	Venlafaxine HCL	Effexor
	SNRIs	Venlafaxine HCL	Effexor XR†
	MAOIs	Selegiline	Emsam†
	SSRIs	Escitalopram Oxalate	Lexapro†
	SSRIs	Fluvoxamine Maleate	Luvox CR
	Antidepressants - Misc.	Maprotiline HCL	Maprotiline HCL
	MAOIs	Isocarboxazid	Marplan
	MAOIs	Phenelzine Sulfate	Nardil
	Modified Cyclics	Nefazodone HCL	Nefazodone HCL
	Tricyclic Agents	Desipramine HCL	Norpramin
	Tricyclic Agents	Nortriptyline HCL	Pamelor
	MAOIs	Tranylcypromine Sulfate	Parnate
	SSRIs	Paroxetine HCL	Paxil
	SSRIs	Paroxetine HCL	Paxil CR
	SSRIs	Paroxetine Mesylate	Pexeva
	SNRIs	Desvenlafaxine Succinate	Pristiq†
	SSRIs	Fluoxetine HCL	Prozac†
	Tetracyclics	Mirtazapine	Remeron†
	Tricyclic Agents	Trimipramine Maleate	Surmontil
	Tricyclic Agents	Imipramine HCL	Tofranil
	Tricyclic Agents	Imipramine Pamoate	Tofranil-PM
	Tricyclic Agents	Protriptyline HCL	Vivactil
	Antidepressants - Misc.	Bupropion HCL	Wellbutrin
	Antidepressants - Misc.	Bupropion HCL	Wellbutrin SR
	Antidepressants - Misc.	Bupropion HCL	Wellbutrin XL
	SSRIs	Sertraline HCL	Zoloft†
Antidiabetics		*Generic drugs:*	
	Alpha-Glucosidase Inhibitors	Acarbose	
	Sulfonylureas	Glimepiride	
	Sulfonylureas	Glipizide	
	Sulfonylureas	Glipizide ER	
	Sulfonylureas	Glipizide XL	
	Sulfonylurea-Biguanide Combinations	Glipizide-Metformin HCL	
	Sulfonylureas	Glyburide	
	Sulfonylureas	Glyburide Micronized	

Table A.1 (Continued)

Drug category	Drug class	Generic name	Brand name
	Sulfonylurea-Biguanide Combinations	Glyburide-MetFormin HCL	
	Biguanides	Metformin HCl	
	Biguanides	Metformin HCl ER	
	Meglitinide Analogues	Nateglinide	
	Sulfonylureas	Tolazamide	
		Brand drugs:	
	Thiazolidinedione-Biguanide Combinations	Pioglitazone HCL/Metformin HCL	Actoplus Met†
	Thiazolidinediones	Pioglitazone HCL	Actos†
	Sulfonylureas	Glimepiride	Amaryl
	Thiazolidinedione-Biguanide Combinations	Rosiglitazone/Metformin HCL	Avandamet†
	Sulfonylurea-Thiazolidinedione Combinations	Rosiglitazone/Glimepiride	Avandaryl†
	Thiazolidinediones	Rosiglitazone Maleate	Avandia
	Sulfonylureas	Chlorpropamide	Chlorpropamide
	Sulfonylureas	Glyburide	Diabeta
	Sulfonylurea-Thiazolidinedione Combinations	Pioglitazone/Glimepiride	Duetact
	Biguanides	Metformin HCL	Fortamet
	Biguanides	Metformin HCL	Glucophage XR
	Biguanides	Metformin HCL	Glucophage†
	Sulfonylureas	Glipizide	Glucotrol
	Sulfonylureas	Glipizide	Glucotrol XL
	Sulfonylurea-Biguanide Combinations	Glyburide/Metformin HCL	Glucovance†
	Biguanides	Metformin HCL	Glumetza
	Sulfonylureas	Glyburide	Glynase†
	Alpha-Glucosidase Inhibitors	Miglitol	Glyset
	Dipeptidyl Peptidase-4 Inhibitor-Biguanide Combinations	Sitagliptin Phosphate/Metformin HCL	Janumet†
	Dipeptidyl Peptidase-4 (DPP-4) Inhibitors	Sitagliptin Phosphate	Januvia†
	Sulfonylurea-Biguanide Combinations	Glipizide/Metformin HCL	Metaglip
	Dipeptidyl Peptidase-4 (DPP-4) Inhibitors	Saxagliptin HCL	Onglyza†
	Meglitinide-Biguanide Combinations	Repaglinide/Metformin HCL	Prandimet
	Meglitinide Analogues	Repaglinide	Prandin†
	Alpha-Glucosidase Inhibitors	Acarbose	Precose

Table A.1 (Continued)

Drug category	Drug class	Generic name	Brand name
	Biguanides	Metformin HCL	Riomet
	Meglitinide Analogues	Nateglinide	Starlix
	Antidiabetic - Amylin Analogs	Pramlintide Acetate	Symlinpen†
	Sulfonylureas	Tolbutamide	Tolbutamide
Statins		*Generic drugs:*	
	HMG CoA Reductase Inhibitors	Lovastatin	
	HMG CoA Reductase Inhibitors	Pravastatin Sodium	
	HMG CoA Reductase Inhibitors	Simvastatin	
		Brand drugs:	
	HMG CoA Reductase Inhibitor Combinations	Niacin/Lovastatin	Advicor
	HMG CoA Reductase Inhibitors	Lovastatin	Altoprev
	Calcium Channel Blocker & HMG CoA Reductase Inhibit Comb	Amlodipine/Atorvast Calcium	Caduet†
	HMG CoA Reductase Inhibitors	Rosuvastatin Calcium	Crestor†
	HMG CoA Reductase Inhibitors	Fluvastatin Sodium	Lescol
	HMG CoA Reductase Inhibitors	Fluvastatin Sodium	Lescol XL
	HMG CoA Reductase Inhibitors	Atorvastatin Calcium	Lipitor†
	HMG CoA Reductase Inhibitors	Lovastatin	Mevacor
	HMG CoA Reductase Inhibitors	Pravastatin Sodium	Pravachol†
	HMG CoA Reductase Inhibitor Combinations	Niacin/Simvastatin	Simcor†
	Intest Cholest Absorp Inhib-HMG CoA Reductase Inhib Comb	Ezetimibe/Simvastatin	Vytorin†
	HMG CoA Reductase Inhibitors	Simvastatin	Zocor

* Drug name, category, and brand/generic status designation were based on the Medi-Span® database.
† Drugs with any prior authorization requirement.

Table A.2: Prediction of generic use for all hypothetical plans*

Benefit design scenario	Cost-sharing for a generic drug ($)	Cost-sharing difference ($)	Prior authorization	Step therapy	Predicted generic use
		Antidepressants			
1	7	26	N	N	75.3%
2	7	26	N	Y	76.6%
3	7	26	Y	N	79.7%
4	7	26	Y	Y	80.8%
5	7	33	N	N	77.1%
6	7	33	N	Y	78.4%
7	7	33	Y	N	81.3%
8	7	33	Y	Y	82.4%
9	5	26	N	N	76.5%
10	5	26	N	Y	77.8%
11	5	26	Y	N	80.8%
12	5	26	Y	Y	81.9%
13	5	33	N	N	78.3%
14	5	33	N	Y	79.5%
15	5	33	Y	N	82.3%
16	5	33	Y	Y	83.3%
		Antidiabetics			
1	7	26	N	N	79.0%
2	7	26	N	Y	79.6%
3	7	26	Y	N	81.1%
4	7	26	Y	Y	81.7%
5	7	33	N	N	80.4%
6	7	33	N	Y	81.0%
7	7	33	Y	N	82.4%
8	7	33	Y	Y	83.0%
9	4	26	N	N	80.4%
10	4	26	N	Y	81.0%
11	4	26	Y	N	82.5%
12	4	26	Y	Y	83.0%
13	4	33	N	N	81.8%
14	4	33	N	Y	82.3%
15	4	33	Y	N	83.7%
16	4	33	Y	Y	84.2%
		Statins			
1	7	25	N	N	55.9%
2	7	25	N	Y	58.9%
3	7	25	Y	N	58.8%
4	7	25	Y	Y	61.7%
5	7	32	N	N	58.9%
6	7	32	N	Y	61.8%
7	7	32	Y	N	61.7%

Table A.2 (Continued)

Benefit design scenario	Cost-sharing for a generic drug ($)	Cost-sharing difference ($)	Prior authorization	Step therapy	Predicted generic use
8	7	32	Y	Y	64.6%
9	5	25	N	N	59.0%
10	5	25	N	Y	61.9%
11	5	25	Y	N	61.8%
12	5	25	Y	Y	64.6%
13	5	32	N	N	61.9%
14	5	32	N	Y	64.8%
15	5	32	Y	N	64.6%
16	5	32	Y	Y	67.4%

*For each drug category, we calculated marginal effects of plan features on the use of generic drugs for 16 scenarios. We chose different combinations of the 25^{th} and 75^{th} percentiles of the cost-sharing for generic drugs, the 25^{th} and 75^{th} percentiles of the cost-sharing difference between brand and generic drugs, and whether or not prior authorization or step therapy was used. All covariates were adjusted for the predictions.

APPENDIX B: TABLES FOR CHAPTER 2

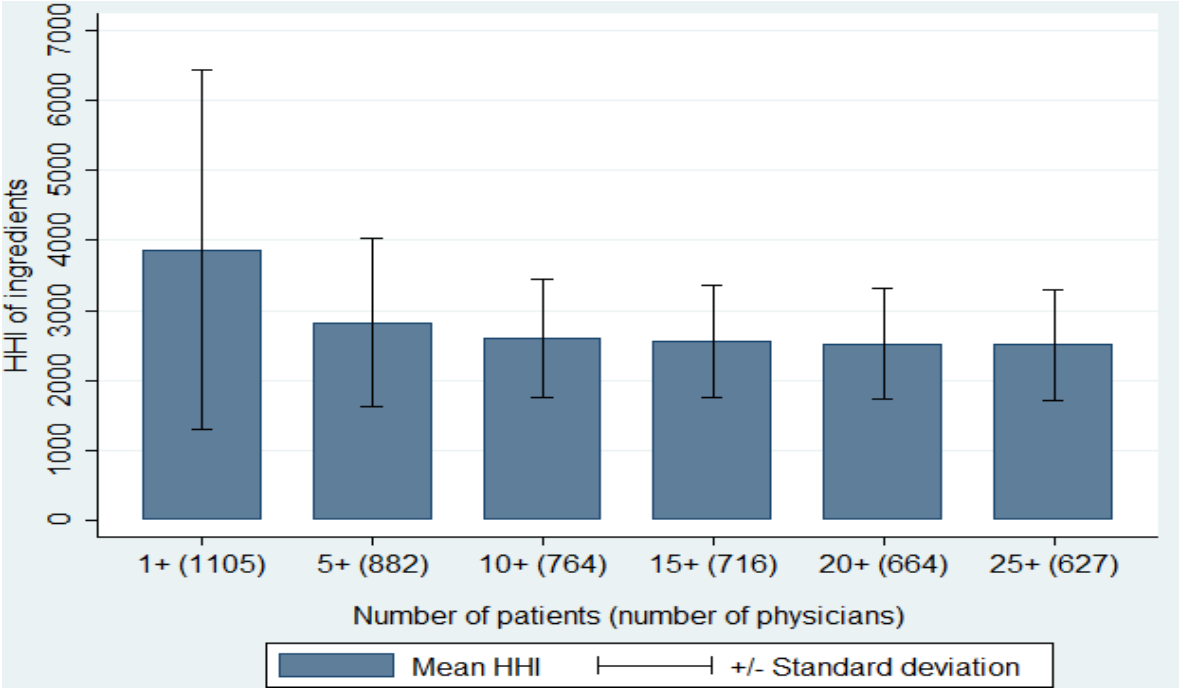


Figure B.1: Change of concentration (HHI) by number of patients

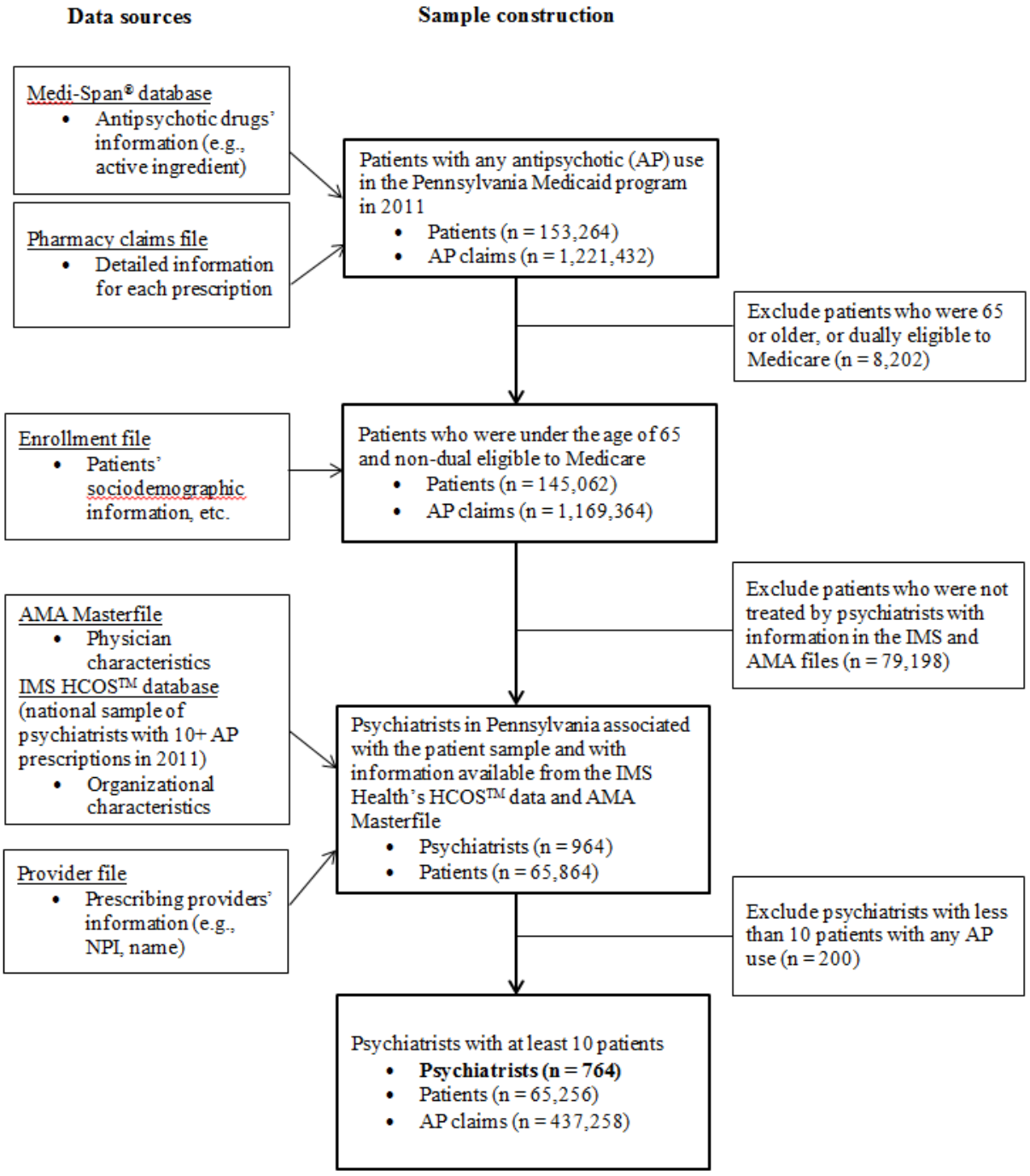


Figure B.2: Flow chart for the study sample

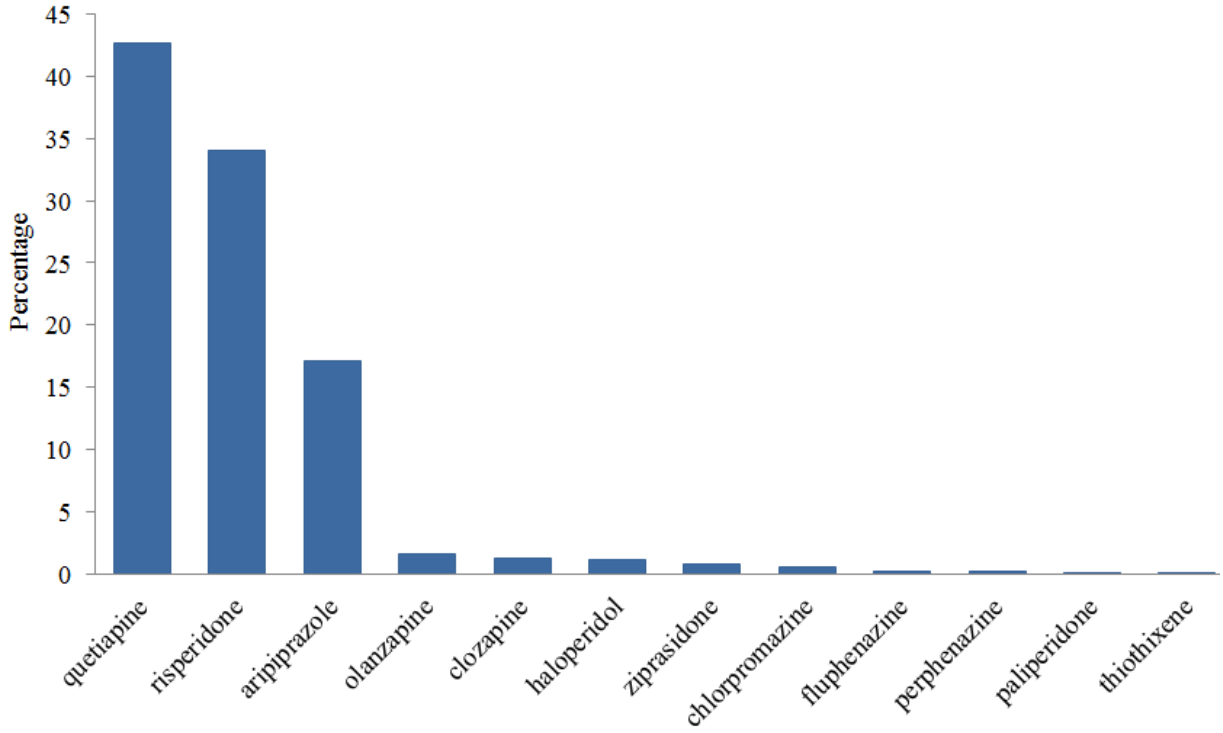


Figure B.3: Most preferred antipsychotics by psychiatrists

Table B.1: Sensitivity analysis results for number of ingredients

Variables	Coefficients (standard errors)		
	Equal weights 1:1	**Weighting ratio 10:1**	**Weighting ratio 2:1**
Characteristics of provider's treated patients			
Share of female patients (%)	-0.01 (0.01)	-0.01 (0.01)	-0.01 (0.01)
Share of SSI-eligible patients (%)	0.02 (0.01)**	0.02 (0.01)**	0.02 (0.01)**
Share of non-Hispanic whites (%)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
Share of patients <18 years old (%)	-0.03 (0.00)***	-0.03 (0.00)***	-0.03 (0.00)***
Share of patients ≥50 years old (%)	0.00 (0.01)	0.00 (0.01)	0.00 (0.01)
Share of patients with serious mental illnesses (%)	0.02 (0.01)***	0.02 (0.01)***	0.02 (0.01)***
Share of patients with 2+ non-mental comorbidities (%)	0.01 (0.01)	0.01 (0.01)	0.01 (0.01)
Share of patients enrolled in fee-for-services (%)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
Physician characteristics			
Physician sex (ref = male)			
Female	-0.29 (0.18)*	-0.29 (0.18)*	-0.29 (0.18)*
Physician age (ref = <40)			
40–49	0.19 (0.25)	0.17 (0.25)	0.18 (0.25)
50–59	-0.03 (0.25)	-0.06 (0.25)	-0.04 (0.25)
≥60	0.27 (0.27)	0.24 (0.27)	0.26 (0.27)
Attended medical school (ref = ranked ≥21)			
US top 20	-0.27 (0.30)	-0.26 (0.3)	-0.26 (0.30)
Foreign schools	0.12 (0.17)	0.11 (0.17)	0.11 (0.17)
Total number of antipsychotic prescriptions	0.00 (0.00)***	0.00 (0.00)***	0.00 (0.00)***
Number of other antipsychotic prescribers in the same organizations (ref = 0)			
1–9	0.17 (0.33)	0.18 (0.33)	0.18 (0.33)
≥10	0.30 (0.34)	0.35 (0.34)	0.32 (0.34)
Practice location (ref = otherwise)			
Urban only	-0.24 (0.27)	-0.24 (0.27)	-0.24 (0.27)
Organizational setting			
Organization specialty (ref = otherwise)			
Any affiliation with a behavioral health organization	0.79 (0.45)*	0.80 (0.45)*	0.79 (0.45)*
Organizational affiliation type (ref = outpatient only)			
Inpatient only	0.35 (0.48)	0.36 (0.49)	0.36 (0.49)
Both inpatient and outpatient	0.12 (0.28)	0.05 (0.28)	0.09 (0.28)
Organization size	0.00 (0.00)*	0.00 (0.00)	0.00 (0.00)*
Intercept	5.13 (0.95)***	5.07 (0.96)***	5.11 (0.96)***

*p<.1, **p<.05, ***p<.01.

Table B.2: Sensitivity analysis results for share of most preferred ingredient

Variables	Coefficients (standard errors)		
	Equal weights 1:1	**Weighting ratio 10:1**	**Weighting ratio 2:1**
Characteristics of provider's treated patients			
Share of female patients (%)	0.02 (0.03)	0.02 (0.00)	0.02 (0.03)
Share of SSI-eligible patients (%)	-0.16 (0.03)***	-0.16 (0.00)***	-0.16 (0.03)***
Share of non-Hispanic whites (%)	-0.03 (0.02)*	-0.03 (0.00)**	-0.03 (0.02)*
Share of patients <18 yrs (%)	0.07 (0.02)***	0.07 (0.00)***	0.07 (0.02)***
Share of patients ≥50 yrs (%)	-0.08 (0.04)**	-0.08 (0.00)**	-0.08 (0.04)**
Share of patients with serious mental illnesses (%)	-0.11 (0.03)***	-0.11 (0.00)***	-0.11 (0.03)***
Share of patients with 2+ non-mental comorbidities (%)	0.06 (0.04)	0.06 (0.00)	0.06 (0.04)
Share of patients enrolled in fee-for-services (%)	0.02 (0.01)	0.02 (0.00)	0.02 (0.01)
Physician characteristics			
Physician sex (ref = male)			
Female	1.22 (0.80)	1.23 (1.00)	1.22 (0.80)
Physician age (ref = <40)			
40–49	1.06 (1.14)	1.05 (1.00)	1.05 (1.14)
50–59	1.26 (1.13)	1.24 (1.00)	1.24 (1.13)
≥60	1.92 (1.22)	1.92 (1.00)	1.92 (1.22)
Attended medical school (ref = ranked ≥21)			
US top 20	1.89 (1.33)	1.9 (1.00)	1.90 (1.33)
Foreign schools	1.40 (0.76)*	1.41 (1.00)*	1.40 (0.76)*
Total number of antipsychotic prescriptions	0.00 (0.00)***	0.00 (0.00)***	0.00 (0.00)***
Number of other antipsychotic prescribers in the same organizations (ref = 0)			
1–9	0.07 (1.46)	0.06 (1.00)	0.06 (1.46)
≥10	1.27 (1.47)	1.26 (1.00)	1.28 (1.47)
Practice location (ref = otherwise)			
Urban only	0.78 (1.20)	0.79 (1.00)	0.78 (1.20)
Organizational setting			
Organization specialty (ref = otherwise)			
Any affiliation with a behavioral health organization	1.46 (1.95)	1.42 (2.00)	1.44 (1.95)
Organizational affiliation type (ref = outpatient only)			
Inpatient only	2.77 (2.08)	2.74 (2.00)	2.76 (2.08)
Both inpatient and outpatient	1.48 (1.23)	1.50 (1.00)	1.49 (1.22)
Organization size	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
Intercept	50.75 (4.23)***	50.85 (4.00)***	50.79 (4.23)***

*p<.1, **p<.05, ***p<.01.

Table B.3: Sensitivity analysis results for HHI of ingredients

Variables	Coefficients (standard errors)		
	Equal weights 1:1	**Weighting ratio 10:1**	**Weighting ratio 2:1**
Characteristics of provider's treated patients			
Share of female patients (%)	3.80 (2.24)*	3.80 (2.24)*	3.80 (2.24)*
Share of SSI-eligible patients (%)	-13.14 (2.32)***	-13.14 (2.32)***	-13.14 (2.32)***
Share of non-Hispanic whites (%)	-2.03 (1.27)	-2.12 (1.26)*	-2.07 (1.27)*
Share of patients <18 yrs (%)	8.04 (1.61)***	8.00 (1.61)***	8.03 (1.61)***
Share of patients ≥50 yrs (%)	-5.63 (3.03)*	-5.59 (3.03)*	-5.60 (3.03)*
Share of patients with serious mental illnesses (%)	-9.00 (2.26)***	-9.00 (2.25)***	-9.00 (2.26)***
Share of patients with 2+ non-mental comorbidities (%)	3.77 (3.07)	3.69 (3.08)	3.74 (3.08)
Share of patients enrolled in fee-for-services (%)	1.73 (1.09)	1.80 (1.09)*	1.77 (1.09)
Physician characteristics			
Physician sex (ref = male)			
Female	96.15 (58.85)*	97.88 (58.88)*	96.77 (58.87)*
Physician age (ref = <40)			
40–49	66.89 (83.84)	61.14 (83.81)	64.86 (83.87)
50–59	81.43 (82.90)	75.34 (82.84)	78.99 (82.91)
≥60	107.42 (89.67)	102.16 (89.71)	105.51 (89.73)
Attended medical school (ref = ranked ≥21)			
US top 20	127.76 (97.91)	132.42 (97.91)	129.44 (97.92)
Foreign schools	62.04 (55.90)	62.31 (56.00)	62.18 (55.94)
Total number of antipsychotic prescriptions	-0.22 (0.03)***	-0.22 (0.03)***	-0.22 (0.03)***
Number of other antipsychotic prescribers in the same organizations (ref = 0)			
1–9	-65.34 (107.82)	-66.78 (107.66)	-65.97 (107.79)
≥10	-36.41 (110.21)	-32.50 (109.72)	-34.82 (110.08)
Practice location (ref = otherwise)			
Urban only	39.62 (88.73)	41.70 (88.82)	40.30 (88.77)
Organizational setting			
Organization specialty (ref = otherwise)			
Any affiliation with a behavioral health organization	52.18 (145.26)	45.43 (145.65)	49.71 (145.51)
Organizational affiliation type (ref = outpatient only)			
Inpatient only	135.49 (155.87)	136.15 (155.77)	135.49 (155.94)
Both inpatient and outpatient	95.71 (91.53)	102.52 (90.58)	98.63 (91.14)
Organization size	0.07 (0.07)	0.04 (0.07)	0.06 (0.07)
Intercept	3737.34 (312.77)***	3754.72 (312.65)***	3744.86 (312.81)***

*p<.1, **p<.05, ***p<.01.

APPENDIX C: TABLES FOR CHAPTER 3

Table C.1: Provider clozapine and polypharmacy practices by schizophrenia-related hospitalization among patient population (quartiles), 2010-2012

Share of patients with schizophrenia-related hospitalization (%)	Any clozapine prescribing (%)	Any polypharmacy prescribing (%)	Share of patients w/ clozapine use (%)*	Share of patients w/ polypharmacy use (%)*
Year 2010				
1st quartile (0.0-24.7%)	46.20	60.76	4.98 (7.13)	6.50 (7.79)
2nd quartile (25.0-36.0%)	60.00	66.67	7.06 (11.94)	7.59 (8.26)
3rd quartile (36.1-53.3%)	58.39	68.94	6.53 (9.01)	7.20 (7.91)
4th quartile (53.8-100.0%)	59.63	29.19	4.89 (7.40)	2.08 (3.92)
Year 2011				
1st quartile (0.0-25.6%)	57.59	76.58	7.28 (10.14)	9.30 (8.97)
2nd quartile (25.8-38.5%)	67.50	75.63	8.69 (11.85)	9.80 (9.34)
3rd quartile (38.9-61.1%)	58.60	61.15	6.67 (11.18)	6.72 (8.29)
4th quartile (61.4-100.0%)	56.05	24.2	5.07 (7.56)	1.75 (4.04)
Year 2012				
1st quartile (0.0-25.0%)	61.21	73.33	9.32 (12.29)	9.45 (9.28)
2nd quartile (25.5-37.3%)	63.06	74.52	6.84 (9.48)	9.18 (8.33)
3rd quartile (37.5-60.0%)	59.64	63.25	6.40 (9.50)	7.73 (9.00)
4th quartile (60.7-100.0%)	56.79	20.37	4.82 (6.10)	1.70 (4.58)

*Figures within parentheses are means and SDs.

Table C.2: GEE regression results for subset cohort (antipsychotic prescribers with 3 years' data): predictors of clozapine and antipsychotic polypharmacy prescribing

Variables	Odds Ratios (robust standard error)	
	Clozapine prescribing	**Antipsychotic polypharmacy prescribing**
Characteristics of provider's treated patients		
Demographic information		
Share of female patients (%)	1.00 (0.00)	1.00 (0.00)
Share of SSI-eligible patients (%)	1.02 (0.00)***	1.01 (0.00)***
Share of Hispanic patients (%)	0.98 (0.00)***	0.99 (0.00)***
Share of non-Hispanic black patients (%)	0.99 (0.00)***	1.00 (0.00)
Mean age of patients	0.98 (0.01)	0.99 (0.01)
Health status and hospitalization		
Share of patients with affective disorders (%)	0.99 (0.00)***	1.00 (0.00)
Share of patients with anxiety disorders (%)	0.99 (0.00)*	0.99 (0.00)*
Share of patients with other psychiatric disorders (%)	1.00 (0.01)	1.01 (0.01)
Share of patients with substance use disorders (%)	0.99 (0.00)***	1.00 (0.00)
Share of patients with brain impairment comorbidity (%)	1.00 (0.00)	1.01 (0.00)**
Mean number of non-mental health comorbidities	1.25 (0.10)***	1.01 (0.07)
Share of patients with schizophrenia-related hospitalization (%)	1.01 (0.00)**	0.99 (0.00)***
Health insurance		
Number of plans for treated patients	1.05 (0.03)**	0.94 (0.02)***
The predominant plan among patient population (ref = FFS)		
MCO plan A	0.91 (0.18)	1.55 (0.18)***
MCO plan B	0.93 (0.22)	1.67 (0.59)
MCO plan C	1.03 (0.17)	1.36 (0.16)***
MCO plan E	0.90 (0.20)	0.59 (0.12)***
MCO plan F	2.48 (1.54)	2.70 (1.10)**
MCO plan G	1.15 (0.23)	0.73 (0.11)**
MCO plan H	1.01 (0.21)	1.49 (0.23)***
MCO plan I	1.51 (0.48)	1.38 (0.26)*
MCO plan J (combined)†	1.51 (0.36)*	0.69 (0.32)
Provider characteristics		
High prescription volume (ref = low prescription volume)	1.50 (0.15)***	2.29 (0.20)***
Female (ref = male)	1.12 (0.17)	1.02 (0.09)
Specialty (ref = psychiatrist)		
Primary care provider	0.40 (0.09)***	0.84 (0.27)
Other	0.77 (0.20)	1.01 (0.19)

Table C.2 (Continued)

Variables	Odds Ratios (robust standard error)	
	Clozapine prescribing	**Antipsychotic polypharmacy prescribing**
Practice in urban only (ref=otherwise)	0.98 (0.25)	0.99 (0.18)
Year (ref = 2010)		
2011	0.97 (0.05)	1.20 (0.06)***
2012	0.95 (0.07)	1.18 (0.07)***
Intercept	0.04 (0.03)***	0.05 (0.03)***
N obs	*1,278*	*1,278*
N groups	*426*	*426*

*p<.1, **p<.05, ***p<.01.
†MCO plan J combined plans with only 1-3 observations in a year.

Table C.3: GEE regression results for psychiatrists: predictors of share of patients with clozapine use and share of patients with antipsychotic polypharmacy prescribing

Variables	Odds Ratios (robust standard error)	
	Clozapine prescribing	**Antipsychotic polypharmacy prescribing**
Characteristics of provider's treated patients		
Demographic information		
Share of female patients (%)	1.00 (0.00)	1.00 (0.00)
Share of SSI-eligible patients (%)	1.02 (0.00)***	1.02 (0.00)***
Share of Hispanic patients (%)	0.98 (0.00)***	0.99 (0.00)***
Share of non-Hispanic black patients (%)	0.99 (0.00)***	1.00 (0.00)
Mean age of patients	0.99 (0.01)	0.98 (0.01)**
Health status and utilization		
Share of patients with affective disorders (%)	0.99 (0.00)***	1.00 (0.00)
Share of patients with anxiety disorders (%)	0.99 (0.00)*	0.99 (0.00)**
Share of patients with other psychiatric disorders (%)	1.00 (0.00)	1.00 (0.01)
Share of patients with substance use disorders (%)	0.99 (0.00)***	0.99 (0.00)***
Share of patients with brain impairment comorbidity (%)	1.00 (0.00)	1.00 (0.00)
Mean number of non-mental health comorbidities	1.12 (0.08)	1.12 (0.07)*
Share of patients with schizophrenia-related hospitalization (%)	1.01 (0.00)***	0.99 (0.00)***
Health insurance		
Number of plans for treated patients	1.04 (0.03)	0.96 (0.02)*
The predominant plan among patient population (ref = FFS)		
MCO plan A	0.95 (0.16)	1.61 (0.18)***
MCO plan B	0.76 (0.18)	1.63 (0.63)
MCO plan C	1.14 (0.18)	1.54 (0.17)***
MCO plan D	2.68 (0.91)***	0.64 (0.25)
MCO plan E	0.85 (0.16)	0.76 (0.13)
MCO plan G	1.17 (0.19)	0.83 (0.12)
MCO plan H	1.17 (0.21)	1.54 (0.21)***
MCO plan I	1.67 (0.45)*	1.35 (0.25)
MCO plan J (combined)†	1.30 (0.31)	0.81 (0.34)
Provider characteristics		
High prescription volume (ref = low prescription volume)	1.40 (0.12)***	2.64 (0.22)***
Female (ref = male)	1.15 (0.13)	0.94 (0.08)
Practice in urban only (ref=otherwise)	1.04 (0.22)	1.09 (0.15)
Year (ref = 2010)		
2011	1.00 (0.05)	1.14 (0.06)**
2012	0.96 (0.07)	1.08 (0.07)

Table C.3 (Continued)

Variables	Odds Ratios (robust standard error)	
	Clozapine prescribing	**Antipsychotic polypharmacy prescribing**
Intercept	0.04 (0.02)***	0.04 (0.02)***
N obs	*1,584*	*1,584*
N groups	*695*	*695*

*p<.1, **p<.05, ***p<.01.
†MCO plan J combined plans with only 1-3 observations in a year.

Table C.4: GEE regression results controlling for practice region: predictors of share of patients with clozapine use and share of patients with antipsychotic polypharmacy prescribing

Variables	Odds Ratios (robust standard error)	
	Clozapine prescribing	**Antipsychotic polypharmacy prescribing**
Characteristics of provider's treated patients		
Demographic information		
Share of female patients (%)	1.00 (0.00)	1.00 (0.00)
Share of SSI-eligible patients (%)	1.02 (0.00)***	1.02 (0.00)***
Share of Hispanic patients (%)	0.98 (0.00)***	0.99 (0.00)***
Share of non-Hispanic black patients (%)	0.99 (0.00)***	1.00 (0.00)*
Mean age of patients	0.98 (0.01)**	0.99 (0.01)
Health status and utilization		
Share of patients with affective disorders (%)	0.99 (0.00)***	1.00 (0.00)
Share of patients with anxiety disorders (%)	0.99 (0.00)*	0.99 (0.00)***
Share of patients with other psychiatric disorders (%)	1.00 (0.01)	1.01 (0.01)
Share of patients with substance use disorders (%)	0.99 (0.00)***	0.99 (0.00)***
Share of patients with brain impairment comorbidity (%)	1.00 (0.00)	1.01 (0.00)**
Mean number of non-mental health comorbidities	1.15 (0.07)**	1.12 (0.06)*
Share of patients with schizophrenia-related hospitalization (%)	1.01 (0.00)***	0.99 (0.00)***
Health insurance		
Number of plans for treated patients	1.04 (0.02)*	0.96 (0.02)**
The predominant plan among patient population (ref = FFS)		
MCO plan A	0.81 (0.14)	1.46 (0.19)***
MCO plan B	0.76 (0.16)	1.39 (0.45)
MCO plan C	1.00 (0.15)	1.29 (0.15)**
MCO plan D	2.67 (0.95)***	1.26 (0.57)
MCO plan E	1.10 (0.23)	0.88 (0.15)
MCO plan F	1.76 (0.64)	1.33 (0.40)
MCO plan G	1.35 (0.24)*	0.95 (0.13)
MCO plan H	1.24 (0.22)	1.56 (0.20)***
MCO plan I	1.72 (0.45)**	1.47 (0.24)**
MCO plan J (combined)†	1.29 (0.30)	0.80 (0.32)
Provider characteristics		
High prescription volume (ref = low prescription volume)	1.43 (0.11)***	2.65 (0.19)***
Female (ref = male)	1.08 (0.12)	1.01 (0.07)

Table C.4 (Continued)

Variables	Odds Ratios (robust standard error)	
	Clozapine prescribing	**Antipsychotic polypharmacy prescribing**
Specialty (ref = psychiatrist)		
Primary care provider	0.54 (0.12)***	1.11 (0.20)
Other	1.00 (0.17)	0.83 (0.11)
Practice county (ref = Philadelphia)		
Allegheny	1.63 (0.31)**	1.37 (0.21)**
Other	1.14 (0.16)	1.24 (0.14)*
Practice in urban only (ref=otherwise)	0.98 (0.19)	0.95 (0.13)
Year (ref = 2010)		
2011	1.02 (0.05)	1.15 (0.06)***
2012	0.98 (0.07)	1.12 (0.06)**
Intercept	0.05 (0.03)***	0.03 (0.01)***
N obs	*1,927*	*1,927*
N groups	*892*	*892*

*p<.1, **p<.05, ***p<.01.
†MCO plan J combined plans with only 1-3 observations in a year.

BIBLIOGRAPHY

1. Kesselheim AS, Misono AS, Lee JL, et al. Clinical equivalence of generic and brand-name drugs used in cardiovascular disease: a systematic review and meta-analysis. *JAMA : the journal of the American Medical Association.* Dec 3 2008;300(21):2514-2526.

2. The Medical Letter on Drugs and Therapeutics. Generic Drugs Revisited. Oct 19 2009(1323):211-2769.

3. Congressional Budget Office. *Effects of using generic drugs on Medicare's prescription drug spending.* Washington, DC Sep 2010.

4. Kaiser Family Foundation. Medicare Part D spending trends: understanding key drivers and the role of competition. 2012; http://kaiserfamilyfoundation.files.wordpress.com/2013/01/8308.pdf. Accessed Jul 19, 2013.

5. Gellad WF, Donohue JM, Zhao X, et al. Brand-name prescription drug use among veterans affairs and medicare part d patients with diabetes: a national cohort comparison. *Annals of internal medicine.* Jul 16 2013;159(2):105-114.

6. United States Government Accountability Office. *Drug pricing: research on savings from generic drug use.* Washington, DC Jan31 2012.

7. Shrank WH, Hoang T, Ettner SL, et al. The implications of choice: prescribing generic or preferred pharmaceuticals improves medication adherence for chronic conditions. *Archives of internal medicine.* Feb 13 2006;166(3):332-337.

8. Griliches Z, Cockburn I. Generics and new goods in pharmaceutical price indexes. *The American Economic Review.* 1994;84(5):1213-1232.

9. Gaither CA, Kirking DM, F.J. A, L.S. W. Consumers' views on generic medications. *J Amer Pharm Assoc* 2001;41(5):729-736.

10. Ganther JM, Kreling DH. Consumer perceptions of risk and required cost savings for generic prescription drugs. *J Amer Pharm Assoc* 2000;40(3):378-383.

11. Shrank WH, Cox ER, Fischer MA, Mehta J, Choudhry NK. Patients' perceptions of generic medications. *Health affairs.* Mar-Apr 2009;28(2):546-556.

12. Shrank WH, Stedman M, Ettner SL, et al. Patient, physician, pharmacy, and pharmacy benefit design factors related to generic medication use. *Journal of general internal medicine.* Sep 2007;22(9):1298-1304.

13. Hellerstein JK. The importance of the physician in the generic versus trade-name prescription decision. *The Rand journal of economics.* Spring 1998;29(1):108-136.

14. Shrank WH, Liberman JN, Fischer MA, Girdish C, Brennan TA, Choudhry NK. Physician perceptions about generic drugs. *The Annals of pharmacotherapy.* Jan 2011;45(1):31-38.

15. Kaiser Family Foundation. Medicare prescription drug plans in 2009 and key changes since 2006: summary of findings. 2009; http://kaiserfamilyfoundation.files.wordpress.com/2013/01/7917.pdf. Accessed Jul 20, 2013.

16. Kaiser Family Foundation. Medicare Part D 2009 data spotlight: ten most common brand-name drugs. 2009; http://kaiserfamilyfoundation.files.wordpress.com/2013/01/7918.pdf. Accessed Jul 22, 2013.

17. Choudhry NK, Fischer MA, Avorn J, et al. At Pitney Bowes, value-based insurance design cut copayments and increased drug adherence. *Health affairs.* Nov 2010;29(11):1995-2001.

18. Cole JA, Norman H, Weatherby LB, Walker AM. Drug copayment and adherence in chronic heart failure: effect on cost and outcomes. *Pharmacotherapy.* Aug 2006;26(8):1157-1164.

19. Donohue JM, Zhang Y, Lave JR, et al. The Medicare drug benefit (Part D) and treatment of heart failure in older adults. *American heart journal.* Jul 2010;160(1):159-165.

20. Goldman DP, Joyce GF, Zheng Y. Prescription drug cost sharing: associations with medication and medical utilization and spending and health. *JAMA : the journal of the American Medical Association.* Jul 4 2007;298(1):61-69.

21. Huskamp HA, Deverka PA, Epstein AM, Epstein RS, McGuigan KA, Frank RG. The effect of incentive-based formularies on prescription-drug utilization and spending. *The New England journal of medicine.* Dec 4 2003;349(23):2224-2232.

22. Maciejewski ML, Farley JF, Parker J, Wansink D. Copayment reductions generate greater medication adherence in targeted patients. *Health affairs.* Nov 2010;29(11):2002-2008.

23. Maciejewski ML, Wansink D, Lindquist JH, Parker JC, Farley JF. Value-based insurance design program in north Carolina increased medication adherence but was not cost neutral. *Health affairs.* Feb 2014;33(2):300-308.

24. Sacks NC, Burgess JF, Jr., Cabral HJ, Pizer SD, McDonnell ME. Cost sharing and decreased branded oral anti-diabetic medication adherence among elderly part d medicare beneficiaries. *Journal of general internal medicine.* Jul 2013;28(7):876-885.

25. Smalley WE, Griffin MR, Fought RL, Sullivan L, Ray WA. Effect of a prior-authorization requirement on the use of nonsteroidal antiinflammatory drugs by Medicaid patients. *The New England journal of medicine.* Jun 15 1995;332(24):1612-1617.

26. Williams J, Steers WN, Ettner SL, Mangione CM, Duru OK. Cost-related nonadherence by medication type among Medicare Part D beneficiaries with diabetes. *Medical care.* Feb 2013;51(2):193-198.

27. Hoadley JF, Merrell K, Hargrave E, Summer L. In Medicare Part D plans, low or zero copays and other features to encourage the use of generic statins work, could save billions. *Health affairs.* Oct 2012;31(10):2266-2275.

28. The IMS Institute for Healthcare Informatics. Medicare Part D at age five: what has happened to seniors' prescription drug prices? 2011; http://www.imshealth.com/ims/Global/Content/Home Page Content/IMS News/IHII_Medicare_Part_D2.pdf. Accessed Aug 16, 2013.

29. Medicare Payment Advisory Commission. A data book: Medicare Part D program. 2010; http://www.medpac.gov/documents/Mar10_PartDDataBook.pdf. Accessed Jul 15, 2013.

30. Medi-Span database (Medi-Span). http://www.medispan.com.

31. U.S. Census Bureau -ACS. 2010; http://www.census.gov. Accessed Mar 4, 2013.

32. Dartmouth Medical School Center for the Evaluative Clinical Sciences. The Dartmouth atlas of health care. http://www.dartmouthatlas.org. Accessed Dec 12, 2012.

33. Centers for Medicare & Medicaid Services. RxHCC model software. 2013; http://www.cms.gov/Medicare/Health-Plans/MedicareAdvtgSpecRateStats/Risk_adjustment.html. Accessed Nov 17, 2012.

34. Robst J, Levy JM, Ingber MJ. Diagnosis-based risk adjustment for medicare prescription drug plan payments. *Health care financing review.* Summer 2007;28(4):15-30.

35. Donohue JM, Morden NE, Gellad WF, et al. Sources of regional variation in Medicare Part D drug spending. *The New England journal of medicine.* Feb 9 2012;366(6):530-538.

36. Neter J, Wasserman W, Kutner MH. *Applied Linear Regression Models.* Homewood, IL: Irwin1989.

37. Mager DE, Cox ER. Relationship between generic and preferred-brand prescription copayment differentials and generic fill rate. *The American journal of managed care.* Jun 2007;13(6 Pt 2):347-352.

38. Centers for Medicare & Medicaid Services. *Medicare Prescription Drug benefit manual chapter 6 - Part D drugs and formulary requirements.* Baltimore, MD Feb 19 2010.

39. Centers for Medicare & Medicaid Services. Fact sheet: CMS proposes program changes for Medicare Advantage and Prescription Drug Benefit Programs for contract year 2015. 2014; http://www.cms.gov/Newsroom/MediaReleaseDatabase/Fact-Sheets/2014-Fact-sheets-items/2014-01-06.html. Accessed Feb 2, 2014.

40. Simon G. Choosing a first-line antidepressant: equal on average does not mean equal for everyone. *JAMA : the journal of the American Medical Association.* Dec 19 2001;286(23):3003-3004.

41. Simon GE, Perlis RH. Personalized medicine for depression: can we match patients with treatments? *The American journal of psychiatry.* Dec 2010;167(12):1445-1455.

42. Abaluck J, Gruber J. Choice inconsistencies among the elderly: evidence from plan choice in the Medicare Part D program. *Am Econ Rev.* 2011;101(4):1180-1210.

43. Heiss H, Leive A, McFadden D, Winter J. Plan selection in Medicare Part D: evidence from administrative data. *NBER working paper.* 2012;w18166.

44. Rice T, Cummings J. Reducing the number of drug plans for seniors: a proposal and analysis of three case studies. *J Health Polit Policy Law.* 2010;35(6):961-997.

45. Polinski JM, Bhandari A, Saya UY, Schneeweiss S, Shrank WH. Medicare beneficiaries' knowledge of and choices regarding Part D, 2005 to the present. *Journal of the American Geriatrics Society.* May 2010;58(5):950-966.

46. Zhou C, Zhang Y. The vast majority of Medicare Part D beneficiaries still don't choose the cheapest plans that meet their medicatin needs. *Health affairs.* 2012;31(10):2259-2265.

47. Reid RO, Deb P, Howell BL, Shrank WH. Association between Medicare Advantage plan star ratings and enrollment. *JAMA : the journal of the American Medical Association.* Jan 16 2013;309(3):267-274.

48. Centers for Medicare & Medicaid Services. *Medicare 2014 Part C & D Star Rating technical notes.* Baltimore, MD Sep 9 2013.

49. Landon BE, Reschovsky J, Reed M, Blumenthal D. Personal, organizational, and market level influences on physicians' practice patterns: results of a national survey of primary care physicians. *Medical care.* Aug 2001;39(8):889-905.

50. Zhang Y, Gellad WF, Zhou L, Lin YJ, Lave JR. Access to and use of $4 generic programs in Medicare. *Journal of general internal medicine.* Oct 2012;27(10):1251-1257.

51. Consumer Reports Best Buy Drugs. Using ACE inhibitors to treat: high blood pressure and heart disease. 2011; https://http://www.consumerreports.org/health/resources/pdf/best-buy-drugs/ACEI-full-report.pdf. Accessed Dec 20, 2014.

52. Hodgkin D, Merrick EL, Hiatt D. The relationship of antidepressant prescribing concentration to treatment duration and cost. *The journal of mental health policy and economics.* Mar 2012;15(1):3-11.

53. Merrick EL, Hodgkin D, Panas L, Soumerai SB, Ritter G. Is Customization in Antidepressant Prescribing Associated with Acute-Phase Treatment Adherence? *Journal of pharmaceutical health services research: an official journal of the Royal Pharmaceutical Society of Great Britain.* Mar 1 2012;3(1):11-16.

54. Frank RG, Zeckhauser RJ. Custom-made versus ready-to-wear treatments: behavioral propensities in physicians' choices. *Journal of health economics.* Dec 1 2007;26(6):1101-1127.

55. Donohue J, O'Malley AJ, Horvitz-Lennon M, Taub AL, Berndt ER, Huskamp HA. Changes in physician antipsychotic prescribing preferences, 2002-2007. *Psychiatric services.* Mar 1 2014;65(3):315-322.

56. IMS Institute for Healthcare Informatics. The use of medicines in the United States: review of 2010. 2011; http://www.imshealth.com/deployedfiles/imshealth/Global/Content/IMS Institute/StaticFile/IHII_UseOfMed_report.pdf. Accessed Aug 16, 2013.

57. Alexander GC, Gallagher SA, Mascola A, Moloney RM, Stafford RS. Increasing off-label use of antipsychotic medications in the United States, 1995-2008. *Pharmacoepidemiol Drug Saf.* Feb 2011;20(2):177-184.

58. Leslie DL, Mohamed S, Rosenheck RA. Off-label use of antipsychotic medications in the department of Veterans Affairs health care system. *Psychiatric services.* Sep 2009;60(9):1175-1181.

59. Aparasu RR, Bhatara V, Gupta S. U.S. national trends in the use of antipsychotics during office visits, 1998-2002. *Annals of clinical psychiatry : official journal of the American Academy of Clinical Psychiatrists.* Jul-Sep 2005;17(3):147-152.

60. Rosenheck RA, Leslie DL, Doshi JA. Second-generation antipsychotics: cost-effectiveness, policy options, and political decision making. *Psychiatric services.* May 2008;59(5):515-520.

61. Kahn RS, Fleischhacker WW, Boter H, et al. Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: an open randomised clinical trial. *Lancet.* Mar 29 2008;371(9618):1085-1097.

62. Hamann J, Adjan S, Leucht S, Kissling W. Psychiatric decision making in the adoption of a new antipsychotic in Germany. *Psychiatric services.* May 2006;57(5):700-703.

63. Franz M, Ranger J, Hanewald B, Gallhofer B, Lay B. Influences on therapist's decisions for neuroleptic treatment in schizophrenia: the role of characteristics of the patient and the physician. *Pharmacopsychiatry.* Nov 2012;45(7):261-268.

64. National Institute of Mental Health. The National Institute of Mental Health Strategic Plan. 2008; http://www.nimh.nih.gov/about/strategic-planning-reports/index.shtml. Accessed Dec 20, 2014.

65. Taub AA, Kolotilin A, Gibbons RS, Berndt ER. The diversity of concentrated prescribing behavior: an application to antipsychotics. *NBER working paper.* 2011:w16823.

66. Eisenberg JM. Changing physicians' practices. *Tobacco control.* 1997;6 Suppl 1:S68-70.

67. Greving JP, Denig P, van der Veen WJ, Beltman FW, Sturkenboom MC, Haaijer-Ruskamp FM. Determinants for the adoption of angiotensin II receptor blockers by general practitioners. *Social science & medicine.* Dec 2006;63(11):2890-2898.

68. Arrow K. Uncertainty and the welfare economics of medical care. *The American economic review.* 1964;53(5):941-973.

69. Greenhalgh T, Robert G, Macfarlane F, Bate P, Kyriakidou O. Diffusion of innovations in service organizations: systematic review and recommendations. *The Milbank quarterly.* 2004;82(4):581-629.

70. Medi-span® Electronic Drug File (MED-File) v2. Indianapolis, IN: Wolters Kluwer Health, Inc.; c2011; Accessed November 7,2012.

71. American Medical Association. AMA physician masterfile. Chicago2012.

72. IMS Health. Healthcare Organizational ServicesTM (HCOS) database http://www.imshealth.com/portal/site/imshealth. Accessed Sep 1, 2013.

73. Centers for Medicare and Medicaid Services. Hospital Compare. https://data.medicare.gov/data/hospital-compare. Accessed Jul 22, 2014.

74. Huskamp HA, O'Malley AJ, Horvitz-Lennon M, Taub AL, Berndt ER, Donohue JM. How quickly do physicians adopt new drugs? The case of second-generation antipsychotics. *Psychiatric services.* Apr 1 2013;64(4):324-330.

75. Nauenberg E, Alkhamisi M, Andrijuk Y. Simulation of a Hirschman-Herfindahl index without complete market share information. *Health economics.* Jan 2004;13(1):87-94.

76. Gaynor M, Town RJ. Competition in health care markets. *NBER working paper.* 2011:w17208.

77. Gaynor M, Anderson GF. Uncertain demand, the structure of hospital costs, and the cost of empty hospital beds. *Journal of health economics.* Aug 1995;14(3):291-317.

78. The U.S. Department of Justice. Concentration and market share. http://www.justice.gov/atr/public/guidelines/horiz_book/15.html. Accessed Aug 20, 2013.

79. Jha AK, Joynt KE, Orav EJ, Epstein AM. The long-term effect of premier pay for performance on patient outcomes. *The New England journal of medicine.* Apr 26 2012;366(17):1606-1615.

80. Jha AK, Orav EJ, Li Z, Epstein AM. The inverse relationship between mortality rates and performance in the Hospital Quality Alliance measures. *Health affairs.* Jul-Aug 2007;26(4):1104-1110.

81. Volpp KG, Rosen AK, Rosenbaum PR, et al. Mortality among patients in VA hospitals in the first 2 years following ACGME resident duty hour reform. *JAMA : the journal of the American Medical Association.* Sep 5 2007;298(9):984-992.

82. Leckie G. Multiple membership multilevel models - concepts. *LEMMA VLE Module 13.* 2013:1-61. http://www.bristol.ac.uk/cmm/learning/course.html.

83. Phelps CE. Diffusion of information in medical care. *The Journal of Economic Perspectives.* 1992;6(3):23-42.

84. Hauck K, Street A. Performance assessment in the context of multiple objectives: a multivariate multilevel analysis. *Journal of health economics.* Nov 2006;25(6):1029-1048.

85. Marcin JP, Li Z, Kravitz RL, Dai JJ, Rocke DM, Romano PS. The CABG surgery volume-outcome relationship: temporal trends and selection effects in California, 1998-2004. *Health services research.* Feb 2008;43(1 Pt 1):174-192.

86. Sullivan LM, Dukes KA, Losina E. Tutorial in biostatistics. An introduction to hierarchical linear modelling. *Statistics in medicine.* Apr 15 1999;18(7):855-888.

87. Meyers JL, Beretvas SN. The impact of inappropriate modeling of cross-classified data structures. *Multivariate Behavioral Research.* 2006;41(4):473-497.

88. Rasbash J, Browne W. Non-hierarchical multilevel models. *Handbook of multilevel analysis*. New York: Springer; 2008:301-334.

89. Rasbash J, Goldstein H. Efficient analysis of mixed hierarchical and cross-classified random structures using a multilevel model. *J Educ Behav Stat.* 1994;19:337-350.

90. Carey K. A multilevel modelling approach to analysis of patient costs under managed care. *Health economics.* Jul 2000;9(5):435-446.

91. Rabe-Hesketh S, Skrondal A. *Multilevel and longitudinal modeling using stata third edition.* Vol I. College Station, Texas: Stata Press; 2012.

92. Berndt ER, Gibbons RS, Kolotilin A, Taub AL. The heterogeneity of concentrated prescribing behavior: theory and evidence from antipsychotics. *Journal of health economics.* 2015;40:26-39.

93. Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *The New England journal of medicine.* Sep 22 2005;353(12):1209-1223.

94. Lehman AF, Kreyenbuhl J, Buchanan RW, et al. The Schizophrenia Patient Outcomes Research Team (PORT): updated treatment recommendations 2003. *Schizophrenia bulletin.* 2004;30(2):193-217.

95. Cutler DM, Skinner J, Stern AD, Wennberg D. Physician beliefs and patient preferences: a new look at regional variation in health care spending. *NBER working paper.* 2013:w19320.

96. Wu E, Birnbaum H, Shi L. The economic burden of schizophrenia in the United Sates in 2002. *The Journal of clinical psychiatry.* Mar 2006;66:1122-1129.

97. The IMS Institute for Healthcare Informatics. Medicare Part D at age five: what has happened to seniors' prescription drug prices? 2011; http://www.imshealth.com/ims/Global/Content/Home Page Content/IMS News/IHII_Medicare_Part_D2.pdf. Accessed August 16, 2013.

98. Jones PB, Barnes TR, Davies L, et al. Randomized controlled trial of the effect on Quality of Life of second- vs first-generation antipsychotic drugs in schizophrenia: Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1). *Archives of general psychiatry.* Oct 2006;63(10):1079-1087.

99. American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, North American Association for the Study of Obesity. Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes care.* Feb 2004;27(2):596-601.

100. Essali A, Al-Haj Haasan N, Li C, Rathbone J. Clozapine versus typical neuroleptic medication for schizophrenia (Review). 2000:435-434.

101. Essock SM, Hargreaves WA, Dohm FA, Goethe J, Carver L, Hipshman L. Clozapine eligibility among state hospital patients. *Schizophrenia bulletin.* 1996;22(1):15-25.

102. Mistry H, Osborn D. Underuse of clozapine in treatment-resistant schizophrenia. *Advances in Psychiatric Treatment.* 2011;17(4):250-255.

103. Association. AP. *Practice guideline for the tratment of patients with schizohrenia (2nd edn).* American Psychiatric Publishing Feb 2004.

104. Lewis SW, Barnes TR, Davies L, et al. Randomized controlled trial of effect of prescription of clozapine versus other second-generation antipsychotic drugs in resistant schizophrenia. *Schizophrenia bulletin.* Oct 2006;32(4):715-723.

105. McEvoy JP, Lieberman JA, Stroup TS, et al. Effectiveness of clozapine versus olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia who did not respond to prior atypical antipsychotic treatment. *The American journal of psychiatry.* Apr 2006;163(4):600-610.

106. Leucht S, Komossa K, Rummel-Kluge C, et al. A meta-analysis of head-to-head comparisons of second-generation antipsychotics in the treatment of schizophrenia. *The American journal of psychiatry.* Feb 2009;166(2):152-163.

107. Chakos M, Lieberman J, Hoffman E, Bradford D, Sheitman B. Effectiveness of second-generation antipsychotics in patients with treatment-resistant schizophrenia: a review and meta-analysis of randomized trials. *The American journal of psychiatry.* Apr 2001;158(4):518-526.

108. Swartz MS, Stroup TS, McEvoy JP, et al. What CATIE found: results from the schizophrenia trial. *Psychiatric services.* May 2008;59(5):500-506.

109. Nielsen J, Dahm M, Lublin H, Taylor D. Psychiatrists' attitude towards and knowledge of clozapine treatment. *Journal of psychopharmacology.* Jul 2010;24(7):965-971.

110. Manuel JI, Essock SM, Wu Y, Pangilinan M, Stroup S. Factors associated with initiation on clozapine and on other antipsychotics among Medicaid enrollees. *Psychiatric services.* Nov 2012;63(11):1146-1149.

111. Correll CU, Rummel-Kluge C, Corves C, Kane JM, Leucht S. Antipsychotic combinations vs monotherapy in schizophrenia: a meta-analysis of randomized controlled trials. *Schizophrenia bulletin.* Mar 2009;35(2):443-457.

112. Essock S, Covell N, Leckman-Westin E, et al. Identifying clinically questionable psychotropic prescribing practices for Medicaid recipients in New York State. *Psychiatric services.* Jan 2009;60:1595-1602.

113. Jaffe AB, Levine J. Antipsychotic medication coprescribing in a large state hospital system. *Pharmacoepidemiol Drug Saf.* Jan-Feb 2003;12(1):41-48.

114. Leckman-Westin E, Kealey E, Gupta N, et al. Validation of a claims-based antipsychotic polypharmacy measure. *Pharmacoepidemiol Drug Saf.* Jun 2014;23(6):628-635.

115. Ganguly R, Kotzan JA, Miller LS, Kennedy K, Martin BC. Prevalence, trends, and factors associated with antipsychotic polypharmacy among Medicaid-eligible schizophrenia patients, 1998-2000. *The Journal of clinical psychiatry.* Oct 2004;65(10):1377-1388.

116. Velligan DI, Carroll C, Lage MJ, Fairman K. Outcomes of Medicaid Beneficiaries With Schizophrenia Receiving Clozapine Only or Antipsychotic Combinations. *Psychiatric services.* 2014.

117. Leslie DL, Rosenheck RA. Use of pharmacy data to assess quality of pharmacotherapy for schizophrenia in a national health care system: individual and facility predictors. *Medical care.* Sep 2001;39(9):923-933.

118. Centers for Medicare & Medicaid Services. National plan and provider enumeration system. 2013; http://www.cms.gov/Regulations-and-Guidance/HIPAA-Administrative-Simplification/NationalProvIdentStand/DataDissemination.html. Accessed Apr 21, 2013.

119. Cleveland WS, Devlin SJ. Locally weighted regression: an approach to regression analysis by local fitting. *Journal of the American Statistical Association.* 1988;83(403):596-610.

120. Papke L, Wooldridge J. Econometric methods for fractional response variables with an application to 401 (k) plan participation rates. *Journal of applied econometrics.* 1996;11:619-632.

121. Huh D, Flaherty BP, Simoni JM. Optimizing the analysis of adherence interventions using logistic generalized estimating equations. *AIDS and behavior.* Feb 2012;16(2):422-431.

122. Simoni JM, Huh D, Wilson IB, et al. Racial/Ethnic disparities in ART adherence in the United States: findings from the MACH14 study. *Journal of acquired immune deficiency syndromes.* Aug 15 2012;60(5):466-472.

123. Horvitz-Lennon M, Donohue JM, Lave JR, Alegria M, Normand SL. The effect of race-ethnicity on the comparative effectiveness of clozapine among Medicaid beneficiaries. *Psychiatric services.* Mar 1 2013;64(3):230-237.

124. Daumit GL, Goff DC, Meyer JM, et al. Antipsychotic effects on estimated 10-year coronary heart disease risk in the CATIE schizophrenia study. *Schizophrenia research.* Oct 2008;105(1-3):175-187.

125. Mangurian C, Giwa F, Shumway M, et al. Primary care providers' views on metabolic monitoring of outpatients taking antipsychotic medication. *Psychiatric services.* Jun 2013;64(6):597-599.

126. Parameswaran SG, Chang C, Swenson AK, Shumway M, Olfson M, Mangurian CV. Roles in and barriers to metabolic screening for people taking antipsychotic medications: a survey of psychiatrists. *Schizophrenia research.* Feb 2013;143(2-3):395-396.