Elucidating the Role of Patients, Providers, and Policies in Predicting (mis)Use of High Risk Prescription Medications

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Curriculum Vitae

Danya Mazen Qato grew up between Chicago, Illinois and Tulkarm, Palestine. She completed undergraduate coursework at the University of Illinois at Urbana-Champaign where she was an Illinois State Scholar and a University James Scholar. She received her clinical pharmacy doctorate (PharmD) in 2002 from the University of Illinois at Chicago (UIC) College of Pharmacy. At UIC, she was inducted into the Rho Chi Pharmacy Honor Society, and was the recipient of both the George M. Pullman Foundation Scholarship and Chicago Schweitzer Humanities Fellowship. It is during this time that Danya founded the Chicago Palestine Film Festival, the longest, consistently held film festival of its kind in the world. Upon graduation from pharmacy school, Danya began working at the University of Chicago Hospitals as a clinical pharmacist.

In 2003, she was awarded the Paul and Daisy Soros Fellowship to study for a Master of Public Health at the Harvard University School of Public Health (HSPH) in Boston, Massachusetts. At HSPH, she focused her studies on International Health and Humanitarian Aid, receiving a certificate in Humanitarian Studies from the Francois-Xavier Bagnoud Center for Health and Human Rights. As a student, she interned with the Union of Palestinian Medical Relief Committees and brought to bear her pharmacy background to serve communities isolated from formal healthcare services.

Danya began work as a community pharmacist in 2004 at CVS/Caremark and continues to practice pharmacy in that setting. She began the doctoral program in Health Services Research with a concentration in Pharmaceutical Services at the Brown University School of Public Health in 2009. Her research focus is broadly related to pharmacy practice, epidemiology, pharmaceutical policy, and drug use and misuse. Other

areas of her research pay particular attention to the quality of healthcare in elderly and minority populations. She has also conducted research that lies at the intersections of health, human rights, and health systems development. Her work has been featured in the Lancet, the New York Times, the Journal of General Internal Medicine, the Journal of the American Geriatrics Society, and National Public Radio.

At Brown, Danya is a Spatial Structures for the Social Sciences (S4) Fellow and her work has been funded by the Agency for Healthcare Research and Quality and the National Institutes of Health. For two years of the doctoral program, she received support as a Postdoctoral Fellow in Comparative Effectiveness Research from the American Recovery and Accountability Act. As a student, she has given guest lectures in the Department of Health Services, Policy & Practice, and has presented at several national and international conferences.

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Introduction

This dissertation is composed of three chapters unified by the central themes of patient safety and disparities in use of prescription medicines. The overarching goals of my dissertation were to explore the consequences of state and national pharmaceutical policy changes on prescribing patterns of drugs with important adverse effects and ask how disparities in healthcare provision may influence such patterns of use. I undertook a series of studies that utilize a selection of diverse data sources and analytic techniques, including survival analysis and difference-in-difference design, to examine the implications of two specific pharmaceutical policies on utilization patterns of high risk drugs. One of these policies was instituted nationally (a risk minimization strategy employed by the Food and Drug Administration- Chapter 1), and the other at the state level (expansion of state 'scope-of-practice' laws-Chapter 2). I selected these two pharmaceutical policies because they operate within two important and distinct dimensions of the healthcare system, and therefore have unique policy and practice implications. Further, inasmuch as determinants of patient care and health outcomes are multifactorial so are factors that may predispose patients, on an individual, population, and systems level, to receipt of high risk medications. An additional aim of my dissertation was thus to identify these predictors of high risk drug use in a sample of elderly Medicare managed care enrollees (Chapter 3).

As a result of the increased use of pharmaceuticals nationally concurrent with the expansion of the pharmaceutical market, the aging population reliant on such medications, and the centrality of medication therapy to overall population health and

soaring healthcare expenditures; balancing the risk-benefit ratio in the use of prescription drugs has increasingly become a foundational mandate of governmental and non-governmental health organizations alike[1]. The delicate balance of improving access to medications by (for example) streamlining drug approval processes and expanding the scope of provider privileges whilst minimizing risk associated with potentially inappropriate medication use continues to be played out in both the legislative and public space. It is within this dimension of health services research that my interest in these broad, yet intersecting, research questions emerges.

Generally speaking, high risk medications are medications where the associated adverse effects outweigh the potential benefits among certain subgroups of the population[2]. The specification of the high risk medication of interest differs based on the research question. In the context of newly formulated drug safety legislation, embodied in the Food and Drug Administration Amendments Act (FDAAA) of 2007, high risk medications are identified as such when emerging post-marketing evidence suggests strong safety concerns in certain subpopulations, as was the case with the diabetic medication rosiglitazone in 2007 (Chapter 1). High risk drugs can also be defined as those medications, collectively referred to as controlled substances, where risk of dependence and abuse is high. These drugs include the opioid pain reliever medications that form the locus of my second chapter (Chapter 2). In the more commonly consulted and cited use of the term in the literature, high risk medications (often referred to as potentially inappropriate medications) are those drugs that, while considered safe in the general population, are of particular concern when consumed by the elderly (Chapter 3). The core principles informing the classification of such drugs were codified initially,

iteratively, and most prominently by the Beers criteria[3], starting in the early 1990s and most recently in 2012. The Beers criteria have been incorporated into the Healthcare Effectiveness Data and Information Set (HEDIS) quality of prescribing measures, in particular the HEDIS 'Drugs to Avoid in the Elderly' quality metric utilized in Chapter 3.

Specifically, in Chapter 1, I ask whether there exist racial and socioeconomic disparities in rates of discontinuation of the diabetic medication rosiglitazone (Avandia) among at-risk, elderly Medicare fee-for-service enrollees after the issuance of a safety advisory by the Food and Drug Administration (FDA) in 2007. In the wake of the highly publicized withdrawal of the popular anti-inflammatory medication Vioxx in 2004[4], and the avalanche of negative public attention that followed[5,6]; the FDA has been at the forefront of wrestling the sometimes competing public interests of drug access and risk minimization. In this Chapter, I capitalized on the placement of the high-profile safety warning resultant from policies enacted by the FDAAA, and in part legislated because of the events brought about by the Vioxx scandal, to examine the effectiveness of FDA policy in achieving its goal of maximizing patient safety. The primary research aim was to identify whether disparities exist, whereby minorities are less influenced by FDA risk minimization strategy, potentially placing them at higher risk of adverse health outcomes. Encouraged by calls made by the Institute of Medicine to rigorously address approved drug safety[7], such work provides critical evidence for the FDA as it seeks to optimize the relevance of such bluntly employed risk mitigation tools as safety advisories, across all sectors of the patient population.

In Chapter 2, I estimated the effect of changing state scope-of-practice laws on use of high risk opioid medications. I utilized 2004-2010 health utilization and

prescription claims data from the MarketScan commercially insured population and applied a difference-in-difference analytic design in order to arrive at utilization estimates.

Scope-of-practice is the legal framework used by states to define what activities an individual healthcare practitioner is permitted to undertake- including, the prescribing of medications to patients. Against the backdrop of an epidemic of opioid abuse and misuse and wide geographic variation in their use, my goal was to clarify the role of newly authorized controlled substance prescribers on utilization of opioids. Such research is instructive to understand the role of state policy in eliciting changes in opioid drug utilization and may help in explaining the wide interstate variation in both opioid utilization rates and opioid overdose deaths nationally. If in fact nonphysician clinicians are contributing significantly to utilization of OPRs, the necessity for additional research to examine their role in safely and responsibly prescribing such medications is heightened. Further, the continuing and often fraught debate over expansion of prescribing privileges to nonphysician clinicians most vociferously and recently played out in Florida (one of only two states- the other being Kentucky-where neither physician assistants nor nurse practitioners have the authority to prescribe controlled substances)[8]; has highlighted the relevance of such work.

In Chapter 3, I took a macro-analytic approach to examine a multiplicity of sociodemographic, geographic, and health-plan level predictors of high risk drug use, as reported by 2009 HEDIS data from a nationally representative sample of Medicare managed care plan enrollees. Avoiding use of high risk medications has been shown to be an effective and simple way to reduce the costly and burdensome adverse-drug events

in the elderly population[9]. Successful efforts to reduce inappropriate drug use in the elderly require knowledge of how prescribing of these agents varies geographically and the factors that predict their use. However, there are few comprehensive and nationally representative studies of the prevalence and predictors of inappropriate drug use, particularly following the implementation of the Medicare prescription drug benefit in 2006.

This chapter provides current up-to-date evidence to help policy makers and clinicians better understand the range of predictors that may predispose certain populations to poor prescribing practices. In addition, because identifying and reducing unexplained levels of geographic variation continues to be a major goal of quality improvement efforts; an additional aim of this chapter was to assess geographic variation in quality prescribing utilizing the same measures from HEDIS. Quality improvement efforts aimed at improving prescribing practices can incorporate such information to target interventions to low-performing areas and coordinate research efforts aimed at understanding the cultures of prescribing that may promote poor prescribing practices.

There has been a paucity of research examining the specific structural and policy factors associated with high risk prescription drug use. I contend that the totality of my dissertation work contributes importantly to the health services literature in several ways that are detailed fully within the justification and background for each chapter. Briefly, by further understanding the state, federal, and individual level factors associated with use of high risk medications, however defined, we can take a more critical approach to enriching and improving subsequent policies related to mitigating their use. This work

can be utilized to refine and target policy efforts that promote access and judicious use of high risk medications without perpetuating disparities in healthcare.

Chapter 1

Response to the Rosiglitazone Safety Warning: Are there Differences across Socioeconomic, Demographic, and Racial groups?

INTRODUCTION

On May 21, 2007, concurrent with the online publication of a widely-anticipated meta-analysis[10], the Food and Drug Administration (FDA) issued a safety advisory online and in the form of letters to providers, conveying concern about the cardiovascular risks of rosiglitazone (Avandia), particularly in patients with a history of heart disease. The safety alert warned of a "potentially significant increase in the risk of heart attack and heart-related deaths in patients taking Avandia."[11] On November 14, 2007 a 'black-box' warning was added to the drug's label and product information (this warning appeared in the product information label as shown in Appendix 1.1), which stated that any consumer with type II diabetes, and especially those who had underlying heart disease or who were at high risk of a myocardial infarction, should talk to their health care provider about the appropriateness of discontinuing rosiglitazone, modifying concomitant pharmacotherapy, and/or switching to an alternative medication.[11] Because other treatment options were available, and because most people with diabetes are at high risk for cardiovascular disease[12,13], the expectation was that most patients on rosiglitazone would discontinue use of the drug[14].

Aggregate utilization of rosiglitazone nationally decreased from 11% to 3% of total drug dispensings for oral diabetes medications within two years after the May safety alert[15]. This decrease was most attributable to discontinuation, and only minimally explained by switches to pioglitazone (Actos)- the alternative drug in the thiazolidinedione class[15]. In a commercially insured population, age, sex, region, cardiovascular comorbidities, and prescriber specialty predicted discontinuation of either rosiglitazone or pioglitazone in the 6-month period after the May safety alert[16]. Yet, one in five rosiglitazone users still had a cardiovascular risk factor in December 2007 and in May 2008[17].

Little research has evaluated whether the effectiveness of FDA safety communications may be modified by important racial and sociodemographic characteristics, especially among the most vulnerable elderly. The pervasiveness and scope of racial and socioeconomic disparities in healthcare is well known, and may extend to exposure to high risk drugs.[18-24] Previous research has found geographic variation and socioeconomic differences in utilization of potentially inappropriate medications in the elderly that is unexplained by patient clinical condition, but may be explained by other sociodemographic factors.[25,26] A recently published systematic review further emphasized the apparently varied and unpredictable impact of FDA advisories[27] and the need to characterize the nature of the variation in responses[28].

As of December 2013, the FDA had recommended lifting restrictions on rosiglitazone based on findings from an advisory panel[29,30]. However, given that drugs are issued a warning because of serious concerns about safety and given that vulnerable populations may respond differentially to such warnings, understanding whether these

interventions change behavior equitably across patient subgroups remains of great interest to providers, policy-makers, and patient advocates alike, as they consider the construction of future risk mitigation strategies. We used data from Medicare fee-for-service to quantify differences in time to discontinuation of rosiglitazone between black and white enrollees and enrollees of different sociodemographic, economic, and geographic subgroups after the May 2007 FDA safety alert.

METHODS

Data sources

We obtained the 2007 Medicare Part D Prescription Event File for a national random sample of 20% of Medicare fee-for-service (FFS) enrollees. This file contains pharmacy claims for every outpatient Medicare FFS-covered prescription filled for an enrollee in the sample. We linked the Part D file to the Medicare enrollment file, Medicare Prescriber Characteristics file, and Medicare Part A, Part B outpatient, and carrier claims files for the same year. The Medicare Enrollment file includes information on sociodemographic characteristics of enrollees, including the core variables of enrollee race[31] and enrollee zip code of residence. Diagnosis codes and healthcare utilization variables came from Medicare Part A inpatient claims and the Medicare Part B outpatient and carrier (provider) files. The Medicare Prescriber Characteristics File contains the provider specialty information.[32]

We constructed the Agency for Healthcare Research Quality (AHRQ) socioeconomic status (SES) index score for each beneficiary using zip-code information linked to the 2000 U.S. Census data. The SES index score is created based on principal

components of unemployment, poverty, median income, property values, low education, high education, and crowded households calculated at the census block level. The score can theoretically range from 0-100, with a greater score associated with better neighborhood SES position. Composition and justification of the score is described in detail by AHRQ.[33] The score has been shown to be well correlated with, among other healthcare factors, access to quality healthcare services[34] and is considered a valid composite measure of community-level SES status.

Study population

The study population consisted of black and white enrollees who were established users of rosiglitazone on the date of the May 21, 2007 safety advisory. An enrollee was considered an established user if they had at least two claims for rosiglitazone between January 1, 2007 and May 21, 2007 and if the period defined by the dispensing date plus the days supply of the last dispensing in this period (the index rosiglitazone claim) included the date of the advisory. We required at least two fills of rosiglitazone to identify enrollees with a persistent pattern of use of rosiglitazone. Many patients discontinue a new chronic disease medicine after one dispensing[35] and their inclusion in this analysis may have obscured the effect of the advisory on discontinuation.

We excluded enrollees younger than 65 years of age, those whose index fill days supply was >31 days, anyone that had two or more claims for pioglitazone in the pre-advisory period, and anyone that died before the May 21, 2007 advisory date or before the end of the index prescription. Because of the difficulty in determining the precise date of disenrollment from Medicare Part D, we also excluded any enrollees who did not die

during the measurement year and were not continuously enrolled in a Medicare Part D plan for the full twelve-month study period (n=750).

The four-month period prior to the May advisory date was used to ascertain sociodemographic information, baseline clinical history, and healthcare utilization covariates. We classified enrollees as having a history of cardiovascular disease (dichotomous indicator) if there were International Classification of Diseases, Ninth Revision diagnosis codes of any of the following in the Medicare Part A, Part B outpatient or carrier files between January 1, 2007, and the date of the FDA warning:

- Acute myocardial infarction [AMI (410.x)]
- Coronary Atherosclerosis and ischemic heart disease [IHD (410.x-414.x, 429.2, V45.81, V45.82)]
- Congestive Heart Failure [CHF (398.91, 402.01, 402.11, 402.91, 404.01, 404.11, 404.91, 404.03, 404.13, 425.x, 428.9)]
- Peripheral and Visceral Atherosclerosis [ATH (440.1-440.23)]

or

- Surgical procedure codes [36.0x through 36.3x for removal of obstruction and insertion of stents, bypass surgery, and revascularization]

Discontinuation of Rosiglitazone

Our outcome of interest was time to discontinuation of rosiglitazone after the May safety advisory among established users of rosiglitazone. We defined this outcome as the number of days from the end of the days supply of the index rosiglitazone claim (the index end date) to the end of the days supply for the last rosiglitazone claim during the study period (May 21, 2007-December 31, 2007), the date of death, or end of study period- whichever came first. If the days supply of the last prescription claim came after the end of the study period, the patient follow-up time was censored on December 31, 2007.

Race, Low personal income, and Socioeconomic Status

The primary independent variables of interest were enrollee race (black or white), a history of low personal income (LPI) defined by at least one month of enrollment in Medicaid or any state subsidy assistance during the baseline period[36], and socioeconomic (SES) index score (by quintile).

Covariates

Selection of additional covariates of interest was guided by a priori considerations and included age (65-69, 70-74, 75-79, 80-85, ≥85), sex (male/female), U.S. Census division of residence (nine divisions total, refer to Appendix 1.2 for list of states in each division), medication adherence history of high/low medication possession ratio (MPR) for rosiglitazone in the four-month baseline period prior to the May warning, and receipt of any oral non-thiazolidinedione diabetes medication in the pre-period (yes/no). The MPR was calculated in the baseline period as the number of days supply of rosiglitazone over the 140 days of the baseline period. The final MPR covariate was designated as a binary indicator with an average MPR greater than or equal to one representing enrollees with near perfect adherence to rosiglitazone in the pre-period, and those with an MPR less than one with comparatively lower adherence. This binary assignment was based empirically on the distribution of adherence in the pre-advisory period.

Health systems parameters of interest were number of outpatient visits to a healthcare provider in the baseline period (≤ 2 outpatient evaluation and management claims or >2 claims) and prescriber specialty (categorized as endocrinology/cardiology or

other). Prescriber information was derived from the prescriber assigned to the index claim of rosiglitazone.

Observation periods

There are two relevant dates related to the rosiglitazone safety warnings. The first was May 21, 2007, when the Nissen and Wolski meta-analysis was published online[10] and the FDA safety alert was communicated to healthcare providers via multiple media outlets. The second date of interest was November 14, 2007, when the 'black-box' warning was added to product label and prescribing information. We conducted the analysis using both the May advisory date and the November black-box date as index dates. For the sake of clarity, we focus on the six-month period after the May advisory, because that event was the catalyst for the subsequent changes made by the FDA and because the results were similar in both analyses. Much of the limited work that has examined effectiveness of the FDA rosiglitazone risk management strategy has chosen the May advisory date as the index date as well[16,17].

Statistical Analysis

Univariate and multivariate survival analysis was employed using Kaplan-Meier estimation with log-rank tests of equality of the cumulative hazards functions, as well as Cox proportional hazards regression analysis. We compared crude and adjusted time to discontinuation of rosiglitazone in the full analytic sample and among enrollees with a history of cardiovascular disease. The adjusted models included the covariates described previously. In both samples, our primary comparisons of interest were between black and

white racial groups, those with or without a history of low personal income, and across quintiles of the SES index score. Follow-up time for each patient was defined as the period from the index date until the earlier of the end of the study or the date of death.

To better understand the impact of the advisories among the patient populations most at risk for adverse cardiovascular outcomes, we repeated analyses after subsetting to enrollees with any history of cardiovascular disease in the baseline period. We also fit the Cox models with a parameter for cost in order to better understand the impact of copay levels in explaining differences in discontinuation rates across subgroups. For these exploratory models enrollee copayment for the index rosiglitazone prescription (binary indicator, $0-11, >$11) was incorporated in the model. The appropriateness of the Cox model assumption of proportional hazards was confirmed using a series of crude models fit with the primary independent variables and a log-time interaction term.

All analyses were conducted using SAS software, version 9.2 (Cary, NC SAS Inc., 2013) or STATA software, version 13 (College Station, TX StataCorp LP, 2013). The Brown University Institutional Review Board and the CMS Privacy Board approved the study protocol.

RESULTS

Figure 1.1 plots the percentage of total oral antihyperglycemic medication claims that were rosiglitazone or pioglitazone among black and white enrollees in the entire 2007 Medicare Part D fee-for-service 20% sample (n=784,159). Following the warning, rosiglitazone use decreased markedly among all Medicare fee-for-service enrollees, while pioglitazone use remained relatively stable with a slight increase in use apparent after the

warning. Such patterns of use suggest that the safety warning impact extended to the entire thiazolidinedione class.

Our analytic sample consisted of 37,412 white users of rosiglitazone among whom 23% had a history of cardiovascular disease and 7,862 black users of rosiglitazone among whom 19% had cardiovascular disease. In the full sample and among those with a history of cardiovascular disease, black enrollees were more likely to be female, have a history of low personal income, live in areas of lower SES, live in the Southern U.S. census divisions, have lower average adherence to rosiglitazone in the pre-period, and have fewer outpatient evaluation and management visits (Table 1.1). The median follow-up time for all current users was 209 days, and was consistent between racial groups. Approximately 4% of white and 3% of black enrollees died during the study period. The follow-up time was censored for those that died during the study period and a further 29% of white and 29% of black enrollees whose calculated discontinuation date came after January 1, 2008 (the study end).

The median time to discontinuation of rosiglitazone among all current users, including those whose follow-up time was censored, was 107 days. Among all white enrollees, median time to discontinuation was 110 days, 12 days later than the median time for black enrollees (Figure 1.2a). Among the study population not censored, 30,491 enrollees or 67% of the entire sample discontinued rosiglitazone by the end of the study period (i.e. within the six-month period after the safety advisory); 67% of white enrollees (n=25,105) and 69% of black enrollees (n=5,386).

In unadjusted analysis, enrollees with a history of low personal income discontinued appreciably later than those with no history of low personal income (31 day

difference in median time to discontinuation) and those in the lowest SES quintile discontinued later than those in the highest SES category- 30 day difference (Figures 1.2b,1.2c). In the sample of enrollees with a history of cardiovascular disease, white enrollees had a median time to discontinuation of 92 days, relative to 91 days for black enrollees (Figure 1.2d). Differences among those with low personal income and SES groups remained comparable to the full sample results (Figures 1.2e, 1.2f). In analysis stratified by race, we found that there were no differences by sex, but that differences existed across categories of personal income and SES groups (not shown).

In the fully adjusted Cox proportional hazards analysis (Figure 1.3), we found that white (vs. black) enrollees (Hazard Ratio [HR]: 0.92, 95% CI:0.88-0.95), male enrollees (HR: 0.96, 95% CI: 0.93-0.99), those with no history of cardiovascular disease (HR:0.90, 95% CI:0.87-0.94), and those with no claims for a concomitant non-thiazolidinedione oral diabetic medication in the pre-period (HR:0.89, 95% CI:0.86-0.92) discontinued rosiglitazone later than their respective comparator groups. Enrollees without a history of low personal income discontinued significantly earlier than those with a history of low personal income (HR: 1.19, 95% CI: 1.15-1.23). We found that age showed a graded response with enrollees in each of the progressively older categories discontinuing rosiglitazone later than the referent age category (65-69 years of age); with the greatest difference observed between the reference group and enrollees ≥ 85 years of age (HR: 0.83, 95% CI: 0.78-0.88). Enrollees residing in the West North Central (HR:0.79, 95% CI:0.73-0.86) and East South Central census division (HR:0.86, 95% CI:0.79-0.94) discontinued later than enrollees in referent New England division; and enrollees residing in the Middle Atlantic region (HR:1.1, 95% CI:1.02-1.18) discontinued significantly

earlier. There did not appear to be marked differences across quintiles of SES, provider type, and other census division groups.

Not surprisingly, a high medication possession ratio of ≥ 1 (vs. <1) of rosiglitazone in the pre-advisory period predicted later discontinuation (HR: 0.88, 95% CI: 0.85-0.91). Enrollees with >2 outpatient visits in the pre-advisory period (vs. ≤2 visits) discontinued rosiglitazone earlier than their comparator group (HR: 1.05, 95% CI: 1.02-1.09).

Among enrollees with a history of heart failure (Figure 1.4) we found that the strongest factors related to earlier discontinuation were similar to those in the full sample and included race, with white race (HR:0.88, 95% CI:0.81-0.97) predictive of later discontinuation and higher outpatient healthcare use (HR:1.11, 95% CI:1.04-1.19) and no low personal income (HR:1.12, 95% CI:1.05-1.19), both predictive of earlier discontinuation of rosiglitazone.

As an exploratory analysis we fit a model in the full sample that included a covariate of copay level for index rosiglitazone claim and found that when the full model included copay, most of the estimates remained the same, while the estimate for low personal income was notably reduced to a null value (results not shown). To further tease out the relationship between low personal income, copay level, and discontinuation rates, we also ran two separate models: one included only enrollees with a copay level of $0, the second model only included enrollees with a copay level >$0. We found that in the sample of enrollees with no copay, those with no history of low personal income discontinued marginally earlier (HR:1.14, 95% CI:1.0-1.3) than those with a history of low personal income. In the sample of enrollees with a copay greater than zero, a history

of low personal income had a slightly greater effect with enrollees of no history of low personal again discontinuing significantly earlier than enrollees with a history of low personal income (HR:1.14, 95% CI:1.10-1.18).

DISCUSSION

In this study, we found that the majority of current Medicare fee-for-service elderly users of rosiglitazone had discontinued use of the medication by the end of 2007, nearly six months after the safety advisory. We also found that black enrollees discontinued rosiglitazone modestly earlier than white enrollees and that those with no history of low personal income discontinued appreciably earlier. In the fully-adjusted analysis, there was no evidence of any differences across socioeconomic status levels; yet we found that sex (men), older age, no history of cardiovascular disease, no receipt of other diabetic medications in the pre-period, and higher medication adherence may play a role in explaining later time to discontinuation of rosiglitazone; however, the magnitude of all of these associations were small. Similar to the full sample analysis, among those with a history of cardiovascular disease, race, low personal income, and health systems factors of greater healthcare use appeared to be the primary drivers of differences in time to discontinuation.

To our knowledge this is the first study to examine effectiveness of FDA safety advisories exclusively in an elderly population. The results of this analysis are consistent with analysis conducted in a Veterans Affairs population that found black race and presence of a clinical history of cardiovascular disease were predictive of earlier discontinuation of rosiglitazone after the safety advisory.[37] Previous work utilizing a

large commercial data source, also found younger age, female sex, receipt of concomitant non-thiazolidinedione diabetic medications in the pre-period, as well as geographic region of residence, predictive of earlier discontinuation of rosiglitazone[16].

The underlying mechanism and principal factors motivating these differences is uncertain. Prior research exploring racial differences in long-term adherence to diabetic medications among black and white enrollees in a managed care setting, found consistent earlier discontinuation of incident diabetic medication therapy among black enrollees with equal access to medications as white enrollees; and suggested that education and other factors related to health literacy and larger mistrust of the healthcare system may help explain these differences.[38] Receipt of poorer quality care in general may also impact enrollee perceptions of the veracity of provider instructions and may exacerbate premature discontinuation of medications.[39,40] The clinical consequences, if any, of black enrollees discontinuing earlier than white enrollees, warrants further investigation, especially if the earlier discontinuation is related to self-motivated changes that do not rely on clinician consultation and appropriate modification of concomitant diabetic therapy. An analysis investigating the clinical consequences of the FDA safety advisory lends credence to this concern finding that the decision to discontinue rosiglitazone was as likely to be initiated by the patient acting alone as by the physician.[41] An alternative explanation for the racial differences may be that white enrollees, aware of the safety advisory and the risk associated with rosiglitazone use, are discontinuing comparatively later because they have actively chosen, either alone or after consultation with a healthcare provider, to continue taking the medication. Substantial variation in patient preferences for shared clinical decision-making supports this alternate explanation. [42]

Our findings suggest that enrollees with no history of low personal income discontinue significantly earlier than enrollees with a history of low personal income. When we included a cost parameter in the fully adjusted model, differences by low personal income were essentially nonexistent, suggesting that the differences by low personal income are explained by cost. The consumer behavior motivated by what economists refer to as "moral hazard," whereby enrollees may be reluctant to forgo even unnecessary or dangerous care because of the negligible costs associated with it, may help explain this phenomenon. However, in the two analyses that examined the impact of low personal income on discontinuation among those that had zero copay and greater than zero copay separately, we found an independent effect of low personal income on later discontinuation regardless of copay level.

Although our fully adjusted analysis did not find evidence of differences by community-level socioeconomic status, unadjusted results suggested a pattern of significantly earlier discontinuation among enrollees living in areas of higher SES. When controlling for healthcare utilization, differences in access that are amplified in the crude analysis are no longer apparent because we may have controlled for the mediating effect of access on the relationship between SES and responsiveness to the FDA advisory.

Because females and younger enrollees may be more likely to utilize healthcare information from social media and online sources, they also may be more likely to initiate discontinuation of rosiglitazone of their own volition.[43,44] The regional-level variation we found may be mediated by a multitude of likely interconnected factors, including variation in prescribing cultures, patient demand, differences in pharmaceutical marketing practices all of which may impact responsiveness to a nationally implemented

safety advisory. Previous work examining geographic variation in rosiglitazone discontinuation suggested that differences might result from formulary and insurance coverage of rosiglitazone following the advisory.[15]

The key strength of our study is that we investigated the impact of FDA safety advisories in a nationally representative elderly population, a population of which little is known in terms of responsiveness to FDA risk policy. In addition, we sought to characterize responsiveness in a population most at risk for adverse health outcomes associated with use of rosiglitazone, i.e. enrollees with a history of cardiovascular disease. Given greater polypharmacy among the elderly and the physiological changes with respect to drug metabolism that accompany older age, this population is of particular vulnerability with respect to adverse drug events. We also include a broad set of sociodemographic, clinical, and health utilization factors that may mediate the impact of FDA advisories and enabling us to provide a rich perspective on the multitude of potential determinants of responsiveness to a bluntly employed risk management policy. An additional strength of our study is the utilization of pharmaceutical drug claims, which are considered highly accurate estimates of medication dispensing patterns.

Much of the previous work examining impact of FDA warnings on use of high risk medications either predates the Food and Drug Administration Amendment Acts of 2007[45] and thus does not represent the current regulatory environment; or has limited generalizability because it has focused on small patient populations in unique settings[37], examined only aggregate measures (using for example sales data, or Medicaid data)[15,46], or did not include important sociodemographic and provider-level information.[16] Further, most of the studies that have examined responsiveness to FDA advisories have utilized

logistic regression methods that emphasize whether or not patients discontinue medications within an arbitrary time period after the release of the advisory or the warning. We used survival analysis, because we recognized that responsiveness may vary over time.

LIMITATIONS

This study has some limitations that warrant discussion. First, we examined rates of discontinuation utilizing prescription drug claims. While prescription claims are the single most widely available marker for receipt of prescriptions, they do not reflect consumption by the enrollee. Enrollees may discontinue taking their medication earlier or later (if there are reserves on hand) than the period covered by their previous prescription claims day supply. Such a limitation is bound by the 30-day supply condition imposed by the inclusion criteria and it is not clear if this difference may be mediated by race. Despite the limitations of prescription claims, they remain the gold standard in terms of ascertaining outpatient medication exposure in secondary data sources.[47]

A further limitation of the Medicare Part D prescription claims information is that prescriptions purchased outside the insurance plan adjudication process, such as generics purchased from large retailers, or prescriptions purchased cash-only, are not captured. We believe the impact of such a limitation may be minimal, as the primary drug of interest- rosiglitazone- is a brand name medication that was not likely covered by retailers under their low-cost formularies.

While there is always concern that primary independent variables of interest may be misclassified; we are confident that the race variable for black and white is fairly

accurate given previous research that has validated the indicator for these racial groups in a sample of Medicare beneficiaries.[48] We relied on the pre-advisory covariate information and used enrollment in Medicaid or any low-income subsidy as a surrogate for low personal income. Such an approach while highly specific to our variable of interest[49], may reflect other conditions apart from low personal income, such as asset depletion in anticipation of future high healthcare spending or nursing home placement. Without personal income information, this limitation cannot be overcome yet the impact on our findings may be marginal because the parameter of interest is still reflective of a precarious income condition that stands in contrast to those of higher income levels. Because we utilized zip-code level measures of SES, there may be some misclassification due to heterogeneity of social environments within zip-codes that cover larger geographic areas. Although there are limitations to such an approach, the validity of this measure has been well-established as being predictive of the SES environment that a Medicare enrollee may live in. It thus reflects potential health systems environments and other social determinants of health captured at the neighborhood-level.

Another potential limitation is that we controlled for a number of factors that may be downstream to the racial experience of black Medicare enrollees, such as the number of outpatient visits and adherence in the pre-advisory period. By doing so, our adjusted analyses may have underestimated the racial differences in our outcome of interest. For example, if differences in adherence are related to poor patient education[39] then by controlling for it in the analysis, we have potentially underestimated the racial differences, because the minority race experience results in lower educational attainment, on average. In this case, adherence may be a mediator of the effect of being black, and we

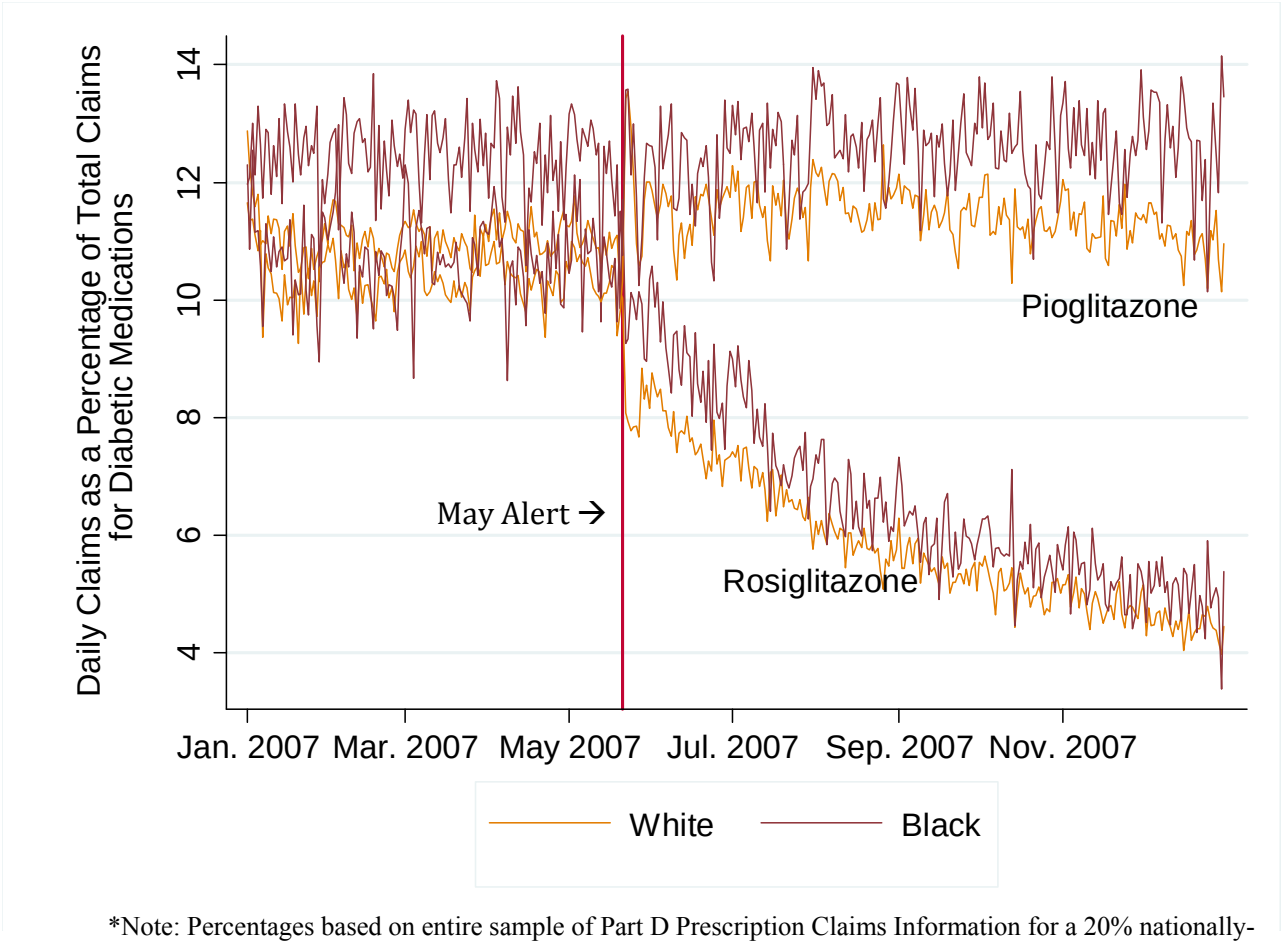
may not wish to adjust for its effect. We have included the unadjusted Cox results and the crude differences in median times to discontinuation to reflect baseline differences.

Because we did not have prescription drug information for 2006, we were only able to characterize enrollees' history of diabetes pharmacotherapy for the five months before the date of advisory. Longer pre-advisory prescription claims information would have enabled a better understanding of an enrollee's history of pharmaceutical use; which may be related to the ultimate decision to discontinue rosiglitazone. For example, enrollees who have exhausted all other diabetes therapies may be less likely to discontinue rosiglitazone in comparison to those who have more recently begun therapy altogether. Importantly, we cannot explain the causal mechanisms underlying the racial differences and cannot discount the potential for residual confounding in our study findings.

CONCLUSION

Our findings suggest that the FDA rosiglitazone warning effectively encouraged current users to discontinue rosiglitazone. However, certain segments of the population appeared more responsive, especially black Medicare fee-for-service enrollees, younger enrollees, enrollees with greater healthcare utilization, and enrollees with no history of low personal income. Further research to understand the causal mechanisms and the implications of differential responsiveness to FDA safety advisories is warranted.

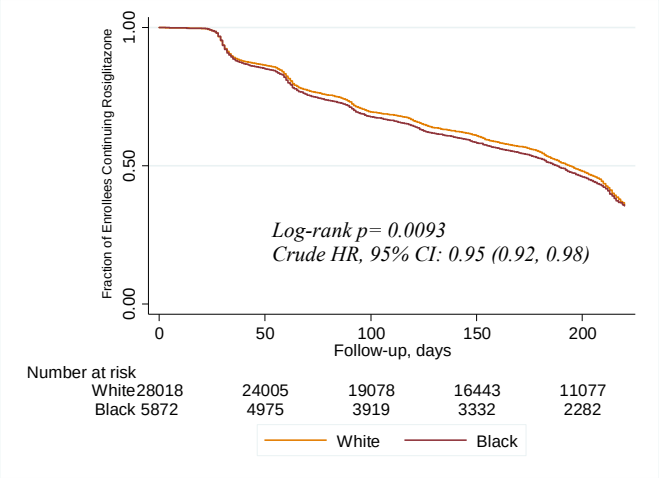
Figure 1.1. Daily Percentage of Rosiglitazone and Pioglitazone Claims per Total Oral Diabetic Medication Claims, All Black and White 2007 Medicare Part D Fee-for-Service Enrollees in a 20% National Sample (n=784, 159 enrollees)*



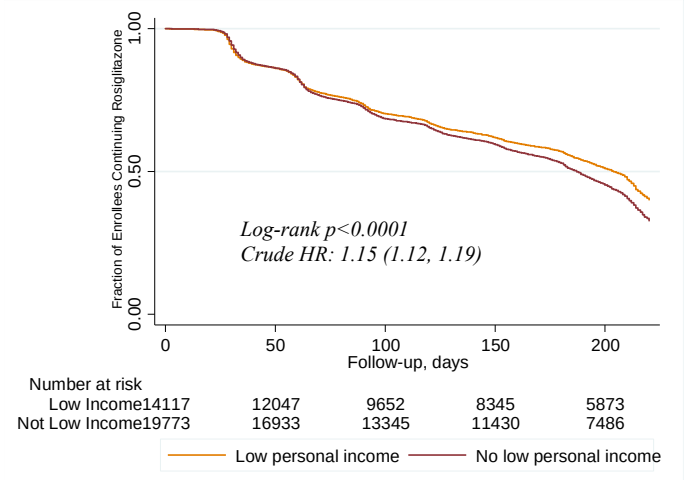
*Note: Percentages based on entire sample of Part D Prescription Claims Information for a 20% nationally-representative sample of Medicare fee-for-service enrollees available to investigators; Denominator does not include claims for insulin-based pharmaceutical products

Figures 1.2a-1.2f. Kaplan-Meier Curves of Discontinuation of Rosiglitazone in Black and White Medicare Fee-for-service Enrollees and Among Enrollees with History of Heart Failure

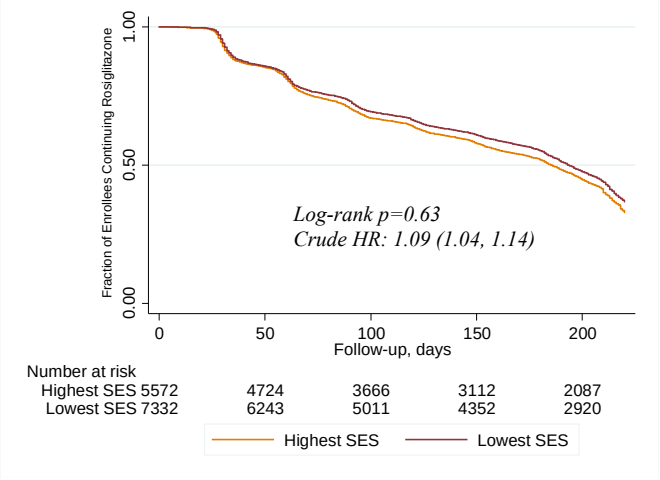
2a. Black vs. White



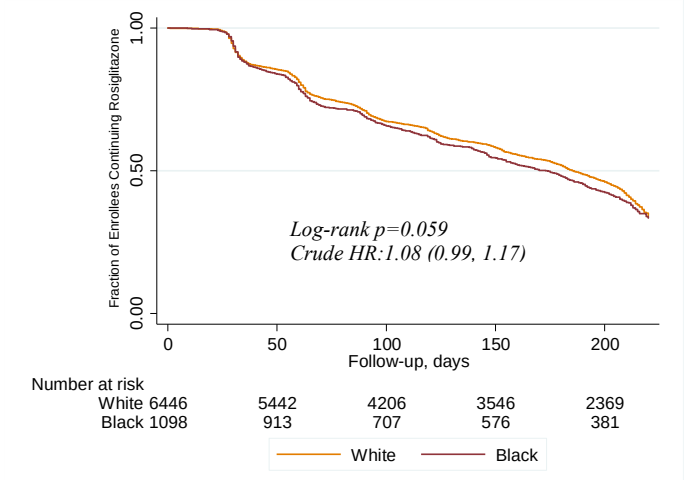
2b. Low vs. not low personal income status



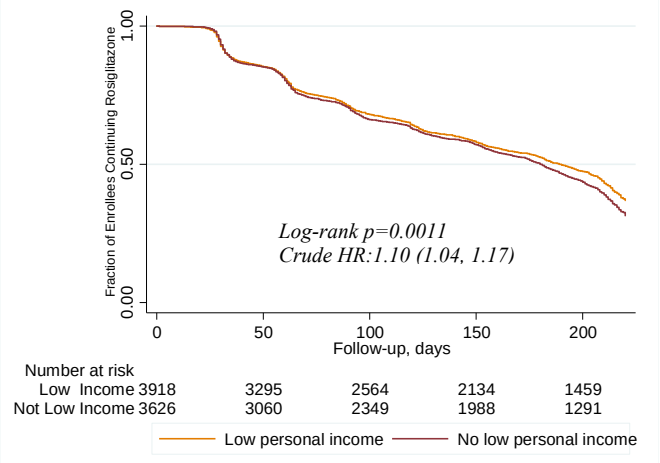
2c. Highest vs. Lowest socioeconomic status (SES) index score



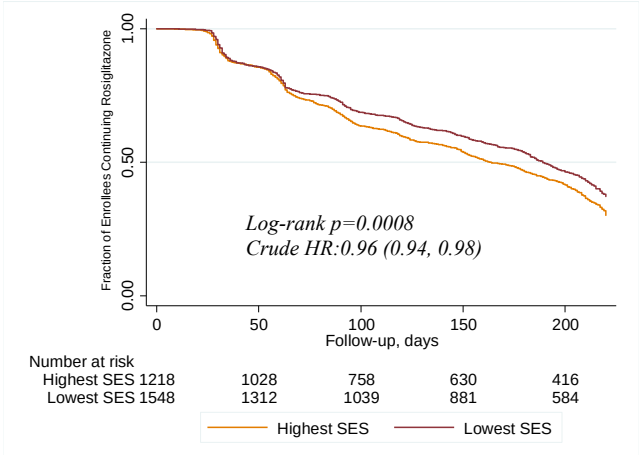
2d. With History of Cardiovascular disease, by race



2e. With History of Cardiovascular disease, by low personal income status



2f. With History of Cardiovascular disease, by socioeconomic status index score (highest vs. lowest)



Notes: Low personal income is defined as at least one month of Medicaid enrollment or low income subsidy from January 1-May 21,2007; the SES index score is derived from zip code-level US census variables based on the Agency for Healthcare Research and Quality's specifications; they represent community-level indices of socioeconomic status

Table 1.1. Baseline Sociodemographic, Clinical, and Geographic Characteristics of Current Users of Rosiglitazone in Medicare Fee-for-Service Study Sample at Index Date by Race *

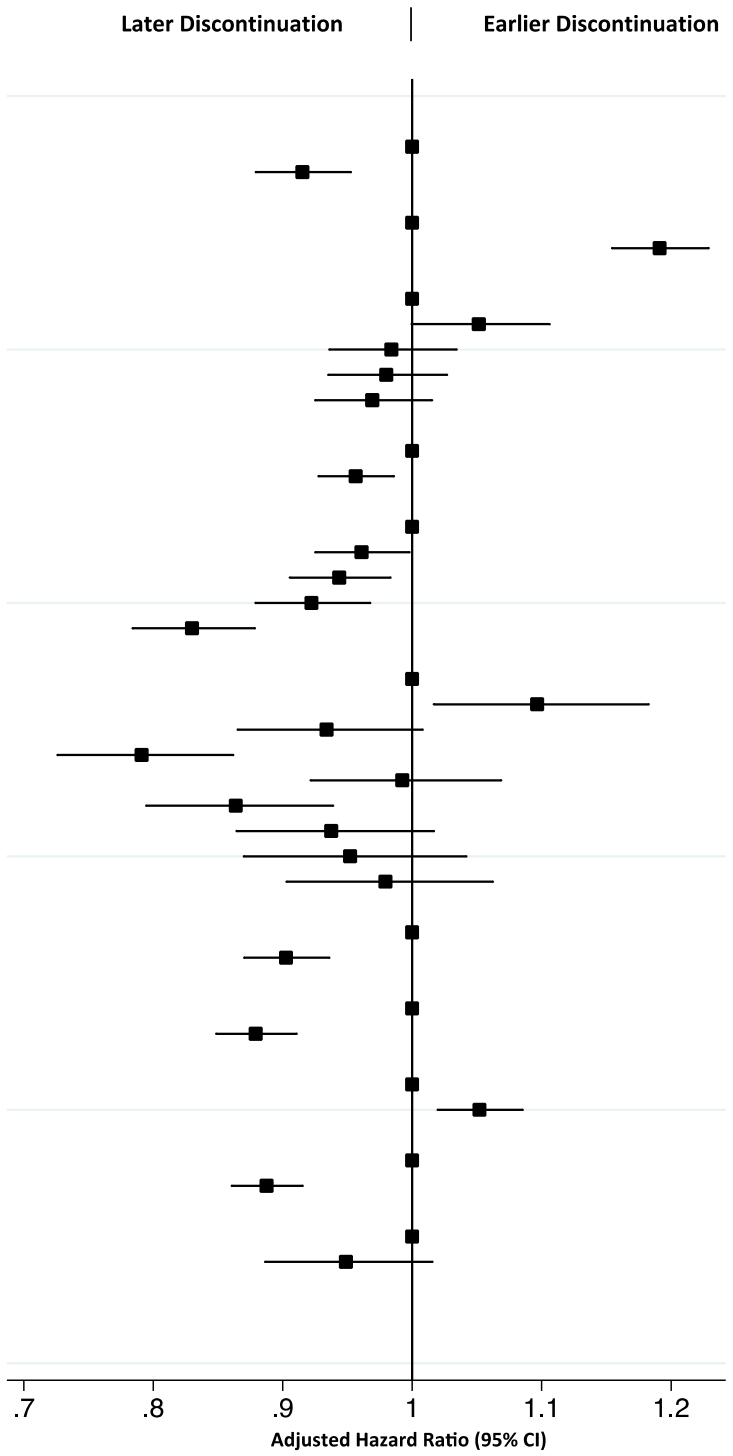
Characteristics	White Rosiglitazone Users (n=37 412)	Black Rosiglitazone Users (n=7 862)	White Rosiglitazone Users with History Cardiovascular Disease (n=8 776)	Black Rosiglitazone Users with History Cardiovascular Disease (n=1 471)
Women (%)	61	70	57	72
Age group, years(%) 65-69	31	35	25	31
70-74	26	28	25	28
75-79	20	19	22	19
80-84	13	11	17	13
≥85	9	8	11	10
Low Personal Income (%)	35	61	46	72
SES Index Score by zip code, mean (SD)	49.68 (4.0)	48.1(3.8)	49.77 (3.8)	47.95 (3.5)
Geographic division (%)				
New England	5	2	6	2
Middle Atlantic	15	19	16	16
East North Central	15	12	16	15
West North Central	9	2	10	2
South Atlantic	19	35	18	34
East South Central	9	14	9	13
West South Central	11	11	12	13
Mountain	6	1	4	1
Pacific	11	4	10	4
History of Cardiovascular Disease (%)	23	19	--	--
Medication Possession Ratio				
Higher adherence MPR≥1	44	38	42	36
Lower adherence MPR<1	56	62	58	64
Number of Outpatient Visits (%)				
Less than or equal to 2	60	65	30	33
Greater than 2	40	35	70	67
Provider Type (%)				
Endocrinology/Cardiology	5	4	6	6
Other	95	96	94	94
Receipt of >=1 non-TZD oral DM claim in pre-period (%)	33	39	64	55

Abbreviations: SES socioeconomic status, non-TZD a medication not in the thiazolidinedione class, DM diabetes mellitus Note: The SES index score is derived from zip code-level US census variables based on the Agency for Healthcare Research and Quality's specifications; higher SES values imply higher SES (U.S. mean, 50), All numbers refer to percentages, with the exception of SES index score; values rounded to nearest whole number

*To compare baseline characteristics in both study samples among black and white enrollees, p-values were computed for dichotomous variables using the $\chi 2$ test and for continuous variables using the t test;
except where italicized, all p-values<0.05

Figure 1.3. Multivariate Cox Proportional Hazards Analysis of Variable Association with Time to Discontinuation of Rosiglitazone after May 21, 2007 safety advisory in Black and White Medicare Fee-for-Service Enrollees

Variable	Total, n	Cases, n*	Follow-up time (person-years)	Crude Difference in Median Time to Discontinuation (days)	Adjusted HR (95 % CI)†
Race					
Black (ref.)	7862	5386	4387	-	-
White	37412	25 105	20787	12	0.92 (0.88, 0.95)
Personal Income					
Low (ref.)	17823	11088	9799	-	-
Not Low	27451	19403	15374	-31	1.19 (1.15, 1.23)
SES Index Score Quintile					
Quintile 5- Lowest (ref.)	9560	6348	5340	-	-
Quintile 1 -Highest	7784	5506	4337	-30	1.05 (1.00, 1.11)
Quintile 2	8281	5589	4578	-15	0.98 (0.94 1.03)
Quintile 3	10390	6939	5773	-7	0.98 (0.94, 1.03)
Quintile 4	9259	6109	5146	-1	0.97 (0.93, 1.02)
Sex					
Female (ref.)	28149	18970	15676	-	-
Male	17 125	11521	9497	8	0.96 (0.93, 0.99)
Age Group, years					
65-69 (ref.)	14300	9989	8096	-	-
70-74	12009	8228	6763	6.5	0.96 (0.93, 1.00)
75-79	9161	6185	5094	0.5	0.94 (0.91, 0.98)
80-84	5866	3789	3185	15.5	0.92 (0.88, 0.97)
≥ 85	3938	2300	2035	34.5	0.83 (0.78, 0.88)
U.S. Census Division of Residence					
New England (ref.)	2144	1472	1186	-	-
Middle Atlantic	6854	4932	3826	-19.5	1.10 (1.02, 1.18)
East North Central	6312	4151	3498	28.5	0.93 (0.87, 1.01)
West North Central	3346	2014	1859	67.5	0.79 (0.73, 0.86)
South Atlantic	9758	6740	5438	2.5	0.99 (0.92, 1.07)
East South Central	4266	2695	2377	34.5	0.86 (0.79, 0.94)
West South Central	4815	3210	2665	14.5	0.94 (0.86, 1.02)
Mountain	2338	1559	1295	32.5	0.95 (0.87, 1.04)
Pacific	4200	2859	2328	4.5	0.98 (0.90, 1.06)
History of Cardiovascular Disease					
History of CV disease (ref.)	10247	7044	5633	-	-
No history of CV Disease	35 027	23447	19540	24	0.90 (0.87, 0.94)
Medication Adherence					
Low Adherence (ref.)	25903	18141	14575	-	-
High Adherence (MPR)	19371	12350	10599	38	0.88 (0.85, 0.91)
Health Service Utilization					
≤2 Outpatient visits (ref.)	27359	18084	15180	-	-
>2 Outpatient Visits	17915	12407	9993	-26	1.05 (1.02, 1.09)
Receipt of non-TZD DM medication‡					
Yes (ref.)	29730	20504	16597	-	-
No	15544	9987	8576	26	0.89 (0.86, 0.92)
Provider type					
Endocrinology/ Cardiology (ref.)	2198	1588	1228	-	-
Other	43076	28903	23945	25.5	0.95 (0.89, 1.02)



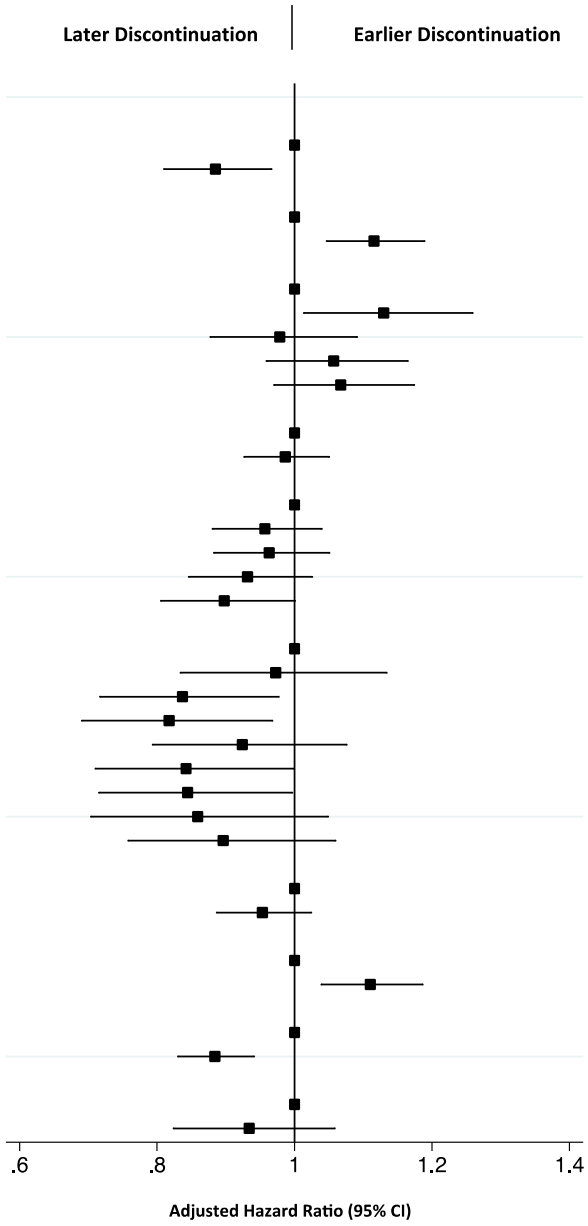
*Cases defined as enrollees who discontinue rosiglitazone before the end of study period, includes individuals with censored and non-censored individuals

†We fit Cox-proportional hazard models to adjust for the selected covariates; confidence intervals that do not cross 1 are significant at P<0.05

‡Receipt of at least one claim for a non-thiazolidinedione oral diabetic medication in the baseline period prior to the May 21, 2007 advisory.

Figure 1.4. Univariate and Multivariate Proportional Hazards Analysis of Variable Association with Time to Discontinuation of Rosiglitazone after May 21, 2007 safety advisory in Black and White Medicare Fee-for-Service Enrollees with a History of Cardiovascular Disease

Variable	Total, n	Cases, n	Follow-up time (person-years)	Crude Difference in Median Time to Discontinuation (days)	Adjusted HR (95% CI)†
Race					
Black (ref.)	1471	1032	813	-	-
White	8776	6012	4820	1	0.88 (0.81, 0.97)
Personal Income					
Low (ref.)	5059	3292	2748	-	-
Not Low	5188	3752	2884	-23	1.12 (1.05, 1.19)
SES Index Score Quintile					
Quintile 5-Lowest (ref.)	2033	1347	973	-	
Quintile 1-Highest	1750	1284	948	-32	1.13 (1.01, 1.26)
Quintile 2	1733	1175	1359	-16	0.98 (0.88, 1.09)
Quintile 3	2475	1697	1235	-18	1.06 (0.96, 1.16)
Quintile 4	2256	1541	1118	-14	1.07 (0.97, 1.17)
Sex					
Female (Ref)	6108	4192	3365	-	-
Male	4139	2852	2268	1	0.99 (0.93, 1.05)
Age group, years					
65-69 (ref.)	2653	1898	1492	-	-
70-74	2560	1785	1432	5	0.96 (0.88, 1.04)
75-79	2245	1555	1236	5	0.96 (0.88, 1.05)
80-84	1656	1101	890	8	0.93 (0.85, 1.03)
≥ 85	1133	705	582	25	0.90 (0.81, 1.00)
U.S. Census Division					
New England (ref.)	526	387	291	-	-
Middle Atlantic	1597	1148	884	10	0.97 (0.83, 1.13)
East North Central	1619	1095	884	32	0.84 (0.72, 0.98)
West North Central	867	559	477	74	0.82 (0.69, 0.97)
South Atlantic	2060	1449	1142	24.5	0.92 (0.79, 1.08)
East South Central	983	654	544	39	0.84 (0.71, 1.00)
West South Central	1212	806	654	31	0.84 (0.72, 1.00)
Mountain	386	255	210	58	0.86 (0.70, 1.05)
Pacific	964	665	528	22.5	0.90 (0.76, 1.06)
Medication Adherence					
Low Adherence (ref.)	6069	4281	344	-	-
High Adherence (MPR)	4178	2763	2276	7	0.95 (0.89, 1.02)
Health Service Utilization					
≤2 Outpatient visits (ref.)	3118	1975	1665	-	-
>2 Outpatient Visits	7129	5069	3968	-33	1.11 (1.04, 1.19)
Receipt of non-TZD DM medication‡					
Yes (ref.)	6414	4524	3542	-	-
No	3833	2520	2091	20	0.88 (0.83, 0.94)
Provider type					
Endocrinology/ Cardiology (ref.)	653	488	361	-	-
Other	9594	6556	5272	29	0.93 (0.82, 1.06)



*Cases defined as enrollees not censored who discontinue rosiglitazone before the end of study period
†We fit Cox-proportional hazard models to adjust for the selected covariates; confidence intervals that do not cross 1 are significant at P<0.05
‡Receipt of at least one claim for a non-thiazolidinedione oral diaebtic medication in the baseline period prior to the May 21, 2007 advisory.

Chapter 2

State Expansion of Schedule II Prescriptive Authority to Nonphysician Clinicians and Impact on Utilization of Opioid Pain Relievers

Introduction

In the past decade, increasing prescription opioid use and misuse has emerged as a major public health conundrum. While advocates for increased access emphasize aggressive treatment of pain, policy makers face the widening predicament of misuse, increased overdose deaths[50], and drug diversion[51]. Indeed, there is wide variation among states in overdose rates and use of opioid pain relievers[52,53] that is not explained by demographic or clinical differences between populations.

State scope-of-practice (SOP) laws define which activities a trained healthcare practitioner may undertake, in which settings, and under what parameters. Activities legislated by SOP laws include the prescribing of medications, either independently or with a supervising physician. SOP laws differ by state and by profession, resulting in variation in authority given to nonphysician clinicians to prescribe controlled substances[54].

Since the 1990's, there has been an increase in the number of nonphysician clinicians providing primary healthcare.[55] This increased provision of care has been

accompanied by SOP legislation that has given more authority to nurse practitioners (NPs) and physician assistants (PAs) to prescribe medications[56]. Before the year 2000, the majority of states allowed for NPs and PAs to prescribe non-controlled prescription medications to their patients, but did not allow for prescribing of controlled substances. Controlled substances are drugs with the potential for abuse and are regulated under the Controlled Substances Act with enforcement by the Drug Enforcement Agency. A drug is placed in its respective schedule (five in total) based on both, "whether it has a currently accepted medical use in treatment in the United States" *and* its "relative abuse potential and likelihood of causing dependence."[57] Refer to Appendix 2.1 for overview of controlled substance classification scheme. Prescribing by PAs and NPs of schedules III-V drugs was enabled first, and then schedule II—the most highly regulated of prescription products with recognized medical use. Schedule II drugs, including opioid pain relievers (OPRs), have a high potential for abuse that may lead to severe psychological or physical dependence. They are also the class of medications most responsible for the rise in overdose deaths and opioid misuse nationally.

Although a variety of policy approaches aimed at curbing inappropriate use of opioid pain relievers are being considered[58], there have been few investigations on determinants of utilization of schedule II opioid pain relievers. In this study, we evaluated the impact of scope-of- practice laws that newly allow nurse practitioners and physician assistants to prescribe schedule II medications on utilization of OPRs.

METHODS

Data Sources

We utilized data from the MarketScan Enrollment, Outpatient, and Prescription Claims Commercial Databases from 2004-2010 to compare differences in opioid utilization before and after expansion of scope-of- practice laws that newly enable nurse practitioners and physician assistants to prescribe schedule II OPRs on prescribing of these medications. The MarketScan claims database is a nationwide United States-based dataset on nearly 30 million commercially insured enrollees under the age of 65 comprised of claims information principally from employers. The data include de-identified patient enrollment information as well as inpatient, outpatient, and pharmacy claims information. The databases were linked using the unique patient identifier found across data files types. The Enrollment Summary File included individual-level demographic information and was used to ascertain covariates of interest such as sex and age. The Outpatient Prescription Drug File included prescription claims information, such as prescription drug name, and was used to estimate total counts of schedule II OPR prescription claims per enrollee and at the state level. The outpatient visits file was utilized to create aggregate and person-level covariate measures of clinical interest. Albeit representative only of the experience of the commercially insured population, MarketScan is a suitable database for this work because the vast majority of opioid users are below the age of 65[50].

We identified change in SOP laws from the DEA's "Mid-level Practitioners Authorization by State"[59] documents published and archived online. These documents, updated upon any change in a state's prescriptive SOP policy, include information on all

nonphysician clinicians and were used to identify states that expanded their SOP laws to allow PAs or NPs to prescribe schedule II OPRs during the study period along with control states that did not allow NPs or PAs to prescribe these medications. Precise dates of enactment were verified through review of Boards of Pharmacy and Department of Public Health websites for the selected states.

Case and Control State Selection

The primary exposure variable was assigned at the state level and was defined by an expansion in SOP prescriptive authority to allow for prescribing of schedule II medications for either NPs or PAs in any period from 2004-2010. We identified three case states in the study period that fit these criteria. In 2006, Virginia enacted legislation allowing NPs to prescribe schedule II drugs, in mid-2007 Pennsylvania expanded the same prescriptive authority to PAs, and in the final week of 2007 New York expanded authority to PAs as well. All states required that prescriptions be written under the supervision of a physician through a collaborative agreement. We were limited in the selection of control states because by 2004 most states were already allowing the prescribing of controlled substances under physician supervision. Further, because New York served as the most appropriate control state for Pennsylvania, we decided to exclude it from the analysis as a case state for methodological reasons. We therefore matched Virginia and Pennsylvania as case states to West Virginia and New York as control states, respectively. These control states saw no change in their scope of practice laws in the same time periods and did not allow the relevant nonphysician clinician group to prescribe schedule II drugs in the same period (Figure 2.1).

The primary determinant of control state selection was geographic proximity to case state. An additional consideration that we made in selection were that the case and control states could not differ markedly with respect to other pharmaceutical policy changes related to prescribing of opioids such as the presence of a prescription monitoring program[60] and concurrent change in the ability of other nonphysician clinicians to prescribe controlled substances in the time period of interest.

We chose to focus our analysis on comparing patterns of use of OPR in the same year of the policy change for each case and control state selection. Specifically, we focused on a two-month period before and after the date of the policy enactment, with a one-month before and two-month after policy change buffer time. The buffer is intended to mitigate any issues related to anticipatory changes in prescribing prior to the policy change as well as offers a lag period to give time for the policy effect to be implemented. For enrollees residing in case states, utilization following the change in the SOP laws was classified as "exposed."

Study population

Our analysis consisted of quantifying patient-level dispensing patterns of schedule II opioid medications among all beneficiaries aged 15 years to 65 years of age who had at least one prescription claim for any medication in both the pre- and post-period of the case and control states. Because it is rare for oral opioids to be used in children, we excluded enrollees younger than 15 years old[50].

Main outcome measures

Our main outcome variables were 1) a binary indicator of whether an enrollee received any schedule II OPR in the pre and post- period; and 2) the mean number of schedule II prescriptions per person received in the pre- and post-policy period among enrollees with at least one claim for any schedule II OPR in both periods. Neither outcome differentiated between the dose or type of schedule II OPR.

Schedule II OPR prescription names were identified using the RedBook Drug Reference and pulled from the MarketScan pharmacy claims. Cough preparations, injectables, transbuccal products, inpatient opioid use, and methadone dispensed by opiate detoxification or maintenance programs were not included in the analysis, because they are not recorded in the data (i.e., inpatient products and methadone maintenance) or because these products are often administered in unusual situations of care (i.e., transbuccal products). The specific drug names included in this measure were all single and combination Schedule II products including oxycodone, meperedine, morphine, hydromorphone, oxymorphone, and codeine.

Primary Independent variables

The primary independent variables indicated whether enrollee state of residence was a case or control state, an indicator variable for period (0 for the period before the policy change and 1 in the period after), and a term of interaction between these two variables (the difference-in-difference estimate). The difference-in-difference interaction term reflects the marginal effect of the policy on enrollees residing in case states as compared to enrollees residing in control states for our outcomes of interest.

Covariates included in the analysis were age, sex (male/female), prescription claim for any oral non-steroidal anti-inflammatory prescription in either period, and associated pain comorbidities (a dichotomous variable indicating an outpatient claim with ICD-9 code for any of these chronic pain conditions: chronic lower back pain (720-724.8, 738.4, 739.3-739.4,756.11-756.12, 805.4-805.6, 846-847.4), generalized pain (780.06); and specific chronic pain conditions (338.0-338.4); and a dichotomous indicator of any diagnosis claims for cancer[61].

STATISTICAL ANALYSIS

We employed a difference-in-difference method to assess both the crude and adjusted impact of expansion of state scope-of-practice prescriptive authority laws on an enrollee's propensity to receive a schedule II OPR and the frequency of receipt of schedule II OPRs in enrollees with a history of use. We compared enrollees residing in case states that expanded their SOP laws to allow for NP or PAs to prescribe schedule II OPRs to enrollees in control states that made no changes to their SOP laws in the same period. A difference-in-difference (DID) is a quasi-experimental study design that accounts for the secular trends in utilization and prescribing patterns over time. The central premise of the DID method is that observations for two relatively comparable groups are collected for two periods. One group (enrollees residing in case states in our study) is subjected to a policy change, while the other group (enrollees in control states) is not. The difference in the change in the outcome of interest between the pre- and post-period in the control group is subtracted from the change in the outcome in the case group

to arrive at a DID estimate. By comparing two groups contemporaneously the DID design attempts to remove biases related to secular changes in the outcome of interest in the case group that may be unrelated to the policy change, assuming the differences between the case states and control states would have remained constant in the absence of the policy change (referred to as the same-trend assumption).

Using this design, we fit two sets of models in our analysis. To examine propensity to receive a schedule II OPR, we fit linear probability models that included the binary outcome variable of receipt or non-receipt of any schedule II OPR in the before and after period as well as the independent variables and covariates described previously. The DID estimate derived from this model reflects the comparative prevalence of schedule II OPR receipt for enrollees in a case state receiving a schedule II OPR after the policy change relative to before, adjusting for secular changes in use as measured from the control state. To examine the impact of changing SOP laws on frequency of receipt of schedule II OPRs among enrollees with at least one claim of any schedule II OPR in both the pre- and post-period, we fitted generalized linear models with the linear outcome variable and the same parameters as the first model. The difference-in-difference estimate derived from this model reflects the marginal effect of the policy on the mean number of schedule II OPRs received by enrollees in case states as compared to the difference in the mean number of schedule II OPRs in the control states in the before and after period. For the first model, we separately assessed the difference-in-difference estimates among younger age categories (15-34 years) versus the oldest age category (35-65 years). For all models, we used generalized estimating equations to account for clustering of observations by state using PROC GENMOD in SAS software.

All analyses were conducted using SAS software, version 9.2 (Cary, NC SAS, Inc 2013) and STATA software, version 13 (College Station, TX StataCorp LP, 2013). The Brown University Human Research Protection Office approved the study protocol.

RESULTS

To test the appropriateness of the selection of controls and to test the common trend assumption of a difference-in-difference analysis, we first plotted weekly prevalence of oral Schedule II OPR utilization in each of the case states and each of the potential control states in the yearly period prior and after the change in policy (Figure 2.2). For both pairs, there appeared to be a similarity of trends prior to the case state change in policy, thus we felt confident that the matches were appropriate. Rates of use of schedule II opioid pain relievers steadily rose over the study period for both the case and control states, with no discernable change in pattern evident immediately after the expansion in SOP legislation.

Our final analytic sample included 377,141 enrollees residing in case states and 183,471 enrollees in control states (Table 2.1). For our sample that included only enrollees with at least one schedule II OPR claim in both the before and after period, our analytic sample consisted of 3,509 enrollees residing in case states and 1,093 in control states. Although there were few striking differences between the groups of states, residents in case states were more likely to be female, younger, have more non-steroidal anti-inflammatory claims per 10,000 enrollees, and have less pain and cancer diagnoses claims as compared to enrollees residing in control states. Overall, there was a modest absolute increase of 0.16% in the proportion of enrollees residing in case states receiving

a schedule II OPR between the before and after period (3.32 to 3.48 % of cases); and an absolute increase of 0.17% in control states (from 1.95 to 2.12%).

In the first analysis where we examined the impact of policy change on the likelihood of receipt of schedule II OPRs, we found no evidence that enrollees residing in case states had a change in the likelihood of receipt of a schedule II OPR as a result of the policy change (Table 2.2) as compared to enrollees residing in control states. However, our analysis for each case/control state pair showed mixed results. We found evidence of a 0.01% (95% CI:-0.0002, -0.0001) decline in prevalence of receipt of a schedule II OPR in Virginia as a result of the policy enabling NPs to prescribe schedule II medications compared to the change in prevalence in West Virginia control state. There was no evidence however of a significant decline or increase in prevalence of receipt of a schedule II OPR in Pennsylvania versus New York as a result of expansion to PAs.

In the second analysis where we examined differences in frequency of receipt of schedule II OPRs, we found evidence of a slight increase of 0.06 (95% CI: 0.0255-0.0865) in the mean per person frequency of schedule II OPR receipt after the policy change in the full sample (Table 2.3). When we stratified the analysis by each case/control state pair, we found that enrollees residing in Virginia (case state) saw a significant, albeit very small, increase in use with a DID estimate of 0.0296 (95% CI: 0.0292-0.0299) as compared to residents of West Virginia; while residents in Pennsylvania also saw an increase in use as compared to their counterparts in New York with a DID estimate of 0.0608 (95% CI: 0.0595- 0.0621).

When we fit the models for each age group separately; we found that among both the youngest enrollees (15-34 years of age) and among the older age groups (34-65 years

of age) there was no evidence of a change in prevalence of receipt of a schedule II OPR as a result of the policy change (Table 2.4).

DISCUSSION

In this analysis, we sought to examine the potential impact of state level expansion of SOP prescriptive authority to nonphysician clinicians on utilization patterns of schedule II opioid pain relievers. Overall, we found no meaningful change in utilization of schedule II OPRs attributable to the expanded SOP laws. In our combined sample, we found no evidence in a change in the likelihood of receipt of a schedule II OPR among enrollees residing in states that had newly allowed nonphysician clinicians, either PAs or NPs, to prescribe the medications. In Virginia, which expanded use to NPs, we found a slight decrease in prevalence of use; and in Pennsylvania, which expanded authority to PAs we found no change in the prevalence of use. Among enrollees with a history of receipt of a schedule II OPR we found increased use, in the combined sample, with results consistent in both case/control pair analyses.

There has been little research elucidating the impact of nonphysician providers on prescription medication utilization, especially controlled substances. In one of the few papers that specifically examined PA and NP prescribing patterns, investigators used data from the National Ambulatory Medical Care Survey, and found that in comparison to physicians and PAs, NPs appeared to prescribe more total prescriptions[56]; and in comparison to NPs and physicians, PAs prescribe controlled substances (all categories) at a greater percentage of total prescriptions written. The authors hypothesized that the greater time availability of both NPs and PAs allows them to treat patients for urgent

matters that often may require controlled substance treatment (for example, in cases of severe pain). Our results do not provide sufficient evidence to support the idea that either PAs or NPs are more likely to prescribe controlled substances, in this case schedule II OPRs. In our analysis examining the impact of expanded scope-of-practice on frequency of receipt of schedule II, we found a decrease in use in the case state that expanded prescriptive authority of schedule II prescriptions to NPs (Virginia). The underlying mechanism for this difference is unclear.

In general, however, we found modest increases in frequency of utilization of schedule II OPRs in states that expanded prescribing authority to nonphysician clinicians among a sample of established users of schedule II OPRs; but decreases in prevalence of receipt in general. These seemingly paradoxical findings can be explained in several ways. For non-established, perhaps naïve users of schedule II OPRs, enabling nonphysician clinicians prescribing authority may motivate more careful consideration of initiating use in favor of alternative medications with less addictive potential. Our results from the stratified analysis also suggest that expansion of prescriptive authority may in some circumstances result in more judicious use of schedule II OPRs. Because the prescribing of schedule II medications can only happen with the supervision of a physician, it may be that nonphysician clinicians such as PAs are able to complement and supplement the care provided by the physician and more methodically address some of the complex issues related to prescribing of pain medications, including schedule II OPRs. Although we were unable to examine the quality of prescribing across practitioner type, this theory seems plausible given previous research that has found that

multidisciplinary care models, if well-integrated and not fragmented, may improve quality of care.[62]

The marginal differences in usage we found among established users (Table 2.3) are corroborated by a Kentucky state sanctioned report commissioned in 2004. In this cross-sectional research analysis which was undertaken by the Legislative Research Commission to study differences in utilization of controlled substances between states that allow NPs to prescribe controlled substances and states that do not, researchers concluded that states that allow NPs to prescribe schedule II medications, including attention-deficit disorder medications, have about 1.4 % more schedule II prescriptions sold and 6.6 more grams per capita dispensed than states that have not granted NPs this authority[63]. We found even smaller estimates of changes; again, underscoring the potentially minimal role nonphysician clinicians may be playing in the opioid epidemic.

One of the reasons why we may not have seen a more dramatic increase or decline in use may be related to the relatively small number of NPs and PAs practicing in each state in comparison to physicians. In comparison to physicians (2009 national total: 785,326)[64], PAs (2008 total: 73,893)[65] and NPs (2009 total: 167,857)[65] practicing in each state are a small minority of practicing health practitioners[66]. In our sample, Virginia had 5,167 NPs to 24,091 physicians (a 1:5 ratio) and West Virginia had 1,075 NPs to 5,387 physicians (a 1:5 ratio); for each 10,000 residents there were 6.3 and 5.8 NPs practicing in Virginia and West Virginia respectively. Pennsylvania had 4,023 PAs practicing in 2007 to 49,575 physicians (a 1:12 ratio) and New York had 7,359 PAs to 88,179 physicians (a 1:12 ratio); for each 10,000 residents there were 3 and 4 PAs that were practicing in Pennsylvania and New York respectively. Only a portion of these

nonphysician clinicians seeks a DEA license that would enable them to prescribe controlled substances[67]. It is not surprising then that the effects we found, regardless of the policy change, were very small.

LIMITATIONS

The proposed work has some limitations. First, some OPR prescriptions may be purchased outside the insurance adjudication process and are therefore not captured in any claims database. We are therefore not able to estimate the full utilization of schedule II OPRs. Estimates likely vary as to what percent of prescription opioid claims are purchased entirely out-of-pocket versus through insurance. In a report from the New York City Department of Health and Mental Hygiene, researchers noted that more than half of schedule II opioid analgesics were paid for with commercial insurance, 21% by Medicaid, 5% by Medicare and the remainder by cash or other sources. If the primary driver of diversion of schedule II OPRs are prescriptions purchased outside the insurance system and if the policy encouraged greater OPR seeking behavior among those residents paying fully out-of-pocket, then our analysis will at minimum underestimate the effects of the policy on potential diversion.

Second, it is not within the scope of our research aims to seek out the role of interstate variability in OPR utilization resulting from prescription benefit design differences. However, because MarketScan is a database reflecting an assortment of commercial plans from privately insured individuals, there is reason to believe variability in plan design for what are almost exclusively generic medications will not differ across state lines. As a result of limitations with the dataset, we are unable to match a provider

to a particular prescription dispensing and as a result cannot assess the direct impact of the policy change in terms of specific portion of OPR prescriptions that are written by nonphysician clinicians. The generalizability of our findings to other patient populations may also be limited in that MarketScan data only captures the healthcare experience of commercially insured individuals. Further, our analysis was not designed to identify whether or not these policies impacted diversion of schedule II OPRs which is one of the seminal problems now facing law enforcement and public health departments. Given the scope of the national epidemic, further research in this area is warranted.

Conclusion

The objective of this study was to evaluate the association between changing state level scope of prescriptive authority laws on utilization patterns of schedule II OPRs. As payers and providers aim to improve access and appropriate use of medications with high risk of abuse, it is instructive to understand the role of state policy in explaining use of OPRs; and the wide interstate variation in both opioid utilization and opioid overdose deaths nationally may partially be understood as a result. By elucidating the potentially minimal role of SOP laws on the utilization patterns of these medications, we provide preliminary evidence that allowing nonphysician providers expanded prescribing privileges does not contribute to this emerging epidemic. This work therefore discounts the rationale among opponents of expansion of controlled substance prescribing privileges to nonphysician clinicians; namely, that such expansion opens the floodgates to further expansive and irrational use of high risk opioids. We found no evidence for that to be the case. On the contrary, our work tentatively suggests that expansion in SOP laws

may in fact result in more judicious use of schedule II OPRs. The underlying mechanism for this phenomenon warrants further investigation. In light of the impending expansion of primary care afforded by the Accountable Care Act and the shortage of primary care providers anticipated as a result, better understanding the intersecting roles of nonphysicians and physicians in improving access to quality care is paramount to improving health.

Figure 2.1. Timeline for Examining Change in Utilization of Schedule II Opioid Pain Reliever Prescriptions after Expansion of Scope-of-Practice Laws, utilizing MarketScan Commercial Healthcare claims

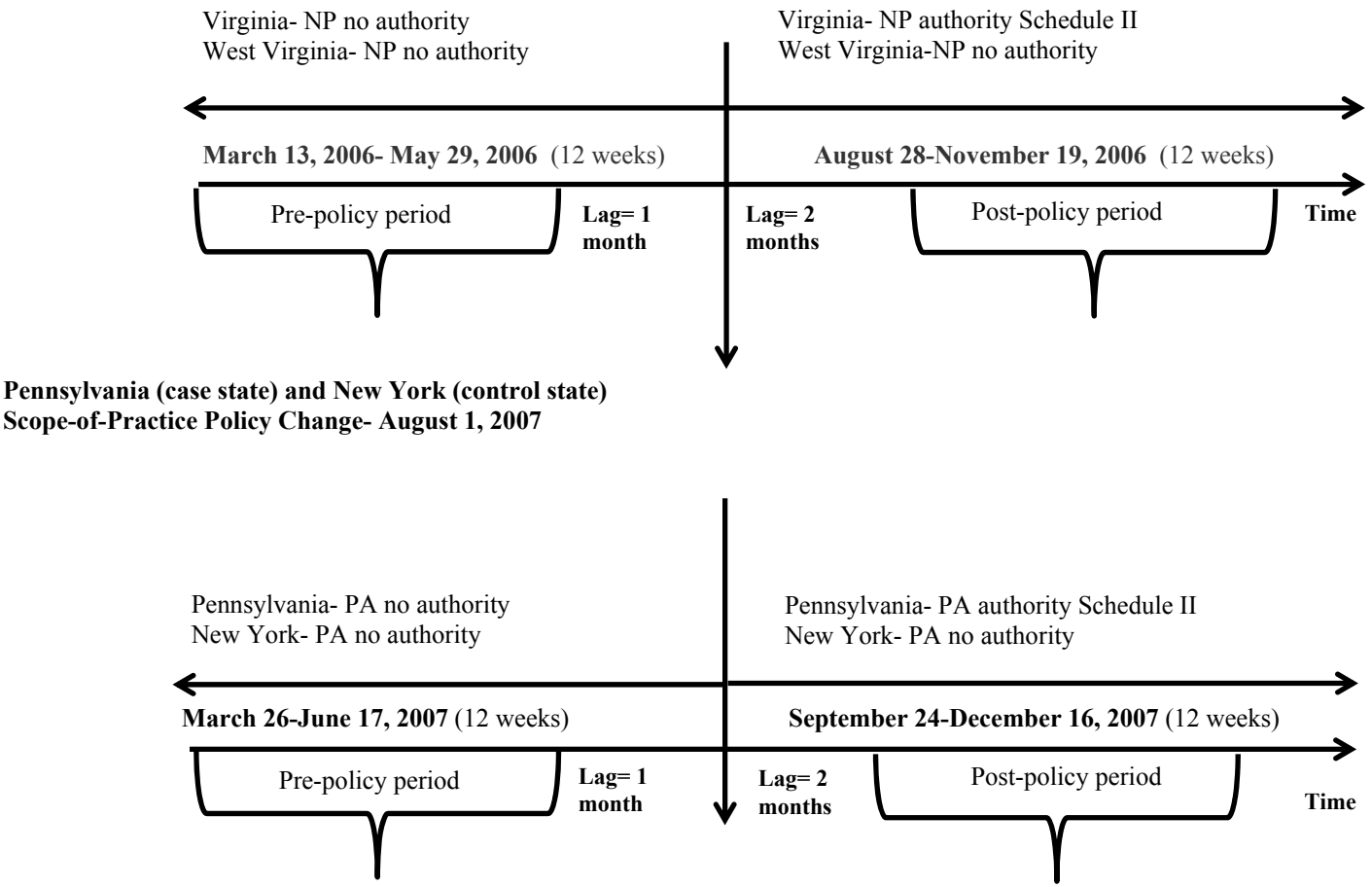
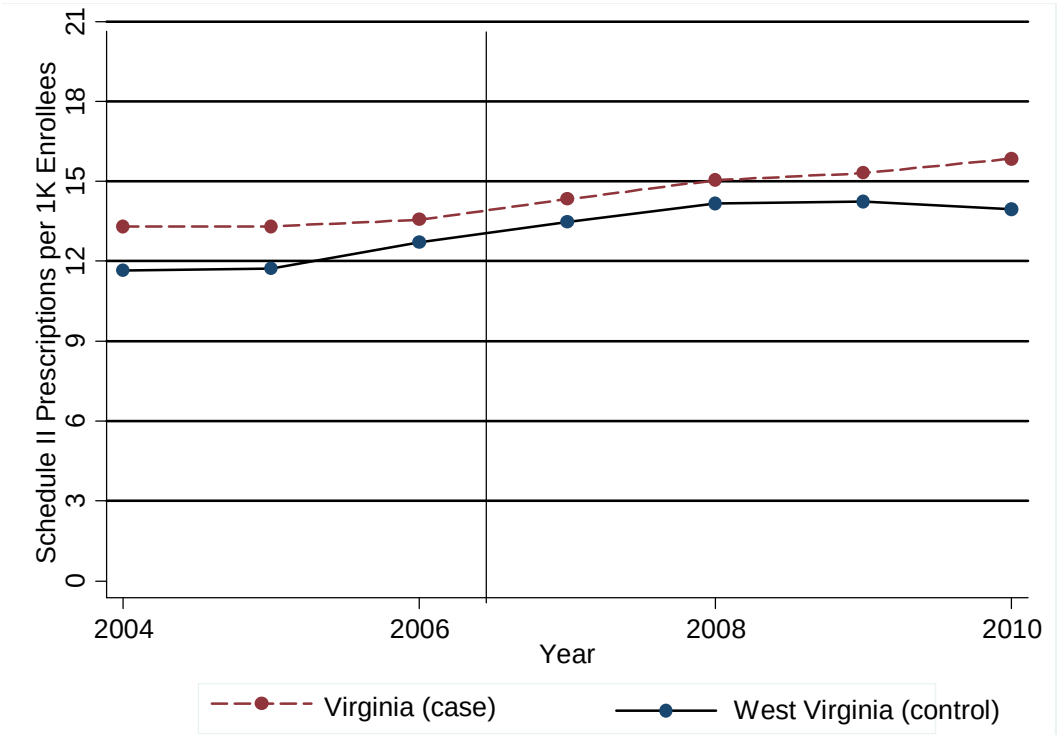


Figure 2.2 Unadjusted Yearly Rate of Schedule II Opioid Prescriptions* per 1,000 Enrollees in Case and Control States 2004-2010, MarketScan Commercial Database



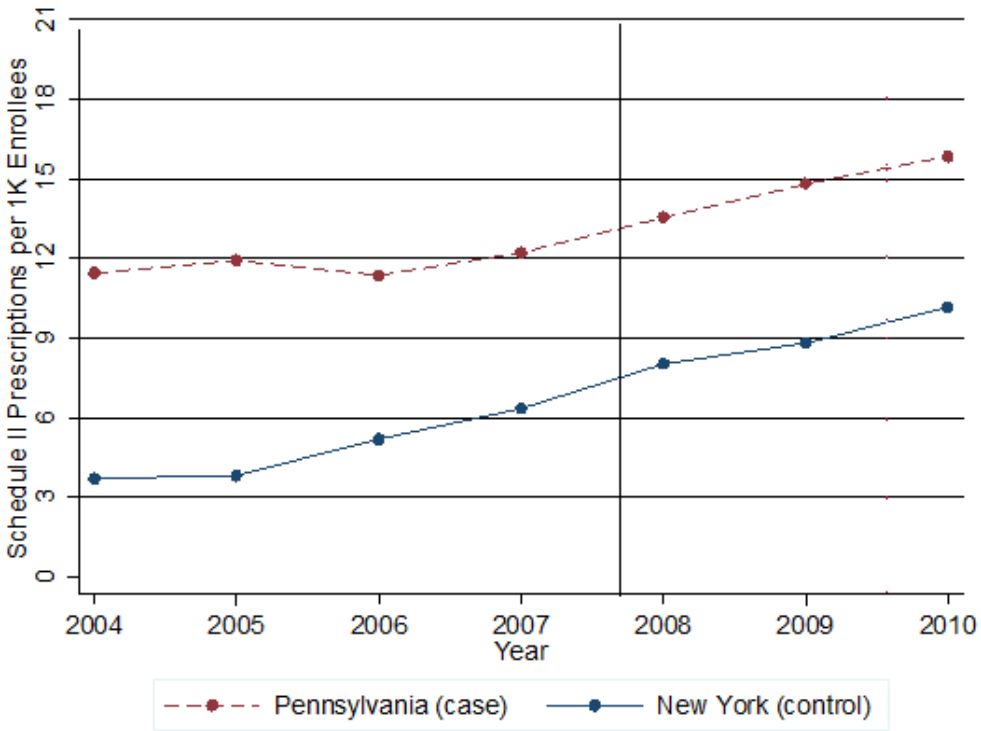


Table 2.1. Baseline Characteristics of Enrollees in Case and Control States*

Characteristic		Case Expansion States[a] (n=377,141)	Control States[b] (n=183,471)
Mean age, years (SD)		44(13)	45 (13)
Male sex (%)		40	41
Age Group, years (%)			
	15-24	10	10
	25-34	14	13
	35-44	21	20
	45-54	28	29
	55-65	27	30
NSAID Claims per 10,000 population*		885 (total=33365)	836 (total=15,358)
Pain Diagnosis per 10,000		130 (total=4919)	165 (total=3,030)
Cancer Diagnosis per 10,000		230(total=8,688)	261 (total=4,787)

*Measured in two-month baseline period; inclusion defined based on beneficiaries with at least one prescription claim in each period of that calendar year;

χ^2 or *t* test was performed to compare the characteristics of individuals in case and control states; all tests resulted in *P* values of less than 0.05.

Abbreviations: NSAID nonsteroidal anti-inflammatory; ICD-9 International Classification of Diseases, Clinical Modification

a. Case states, Virginia (2006) and Pennsylvania (2007)
b. Control states, West Virginia (2006) and New York (2007)

Table 2.2 Prevalence of Use of Schedule II Opioid Pain Relievers in Case States and Control States, before and after change in Scope-of-Practice Laws

	Percent Enrollees with Schedule II OPR claim									
Sample	**Case State(s)**				**Control State(s)**					
	Total enrollees, n	Before	After	Net Change	Total enrollees, n	Before	After	Net Change	**Between-Group change**	**Adjusted Between-group change (95% CI)**
Full Sample	377,141	3.32	3.48	0.16	183,471	1.95	2.12	0.17	**-0.01**	**0.0001** (-0.0003, 0.0002)
Virginia vs. West Virginia	149,350	3.70	3.89	0.19	25,926	3.12	3.36	0.24	**-0.05**	**-0.0001** (-0.0002, -0.0001)
Pennsylvania vs. New York	227,791	3.07	3.22	0.15	157,545	1.76	1.92	0.16	**-0.01**	**-0.0002** (-0.0003, 0.00004)

*Confidence intervals that do not cross the null value are significant at $p<0.001$, except where noted; Results in last column adjusted for age, sex, receipt of non-steroidal anti-inflammatory in period, any diagnosis claim for pain, any diagnosis claim for cancer; generalized estimating equations accounted for clustering by state

Table 2.3. Frequency of Receipt of Schedule II Opioid Pain Relievers among enrollees with History of Receipt

	Mean Number of Schedule II OPR claims									
Sample	**Case State(s)**				**Control State(s)**					
	Total enrollees, n	Before	After	Net Change	Total enrollees, n	Before	After	Net Change	**Between-Group change**	**Adjusted Between-group change (95% CI)**
Full Sample	3509	2.52	2.55	0.03	1093	2.49	2.47	-0.02	**0.05**	**0.056** (0.0255, 0.0865)[a]
Virginia vs. West Virginia	1436	2.49	2.53	0.04	260	2.57	2.58	0.01	**0.03**	**0.0296** (0.0292, 0.0299)
Pennsylvania vs. New York	2073	2.55	2.57	0.02	833	2.48	2.44	-0.04	**0.06**	**0.0608** (0.0595,0.0621)

*Confidence intervals that do not cross the null value of 0 are significant at p<0.001, except where noted; Results in last column adjusted for age, sex, receipt of non-steroidal anti-inflammatory in period, any diagnosis claim for pain, any diagnosis claim for cancer; generalized estimating equations accounted for clustering of enrollees by state

a. Significant at p=0.01

Table 2.4. State-level Changes in Use of Schedule II Prescriptions in Case States with Change in Scope-of-Practice Laws, Prevalence of receipt of Schedule II Opioid Pain Relievers, Youngest vs. Oldest Age groups

Age Group, 15-34 years										
	Percent Enrollees with Schedule II OPR claim									
Sample	**Case State(s)**				**Control State(s)**					
	Total enrollees, n	Before	After	Net Change	Total enrollees, n	Before	After	Net Change	**Between-Group change**	**Adjusted Between-group change (95% CI)**
Full Sample	89,660	3.00	3.31	0.31	41,113	1.60	1.81	0.21	**0.10**	**0.0009** (-0.0002,0.0020)

Age group, 35-65 years										
Sample	**Case State(s)**				**Control State(s)**					
	Total enrollees, n	Before	After	Net Change	Total enrollees, n	Before	After	Net Change	**Between-Group change**	**Adjusted Between-group change (95% CI)**
Full Sample	287,481	3.42	3.54	0.12	142,358	2.06	2.21	0.15	**-0.03**	**0.0** (-0.0011, 0.0012)

Chapter 3

Receipt of High Risk Medications among Elderly Enrollees in Medicare Advantage Plans

Introduction

Adverse drug events resulting from poor quality prescribing are a significant public health problem[68]. An increased burden of chronic diseases and age-related changes in drug metabolism predispose the elderly to adverse drug events precipitated by the use of high risk medications (HRM)[69,70]. HRM use in the geriatric population is associated with increases in morbidity, mortality, hospitalization, inpatient length of stays, and health care spending[71-73].

HRMs in the elderly are broadly defined as medications that should be avoided among people 65 years of age or older because the associated adverse effects outweigh potential benefits or because safer alternatives are available[2], a principle codified most prominently by the Beers[74] and Zhan[75] criteria. To improve the quality of drug prescribing in the elderly, the Centers for Medicare and Medicaid Services (CMS) requires all Medicare Advantage (MA) health plans to report publicly on the prescribing rates of HRMs, as defined by the Healthcare Effectiveness Data and Information Set's (HEDIS) "Drugs to Avoid in the Elderly" quality measure. The term HRM is often used interchangeably with 'potentially inappropriate medication', [74,75] a phrase that

acknowledges the complexity inherent in assessing the quality of patient-specific drug management decisions among heterogeneous patient populations. In this manuscript, we use 'high risk', because that is the specification of the quality measure used in the analysis.

Successful efforts to reduce HRM use in the elderly require knowledge of how prescribing of these agents varies geographically and the factors that predict their use. However, there are few nationally representative studies of the prevalence and predictors of HRM use, particularly following the implementation of the Medicare prescription drug benefit in 2006. Medicare Part D extended prescription drug coverage to the majority of Medicare's approximately 44 million beneficiaries, only one-third of whom had drug coverage previously. More universal access to drug coverage among the elderly has increased pharmaceutical use[76,77] and therefore, by extension, opportunities for receipt of HRMs. Further, there is limited evidence about HRM use in the MA program, which now comprises approximately 25% of the Medicare population. Because such plans assume financial risk for paying for Medicare-covered services and integrate the financing and delivery of care, and because the MA population may be healthier, on average, and younger than traditional Medicare enrollees[78], the rate of HRM use in this population may differ from that observed in the traditional Medicare population.

In this study, we examined predictors of HRM use utilizing the HEDIS quality indicator in a national sample of over 6 million elderly MA enrollees. We also characterized geographic variation in HRM use with the aim of identifying subpopulations at increased risk of receiving these medications.

METHODS

Data Sources

We obtained individual-level Medicare HEDIS data for the 2009 calendar year from CMS. The National Committee for Quality Assurance (NCQA) developed HEDIS to measure and compare the quality of care delivered to enrollees in health plans. Since 1997, all Medicare managed care plans have been required to submit HEDIS data to the CMS. In 2005, NCQA developed two HEDIS quality indicators both entitled "Drugs to Avoid in the Elderly," to measure the percentage of Medicare enrollees in each plan that received at least one HRM or at least two different HRMs. Clinical co-morbidity information and the names of specific medications are not available in the HEDIS data (refer to Appendix 3.1 for a list of medications included in the measure).

Conceptually and operationally, the Beers and Zhan criteria for use of "potentially inappropriate medications in the elderly" form the backbone of the HEDIS measures. Both measures, Beers in particular, are widely used in the literature and have been accepted through various iterations as the best available clinical tools for the screening of HRMs. Research has shown a link between medications on the Beers list and serious adverse effects in the elderly, including falls, fractures, gastrointestinal bleeding, and delirium[79-81]. The final list of 110 medications used to identify claims for HRMs borrows heavily from the Zhan and Beers criteria and was determined by NCQA through a modified Delphi consensus process that included a panel of clinical, methodological, and organizational science experts. A more detailed description of this process[82] and comparison of the HEDIS measure with other criteria can be found elsewhere[83].

Study population

We matched 98% of the HEDIS observations to the Medicare enrollment file from the corresponding year to determine enrollees' demographic characteristics. We used the CMS Medicare Advantage Plan Directory to obtain information on health plan characteristics. If these data were missing, we contacted the health plan directly. Using the Dartmouth Atlas of Healthcare, we assigned each enrollee to a hospital-referral region (HRR) on the basis of zip code of residence. HRRs represent distinct regional health care markets within which residents seek the services of a tertiary hospital or major referral center[84]. HRRs have been utilized widely to characterize geographic variation in healthcare quality and delivery[85-87].

Among 6,514,278 enrollees eligible for the HEDIS measure, we excluded 86,131 who died during the measurement year, who were not residing in the U.S., or those enrolled in health plans outside the U.S. We further excluded 8,707 observations from six plans that erroneously reported a greater rate of enrollees receiving two or more HRMs than the rate of enrollees receiving one or more HRMs. After all exclusions, the final study sample consisted of 6,204,824 enrollees.

Outcome Variables

The two primary dependent variables of interest were: (1) receipt of at least one prescription for a HRM; and (2) receipt of at least two different HRMs during the measurement year as defined by the HEDIS "Drugs to Avoid in the Elderly" quality indicators. To be eligible for inclusion in the denominator for either indicator, enrollees must be 65 years of age or older, continuously enrolled in the managed care plan

throughout the measurement year, and have prescription drug benefits for the duration of the measurement year. To be included in the numerator, enrollees were required to have a prescription drug claim for at least one (for first measure) or at least two HRMs (for second measure).

Independent Variables

Descriptive variables defined at the individual level included age (65-69, 70-74, 75-79, 80-85, ≥85), sex, race (white, black, other), low personal income (defined by receipt of Medicare State Buy-in assistance[36]), U.S. census division of residence (refer to Appendix 1.2 for list of states in each division), and socioeconomic status (SES) index score (by quintile). The SES index score is a composite measure of area-level socioeconomic status derived from zip code-level employment, housing, income, education and crowding data. Composition and creation of the score is described in detail by the Agency for Healthcare Research and Quality[33]. Plan-level independent variables included model type (group/staff, independent practice association, mixed/network), plan age (determined by the date the plan began its operation: before 1980, 1980-1999, and after 2000), beneficiary enrollment per plan (0-24,999, 25,000-99,999, ≥100,000), and plan tax status (for-profit, not-for-profit). All variables were tested for non-collinearity.

Statistical Analysis

We determined the percentage of eligible enrollees who met the numerator criteria for the two HEDIS indicator measures in each sociodemographic and health plan-level subgroup and used χ^2-square or t-tests to compare the characteristics of enrollees

receiving a HRM to those who did not. To identify predictors of HRM use, we fit generalized linear models to predict receipt of a HRM using the independent variables described above. We modeled outcomes on the risk-difference scale and accounted for clustering of enrollees within health plans using generalized estimating equations. Three models were fit: model 1 controlled for the individual-level characteristics of age, sex, race, and low personal income; model 2 included all variables from model 1, as well as community-level characteristics of zip code-based SES index score and census division of enrollee residence; and model 3 included all variables from models 1 and 2, as well as health plan characteristics (model type, profit status, enrollment size, and plan age).

To determine the extent of geographic variation in HRM use, we calculated the proportion of total eligible enrollees in each HRR that met the criteria for each of the HEDIS indicators. National maps were created to reflect the geographic variation in rates of HRM use for each measure.

Statistical tests were two-sided, with only $P < 0.005$ considered statistically significant, due to the large sample size. All analyses were performed using SAS statistical software (version 9.3; Cary, North Carolina) and maps were created using ArcGIS software (version 9.3; Redlands, California). The study was approved by Brown University's Human Research Protections Office.

RESULTS

In the final sample, the rates of receipt of at least one HRM and of at least two HRMs were 21.5% and 4.8%, respectively. The mean age of enrollees was 74.5 years;

58% were women and 83% were white. The characteristics of persons receiving and not receiving HRMs are presented in Table 3.1.

In fully adjusted analyses (Table 3.2), female gender, low personal income, and white race were significant predictors of receipt of a HRM at the individual level. In comparison to the reference age group which included those 65-69 years of age, the oldest age category appeared to have a protective effect, with significantly lower rates of receipt of HRMs among those enrollees. At the community level, SES index quintile showed a graded response with lower SES scores associated with higher rates of receipt of HRMs. Although most of the census divisions had significantly higher rates of receipt of HRMs when compared to the reference New England division (with the exception of Middle Atlantic and the West North Central divisions); the extent of this difference was highest (>10%) among divisions in the Southern U.S. region, including the South Atlantic, East South Central, and West South Central divisions. Plan-level characteristics did not predict use of HRM medications.

HRRs vary substantially with respect to HEDIS measures of quality prescribing. The HRR with the highest proportion of MA enrollees receiving at least one HRM was Albany, Georgia where 38.2% of enrollees received at least one HRM. The HRR with the highest proportion of enrollees receiving at least two HRMS was Alexandria, Louisiana where 13.5% received at least two different HRMs (Figure 3.1). The rate in Albany was approximately four times higher than the HRR with the lowest rate of receipt of at least one HRM- Mason City, Iowa. Of additional note, the rate of receipt of at least two HRMs in Alexandria was 20 times higher as compared to the HRR with the lowest rate- Worcester, Massachusetts (13% vs. 0.7%). The twenty lowest performing HRRs were all

in the Southern region of the U.S. In contrast, only one of the twenty highest performing HRRs was in the South; the remainder were either in the Midwest or Northeast census regions. The results for the use of two or more HRMs were similar and are therefore not shown here.

DISCUSSION

In 2009, of the 6,204,824 eligible Medicare Advantage enrollees included in this population-based, cross-sectional analysis, 21.5% received at least one HRM and 4.8% received at least two, as defined by the HEDIS quality measures. In fully adjusted analyses, females had a 10.6 higher percentage point rate of receipt of at least one HRM (95% CI: 10-11.2) compared to males. Persons residing in the West South Central, East South Central and South Atlantic census divisions had a percentage point rate of 10 or higher of receiving HRMs as compared with those residing in New England. We observed increased rates of use of HRMs among white enrollees, individuals with low personal income, and those residing in areas of lower socioeconomic status.

The direction of the gender difference was not surprising, as some of the medications categorized as high risk by HEDIS are prescribed only to women (e.g. oral estrogens) or are treatments for conditions that are more prevalent in women. Examples include psychopharmacologic agents such as long-acting benzodiazepines[88], analgesics[89], and anticholinergics[90,91]. Previous work examining use of HRMs in the community-dwelling elderly has also consistently identified males as having decreased risk of receipt of HRM medications[75].

The magnitude of the gender difference is of particular note. One study that examined the persistent gender differences in utilization of HRMs reported that even after controlling for sociodemographic characteristics, number of medications, and comorbidities, women remained at significantly higher risk of receipt of HRMs[92]. That racial minority status is associated with lower use of mental health services may also explain the slightly lower risk of HRM use in blacks and other non-white groups[93-95]. More research is needed to better elucidate the process by which these gender and racial differences arise.

In addition to gender, region of residence appears to be one of the strongest potential predictors, with rate differences greater than 10 percentage points for the three Southern census divisions as compared to the reference New England division. This finding is reflected in Figure 3.1, which suggests that geographic variation in HRM use is consistent with patterns described in the Medicare fee-for-service population[86]; where the HRR with the highest rate of inappropriate medication use was also Alexandria, Louisiana. The prevailing maxim for the elderly Medicare population that "geography is destiny" seems applicable to the use of HRMs.

The existence of substantial geographic variation in healthcare quality, costs, and delivery has been well established in the literature[96]. However, the interpretation of such extensive variation remains controversial. It is uncertain who or what principal actors or agents in the process of prescribing may underlie the geographic disparity of the magnitude seen with these HRM measures. One possible explanation is increased poly-pharmacy among those populations in the Southern region with the highest rates of HRM use. This population may also have a greater prevalence of chronic conditions, including

for example obesity[97], that may precipitate use of such medications[98]. Previous research has pointed to both poor health and poly-pharmacy[75,99] as predictors for receipt of HRMs. However, a recent study of the Medicare fee-for-service population did not find an association between increased HRM use and overall expenditures on prescription drugs[86]. Another possible explanation could be prescribing differences mediated organizationally and geographically vis-à-vis clinician training and education. Further, clinician prescribing behavior may reflect differences in patient preferences or formulary structure in health plan prescription drug coverage[100,101]. Additional qualitative and quantitative research to better understand the causes and potential adverse consequences of this variation is warranted.

The primary strength of this study lies in its inclusion of a broad set of predictors of HRM use in a recent, nationally representative sample of all elderly Medicare managed care enrollees. Prior research studies of HRM use in the elderly have used older data,[75,102] or focused on specific healthcare settings[83,103-105] such as nursing homes or home health. In addition, no existing studies have included socioeconomic status and health plan-level variables that may also help explain propensity to receive a HRM. We found that, after accounting for geographic region, the organizational characteristics of health plans are not associated with the likelihood of receiving HRMs.

In 2006, the NCQA reported the use of HRMs among elderly MA enrollees to be 23.1%[106]. In the Medicare fee-for-service population, the rate was estimated at 25.8% in 2010[86]. The relative stability of the estimates over time and across different elderly populations underscores the challenges of changing prescribing behavior, as well as the

need to further emphasize medication management of geriatric patients in clinical training.

Our study has some limitations. HEDIS data lacks information on the number of prescriptions and diagnoses or clinical comorbidities of enrollees; both have been found to be potential predictors of HRM use[75]. As a result, we were not able to determine whether particular medications account for the majority of the HRM use in the MA population. The most recent research utilizing national survey data to assess HRM use in the community-dwelling elderly, determined that the most prevalent HRMs of use include propoxyphene, amitriptyline, antihistamines, diazepam, muscle relaxants, gastrointestinal antispasmodics and indomethacin[99].

We were unable to assess whether and to what extent differences in the prevalence of comorbid conditions may account for the geographic variation in HRM use. If, in fact, increased clinical comorbidities may explain the high rates of use of HRMs in the Southern region of the U.S., further efforts to target those populations for more thorough medication management and review should be supported. That there are in many cases alternative medications to those found on the HEDIS list underscores this point.[107,108] These patients may also be at increased risk for other potentially inappropriate prescribing, including drug-disease interactions and/or drug-drug interactions.

The utility of quality measures of HRM use have been criticized for ignoring contextual factors associated with prescribing by using a "hit list" approach for identifying HRMs[109]. Some clinicians argue that medications on the HEDIS list are in fact appropriate and safe for a subset of their patients; and therefore, the prevalence of

HRM use may overestimate true rates of inappropriate medication use. Empirical evidence definitively linking use of HRMs to adverse health outcomes has also been limited, further mitigating efforts to reduce prescribing of such agents in routine clinical practice.

Notwithstanding these challenges, however, the use of these HEDIS measures allow clinicians, health plans, and policymakers to assess HRM use over time and characterize elderly groups that are more likely to receive medications that may predispose them to increased morbidity and mortality. Moreover, prior studies found significant associations between use of specific HRMs and falls, fractures, and self-reported adverse drug events[79-81]. Most HRMs also have alternatives that are safer for use in the elderly population[107].

CONCLUSION

Understanding predictors of HRM use at the population level can inform quality improvement efforts to reduce the use of these agents. This study examined the prevalence and predictors of HRMs among a national sample of elderly managed care enrollees. We observed wide geographic variation in the use of these medications that were not explained by sociodemographic characteristics, with the Southern region of the United States having markedly higher rates of use of HRMs. Female gender, white race, low SES index score, and low personal income also predicted receipt of HRMs. Efforts to reduce prescribing of these medications among the elderly should consider the role these factors play in predicting their use.

Table 3.1. Sociodemographic, Geographic, and Health Plan Characteristics of Medicare Advantage Enrollees Receiving and Not Receiving at Least 1 High Risk Medication (HRM), based on HEDIS' Drugs to Avoid in the Elderly Measure*

Characteristics	Received ≥1 HRM (n=1 333 307)	Did not receive ≥1 HRM (n=4 871 517)
Women (%)	71	55
Age group, years		
65-69	31	30
70-74	25	25
75-79	20	20
80-84	14	14
≥85	10	10
Race (%)		
White	84	83
Black	10	10
Other	7	7
Low Personal Income (%)	16	11
SES indicator(zip code), mean (SD)	50.7 (4)	51.2 (4)
Geographic division (%)		
New England	3	5
Middle Atlantic	15	21
East North Central	9	10
West North Central	6	7
South Atlantic	21	16
East South Central	6	4
West South Central	11	7
Mountain	9	10
Pacific	20	21
Plan size (%)		
0-24,999	29	28
25,000-99,999	47	46
≥100,000	25	26
Model Type (%)		
Group/Staff	7	10
Independent Practice Association	10	11
Network/Mixed	83	79
Plan Start Year (%)		
Before 1980	<1	<1
1980-1999	60	64
After 2000	39	35
Profit Status (%)		
For Profit	74	70

Abbreviations: HEDIS, Healthcare Effectiveness Data and Information Set

Note: The SES index score is derived from zipcode-level US census variables based on the Agency for Healthcare Research and Quality's specifications, higher SES values imply higher SES(U.S. mean, 50)[22]; all numbers refer to percentages, with the exception of SES index score; values rounded to nearest whole number

*The χ^2 or *t* test was performed to compare the characteristics of individuals who received high risk medications with those who did not; all tests resulted in *P* values of less than 0.001.

Table 3.2. Observed and Adjusted Rates of HEDIS Drugs to Avoid in the Elderly Measure, Receipt of at least 1 High Risk Medication*

Characteristics		Unadjusted Difference, % points	Model 1	Model 2	Model 3
Sex	Women	11.2	10.8 (10.3,11.3)†	10.6(10.1,11.2)	10.6(10,11.2)
Age group, years					
	65-69	Reference	Reference	Reference	Reference
	70-74	-0.4	-0.4(-0.7,0.0)	-0.2 (-0.5,0.1)	-0.2(-0.4,0.1)
	75-79	-0.3	-0.5 (-1.0,0.0)	-0.1 (-0.5,0.2)	-0.1(-0.4,0.3)
	80-84	-0.3	-0.8(-1.4,-0.3)	-0.3(-0.7,0.1)	-0.3(-0.7,0.1)
	≥85	-0.8	-2.1(-2.7,-1.4)	-1.3 (-1.8,-0.8)	-1.2(-1.7,-0.8)
Race					
	White	Reference	Reference	Reference	Reference
	Black	-1.2	-2.6(-3.8,-1.5)	-4.2(-4.8,-3.5)	-4.0(-4.6,-3.3)
	Other	-0.8	-1.7(-3.5,0.1)	-2.1(-3.2,-0.9)	-2.0(-3.1,-1.0)
Personal income	Low	8.6	7.8(6.4,9.2)	6.6(5.6,7.5)	6.5(5.5,7.5)
Zip-code based SES index Score					
	Quintile 1 (low)	6.2	--	2.8(2.0,3.7)	2.7(1.9,3.4)
	Quintile 2	3.4	--	1.9(1.4,2.4)	1.8(1.3,2.3)
	Quintile 3	2.4	--	1.4(0.9,1.9)	1.3(0.8, 1.8)
	Quintile 4	1.4	--	1.1(0.8,1.5)	1.1(0.7,1.4)
	Quintile 5 (high)	Reference	--	Reference	Reference
Geographic division					
	New England	Reference	--	Reference	Reference
	Middle Atlantic	1.2	--	1.3(0.13,2.6)	0.4 (-1.4,2.3)
	East North Central	4.6	--	4.6(3.3,5.9)	3.4 (1.5,5.3)
	West North Central	3.0	--	2.8(1.4,4.2)	1.9(-0.0,3.9)
	South Atlantic	11.9	--	11.3(9,13.5)	10.3(7.7,12.9)
	East South Central	14.0	--	12.4(10.7,14.0)	11.2(9.0,13.2)
	West South Central	14.2	--	13.1(9.7,16.5)	12.0(8.6,15.4)
	Mountain	6.0	--	5.3(3.1,7.6)	4.4(1.5,7.4)
	Pacific	5.9	--	5.6(3.5,7.7)	5.8(3.6,8.1)
Plan size					
	0-24,999	1.6	--	--	0.3(-1.6,2.2)
	25,000-99,999	1.3	--	--	1.0(-0.8,2.9)
	≥100,000	Reference	--	--	Reference
Model Type					
	Group/Staff	Reference	--	--	Reference
	Independent practice association	2.3	--	--	2.9(-0.0,5.8)‡
	Mixed/Network	5.7	--	--	3.1(0.8,5.5)‖
Year HMO began contract					
	Before 1980	Reference	--	--	Reference
	1980-1999	-0.1	--	--	-0.2(-3.9,3.5)
	After 2000	2.8	--	--	0.6(-2.9,4.2)
Profit Status	For Profit	3.7	--	--	0.0(-1.5,1.5)

Abbreviations: HEDIS, Healthcare Effectiveness Data and Information Set; CI, confidence interval; HMO, health maintenance organization

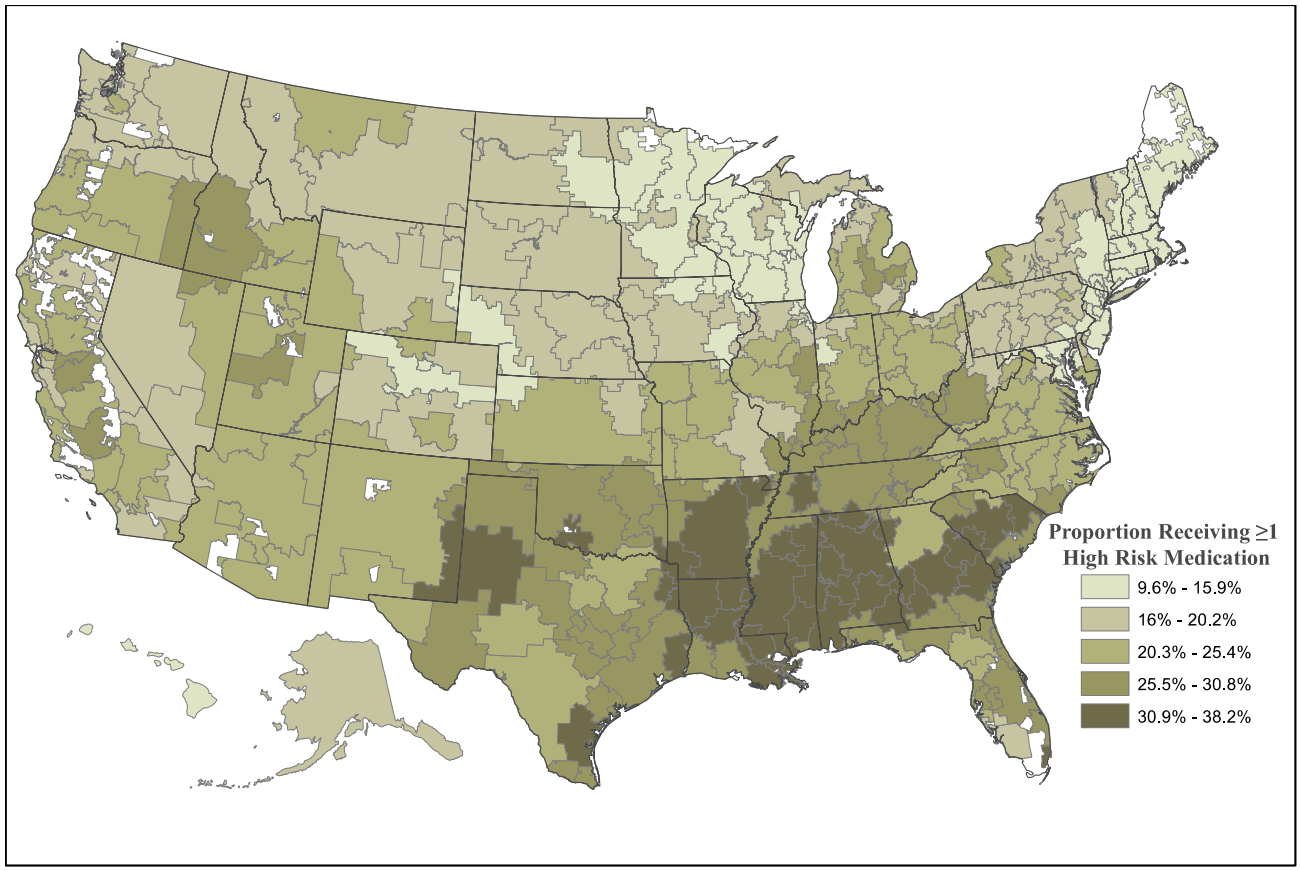
*All estimates on the risk difference scale, reported as percentage point difference (95% Confidence interval)

†Except where noted, confidence intervals that do not cross 0 are significant at P<0.005

‡Confidence interval crosses 0, not significant at P<0.005

‖P-value =0.008

Figure 3.1. Geographic Variation in the Proportion of Medicare Advantage Enrollees Receiving One or More High Risk Medications, 2009



Quintiles of Performance on HEDIS Measure of Quality of Drug Prescribing, According to Hospital-Referral Region, in 2009
Note: Lower rates indicate better quality

<u>Appendix 1.1</u> Rosiglitazone Black Box warning- November 2007[a]

WARNING: CONGESTIVE HEART FAILURE AND MYOCARDIAL ISCHEMIA

●Thiazolidinediones, including rosiglitazone, cause or exacerbate congestive heart failure in some patients (5.1). After initiation of AVANDIA, and after dose increases, observe patients carefully for signs and symptoms of heart failure (including excessive, rapid weight gain, dyspnea, and/or edema). If these signs and symptoms develop, the heart failure should be managed according to current standards of care. Furthermore, discontinuation or dose reduction of AVANDIA must be considered.

●AVANDIA is not recommended in patients with symptomatic heart failure. Initiation of AVANDIA in patients with established NYHA Class III or IV heart failure is contraindicated. (4, 5.1)

●A meta-analysis of 42 clinical studies (mean duration 6 months; 14,237 total patients), most of which compared AVANDIA to placebo, showed AVANDIA to be associated with an increased risk of myocardial ischemic events such as angina or myocardial infarction. Three other studies (mean duration 41 months; 14,067 patients), comparing AVANDIA to some other approved oral antidiabetic agents or placebo, have not confirmed or excluded this risk. In their entirety, the available data on the risk of myocardial ischemia are inconclusive. (5.2)

a.Food and Drug Administration Rosiglitazone Warning. Available at: http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM143413.pdf. Accessed 29 April 2014.

Appendix 1.2 United States Census Bureau Divisions and Regions[a]

REGION I: NORTHEAST

Division I: New England
Connecticut
Maine
Massachusetts
New Hampshire
Rhode Island
Vermont

Division 2: Middle Atlantic
New Jersey
New York
Pennsylvania

REGION 3: SOUTH

Division 5: South Atlantic
Delaware
District of Columbia
Florida
Georgia
Maryland
North Carolina
South Carolina
Virginia
West Virginia

Division 6: East South Central
Alabama
Kentucky
Mississippi
Tennessee

Division 7: West South Central
Arkansas
Louisiana
Oklahoma
Texas

REGION 2: MIDWEST

Division 3: East North Central
Illinois
Indiana
Michigan
Ohio
Wisconsin

Division 4: West North Central
Iowa
Kansas
Minnesota
Missouri
Nebraska
North Dakota
South Dakota

REGION 4: WEST

Division 8: Mountain
Arizona
Colorado
Idaho
Montana
Nevada
New Mexico
Utah
Wyoming

Division 9: Pacific
Alaska
California
Hawaii
Oregon
Washington

a.Census Bureau Regions and Divisions with State FIPS Codes. 2011. Available at: http://www.census.gov/geo/www/reg_div.txt. Accessed 29 April 2014.

Appendix 2.1 Schedules of Controlled Substances[a]

Classification	Potential for abuse	Accepted Medical Use	Degree of Dependence	Examples
I	High	None	High	Heroin Marijuana LSD
II	High	Yes	Severe	Morphine Codeine Demerol Phenobarbital OxyContin
III	Less than Schedule II	Yes	Moderate or Low	Tylenol with Codeine Drugs with limited amounts of narcotics
IV	Low	Yes	Low	Valium Weight Loss Drugs
V	Low	Yes	Low	Cough syrups

Source: The Controlled Substance Act of 1970.

a. US Pharmacist. Drug Rescheduling and Controlled Substances. Available at: http://www.uspharmacist.com/continuing_education/ceviewtest/lessonid/109441/. Accessed 29 April 2014.

Appendix 3.1

List of Medications Included in HEDIS list of High Risk Drugs, 2009[110]

Description	Prescription
Antianxiety (includes combination drugs)	• aspirin-meprobamate • meprobamate
Antiemetics	• scopolamine • trimethobenzamide
Analgesics (includes combination drugs)	• ketorolac
Antihistamines (includes combination drugs)	• APAP/dextromethorphan/diphenhydramine • APAP/diphenhydramine/phenylephrine • APAP/diphenhydramine/pseudoephedrine • acetaminophen-diphenhydramine • carbetapentane/diphenhydramine/phenylephrine • codeine/phenylephrine/promethazine • codeine-promethazine • cyproheptadine • dexchlorpheniramine • dexchlorpheniramine/dextromethorphan/PSE • dexchlorpheniramine/guaifenesin/PSE • dexchlorpheniramine/hydrocodone/phenylephrine • dexchlorpheniramine/methscopolamine/PSE • dexchlorpheniramine-pseudoephedrine • dextromethorphan-promethazine • diphenhydramine • diphenhydramine/hydrocodone/phenylephrine • diphenhydramine-magnesium salicylate • diphenhydramine-phenylephrine • diphenhydramine-pseudoephedrine • hydroxyzine hydrochloride • hydroxyzine pamoate • phenylephrine-promethazine • promethazine
Antipsychotic, typical	• thioridazine
Amphetamines	• amphetamine-dextroamphetamine • benzphetamine • dexmethylphenidate • dextroamphetamine • diethylpropion • methamphetamine • methylphenidate • phendimetrazine • phentermine
Barbiturates	• butabarbital • mephobarbital • pentobarbital • phenobarbital • secobarbital
Long-acting benzodiazepines (includes combination drugs)	• amitriptyline-chlordiazepoxide • chlordiazepoxide • chlordiazepoxide-clidinium • diazepam • flurazepam
Calcium channel blockers	• nifedipine—short-acting only

Gastrointestinal anti-spasmodics	• dicyclomine • propantheline
Belladonna alkaloids (includes combination drugs)	• atropine • atropine/CPM/hyoscyamine/PE/scopolamine • atropine/hyoscyamine/PB/scopolamine • atropine-difenoxin • atropine-diphenoxylate • atropine-edrophonium • belladonna • belladonna/ergotamine/phenobarbital • butabarbital/hyoscyamine/phenazopyridine • hyoscyamine • hyoscyamine/methenam/m-blue/phenyl salicyl
Description	**Prescription**
Skeletal muscle relaxants (includes combination drugs)	• ASA/caffeine/orphenadrine • ASA/carisoprodol/codeine • aspirin-carisoprodol • aspirin-methocarbamol • carisoprodol • chlorzoxazone • cyclobenzaprine • metaxalone • methocarbamol • orphenadrine
Oral estrogens (includes combination drugs)	• conjugated estrogen • conjugated estrogen-medroxyprogesterone • esterified estrogen • esterified estrogen-methyltestosterone • estropipate
Oral hypoglycemics	• chlorpropamide
Narcotics (includes combination drugs)	• ASA/caffeine/propoxyphene • acetaminophen-pentazocine • acetaminophen-propoxyphene • belladonna-opium • meperidine • meperidine-promethazine • naloxone-pentazocine • pentazocine • propoxyphene hydrochloride • propoxyphene napsylate
Vasodilators	• dipyridamole—short-acting only • ergot mesyloid • isoxsuprine
Others (including androgens and anabolic steroids, thyroid drugs, urinary anti-infectives)	• methyltestosterone • nitrofurantoin • nitrofurantoin macrocrystals • nitrofurantoin macrocrystals-monohydrate • thyroid desiccated

Conclusion

My dissertation is composed of three chapters unified by the central themes of patient safety and disparities in the use of high risk prescription medicines. The overarching goal of my dissertation was to challenge the assumption that responsiveness to policies is uniform across patient populations. I achieved this by exploring the consequences of state and national pharmaceutical policy interventions on prescribing patterns of drugs with important adverse effects. I also sought to examine the predictors of high risk medication use among a nationally representative sample of elderly enrollees.

In my first chapter, I showed that a Food and Drug Administration (FDA) safety advisory had effectively encouraged the majority (~70%) of elderly Medicare fee-for-service enrollees who were current users of rosiglitazone to discontinue use of the medication, after it was found to be potentially unsafe. However, certain segments of the population- including black enrollees, younger enrollees, and enrollees with no history of low personal income- appeared more responsive to the warning. While the efficacy of the FDA safety advisory appears promising, the findings from this paper can be utilized by policymakers to refine future advisories and more effectively target those populations that appear latent in their response.

In my second chapter, I found that expanding state level scope-of-practice prescribing authority to nonphysician clinicians did not result in a significant increase in use of the highly-addictive opioid pain reliever medications. Such a finding discounts the rationale among those opposed to expanding to nonphysicians the privilege of prescribing controlled substances; namely, that such expansion opens the floodgates to further irrational use of high risk opioids. I found no evidence for that to be the case. In light of

the impending expansion of primary care afforded by the Accountable Care Act, and the shortage of primary care providers anticipated as a result, better understanding the intersecting roles of nonphysicians in improving access to quality care is paramount to improving population health.

In my final chapter, I sought to examine the prevalence and predictors of high risk medication use in a national sample of elderly Medicare enrollees. I observed wide geographic variation in the use of these medications that were not explained by sociodemographic characteristics, with the Southern region of the United States having markedly higher rates of use of potentially inappropriate high risk medications. Female gender, white race, low socioeconomic status, and low personal income also predicted receiving high risk medications. Efforts to reduce the prescribing of these medications among the elderly can and should consider the role of all these factors in predicting their use.

There has been a paucity of research examining the specific structural and policy factors associated with high risk prescription drug use. I contend that the totality of my dissertation work contributes importantly to the health services literature by unpacking the homogeneity assumption implicit in the operationalization of many pharmaceutical policies and interventions. By further understanding factors at the state, federal, and individual levels associated with use of high risk medications, however defined, we can take a more critical approach to enriching and improving subsequent policies related to mitigating their use. This work can be utilized to refine and target policy efforts that promote drug access and higher quality drug prescribing, especially for the most vulnerable populations.

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