

University of Mississippi

eGrove

Electronic Theses and Dissertations

Graduate School

2011

Market Response to Food and Drug Administration's Safety Warnings: a Case Study Using an Interrupted Time Series Analysis of the Medicare Database for 2006-2008

Hafiz Oko-Osi

Follow this and additional works at: <https://egrove.olemiss.edu/etd>



Part of the [Pharmacy and Pharmaceutical Sciences Commons](#)

Recommended Citation

Oko-Osi, Hafiz, "Market Response to Food and Drug Administration's Safety Warnings: a Case Study Using an Interrupted Time Series Analysis of the Medicare Database for 2006-2008" (2011). *Electronic Theses and Dissertations*. 215.

<https://egrove.olemiss.edu/etd/215>

This Dissertation is brought to you for free and open access by the Graduate School at eGrove. It has been accepted for inclusion in Electronic Theses and Dissertations by an authorized administrator of eGrove. For more information, please contact egrove@olemiss.edu.

MARKET RESPONSE TO FOOD AND DRUG ADMINISTRATION'S SAFETY
WARNINGS: A CASE STUDY USING AN INTERRUPTED TIME SERIES ANALYSIS OF
THE MEDICARE DATABASE FOR 2006-2008

A Thesis
Submitted to the Faculty of
The University of Mississippi
in Partial Fulfillment of the Requirements
for the Degree of Master of Science
in the Department of Pharmacy Administration
The University of Mississippi

by

HAFIZ ADEDOLA OKO-OSI, B.Pharm.

December, 2011

Copyright Hafiz A. Oko-Osi 2011

ALL RIGHTS RESERVED

ABSTRACT

Objectives: To evaluate the impact of a safety warning on the utilization rates of thiazolidinedione oral anti-diabetes medication using an interrupted time series analysis.

Methods: We extracted data from a five percent national sample of Medicare Part D beneficiaries for the periods between January 2006 and December 2008. Beneficiaries with Part D claims for thiazolidinediones were classified into appropriate-use, at risk, and contraindicated groups based on certain comorbid conditions. We assessed the effects of the May 2007 FDA safety warning about an ongoing safety review of rosiglitazone's potential to increase cardiovascular risks on thiazolidinedione utilization rates using an interrupted time series consisting of 32 data points (13 months before and 19 months after the safety warning).

Results: There was an increasing trend in the total utilization rates of thiazolidinediones before the safety warning. Significant decline in drug utilization rates were observed at the end of the study period for all patient groups on rosiglitazone (relative difference -74.78%, -79.93%, and -90.21% respectively in appropriate-use, at risk and contraindicated patient groups). The intervention did not have significant immediate effects on the post-intervention utilization rates of pioglitazone. However, after the intervention, we observed a general decline in utilization of thiazolidinediones.

Conclusions: The initial safety warning about rosiglitazone's cardiovascular safety was effective in decreasing rosiglitazone's utilization in the targeted population and hence its Medicare market share. The safety warning also had spillover effects by reducing utilization of drugs in other patient cohorts not targeted by the warning.

Key Words: Interrupted time series, Safety-warning, Rosiglitazone, Pioglitazone, Market response.

DEDICATION

This thesis is dedicated to Adeshola Onilogbo Oko-Osi and to my colleagues. To Dr. Pat Pace and Dr. Yi Yang, I express my utmost appreciation for their unwavering support and relentless efforts.

LIST OF ABBREVIATIONS AND SYMBOLS

FDA	Food and Drug Administration
AERS	Adverse Event Reporting System
ADR	Adverse Drug Reaction
DM	Diabetes mellitus
TZD	Thiazolidinediones
CHF	Congestive Heart Failure
ESRD	End Stage Renal Disease
CMS	Center for Medicare and Medicaid Services
SMI	Supplementary Medical Insurance
ICD-9-CM	International Classification of Diseases, 9 th Revision, Clinical Modification
MEDPAR	Medicare Provider Analysis and Review
NYHA	New York Heart Association
SAS	Statistical Analysis Software
DW	Durbin-Watson

ACKNOWLEDGEMENTS

I would like to acknowledge the members of this thesis committee who guided my activities in this undertaking. Their constant direction, collegiality, and encouragement are the primary reasons this thesis was completed. I would like to extend special thanks to the thesis committee Chair, Dr. Benjamin Banahan III, and the thesis committee members, Dr. Donna West-Strum and Dr. John P. Bentley.

I would like to express my appreciation to Dr. Rahul Khanna for the articles he provided towards analyzing and expressing the results of the thesis.

TABLE OF CONTENTS

ABSTRACT	ii
DEDICATION	iv
LIST OF ABBREVIATIONS AND SYMBOLS	v
ACKNOWLEDGEMENTS	vi
LIST OF TABLES	viii
CHAPTER	
I. INTRODUCTION	1
II. LITERATURE REVIEW	4
III. METHODS	10
IV. RESULTS	18
V. DISCUSSION	31
VI. CONCLUSIONS	36
BIBLIOGRAPHY	37
VITA	41

LIST OF TABLES

TABLE		PAGE
I.	Group Classification Criteria.....	14
II.	Study Population Demography.....	18
III.	Durbin-Watson statistics for group-specific regression models after controlling for autocorrelation.....	21
IV.	Parameter estimates, standard errors and P-values from the full and most parsimonious segmented regression models predicting the monthly utilization rate of rosiglitazone in appropriate-use patients.....	23
V.	Parameter estimates, standard errors and P-values from the full and most parsimonious segmented regression models predicting the monthly utilization rate of rosiglitazone in patients at risk of developing contraindicated conditions...	24
VI.	Parameter estimates, standard errors and P-values from the full and most parsimonious segmented regression models of the monthly utilization rate of rosiglitazone in contraindicated patients.....	26
VII.	Parameter estimates, standard errors and P-values from the full and most parsimonious segmented regression models of the monthly utilization rate of pioglitazone in appropriate-use patients.....	27

LIST OF TABLES Continued

TABLE	PAGE
VIII. Parameter estimates, standard errors and P-values from the full and most parsimonious segmented regression models of the monthly utilization rate of pioglitazone in patients at-risk of developing contraindicated conditions.....	29
IX. Parameter estimates, standard errors and P-values from the full and most parsimonious segmented regression models of the monthly utilization rate of pioglitazone in contraindicated patients.....	30

CHAPTER I

INTRODUCTION

Patients in the U.S. have access to the safest and most advanced pharmaceutical system in the world.¹ Drugs produced for U.S. markets are subjected to perhaps the most rigorous drug approval process.² The aim of this drug approval process, conducted by the Food and Drug Administration (FDA), is to demonstrate that drugs seeking approval are safe and effective for their indicated use. Safe in this regard means that the benefits associated with the use of a drug outweighs its risk of use.¹

The FDA is responsible for protecting public health by ensuring that drugs, vaccines, and other biological products and medical devices intended for human use are safe and effective. The FDA also shares with pharmaceutical companies, physicians, and pharmacists, the responsibility of helping the public get accurate science-based information required for proper use of medicines and devices.³ The FDA achieves the former role through a rigorous drug approval process and postmarketing surveillance. Communicating important safety information regarding drug use is achieved via FDA safety newsletters and the “MedWatch” program - a web-based resource that provides specific information relating to drugs that have been the subject of a public health advisory or an alert.^{4,5}

The effectiveness of FDA's postmarketing surveillance system can be attributed to key tasks performed during this surveillance period. These tasks include detecting post-approval safety issues and communicating these to the public. Detection of post-approval safety issues occur either during post-marketing clinical/phase IV trials conducted by pharmaceutical companies or through FDA's adverse event reporting system (AERS) and MedWatch. Medwatch also serves as an effective avenue for communicating safety information to the medical community. Following the evaluation of new safety information, the FDA provides postmarket drug safety information to patients and providers. The FDA also issues safety alerts, enforces labeling changes, and/or restricts access to drugs when appropriate. These actions could potentially affect treatment and diagnostic options for both healthcare professionals and patients.

4, 12

The Black box warning, a type of safety warning and a marker of the most serious adverse drug reactions (ADRs),⁷ prompts actionable changes in clinical use of a drug without necessarily requiring an immediate market withdrawal. The overall effects of safety warnings on prescribing habits have prompted studies to evaluate the intended and unintended consequences of such warnings^{8,9} as well as the adequacy of these warnings in restricting use of unsafe drugs.^{10,11}

The body of research that has focused on the use of thiazolidinediones in the management of type II diabetes demonstrates opposing views on the direction of prescription trends and promptness of the medical community in adhering to black box warnings. One of these studies¹⁰ evaluated the utilization of rosiglitazone following black box warnings and found that geographic variations coupled with a modest decline in the number of prescriptions written for

rosiglitazone does exist. Another study¹¹ which evaluated the utilization of troglitazone in response to black box warnings found that initial safety warnings were ineffective in prompting actionable changes.

These studies establish conflicting evidence on the changes in the number of prescriptions for the thiazolidinediones class of drugs following FDA safety warnings. Thus, adequate evidence to infer a logical conclusion on the actual market response to FDA safety warnings for drugs in the thiazolidinedione class of oral hypoglycemic agents is lacking. An appropriate market response to FDA safety warnings is critical in order to assure reasonable safety in the health care system, as well as to protect the drug development investment made by the pharmaceutical product manufacturer. The purpose of this study is to investigate the appropriateness of market response to the FDA black box warning issued for rosiglitazone. This study will use an interrupted time series design to determine whether changes in product use are differentiated by appropriate and inappropriate patient types.

CHAPTER II

LITERATURE REVIEW

Diabetes Mellitus: Prevalence and Cardiovascular Risks

Diabetes mellitus (DM) is a metabolic disorder characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both.¹² About 15.3% of American adults 65 years or above have been diagnosed with DM.¹³ Management of DM involves a multifaceted approach that includes pharmacological therapy and life-style changes. One of the pharmacological interventions for the management of diabetes mellitus are the thiazolidinedione class of oral hypoglycemic agents which were first introduced to the U.S. market in 1997.¹⁶

Historical Overview of Rosiglitazone-specific FDA warnings

Troglitazone (Rezulin®; Parke-Davis/Warner-Lambert), Rosiglitazone (Avandia®; GlaxoSmithKline), and Pioglitazone (Actos®; Takeda), drugs belonging to the anti-diabetic class of thiazolidinediones (TZDs), have received numerous safety alerts and labeling change recommendations from the FDA in order to ensure their safe use. Troglitazone was withdrawn from the U.S. market on March 21, 2000 because of its adverse hepatic effects.¹⁷ Rosiglitazone and pioglitazone are still available in the U.S. market. However, their future market potential

remains uncertain because varied metabolic effects in addition to their hypoglycemic effects have stirred doubts about their cardiovascular safety.¹⁶

In 2007, new safety information on the cardiovascular risks of rosiglitazone was made available by the FDA^{15, 16} following a meta-analysis of 42 trials comparing rosiglitazone to placebo. These studies demonstrated that rosiglitazone was associated with an increased risk of myocardial infarction and death from cardiovascular sources.¹⁸ This disclosure engendered a series of empirical inquiries into the safety of rosiglitazone and its utility in managing Type 2 diabetes mellitus.^{20,21}

Rosiglitazone was first approved by the FDA in May 1999 as an adjunct to diet and exercise to improve glycemic control in patients with Type 2 diabetes mellitus.²² On the 21st of May 2007, FDA issued a safety alert to inform healthcare professionals and the public about an ongoing safety review of rosiglitazone's potential to increase cardiovascular risks.^{18, 19} By August 2007, a boxed warning to include an increased risk of new onset or exacerbations of congestive heart failure (CHF) was approved for rosiglitazone. In November 2007, another boxed warning about an increased potential for heart failure was added to rosiglitazone's labeling.²⁵ More recently, in September 2010, the FDA decided to significantly restrict access to rosiglitazone use.²⁶

The period between the first alert and the end of 2007 could safely be assumed as an adequate period of awareness to the safety issues expressed with rosiglitazone use. In addition, the boxed warnings issued during that year were expected to prompt careful consideration on the part of prescribing physicians. A stream of research has however demonstrated poor adherence to

FDA alerts and warnings regarding the use of rosiglitazone and other classes of drugs, often leaving patients exposed to potentially harmful drugs.⁸⁻¹¹

Response to FDA Safety Warnings

The body of literature on the utilization of thiazolidinedione in response to FDA safety alerts demonstrates conflicting evidence with regards to the adequacy of safety warnings in limiting utilization of implicated drugs. Wilkinson et al.,¹¹ demonstrated that initial safety alerts issued for cisapride and troglitazone were inadequate in preventing the use of these drugs in at risk patients. Their study found that contraindicated use of cisapride was not significantly reduced by the issuance of “Dear healthcare professional” letters and labeling changes; rather, there was a significant increase in the number of new and total prescriptions for cisapride five months after the first alert with growth in total and new prescriptions declining only after the third alert. A similar trend was observed with troglitazone - the total number of prescriptions maintained an upward trend after the first three alerts, decreasing only after the fourth alert. Total number of new prescriptions however began to decline after the second alert.

Shah et al.,¹⁰ found geographical variations in the use of rosiglitazone following FDA warnings. Despite these variations, their study demonstrated a significant decline in the total number of rosiglitazone prescriptions across the U.S. Their study also showed that FDA warnings can be interpreted differently across prescribing physicians, resulting in inconsistent patient protection from unsafe drug use. In their discussion, Shah et al. posit that the variations in prescriptions may be influenced by specialists, key opinion leaders and pharmaceutical marketing activities.

Intended and Unintended consequences of FDA Safety Warnings

Katz et al.,⁸ examined the relationship between prescriptions rates of anti-depressants and FDA regulatory warnings in two groups. One of the groups which was not the focus of the warning served as a “control” group. The prescribing rate in this control group was thus expected to remain fairly constant. Their study however observed a significant decrease in prescriptions rate of anti-depressants for both groups, including the group not targeted by the alerts. In addition, there were no significant differences in prescription rates for both groups. The implication of their findings was that FDA warnings may have similar effect in reducing prescribing rates, and hence utilization of other drugs in the same therapeutic class as drug(s) targeted by warnings.

In another study, Libby et al.⁹ observed significant and persistent declines in anti-depressant prescriptions for both targeted and untargeted cohorts despite an absence of a complementary increase in prescriptions for anti-depressant alternatives such as anxiolytics and atypical psychotics. This finding is indicative of a general decline in depression treatment and a general decrease in case findings of depression among their study population.

Study purpose

Geographical variations in market behaviors and evidence supporting a general decline in the use of rosiglitazone indicate that market response to safety warnings may not be limited to the targeted population. Further, the indiscriminate restriction in the use of a drug raises the question of whether a market, in this case comprised of health professionals and patients, appropriately responds to FDA safety warnings. This study examined changes in the utilization rates of rosiglitazone and pioglitazone during the periods before and after the May 2007 FDA safety warning for rosiglitazone in the following three patient groups (see Table I):

- Patients for whom the use of rosiglitazone was considered appropriate (Appropriate-use group),
- Patients with a medical history of heart failure and/or myocardial infarction, considered to be contraindicated for rosiglitazone use (Contraindicated group), and
- Patients deemed at risk of developing contraindicated condition(s), due to rosiglitazone use, by virtue of the presence of an identifiable medical condition considered to be risk factors for heart failure and myocardial infarction (At risk group). These identifiable risk factors included hypertension, coronary artery disease and metabolic syndrome.

Study objectives

The major objective was to assess the appropriateness in the utilization and/or declining use of rosiglitazone after May 2007. We also examined the changes in the utilization of pioglitazone (a drug in the thiazolidinedione class but not targeted by the warning) in order to determine the “class effect” of the rosiglitazone safety warning.

We utilized an interrupted time series design to evaluate the longitudinal effects of an intervention, that is, an FDA safety warning, on rosiglitazone use in a national sample of the Medicare population. We obtained monthly utilization rates for rosiglitazone and pioglitazone during the period preceding and following the May 2007 safety warning in order to determine the effects of the safety warning on thiazolidinedione utilization. To the best of our knowledge, no study to date has attempted to examine the effects of FDA safety warnings specific to rosiglitazone by comparing the utilization rates in the population or groups being proposed. Thus, this study will contribute significantly to an understanding of the appropriateness of market response to FDA safety warnings.

CHAPTER III

METHODS

The study was approved by the Institutional Review Board (IRB) of the University of Mississippi.

Study population

The study population consisted of all beneficiaries who were continuously enrolled in Medicare Part D during the study period beginning from 1st of January, 2006 through 31st of December, 2008. The study inclusion and exclusion criteria are described below:

Inclusion Criteria

Medicare part D beneficiaries with at least one prescription claim for a thiazolidinedione anti-diabetic during the study period were included in the study. The eligible beneficiaries were identified from the part D event file as all beneficiaries with at least one claim for a thiazolidinedione anti-diabetic during the study period. This group served as the denominator for examining use of thiazolidinediones throughout the observation period. A total of 57,329 beneficiaries were included in the analysis.

Exclusion Criteria

The following exclusion criteria were used for this study:

1. Medicare part D beneficiaries who were in skilled nursing facilities,
2. Medicare beneficiaries who had end stage renal disease (ESRD),
3. Medicare beneficiaries who had Medicaid dual eligibility, or
4. Medicare beneficiaries enrolled in Medicare Advantage programs

Data Sources

The data set used for this study was the five percent national Medicare sample from the Center for Medicare and Medicaid Services (CMS). Use of this data was covered by a data use agreement with CMS. The Medicare program is made up of Part A - hospital insurance, Part B - supplementary medical insurance (SMI), Part C - Managed care, and Part D - outpatient prescription benefits.

The Medicare research identifiable files used for this study consisted of a denominator file and claims files.

The denominator file contained the following information:

- Information on patient enrollment,
- Demographic information, and
- Other beneficiary level data.

The claims files contained claims for:

- Hospital and skilled nursing facilities,
- Physician and other outpatient facilities, and
- Drugs.

The medical claims included diagnoses codes from the International Classification of Diseases, 9th revision, clinical modification (ICD-9-CM).

All of the claims could be linked by encrypted unique beneficiary identification codes.

Study Design

We analyzed claims data for thiazolidinediones in the study population using an interrupted time series design of a 32-month study observation period (Figure 1). The time series consisted of a 13-month pre-intervention period and a 19-month post-intervention period.

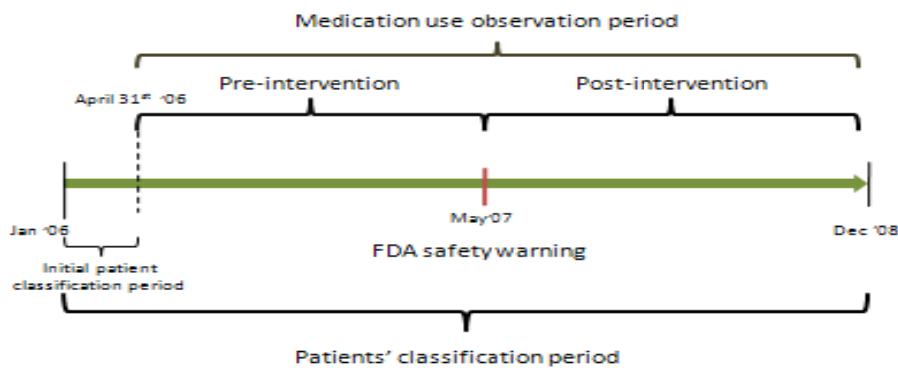


Figure 1. Representation of Study Design

The first four months of available data (January 2006 to April 2006) served as an initial patient classification period (Figure 1). During this period, eligible beneficiaries were classified into appropriate-use, at-risk and contraindicated groups based on appropriateness for using thiazolidinediones. Following this initial classification period, beneficiaries were re-classified as appropriate each month throughout the remainder of the study period.

ICD-9 diagnosis codes from medical office visits (carrier claim files), patient files (MEDPAR), and institutional outpatient visits (outpatient files) were used to classify beneficiaries into respective groups. Once beneficiaries were classified into a group, it was assumed that they remained in that group until the end of the study unless they were re-classified into another group with higher contraindication severity. The groups were ranked in contraindication severity in the following order:

Appropriate-use < At risk < Contraindicated

Table 1 lists the diagnostic criteria used for group classification ('x' was used as an indicator of diseases/conditions belonging to respective groups). These classification criteria were based on the November 2007 FDA safety warning issued for rosiglitazone²⁵. According to this safety warning, rosiglitazone is contraindicated in patients with any of the following conditions: NYHA class III or IV heart failure, symptomatic heart failure, congestive heart failure or myocardial infarction. We also included diagnosis codes for old myocardial infarction (412.xx) in order to adequately identify and classify patients who have had a myocardial infarction before our study initiation period.

Table I. Group Classification Criteria

DISEASE/CONDITION	ICD9 CODES	PATIENT GROUP		
		APPROPRIATE- USE	AT RISK	CONTRAINDICATED
HYPERTENSION	401.XX, 405.XX		X	
CORONARY ARTERY DISEASE	440.XX, 414.XX		X	
OVERWEIGHT & OBESITY	278, 278.00, 278.01, 278.02		X	
METABOLIC SYNDROME	277.7		X	
HEART FAILURE	402.X1, 404.X3, 428.XX			X
OLD MYOCARDIAL INFARCTION	412.XX			X
MYOCARDIAL INFARCTION	410.XX			X

The at-risk patients were identified as patients with identifiable medical conditions (i.e. conditions with ICD-9 codes) considered as risk factors for developing any of the contraindicated diseases/conditions mentioned above.^{14, 27} In addition, metabolic syndrome was included to represent a cluster of other risk factors. These risk factors include overweight, high lipids and diabetes mellitus. The appropriate-use patients were identified as all other patients meeting the inclusion criteria but without a medical diagnosis for any of the above diseases/conditions.

Rationale for selecting rosiglitazone (Avandia ®)

Safety warnings are markers of potentially serious adverse effects of drug use. These warnings, which are not frequently issued, have the potential to alter clinical use of implicated drugs often resulting in intended and unintended effects of such warnings. Some of these effects include an overly restricted use of implicated drugs in populations not targeted by these warnings.

In order to examine the effects of safety warnings or any intervention, adequate time points before and after the intervention are required. The availability of retrospective Medicare data (January 2006 to December 2008) having adequate time points pre and post the safety warnings for rosiglitazone in May 2007, allows the study of these intended and unintended effects of safety warnings. Moreover, the variations in rosiglitazone use reported prompts further investigation into market response to rosiglitazone specific safety warnings.

Evaluation of the safety warning (Intervention)

Time series of thiazolidinedione utilization within each patient group were constructed as a rate by dividing the number of beneficiaries taking thiazolidinediones in each group per month by the number of beneficiaries classified as belonging in the group that month. The resulting time series were analyzed by specifying a segmented regression model.

Segmented regression analysis of interrupted time series enables estimation of, in statistical terms, changes in the level and trend in an outcome of interest immediately and over time following an intervention²⁸. This is achieved by fitting the observations into an adequate regression model. The outcome of interest in this study was the utilization rates (per 100) of both

rosiglitazone and pioglitazone in all patient groups before and after the safety warning.

Following the visual inspection of the plot of the monthly utilization of thiazolidinedione in each group against time, segmented regression models (Model 1) were specified using the general linear models procedure (proc glm) for SAS in order to determine the effects of the intervention while assessing the effect of chance and controlling for other confounders. Initial models were examined for the presence of autocorrelation in error terms using the Durbin-Watson test for autocorrelation. When the Durbin-Watson test statistic was significant, indicating presence of autocorrelation, we included the estimated autocorrelation parameter in the model. Segmented regression models were further examined for significance of parameter estimates, eliminating insignificant variables when appropriate, by means of a backward elimination method. The resulting parsimonious models were then re-specified. All analyses and data management were carried out using SAS 9.2.

Model 1 shows the full segmented regression equation for estimating the level and trend in the utilization rates of thiazolidinediones in each class of patients before and after the rosiglitazone FDA safety warning:

$$Rate_t = \beta_0 + \beta_1 * time_t + \beta_2 * intervention_t + \beta_3 * time\ after\ intervention_t + e_t \text{ (Model 1)}$$

Where:

- $Rate_t$ is the utilization rate of thiazolidinediones anti-diabetic drugs in month t
- $time$ is a continuous variable indicating the time in months from the beginning of the observation period

- *intervention* is an indicator for time t occurring before ($\text{intervention} = 0$) or after ($\text{intervention} = 1$) the safety warning
- *time after intervention* is a continuous variable counting the number of months after the intervention at time t
- β_0 estimates the baseline level of the claims rate at the beginning of the study period (at time zero)
- β_1 estimates the change in claims rates that occurs with each month before the intervention (i.e the baseline trend)
- β_2 estimates the level change in the rate of claims for thiazolidinediones anti-diabetic drugs immediately after the intervention
- β_3 estimates the change in trend in the mean monthly rate of claims for thiazolidinediones anti-diabetic drugs per month after the safety warning, compared with monthly trend before the safety warning.

CHAPTER IV

RESULTS

Population Characteristics

The total population for this study following the application of the inclusion and exclusion criteria was 57,329. Their demographic characteristics are represented in Table II. Women constituted 54.7% of the study population. Eighty-four percent of the beneficiaries were white, 10% were black and 6% were of other races (Asian, Hispanic, North American Native and others). Forty-seven percent of the population were between the ages of 65 and 74, 34% were between the ages of 75-84, 11% were older than 85 years of age while less than 5% were younger than 65 years old.

Table II: Study Population Demography

Demographic Variables	Percentage	
Gender	Female	54.7
	Male	45.3
Race	White	84
	Black	10
	Other	6
Age	< 65 years	5
	65 – 74 years	47
	75 – 84 years	37
	> 85 years	11

Time Series of Thiazolidinedione Utilization

The interrupted time series consisted of 32 data points divided into 2 segments by the FDA safety warning for rosiglitazone (intervention). Thirteen months of data were available prior to the intervention and 19 months of follow up data were available after the intervention for all beneficiaries. The rate of drug utilization was expressed as a monthly percentage of the number of patients in each sub-group. This percentage utilization was obtained for each month during the study period by dividing the number of patients classified into respective groups using a particular drug by the total number of patients classified into each group per month. For example, in the first month of our study period, 9204 patients classified as appropriate-use patients using rosiglitazone, while 8218 patients were classified as appropriate-use patients using pioglitazone. During this month, the total number of patients classified as appropriate was 47108. Hence the utilization rates for rosiglitazone and pioglitazone during this month were 22.18% and 20.42% respectively.

The effects of the intervention were expressed as changes in the level and trend of market utilization of thiazolidinedione as well as the relative effect of the intervention on thiazolidinedione utilization at the end of the study period (post-intervention month 19, study month 32) using the relative model (Model 2). A graph of the monthly utilization rates for all patient groups is shown in Figure 2.

$$RD = [(Y_{32(\text{with safety warning})} - Y_{32(\text{without safety warning})}) / Y_{32(\text{without safety warning})}] * 100 \text{ (Model 2)}$$

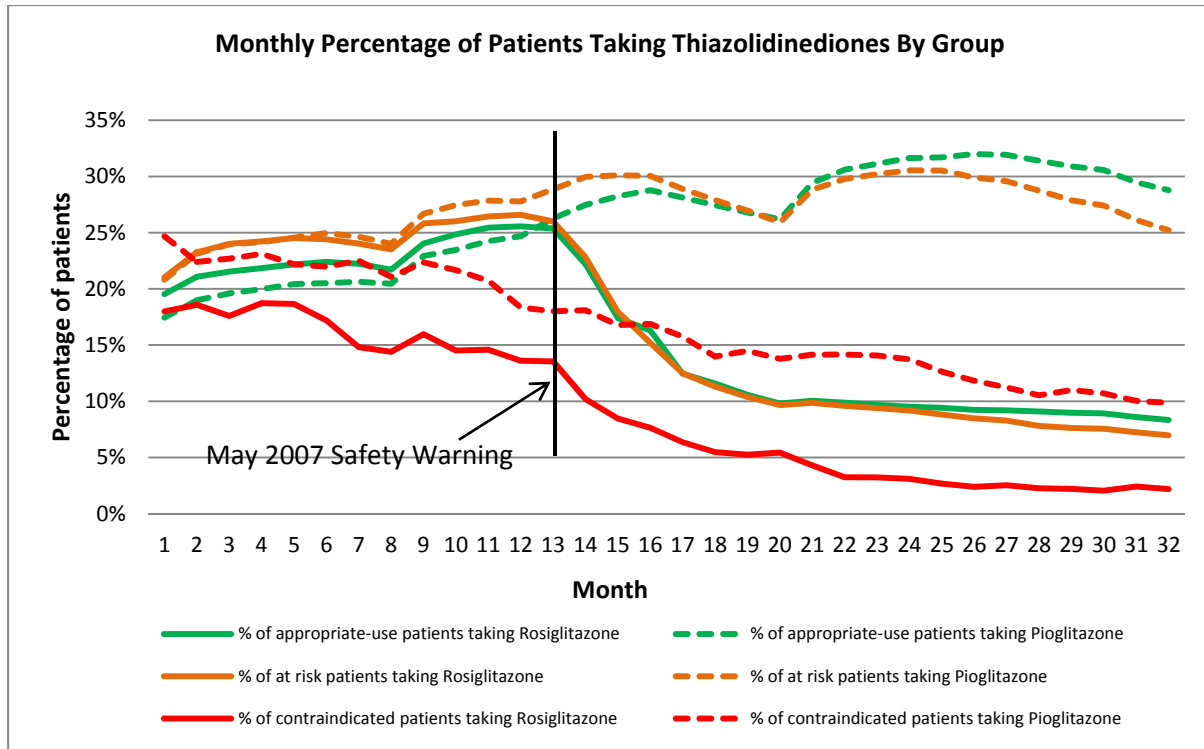


Figure 2: Utilization rates of rosiglitazone and pioglitazone by patient group per month.

The figure shows a slight increasing slope in the utilization rates for indicated and at risk patients taking rosiglitazone and pioglitazone before the intervention. However, following the intervention, there was an immediate, abrupt and consistent decline in the slope for all three groups of patients using rosiglitazone. For patients using pioglitazone, an increasing trend in slope was maintained for both indicated and at-risk patients while the slope for the contraindicated population in this patient population (using pioglitazone) gradually decreased after the intervention.

The time series were analyzed for the presence of serial autocorrelations between observations using the Durbin-Watson statistic. Significant autocorrelations were adjusted for by estimating the autocorrelation parameters for each model and including it in a final regression model. Table III shows the Durbin-Watson statistics for each regression model following correction for autocorrelation.

Table III: Durbin-Watson statistics for group-specific regression models after controlling for autocorrelation.

Drug Group	Regression Model	Durbin-Watson statistic	Pr < DW	Pr > DW
Rosiglitazone	Appropriate-use model	2.1069	0.4697	0.5303
	At-risk model	2.1914	0.6147	0.3853
	Contraindicated model	1.9234	0.2449	0.7551
Pioglitazone	Appropriate-use model	1.7257	0.1076	0.8924
	At-risk model	1.6920	0.0922	0.9078
	Contraindicated model	1.8665	0.1768	0.8232

Pr < DW is the P-value for hypothesis of positive correlation, and Pr > DW is the P-value for hypothesis of negative correlation

Effect of the FDA safety warning on rosiglitazone utilization in appropriate-use patients

The results from Table IV indicate that just before the beginning of the observation period, the monthly utilization rate of rosiglitazone in the patient group classified as appropriate for rosiglitazone use was about 21 patients per 100 patients classified as appropriate patients for rosiglitazone use. Before the intervention, there was no significant month-to-month variation in rosiglitazone use. Before the intervention, there was no significant month-to-month variation in rosiglitazone utilization (p-value = 0.679). Immediately after the intervention, the estimated utilization rate of rosiglitazone dropped by 2.4 patients per 100 patients. Following the intervention, there was a significant and consistent month-to-month decline of 0.87 patients per 100 thiazolidinedione appropriate-use patients per month in comparison to the pre-intervention period. After stepwise elimination of non-significant terms, the most parsimonious model contained only the baseline trend in utilization, the immediate effect of the intervention, and the month-to-month variation in the utilization of rosiglitazone following the intervention (Table IVb).

Table IV: Parameter estimates, standard errors and P-values from the full and most parsimonious segmented regression models predicting the monthly utilization rate of rosiglitazone in appropriate-use patients.

Variable	Estimate	Standard Error	<i>t</i> -statistic	P-value
a. Full segmented regression model				
Intercept	20.562	2.540	8.09	< 0.0001
Time	0.117	0.280	0.42	0.6792
Intervention	-2.445	1.100	-2.22	0.0356
Time after intervention	-0.874	0.408	-2.14	0.0421
b. Most parsimonious segmented regression model				
Intercept	21.506	1.173	18.33	< 0.0001
Intervention	-2.421	1.078	-2.25	0.0333
Time after intervention	-0.719	0.144	-5.01	< 0.0001

Using the most parsimonious model (Table IVb), we estimated the relative change in utilization was -74.78%, indicating that rosiglitazone utilization rate in the appropriate-use patient group decreased by 74.78% at the end of the study period (month 32) compared to what it would have been in the same month had the safety warning not been issued.

Effect of the FDA safety warning on rosiglitazone utilization in patients at risk of developing contraindicated conditions

In this patient population, the monthly utilization rate of rosiglitazone just before the beginning of the observation period was 19.95 patients per 100 patients classified as at-risk (Table V). Before the safety warning was issued, there was no significant month-to-month change in the percentage of patients using rosiglitazone (p-value = 0.646). There was also no significant change in the utilization rate of rosiglitazone (p-value = 0.693) and month-to-month utilization of rosiglitazone after the safety warning was issued (p-value = 0.078). After stepwise elimination of non-significant terms however, we observed a significant month-to-month decrease of less than 1 patient per 100 at-risk patients post-intervention in comparison to the pre-intervention period (Table Vb).

Table V: Parameter estimates, standard errors and P-values from the full and most parsimonious segmented regression models predicting the monthly utilization rate of rosiglitazone in patients at risk of developing contraindicated conditions.

Variable	Estimate	Standard Error	t-statistic	P-value
a. Full segmented regression model				
Intercept	19.946	4.120	4.84	< 0.0001
Time	0.204	0.439	0.47	0.646
Intervention	0.398	0.998	0.40	0.693
Time after intervention	-1.200	0.653	-1.86	0.078
b. Most parsimonious segmented regression model				
Intercept	21.607	2.053	10.53	< 0.0001
Time after intervention	-0.909	0.209	-4.53	< 0.0001

From Table Vb, we estimated the relative change in utilization was -79.93%, indicating that rosiglitazone utilization in the at risk group decreased by 79.93% at the end of the study period (month 32) compared to what it would have been in the same month had the safety warning not been issued.

Effect of the FDA safety warning on rosiglitazone utilization in patients contraindicated to use rosiglitazone

The utilization rate in patients contraindicated for rosiglitazone use in the period just before the beginning of the observation was 19.43 patients per 100 contraindicated patients. Before the intervention, rosiglitazone use decreased at a rate of 0.49 patients per 100 contraindicated patients. In the period immediately following the intervention, the rate of rosiglitazone use dropped abruptly by 4.62 patients per 100 contraindicated patients. There was however, no significant month-to-month change in rosiglitazone utilization after the safety warning (p-value = 0.6419) in comparison to the pre-intervention period (Table VIa).

Table VI: Parameter estimates, standard errors and P-values from the full and most parsimonious segmented regression models of the monthly utilization rate of rosiglitazone in contraindicated patients.

Variable	Estimate	Standard Error	t-statistic	P-value
a. Full segmented regression model				
Intercept	19.428	1.017	19.11	< 0.0001
Time	-0.485	0.119	-4.09	< 0.0001
Intervention	-4.618	0.953	-4.84	< 0.0001
Time after intervention	0.073	0.155	0.47	0.6419
b. Most parsimonious segmented regression model				
Intercept	19.081	0.744	25.64	< 0.0001
Time	-0.437	0.055	-7.94	< 0.0001
Intervention	-4.598	0.941	-4.88	< 0.0001

Using results from Table VIb, we estimated the relative change in utilization was -90.21%, indicating that utilization of rosiglitazone decreased by 90.21% at the end of the study period (month 32) in the contraindicated group compared to what it would have been in the same month had the safety warning not been issued.

Effect of the FDA safety warning on pioglitazone utilization in appropriate-use patients

These results (Table VIIa) indicate that just before the beginning of the observation period, the utilization rate of pioglitazone in patients deemed appropriate to use any type of thiazolidinedione was 16.46 patients per 100 patients per month. Before the warning, there was a significant month-to-month utilization increase of 0.744 patients per 100 appropriate-use patients. Immediately after the warning, there was no significant change in the utilization of pioglitazone (p-value = 0.2869). Following the intervention, there was a significant and consistent month-to-month decline of 0.561 patients per 100 appropriate-use patients using pioglitazone in comparison to the pre-intervention period.

Table VII: Parameter estimates, standard errors and P-values from the full and most parsimonious segmented regression models of the monthly utilization rate of pioglitazone in appropriate-use patients.

Variable	Estimate	Standard Error	<i>t</i> -statistic	P-value
a. Full segmented regression model				
Intercept	16.455	1.433	11.48	< 0.0001
Time	0.744	0.161	4.61	< 0.0001
Intervention	1.247	1.148	1.09	0.2869
Time after intervention	-0.561	0.220	-2.56	< 0.0001
b. Most parsimonious segmented regression model				
Intercept	16.286	1.539	10.59	< 0.0001
Time	0.805	0.163	4.93	< 0.0001
Time after intervention	-0.583	0.236	-2.47	0.0198

From Table VIIb, we further estimated a relative change in utilization of -26.34%, indicating that the utilization of pioglitazone in the appropriate-use group decreased by 26.34% at the end of the study period (month 32) compared to what it would have been in the same month had the safety warning not been issued.

Effect of the FDA safety warning on pioglitazone utilization in patients at risk of developing contraindicated conditions

The pre-observation utilization rate of pioglitazone in the at risk group was 20.85 patients per 100 patients per month. There was a significant month-to-month increase of 0.642 patients per 100 patients per month in the utilization rate within this group. There was however no significant effect of the safety warning on the use of pioglitazone immediately after the safety warning (p-value = 0.2534). Following the intervention, the use of pioglitazone decreased at a rate of 0.845 patients per 100 patients per month (Table VIII).

Table VIII: Parameter estimates, standard errors and P-values from the full and most parsimonious segmented regression models of the monthly utilization rate of pioglitazone in patients at-risk of developing contraindicated conditions.

Variable	Estimate	Standard Error	<i>t</i> -statistic	P-value
a. Full segmented regression model				
Intercept	20.850	1.490	13.99	< 0.001
Time	0.642	0.165	3.90	< 0.001
Intervention	1.287	1.103	1.17	0.2534
Time after intervention	-0.845	0.228	-3.71	< 0.001
b. Most parsimonious segmented regression model				
Intercept	20.707	1.499	13.81	< 0.001
Time	0.699	0.159	4.40	< 0.001
Time after intervention	-0.853	0.230	-3.72	< 0.001

From Table VIIIb, we estimated a relative change in utilization of -37.63%, indicating that pioglitazone utilization rate in the at risk group decreased by 37.63% at the end of the study period (month 32) compared to what it would have been in the same month had the safety warning not been issued.

Effect of the FDA safety warning on pioglitazone utilization in rosiglitazone-contraindicated patients

In the period just before the observation period, the monthly utilization rate of pioglitazone in the patient population identified as contraindicated for rosiglitazone use was 24.79 patients per 100 patients. Before the intervention, there was a significant month-to-month decline of 0.45 patients per 100 patients in pioglitazone utilization. In the period immediately following the intervention, there was no significant change in the rate of pioglitazone use (p-value = 0.1222). There was also no significant month-to-month change in the utilization rate of pioglitazone after the safety warning (p-value = 0.8030) (Table IXa).

Table IX: Parameter estimates, standard errors and P-values from the full and most parsimonious segmented regression models of the monthly utilization rate of pioglitazone in contraindicated patients.

Variable	Estimate	Standard Error	t-statistic	P-value
a. Full segmented regression model				
Intercept	24.790	0.670	36.99	< 0.001
Time	-0.450	0.828	-5.43	< 0.001
Intervention	-1.222	0.766	-1.60	0.1222
Time after intervention	0.025	0.099	0.25	0.8030
b. Most parsimonious segmented regression model				
Intercept	24.856	0.554	44.84	< 0.001
Time	-0.487	0.029	16.83	< 0.001

There was no relative change in pioglitazone utilization within this group since there was no absolute effect of the safety warning on drug utilization in this group.

CHAPTER V

DISCUSSION

In this study, we analyzed the rate (percentage utilization) of rosiglitazone and pioglitazone use among three patient groups (appropriate-use, at risk and contraindicated groups) using a national sample of Medicare during the 13 months before and 19 months following the FDA safety warning about the use of rosiglitazone. The inclusion of the pioglitazone group allowed for assessment of possible class effects of the safety warning.

Findings from this study suggest that the initial safety warning was adequate in reducing the utilization of rosiglitazone in the population targeted by the warning, as well as the other non-targeted groups. The warning however, did not produce significant reductions, immediate or sustained, in the percentage of patients considered to be contraindicated and on pioglitazone. Similarly, the warning had no significant effect in reducing utilization of pioglitazone in other groups in the period immediately after the safety warning. These findings signify that the initial safety warning only had an immediate effect in the group targeted by the warning. Our findings, are thus contrary to previous findings on the overall effects of safety warnings specific to rosiglitazone and troglitazone observed by Shah et al.¹⁰ and Wilkinson et al.¹¹ Both studies demonstrated that initial safety warnings were inadequate in reducing utilization of respective drugs.

We also observed that during the pre-intervention period, the average monthly utilization of pioglitazone was 20.7 patients per 100 patients, marginally surpassing that of rosiglitazone (19.63 patients per 100 patients). We attributed this finding to prior sensitization of the medical and general community to the safety concerns raised about rosiglitazone use during the pre-warning period. Similar assumptions about the insignificant effects of the safety warning in the at risk patient group using rosiglitazone as well as the appropriate-use and at risk groups using pioglitazone can be made because despite an noticeable decline in slope for percentage utilization of rosiglitazone and an increasing slope for percentage utilization of pioglitazone, the effects of the safety warning was insignificant in these groups.

In the appropriate-use group, we estimated that at the end of the study period (month 32), the relative utilization rates of rosiglitazone and pioglitazone decreased significantly by 74.78% and 26.34% respectively in comparison to expected utilization rates in the absence of the safety warning, indicating that the safety warning had spillover effects in this group for both drugs. Similar findings, demonstrated by significant post-intervention decline in drug use in the at risk groups of both drugs were observed. Our findings in this regard supports the findings of Katz et al.⁸ who demonstrated spillover effects of safety warnings to populations not targeted by such warnings.

A secondary effect of implementing a safety warning such as this is, as suggested by Wilkinson et al,¹¹ is a reduction in the frequency of utilization of the implicated drug. Our findings also demonstrate this secondary effect as we observed a general decline in rosiglitazone utilization across all patient groups using rosiglitazone following the safety warning. During the

pre-intervention period, rosiglitazone and pioglitazone use accounted for almost equal shares of the thiazolidinedione market within our study population (accounting for an average of 50.95% and 49.05% of the market share respectively). Following the intervention, market share reduced drastically in the rosiglitazone drug group to 26.66% but increased considerably in the pioglitazone group to 73.34%. Furthermore, the reduction in rosiglitazone utilization at the end of the study relative to the expected utilization rate in the absence of the intervention, in the appropriate-use, at-risk and contraindicated patients were 74.78%, 79.93% and 90.21% respectively. Likewise, we estimated reductions of 26.34% and 37.63% in the utilization of pioglitazone for appropriate-use and at risk patient groups respectively. These support the findings of various investigators who have identified the effects of regulatory warnings on drug utilization. Katz et al. demonstrated a general decline in prescription rates and therefore use of antidepressants following the Health Canada warning. Similarly, Wilkinson et al. and Shah et al. reported decreased utilization of troglitazone and rosiglitazone respectively following safety warnings, however in the case of rosiglitazone the declining use varied geographically.

Over the duration of the study, the market differentiation amongst appropriate-use, at risk patients and contraindicated patients varied considerably between rosiglitazone and pioglitazone group. During the pre-intervention period, there was minimal differentiation in utilization rates among all patient subgroups. Before the safety warning, the average difference in utilization rates between appropriate-use and contraindicated use was 6.7% and -0.2% for rosiglitazone and pioglitazone respectively. Following the intervention, the average difference was 6.8% and 16.30% respectively. This difference, seen with pioglitazone utilization, is an indication of appropriate differentiation of drug use among appropriate-use and contraindicated patient

groups. The same, on the other hand, was not evident with rosiglitazone. From a market perspective, the importance of this patient differentiation in minimizing risks associated with drug use in the event of a safety warning cannot be over emphasized. The significant decrease in utilization rates of pioglitazone in the appropriate and at-risk patient groups (-0.583 (p-value = 0.0198) and -0.853 patients per 100 patients (p-value = 0.0009) respectively) after the warning resulted in 26.34% and 37.63% decrease in pioglitazone utilization in respective groups at the end of the study period compared to expected utilization rates in the same month had the policy not been implemented, despite insignificant immediate effects of the safety warning in these groups could be attributed in part to a “class effect” of the safety warning. We also attributed this finding to the numerous risk management and marketing efforts employed by Takeda pharmaceuticals in the wake of the rosiglitazone safety warnings.

The differential effects of the safety warning on thiazolidinedione utilization observed in our study could be attributed to the fact that our study methods took classification of patients based on their potential drug-use risk profile into consideration. Moreover, the study design, which is the strongest, quasi-experimental design for evaluating longitudinal effects of time-delimited interventions²⁸ as well as the statistical analysis method employed enabled the identification of the immediate and sustained effects of interventions through analysis of change in level and slope pre- and post-intervention.^{28,29} We could thus adequately differentiate between the immediate and sustained effects of the safety warnings.

Study Limitations

This study evaluated the utilization of rosiglitazone and pioglitazone in the Medicare population in light of the safety warning for rosiglitazone; hence the results of the study are only generalizable to the Medicare population. Secondly, since this study relied on following a consistent cohort through the entire duration of the study, we could not determine the overall use pattern of thiazolidinediones during this period. Lastly, the media focus on rosiglitazone safety concerns prior to the FDA safety warning might have confounded the effects observed.

CHAPTER VI

CONCLUSIONS

The initial safety warning issued by the FDA about an ongoing safety review of rosiglitazone's potential to increase cardiovascular risks was effective in decreasing the utilization of the implicated drug in the targeted population and hence rosiglitazone market share within the Medicare thiazolidinedione market. There was no obvious differentiation in rosiglitazone use among different patient groups in response to the safety warning. Similarly, the safety warning had spillover effects, reducing utilization of drugs in other patient cohorts not targeted by the warning, an indication that the response to the safety warning might have been inappropriate in these groups. There was also an in-class shift in thiazolidinedione utilization from rosiglitazone to pioglitazone despite a "class effect". We thus conclude that the Medicare thiazolidinedione market responded promptly and appropriately to the May 2007 FDA safety warning for rosiglitazone resulting in a significant decline in rosiglitazone utilization in the targeted cohort and a general reduction in rosiglitazone market share across patient groups.

BIBLIOGRAPHY

BIBLIOGRAPHY

1. The U.S. FDA. Drug Development and Approval Process: Available at <http://www.fda.gov/drugs/developmentapprovalprocess/default.htm>. Accessed March 11, 2011
2. Spilker B. The Drug Design/Development Process. Available at <http://shrpssb.umdnj.edu/shrpnwk/course/BINF5220/Fall-2001/lecture2/lecture2.PDF>. Accessed February 13, 2011
3. The U.S. FDA. What does the FDA do? Available at <http://www.fda.gov/AboutFDA/Transparency/Basics/ucm194877.htm>. Accessed February 20, 2011
4. The U.S. FDA. The Drug Safety Newsletter. Available at <http://www.fda.gov/Drugs/DrugSafety/DrugSafetyNewsletter/default.htm>. Accessed February, 12, 2011
5. Guidance on Drug Safety Information – Food and Drug Administration’s Communication to the Public; Availability; Food and Drug Administration, Human Health Services; Notice, 72 Federal Register 44 (March 7, 2007), pp. 10224 – 10225
6. The U.S. FDA. “MedWatch” Safety Alert for Human and Medical Products. Available at: <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/default.htm>. Accessed February 22, 2011
7. Lasser KE, Allen PD, Woolhandler SJ, Himmelstein DU, Wolfe SM, Bor DH. Timing of New Black Box Warnings and Withdrawals for Prescription Medications. *JAMA*. 2002;287(17):2215-2220.
8. Katz LY, Kozyrskyj AL, Prior HJ, Murray WE, Cox JB, Sareen J. Effect of regulatory warnings on antidepressant prescription rates, use of health services and outcomes among children, adolescents and young adults. *Canadian Medical Association Journal*. 2008;178(8):1005-1011.
9. Libby AM, Orton HD, Valuck RJ. Persisting Decline in Depression Treatment after FDA Warnings. *Archives of General Psychiatry*. 2009;66(6):633-639.
10. Shah ND, Montori VM, Krumholz HM, Tu K, Alexander CG, Jackevicius CA. Responding to an FDA Warning - Geographic Variation in the Use of Rosiglitazone. *The New England Journal of Medicine*. 2010;363(22):2081-2084.
11. Wilkinson JJ, Force RW, Cady PS. Impact of Safety Warnings on Drug Utilization: Marketplace Life Span of Cisapride and Troglitazone. *Pharmacotherapy*. 2004;24(8):978-986.
12. World Health Organization. Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications. Report of a WHO consultation. Geneva: WHO, 1999.

13. Graham DJ, Ouellet-hellstrom R, Macurdy TE, et al. Risk of Acute Myocardial Infarction, Stroke , Heart Failure , and Death in Elderly Medicare Patients Treated With Rosiglitazone or Pioglitazone. *JAMA* 2010;304(4):411-418.
14. Lloyd-Jones D, Adams R, Carnethon M, et al. Heart Disease and Stroke Statistics -2009 update: A Report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation*. 2009;119:e1-e161.
15. Epstein FH. SPECIAL ARTICLE: Hyperglycemia A Risk Factor in Coronary Heart Disease. *Circulation* 1967;36:609-619.
16. Masoudi FA. Improving Drug Safety Surveillance: Lessons from Rosiglitazone. *Circulation: Cardiovascular Quality and Outcomes*. 2010;3:441-443.
17. The U.S. FDA. Rezulin withdrawn from the market. Available at: http://www.fda.gov/ohrms/dockets/ac/00/backgrd/3634b1a_tab6c.htm. Accessed March 4, 2011.
18. Nissen SE, Wolski K. Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes. *New England Journal of Medicine*. 2007;356(24):2457-2471.
19. The U.S. FDA. New safety information on Diabetes Drug Rosiglitazone. 2007. Available at: <http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm049063.htm>. Accessed February 11, 2011.
20. Drazzen JM, Morrissey S, Curfman GD. Rosiglitazone - Continued Uncertainty about Safety. *New England Journal of Medicine*. 2007;357(1):63-64.
21. Diamond GA, Bax L, Kaul S. Uncertain Effects of Rosiglitazone on the Risk for Myocardial Infarction and Cardiovascular Death. *Annals of Internal Medicine*. 2007;147:578-581.
22. The U.S. FDA. Avandia FDA Approval letter. 1999. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/applletter/1999/21071ltr.pdf. Accessed February 11, 2011.
23. The U.S. FDA. FDA Issues Safety Alert on Avandia. 2007. Available at: <http://www.fda.gov/ScienceResearch/SpecialTopics/WomensHealthResearch/ucm134225.htm>. Accessed February 21, 2011.
24. The U.S. FDA. Information for Healthcare professionals on Rosiglitazone. Available at: <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm143460.htm>. Accessed March 2, 2011.
25. The U.S. FDA. FDA Adds Boxed Warning for Heart-related Risks to Anti-Diabetes Drug Avandia. Available at: <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/ucm109026.htm>. Accessed February 2, 2011.
26. The U.S. FDA. FDA Significantly Restricts Access to the Diabetes Drug Avandia. Available at: <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm226956.htm>. Accessed February 2, 2011.
27. Anand SS, Islam S, Rosengren A, et al. Risk factors for myocardial infarction in women and men: insights from the INTERHEART study. *European Heart Journal*. 2008;29:932-940.

28. Wagner AK, Soumerai SB, Zhang F, Ross-Degnan D. Segmented regression analysis of interrupted time series studies in medication use research. *Journal of Clinical Pharmacy and Therapeutics*. 2002;27:299-309.
29. Ramsay C, Brown E, Hartman G, Davey P. Room for improvement: A systematic review of the quality of evaluations of interventions to improve hospital antibiotic prescribing. *The Journal of Antimicrobial Chemotherapy*. 2003;52:764-71.
30. Ramsay CR, Matowe L, Grilli R, Grimshaw JM, Thomas RE. Interrupted time series designs in health technology assessment: Lessons from two systematic reviews of behavior change strategies. *Int.J.Technol.Assess.Health Care* 2003;19:613-23.

VITA

Hafiz A. Oko-Osi was born July 28, 1981 in Kaduna state, Nigeria. He is the son of Engr. And Mrs. Razaq O. Oko-Osi of Lagos, Nigeria.

Mr. Oko-Osi obtained his Bachelor of Pharmacy degree from the University of Lagos, Lagos, Nigeria in 2006. After graduation from pharmacy school, he worked in Lagos State Health Service Commission, Lagos, before entering the pharmaceutical industry as a Pharmaceutical Sales Representative for Pfizer Inc. He entered graduate school in August, 2009. He received his M.S. in Pharmacy Administration from the University of Mississippi in 2011.