The Thesis Committee for Isaac Pan
Certifies that this is the approved version of the following thesis:

Association Between Race/Ethnicity and the Receipt of Outpatient Second-Generation Antipsychotic Agents Stratified by Metabolic Effects

APPROVED BY
SUPERVISING COMMITTEE:

Supervisor:

Jim M. Koeller

Co-Supervisor:

Stephen R. Saklad

Kelly R. Reveles

Cynthia A. Gutierrez

Association Between Race/Ethnicity and the Receipt of Outpatient Second-Generation Antipsychotic Agents Stratified by Metabolic Effects

by

Isaac Pan, B.S.Bio.; Pharm.D.

Thesis

Presented to the Faculty of the Graduate School of

The University of Texas at Austin

in Partial Fulfillment

of the Requirements

for the Degree of

Master of Science in Pharmaceutical Sciences

The University of Texas at Austin

August, 2016

Dedication

This thesis is dedicated to my parents for their support and prayers.

Acknowledgements

I would like to thank the following people for their guidance and support:

Jim M. Koeller, M.S.
Professor, College of Pharmacy, The University of Texas at Austin; and Adjoint Professor, School of Medicine, The University of Texas Health Science Center at San Antonio, Texas, who served as my thesis committee chairperson

Stephen R. Saklad, Pharm.D., BCPP
Clinical Professor, College of Pharmacy, The University of Texas at Austin; Adjoint Associate Professor, School of Medicine, The University of Texas Health Science Center at San Antonio, Texas; and Clinical Pharmacologist, San Antonio State Hospital, Texas, who served as my residency director and a thesis committee member.

Kelly R. Reveles, Pharm.D., Ph.D., BCPS
Assistant Professor, College of Pharmacy, The University of Texas at Austin; and Adjoint Assistant Professor, School of Medicine, The University of Texas Health Science Center at San Antonio, Texas, who served as a thesis committee member

Cynthia A. Gutierrez, Pharm.D., M.S., BCPP
Clinical Pharmacy Specialist, Psychiatry, South Texas Veterans Health Care System, San Antonio, Texas; Clinical Assistant Professor, College of Pharmacy, The University of Texas at Austin; and Clinical Assistant Professor, School of Medicine, The University of Texas Health Science Center at San Antonio, Texas

Grace C. Lee, Pharm.D., Ph.D., BCPS
Assistant Professor, College of Pharmacy, The University of Texas at Austin; and Adjoint Assistant Professor, School of Medicine, The University of Texas Health Science Center at San Antonio, Texas

Abstract

Association Between Race/Ethnicity and the Receipt of Outpatient Second-Generation Antipsychotic Agents Stratified by Metabolic Effects

Isaac Pan, M.S.P.S.

The University of Texas at Austin, 2016

Supervisor: Jim M. Koeller

Co-Supervisor: Stephen R. Saklad

Background: Use of first-generation antipsychotics (FGAs) has been largely replaced by second-generation antipsychotics (SGAs) in the United States (US) due to the lower risk of extrapyramidal symptoms (EPS) associated with SGAs. However, SGAs have higher risk of metabolic adverse effects than FGAs do, and some SGA agents have higher metabolic risk than the other SGA agents. Historically, patients of racial/ethnic minorities were less likely than those of non-Hispanic White (NHW) to receive adequate mental health care. Our investigation sought to identify if there is an association between the patient race/ethnicity (NHW or 'Others') and the receipt of lower-metabolic-risk SGAs (LMRS) or higher-metabolic-risk SGAs (HMRS) in the outpatient settings.

Methods: This was a retrospective study using the nationally representative data from the Medical Expenditure Panel Survey from 2008 to 2013. The chi-square test was used to determine the relationship between race/ethnicity (NHW or 'Others') and the receipt of LMRS or HMRS.

Results: From 2008 to 2013, we estimated about 4 million patients using SGAs per year. Approximately 2.8 million patients were NHW, and 1.2 million patients were 'Others'. Approximately 29.7% (1.2 million) used LMRS, and 70.3% (2.8 million) used HMRS. The

disproportionate use of LMRS and HMRS was significant between races/ethnicities. More patients of NHW received LMRS than those of 'Others' ($p = 0.021$), and less patients of NHW received HMRS than those of 'Others' ($p = 0.021$).

Conclusion: With our 2-group categorization of LMRS and HMRS, there appeared to be a racial/ethnic disparity in the receipt of LMRS. Patients of racial/ethnic minorities were less likely to receive LMRS than those of NHW.

Table of Contents

List of Tables

List of Figures

Chapter One

Introduction

Therapeutic Uses of Second-Generation Antipsychotics

In 1989, the United States (US) Food and Drug Administration (FDA) approved the first second-generation antipsychotic (SGA), clozapine, for treatment-resistant schizophrenia.[1] Three more SGAs were approved in the 1990s: risperidone, olanzapine, and quetiapine. To date, there are a total of 12 different SGAs in the US market for treatment of schizophrenia (Table 1.1). Since the emergence of SGAs, various schizophrenia guidelines have consistently recommended SGAs as the first-line treatment, and SGAs have become the mainstay agent for schizophrenia since late 1990s.[2-4]

Table 1. 1 SGAs and the FDA Approval Years

Year Approved	Generic Name	Brand Name
1989	Clozapine	Clozaril®
1993	Risperidone	Risperdal®
1996	Olanzapine	Zyprexa®
1997	Quetiapine	Seroquel®
2001	Ziprasidone	Geodon®
2002	Aripiprazole	Abilify®
2006	Paliperidone	Invega®
2009	Asenapine	Saphris®
2009	Iloperidone	Fanapt®
2010	Lurasidone	Latuda®
2015	Brexpiprazole	Rexulti™
2015	Cariprazine	Vraylar™

In addition to their use in schizophrenia, many SGAs are not only FDA-approved but recommended as the first-line treatment for mania episodes, mixed episodes, or depressive episodes associated with bipolar disorder.[5-7] Aripiprazole, brexpiprazole, and quetiapine also have FDA's approval as adjunctive therapy in major depressive disorder.

Besides FDA-approved indications in schizophrenia and mood disorders, SGAs are also often prescribed off-label for agitation, aggression, and other behavioral and psychological symptoms of dementia.[8-13]

As of now, SGAs have become part of the standard of care for treating schizophrenia and bipolar disorder.[2,3,5,14] When comparing toxicity profiles, SGAs have been often preferred over FGAs for their lower risk of antipsychotic-induced movement disorders, or extrapyramidal symptoms (EPS).[15,16] Since the 1990s, use of FGA has largely been replaced by SGA in the US.[17,18]

Metabolic Adverse Effects of SGAs

Despite SGAs' lower risk of inducing EPS, their use is not without other risks. SGAs in general have considerably greater risk of metabolic adverse effects than FGAs, including weight gain, glucose intolerance, and lipid abnormalities (Table 1.2).[19] Patients with serious mental illness (SMI), including schizophrenia, schizoaffective disorder, and bipolar disorder, have higher prevalence of metabolic syndrome (MetS), which is a cluster of metabolic abnormalities that increase risks of cardiovascular diseases, diabetes, and stroke.[20-25] Depending on age, race, ethnicity, country, and antipsychotic treatments, prevalence of MetS in patients with schizophrenia has been reported to be as high as 68% while the prevalence was considerably lower in patients without psychiatric conditions, ranging between 6% and 20.7%.[22,24] Similarly, higher prevalence of MetS has also been described in patients with bipolar disorder and schizoaffective disorder at 22% to 30% and 42%, respectively.[20-23,25]

The cause of higher prevalence of MetS in patients with SMI is likely multifactorial, but it can be partly attributed to the exposure to antipsychotic treatment, especially SGAs.[22,24] Within the class of SGA, the risk of causing metabolic adverse effects varies greatly from one agent to another. There have been a number of studies analyzing and reviewing the metabolic risk in different SGAs. However, there is considerable heterogeneity in their methods of quantifying weight gain, glucose intolerance, and lipid abnormalities. Nonetheless, the general consensus is that clozapine and olanzapine have the greatest metabolic risks compared to other SGAs (Table1.2).[2,4,24,26] For example, one meta-analysis reported the risk ratios of olanzapine causing significant weight gain (7% or more above baseline or as defined by the original studies) were between 1.44 and 4.59 compared to SGAs other than clozapine, and it also suggested clozapine shared similar metabolic risk with olanzapine (Figure 1.1).[15,27,28] On the contrary, aripiprazole and ziprasidone have often been considered "weight neutral" and have lower metabolic risks than other SGAs (Table 1.2).[15,24,29,30]

Table 1. 2 EPS and Metabolic Adverse Effects of Selected FGAs and SGAs[4]

	Medication	EPS	Weight Gain	Glucose Abnormalities	Lipid Abnormalities
FGAs	Haloperidol	+++	+	0	0
	Perphenazine	++	+	+	+
SGAs	Aripiprazole	0	0	0	0
	Clozapine	0	+++	+++	+++
	Olanzapine	0	+++	+++	+++
	Quetiapine	0	++	++	++
	Risperidone	+	++	++	++
	Ziprasidone	0	0	0	0

0 = No risk or rarely cause adverse effects at therapeutic doses

+ = Mild or occasionally causes adverse effects at therapeutic doses

++ = Sometimes causes adverse effects at therapeutic doses

+++ = Frequently causes adverse effects at therapeutic doses

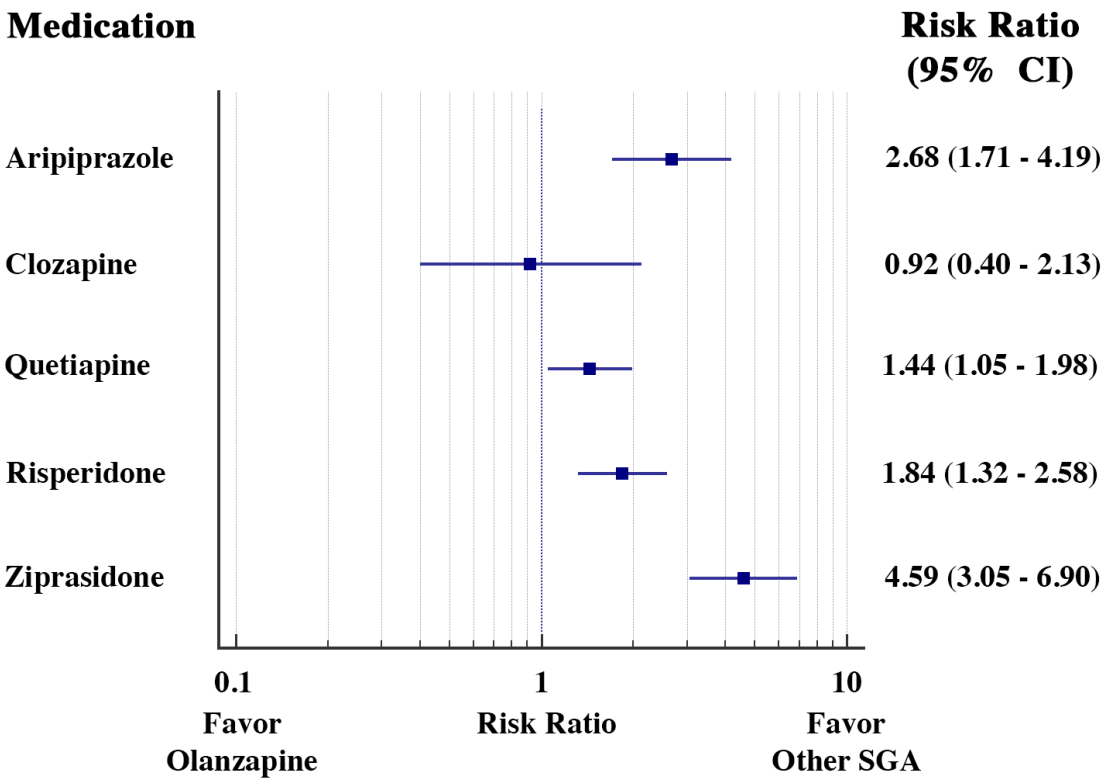

Figure 1. 1 Olanzapine versus other SGAs in Adverse Effect of Causing Significant Weight Gain[28]

Similarly, olanzapine and clozapine have the highest risk in inducing glucose and lipid abnormalities compared to other SGAs.[4] In the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), Lieberman *et al*. reported the outcomes of metabolic adverse effects of three different SGAs and an active FGA control, perphenazine.[15] In their results, the olanzapine treatment group had the highest increase in glycosylated hemoglobin A1c (HbA1c) from baseline with an average increase at 0.41% (quetiapine 0.05%, risperidone 0.08%, ziprasidone -0.1%, and perphenazine 0.1%; $p = 0.01$) (Table 1.3). In the same study, the olanzapine treatment group also had the greatest increase in cholesterol and triglycerides from baseline (Table 1.3). Besides results from CATIE, systematic reviews have also confirmed that aripiprazole and ziprasidone have considerably lower risk of metabolic adverse effects than olanzapine, clozapine, risperidone, and quetiapine.[15,24,29-31] While there are limited studies on the metabolic risk of the newer SGAs approved after aripiprazole, based on the systematic review of De Hert *et al.*, asenapine and lurasidone are likely to have low metabolic risks. In the same systematic review, they also categorized iloperidone and paliperidone to have mild to moderate metabolic risk (Table 1.4).[26,32]

Table 1. 3 Selected Metabolic Adverse Effect Outcomes from CATIE[15]

Outcomes	Olanzapine	Quetiapine	Risperidone	Ziprasidone	Perphenazine	P-Value
HbA1c* (%)	0.41	0.05	0.08	-0.10	0.10	0.01
Cholesterol (mg/dL)	9.7	5.3	-2.1	-9.2	0.5	<0.001

*Mean change from baseline

Table 1. 4 Risk of Metabolic Adverse Effects of SGAs Sorted by Year of FDA Approval [26,32]

Year of FDA Approval	Medication	Risk of Weight Gain	Risk of Glucose and Lipid Abnormalities
1989	Clozapine	High	High
1993	Risperidone	Moderate	Mild
1996	Olanzapine	High	High
1997	Quetiapine	Moderate	Moderate
2001	Ziprasidone	Low	Low
2002	Aripiprazole	Low	Low
2006	Paliperidone	Moderate	Mild
2009	Asenapine	Low	Low
2009	Iloperidone	Moderate	Mild
2010	Lurasidone	Low	Low

Disparities in Antipsychotic Use

Historically, patients of racial/ethnic minority groups have been reported to be less likely to receive adequate mental health care, including antipsychotic treatment, compared to those of non-Hispanic Whites (NHWs).[33,34] Also, based on early retrospective studies in the 1990s, patients of minority groups were less likely than those of NHW to receive SGAs and more likely to receive FGAs.[34-37]

Daumit *et al* assessed the disparities in antipsychotic treatment using the National Ambulatory Medical Care Survey (NAMCS) and National Hospital Ambulatory Medical Care Survey (NHAMCS). [34] Their results demonstrated that patients of non-Hispanic Blacks (NHBs) and Hispanics were less likely than those of NHWs to receive SGAs (odds ratios at 0.50 and 0.43, respectively) in 1992 to 1994. However, they also showed that these disparities became less pronounced throughout the 1990s. In the same study, they reported the odds ratios for minorities to receive SGAs in 1998 and 2000 had increased to 0.88 and 1.05 compared to NHW.[34]

With a similar study design, Cook *et al.* suggested the higher SGA use rate in NHWs between 2005 and 2010 was not statistically different than the rate in NHBs (92.8% vs. 90.0%).[38]

However, agents within the SGA class vary greatly in propensities of inducing metabolic adverse effects. There has yet to be a study examining the racial/ethnic disparities in use of SGAs with lower risk of metabolic adverse effects.

Summary

SGAs are not only the mainstay of schizophrenia treatment, but are also widely used in psychiatric disorders other than psychotic disorders. SGAs have been documented to have comparatively lower EPS adverse effects than FGAs, but their metabolic risks are higher, which can increase cardiometabolic risks in SGA-treated patients. Historically, racial/ethnic minorities, including NHB and Hispanic patients, were less likely than NHW patients to use SGAs. However, studies have suggested this gap in disparities continues to become narrower and could have become insignificant in recent years.

Knowledge Gap

To our best knowledge, there have yet been any studies on the association between races/ethnicities and the receipt of lower-metabolic-risk SGAs (LMRS) or higher-metabolic-risk SGAs (HMRS).

Objective and Hypotheses

Objective: to determine if there is an association between race/ethnicity (non-Hispanic Whites or other races/ethnicities) and the receipt of lower-metabolic-risk SGAs (LMRS) or higher-metabolic-risk SGAs (HMRS)

Hypothesis 1: more non-Hispanic Whites (NHW) using SGAs will receive lower-metabolic-risk SGAs (LMRS) compared to other races/ethnicities ('Others').

Hypothesis 2: more non-Hispanic Whites (NHW) using SGAs will receive higher-metabolic-risk SGAs (HMRS) compared to other races/ethnicities ('Others').

Hypothesis 3: more other races/ethnicities ('Others') using SGAs will receive lower-metabolic-risk SGAs (LMRS) compared to non-Hispanic Whites (NHW).

Hypothesis 4: more other races/ethnicities ('Others') using SGAs will receive higher-metabolic-risk SGAs (HMRS) compared to non-Hispanic Whites (NHW).

Chapter Two

Methods

Study Design

This study was a retrospective, cross-sectional analysis of the US civilian, outpatient population from 2008 to 2013. We examined the SGA utilization using the Medical Expenditure Panel Survey (MEPS). This study was a non-human research based on the regulation of the University of Texas Health Science Center at San Antonio (UTHSCSA) Institutional Review Board (IRB) (protocol number: HSC20160319N).

Data Source

This study utilized data from MEPS. MEPS is a set of large-scale surveys sponsored by the Agency for Healthcare Research and Quality (AHRQ). It provides detailed information of the healthcare use and expenditure from a nationally representative sample of outpatient, civilian Americans. MEPS is designed to produce national estimates of healthcare utilization through its statistical models.[39,40] The design of MEPS is complex and includes stratification, clustering (primary sampling unit, or PSU), multiple stages of selection, and disproportionate sampling. Because of its complex survey design, analyzing MEPS data requires to application of MEPS survey patient-specific weight, stratum variance, and PSU variance. Also, to ensure accurate national estimates, AHRQ requires a minimum of 100 unweighted observations to report the results.[39-41]

MEPS is a relational data source that is publicly accessible on AHRQ's website for research purposes, and its data files are categorized into Household Component Full-Year files, which contain expenditure and utilization data for the calendar year, and Household Component Event files, which contain patient self-reported medical events. [39,40]

Study Subjects and Eligibility

We included any patient who had at least one SGA prescription between 2008 and 2013, based on the Prescribed Medicines files of MEPS. For the SGAs in this study, we included clozapine, risperidone, quetiapine, olanzapine, aripiprazole, ziprasidone, paliperidone, lurasidone, iloperidone, and asenapine. SGAs were identified by the Multum Lexicon drug classification codes: first level category ID 242 (psychotherapeutic agents), second level category ID 251 (antipsychotics), and third level category ID 341 (atypical antipsychotics).

Definitions

Patient's Receipt of SGAs by Metabolic Risks

Based on our review of the existing literature on metabolic adverse effects associated with SGAs, risk of metabolic adverse effects of SGAs can be categorized into low, moderate, and high.[15,26-32] To simplify the classification of metabolic risk in SGAs, we took a step forward and created the two-level category of LMRS and HMRS (Table 2.1). Utilizing the review by De Hert *et al.*, we combined the SGA agents with moderate or high metabolic risks into a single group, HMRS, and then kept the SGA agents with low metabolic risks the same.

Table 2. 1 SGAs Categorized as LMRS and HMRS[15,26-32]

LMRS	HMRS
• Aripiprazole • Asenapine • Lurasidone • Ziprasidone	• Clozapine • Iloperidone • Olanzapine • Paliperidone • Quetiapine • Risperidone

Patient's Race/Ethnicity

- NHW: patient who reported to be of White race (no other race reported) and non-Hispanic ethnicity
- 'Others': patient who reported to be of Hispanic ethnicity or races other than White

Variables

Based on patients' race, Hispanic ethnicity, and antipsychotic prescription records, we created two dichotomous variables to assess the race/ethnicity and individual patient's receipt of SGAs by metabolic risk categories (Table 2.2). Regardless of the numbers of SGA prescription filled, patients were categorized to either using LMRS or using HMRS. Patients who used both LMRS and HMRS were classified as patient using HMRS (Table 2.3).

Table 2. 2 Variables for Statistical Analysis

Variable	Variable Type
Patient's race/ethnicity • NHW • 'Others'	Dichotomous
Patient's receipt of SGAs by metabolic risks • LMRS • HMRS	Dichotomous

Table 2. 3 Examples of Categorizing Patient's Receipt of LMRS or HMRS

Example 1: Patient A had three prescriptions for olanzapine and no other SGAs; patient A was categorized as a patient using HMRS
Example 2: Patient B had only one prescription for aripiprazole; patient B was categorized as a patient using LMRS
Example 3: Patient C had four prescriptions for ziprasidone and one prescription for quetiapine; patient C was categorized as a patient using HMRS

Statistical Methods

To test our hypotheses, we utilized the chi-square test to analyze the relationship between race/ethnicity (NHW or 'Others') and patient's receipt of SGAs with lower or higher metabolic risk category (LMRS or HMRS). We chose race/ethnicity to be the independent variable, and the dependent variable was the receipt of SGAs with lower or higher metabolic risk category (LMRS or HMRS). The chi-square test was adjusted to account for the MEPS complex study design using patient-specific weights, clustering, and stratification to derive national estimates. IBM® SPSS® Statistic 23 was used for all statistical analyses. A p-value that was less than 0.05 indicated statistical significance.

For each cell of the 2x2 chi-square table, we also reported the adjusted residual to assess if an individual cell was significantly above or below the expected value when the null hypothesis was true. Under the null hypothesis that race/ethnicity and receipt of LMRS or HMRS were independent, the adjusted residual would have a normal distribution. Therefore, with a significance level of 0.05, the null hypothesis would be true if the adjusted residual was less than 1.96 and more than -1.96. In addition, odds ratios were also calculated to assess the magnitude of the relationship between races/ethnicities and patient's receipt of LMRS or HMRS.

Chapter Three

Results

Objective: To determine if there is an association between race/ethnicity (NHW or ‘‘Others’’) and the receipt of LMRS or HMRS

Overall, we estimated there were about 4 million patients per year who had at least one prescription for SGAs. Approximately 2.8 million patients were NHW, and 1.2 million patients were considered ‘Others’. Of these 4 million patients, 29.7% (1.2 million) used LMRS, and 70.3% (2.8 million) used HMRS. Table 3.1 depicts the overall results of the chi-square test. Overall, the disproportionate use of LMRS and HMRS between NHW and ‘Others’ was significant (chi-square = 10.745, p = 0.021).

Table 3. 1 Chi-Square Results on Relationship between Patient’s Race/Ethnicity and Patient’s Receipt of LMRS or HMRS

		Patient’s Race/Ethnicity (Number of Patients)		
		NHW	**Other**	**Total**
Patient’s Receipt of SGA by Metabolic Risk Categories (Number of Patients)	**LMRS**	888,370	305,420	1,193,790
	HMRS	1,918,603	911,054	2,829,657
	Total	2,806,973	1,216,474	4,023,447

Chi-square = 10.745, p = 0.021

LMRS: aripiprazole, asenapine, lurasidone, and ziprasidone

HMRS: clozapine, iloperidone, olanzapine, quetiapine, paliperidone, and risperidone

Hypothesis 1: More NHW using SGAs will receive LMRS compared to 'Others'

Of the 1.2 million patients who received only LMRS, approximately 0.9 million were NHW (Table 3.2). This disproportionate use was significantly different from what our bivariate model predicted; more NHW using SGAs received LMRS than what we expected by random chance (adjusted residual = 2.41 > 1.96). Our model showed the odds for NHW to receive LMRS were 1.381 times greater than those for 'Others'. We accepted hypothesis 1.

Table 3. 2 Chi-Square Results on NHW Received LMRS

NHW Patients Received LMRS	
Observed	888,370
Predicted	832,854
Adjusted Residual	2.410

Chi-square = 10.745, p = 0.021, odds ratio = 1.381

LMRS: aripiprazole, asenapine, lurasidone, and ziprasidone

Hypothesis 2: More NHW using SGAs will receive HMRS than 'Others'

Of the 2.8 million patients received HMRS, approximately 1.9 million were NHW (Table 3.3). This disproportionate use was significantly different from what our bivariate model predicted; less NHW using SGAs received HMRS than what we expected by random chance (adjusted residual = -2.41 < -1.96). Our model showed the odds for NHW to receive HMRS were approximately 28% less than those for 'Others'. We rejected hypothesis 2.

Table 3. 3 Chi-Square Results on NHW Received HMRS

NHW Patients Received HMRS	
Observed	1,918,603
Predicted	1,919,184
Adjusted Residual	-2.410

Chi-square = 10.745, p = 0.021, odds ratio = 0.724

HMRS: clozapine, iloperidone, olanzapine, quetiapine, paliperidone, and risperidone

Hypothesis 3: More 'Others' using SGAs will receive LMRS compared to NHW

Of the 1.2 million patients who received only LMRS, approximately 0.3 million were considered 'Others' (Table 3.4). This disproportionate use was significantly different from what our bivariate model predicted; less 'Others' using SGAs received LMRS than we expected by random chance (adjusted residual = -0.241 < -1.96). Our model showed the odds for 'Others' to receive LMRS was approximately 28% less than those for NHW. We rejected hypothesis 3.

Table 3. 4 Chi-Square Results on 'Others' Received LMRS

'Others' Patients Received LMRS	
Observed	305,420
Predicted	360,936
Adjusted Residual	-2.410

Chi-square = 10.745, p = 0.021, odds ratio = 0.724

LMRS: aripiprazole, asenapine, lurasidone, and ziprasidone

Hypothesis 4: More 'Others' using SGAs will receive HMRS compared to NHW

Of the 2.8 million patients who received HMRS, approximately 0.9 million were considered 'Others'. (Table 3.5) This disproportionate use was significantly different from what our bivariate model predicted; more 'Others' using SGAs received HMRS than we expected by random chance (adjusted residual = 2.41 > 1.96). Our model showed the odds for 'Others' to receive HMRS was 1.381 times greater than those for NHW. We accepted hypothesis 4.

Table 3. 5 Chi-Square Results on 'Others' Received HMRS

NHW Patients Received HMRS	
Observed	911,054
Predicted	910,473
Adjusted Residual	2.410

Chi-square = 10.745, p = 0.021, odds ratio = 1.381

HMRS: clozapine, iloperidone, olanzapine, quetiapine, paliperidone, and risperidone

Chapter Four

Discussion

Our study was the first to describe outpatient SGA use by risk of metabolic adverse effects between NHW and 'Others' in the US civilian, outpatient population. Our data demonstrated the disproportionate use of LMRS or HMRS was significant between these two racial/ethnic groups; more NHWs using SGAs received LMRS than 'Others' ($p = 0.021$). More 'Others' patients received HMRS than those of NHW patients did ($p = 0.021$).

Although previous studies suggested there were less or even likely insignificant racial/ethnic disparities in SGA use as compared to FGA use, our study suggested there still may be racial/ethnic disparities in antipsychotic prescribing when considering the receipt of SGA with different metabolic risk categories (LMRS or HMRS). This difference in SGA prescribing patterns could be partly explained by the medication cost and generic availability (Table 4.1). Patients of racial/ethnic minorities are more likely than those of NHW to be uninsured or had lower income levels.[42,43] Risperidone, the first generic SGA other than clozapine, has been approved by the FDA since 2008; however, the first generic LMRS agent was not approved until more recently in 2012. Ziprasidone was the only LMRS agent that had a generic alternative available during our study period. Based on the most recent average wholesale prices of SGAs, the cost of generic ziprasidone was approximately four times of the cost of generic risperidone (Table 4.1).[44] The racial/ethnic disparity in LMRS use observed in our study could be confounded by the high cost of LMRS agents and the disparities of income and health insurance coverage in the 'others' group.[45] In addition to costs and generic availability, aripiprazole and ziprasidone were more likely to be restricted as non-preferred brand antipsychotics in insurance medication formularies compared to risperidone, quetiapine, and olanzapine.[46,47] Also, aripiprazole and ziprasidone were more likely to be restricted by insurance and health care plans with

prior authorization compared to risperidone and quetiapine.[46-48] These formulary restrictions could also further decrease access to LMRS in the 'others' group who already had lower health care access and utilization than NHW.[43]

Table 4. 1 SGAs, Generic Approval Years, and Generic Costs [44]

Generic Name	Year of Generic Approval	Generic Cost*
Clozapine	1996	$ 280.47
Risperidone	2008	$120.70
Olanzapine	2011	$396.48
Quetiapine	2012	$304.43
Ziprasidone	2012	$531.83
Aripiprazole	2015	$897.80
Paliperidone	2015	$915.84
Asenapine	No Generic Available	No Generic Available
Iloperidone	No Generic Available	No Generic Available
Lurasidone	No Generic Available	No Generic Available

*Based on the lowest average wholesale price of 30-day supply at the lowest recommended target daily adult dosage for schizophrenia on the FDA labels

In addition, psychiatric patients of NHB were more likely than those of NHW to receive a psychotic disorder diagnosis instead of mood disorder diagnosis; mood disorders can be potentially underdiagnosed in this minority population. [49,50] Aripiprazole was the most used LMRS agent in our study, which also ranked number two in the US prescription medication sales in 2012.[51] Increased use of aripiprazole may be due to its use for adjunct treatment in depression, which could be underdiagnosed in patients of NHB.

Our study highlighted the importance of examining SGA prescribing patterns by risk of metabolic adverse effects. Use of FGAs has largely been replaced by SGAs in the US, and SGAs have become the standard of care for schizophrenia and bipolar disorder. [2,3,5,14,17,18] Selection of SGAs should be based on patient's previous antipsychotic experience and side effect profile.[2,4] Because of the high prevalence of MetS among patients with SMI, LMRS agents should be preferred over HMRS agents to delay occurrence of MetS, avoid exacerbating existing metabolic symptoms, and decrease long-term healthcare costs associated with antipsychotic induced MetS.[4,52,53] In this study, our results suggested that disparities appeared to still exist in LMRS use between different races/ethnicities. The next step should be using a multivariate model and different data source to confirm our study results. In addition, further research should be directed to identifying other factors affecting equal access to LMRS and innovative mental health practice models and policies to decrease and eliminate the disparities of LMRS in racial/minority groups.

Limitations

There were some limitations to this study. First, MEPS data rely on patient self-reporting.[39,40] In this study, patients' race and ethnicity were solely based on patient self-reporting while prescription records were collected both from patients and their pharmacies. Patient self-reporting could be less robust than information obtained from health professionals. Also, reliability of self-reporting varies in patients with mental disorders. A previous study has suggested that self-reporting of health service use by patients with SMI was most reliable when dealing with service provided, but less consistent on the level of actual service given.[54]

Secondly, MEPS only included civilian, outpatient patients. Institutionalized patients and patients of military or federal services, including Veterans Affairs and Department of Defense, were excluded. Therefore, we were not able to generalize our findings to these populations. It is possible the SGA prescribing patterns are different among institutionalized patients because the acuity and severity of the psychiatric disorders being treated in inpatient settings are different from those in outpatient settings.

Also, because MEPS data from 2008 to 2013 were pooled to increase sample size and decrease variance, we could not detect if there were significant changes in the racial/ethnic disparities of SGA uses between 2008 and 2013. Likewise, we could not detect the trends in SGA prescribing between 2008 and 2013 from the pooled analyses.

In addition, we simplified SGA metabolic risk levels into LMRS and HMRS. Therefore, we could not generalize our results to the receipt of SGA with low, moderate, or high metabolic risk.

Lastly, there were several possible covariates not included in our study design, including income, education, health insurance status, indications of antipsychotic use, and coexisting medical conditions, which can inevitably affect patients' receipt of LMRS or HMRS.

Conclusion

In this study, we took a step forward to simplify the categorization of SGAs into LMRS and HMRS based on their risks of metabolic adverse effects. Applying our two-group SGA categorization and using MEPS data, there still appears to be a racial/ethnic disparity of outpatient prescribing of SGA's with lower or higher metabolic adverse effects. NHW were more likely to receive LMRS compared with other races/ethnicities.

References

1. Kane J, Honigfeld G, Singer J, Meltzer H. Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. *Arch Gen Psychiatry.* 1988;45:789-796.
2. Buchanan RW, Kreyenbuhl J, Kelly DL, et al. The 2009 schizophrenia PORT psychopharmacological treatment recommendations and summary statements. *Schizophr Bull.* 2010;36(1):71-93.
3. Moore TA, Buchanan RW, Buckley PF, et al. The Texas Medication Algorithm Project antipsychotic algorithm for schizophrenia: 2006 update. *J Clin Psychiatry.* 2007;68(11):1751-1762.
4. Lehman AF, Lieberman JA, Dixon LB, et al. Practice guideline for the treatment of patients with schizophrenia, second edition. *Am J Psychiatry.* 2004;161(2 Suppl):1-56.
5. Suppes T, Dennehy EB, Hirschfeld RM, et al. The Texas implementation of medication algorithms: update to the algorithms for treatment of bipolar I disorder. *J Clin Psychiatry.* 2005;66(7):870-886.
6. Hirschfeld RM, Bowden CL, Gitlin MJK, Paul E.; Suppes Trisha; Thase, Michael E.; Wagner, Karen D.; Perlis, Roy H. Practice guideline for the treatment of patients with bipolar disorder (revision). *Am J Psychiatry.* 2002;159(4 Suppl):1-50.
7. Yatham LN, Kennedy SH, Parikh SV, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2013. *Bipolar Disord.* 2013;15(1):1-44.
8. Targum SD, Abbott JL. Efficacy of quetiapine in Parkinson's patients with psychosis. *J Clin Psychopharmacol.* 2000;20(1):54-60.

9. Street JS, Clark WS, Gannon KS, et al. Olanzapine treatment of psychotic and behavioral symptoms in patients with Alzheimer disease in nursing care facilities: a double-blind, randomized, placebo-controlled trial. The HGEU Study Group. *Arch Gen Psychiatry.* 2000;57(10):968-976.

10. McManus DQ, Arvanitis LA, Kowalcyk BB. Quetiapine, a novel antipsychotic: experience in elderly patients with psychotic disorders. Seroquel Trial 48 Study Group. *J Clin Psychiatry.* 1999;60(5):292-298.

11. Katz IR, Jeste DV, Mintzer JE, Clyde C, Napolitano J, Brecher M. Comparison of risperidone and placebo for psychosis and behavioral disturbances associated with dementia: a randomized, double-blind trial. Risperidone Study Group. *The J Clin Psychiatry.* 1999;60(2):107-115.

12. De Deyn PP, Rabheru K, Rasmussen A, et al. A randomized trial of risperidone, placebo, and haloperidol for behavioral symptoms of dementia. *Neurology.* 1999;53(5):946-955.

13. Parsa MA, Bastani B. Quetiapine (Seroquel) in the treatment of psychosis in patients with Parkinson's disease. *J Neuropsychiatry Clin Neurosci.* 1998;10(2):216-219.

14. Practice guideline for the treatment of patients with bipolar disorder (revision). *Am J Psychiatry.* 2002;159(4 Suppl):1-50.

15. Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *NEJM.* 2005;353(12):1209-1223.

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

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

18. Domino ME, Swartz MS. Who are the new users of antipsychotic medications? *Psychiatr Serv.* 2008;59(5):507-514.

19. De Hert M, Dekker JM, Wood D, Kahl KG, Holt RI, Moller HJ. Cardiovascular disease and diabetes in people with severe mental illness position statement from the European Psychiatric Association (EPA), supported by the European Association for the Study of Diabetes (EASD) and the European Society of Cardiology (ESC). *Eur Psychiatry.* 2009;24(6):412-424.

20. Bobes J, Arango C, Aranda P, Carmena R, Garcia-Garcia M, Rejas J. Cardiovascular and metabolic risk in outpatients with schizoaffective disorder treated with antipsychotics: results from the CLAMORS study. *Eur Psychiatry.* 2012;27(4):267-274.

21. Garcia-Portilla MP, Saiz PA, Benabarre A, et al. The prevalence of metabolic syndrome in patients with bipolar disorder. *J Affect Disord.* 2008;106(1-2):197-201.

22. De Hert M, Correll CU, Bobes J, et al. Physical illness in patients with severe mental disorders. I. Prevalence, impact of medications and disparities in health care. *World Psychiatry.* 2011;10(1):52-77.

23. Fagiolini A, Frank E, Scott JA, Turkin S, Kupfer DJ. Metabolic syndrome in bipolar disorder: findings from the Bipolar Disorder Center for Pennsylvanians. *Bipolar Disord.* 2005;7(5):424-430.

24. Meyer JM, Stahl SM. The metabolic syndrome and schizophrenia. *Acta Psychiatr Scand.* 2009;119(1):4-14.

25. Basu R, Brar JS, Chengappa KN, et al. The prevalence of the metabolic syndrome in patients with schizoaffective disorder--bipolar subtype. *Bipolar Disord.* 2004;6(4):314-318.

26. De Hert M, Detraux J, van Winkel R, Yu W, Correll CU. Metabolic and cardiovascular adverse effects associated with antipsychotic drugs. *Nat Rev Endocrinol.* 2012;8(2):114-126.

27. Leucht S, Komossa K, Rummel-Kluge C, et al. A meta-analysis of head-to-head comparisons of second-generation antipsychotics in the treatment of schizophrenia. *Am J Psychiatry.* 2009;166(2):152-163.

28. Komossa K, Rummel-Kluge C, Hunger H, et al. Olanzapine versus other atypical antipsychotics for schizophrenia. *Cochrane Database Syst Rev.* 2010(3):Cd006654.

29. Komossa K, Rummel-Kluge C, Hunger H, et al. Ziprasidone versus other atypical antipsychotics for schizophrenia. *Cochrane Database Syst Rev.* 2009(4):Cd006627.

30. Khanna P, Komossa K, Rummel-Kluge C, et al. Aripiprazole versus other atypical antipsychotics for schizophrenia. *Cochrane Database Syst Rev.* 2013(2):Cd006569.

31. Rummel-Kluge C, Komossa K, Schwarz S, et al. Head-to-head comparisons of metabolic side effects of second generation antipsychotics in the treatment of schizophrenia: a systematic review and meta-analysis. *Schizophr Res.* 2010;123(2-3):225-233.

32. De Hert M, Yu W, Detraux J, Sweers K, van Winkel R, Correll CU. Body weight and metabolic adverse effects of asenapine, iloperidone, lurasidone and paliperidone in the treatment of schizophrenia and bipolar disorder: a systematic review and exploratory meta-analysis. *CNS Drugs.* 2012;26(9):733-759.

33. Horvitz-Lennon M, Volya R, Donohue JM, Lave JR, Stein BD, Normand SL. Disparities in quality of care among publicly insured adults with schizophrenia in four large U.S. states, 2002-2008. *Health Serv Res.* 2014;49(4):1121-1144.

34. Daumit GL, Crum RM, Guallar E, et al. Outpatient prescriptions for atypical antipsychotics for African Americans, Hispanics, and whites in the United States. *Arch Gen Psychiatry.* 2003;60(2):121-128.

35. Copeland LA, Zeber JE, Valenstein M, Blow FC. Racial disparity in the use of atypical antipsychotic medications among veterans. *Am J Psychiatry.* 2003;160(10):1817-1822.

36. Opolka JL, Rascati KL, Brown CM, Gibson PJ. Ethnicity and prescription patterns for haloperidol, risperidone, and olanzapine. *Psychiatr Serv.*2004;55(2):151-156.

37. Kuno E, Rothbard AB. Racial disparities in antipsychotic prescription patterns for patients with schizophrenia. *Am J Psychiatry.* 2002;159(4):567-572.

38. Cook TB, Reeves GM, Teufel J, Postolache TT. Persistence of racial disparities in prescription of first-generation antipsychotics in the USA. *Pharmacoepidemiol Drug Saf.* 2015;24(11):1197-1206.

39. Cohen JW, Cohen SB, Banthin JS. The medical expenditure panel survey: a national information resource to support healthcare cost research and inform policy and practice. *Med Care.* 2009;47(7 Suppl 1):S44-50.

40. Cohen SB. Design strategies and innovations in the medical expenditure panel survey. *Med Care.* 2003;41(7 Suppl):Iii5-iii12.

41. Medical Expenditure Panel Survey (MEPS): MEPS HC-138: 2010 Full Consolidated Data File. https://meps.ahrq.gov/survey_comp/hc_samplecodes_se.shtml. Accessed April 15, 2016.

42. Hargraves JL, Hadley J. The contribution of insurance coverage and community resources to reducing racial/ethnic disparities in access to care. *Health Ser Res.* 2003;38(3):809-829.

43. Chen J, Vargas-Bustamante A, Mortensen K, Ortega AN. Racial and Ethnic Disparities in Health Care Access and Utilization Under the Affordable Care Act. *Med Care.* 2016;54(2):140-146.

44. Red Book Online [database online]. Greenwood Village, CO: Truven Health Analytics. Available at http://www.micromedexsolutions.com. Accessed August 1, 2016.

45. Artiga S. Health coverage by race and ethinicity: the potential impact of the affordable care act. 2013. The Henry J. Kaiser Family Foundation. March 1, 2013. Available at http://kff.org/disparities-policy/issue-brief/health-coverage-by-race-and-ethnicity-the-potential-impact-of-the-affordable-care-act. Accesed August 1, 2016.

46. Wang CC, Kennedy J, Cohen LJ, Sclar DA. Coverage of atypical antipsychotics among medicare drug plans in the state of washington for fiscal year 2007. *Prim Care Companion J Clin Psychiatry.* 2008;10(4):313-317.

47. Wu MY, Kennedy J, Cohen LJ, Wang CC. Coverage of atypical antipsychotics among medicare drug plans in the state of washington: changes between 2007 and 2008. *Prim Care Companion J Clin Psychiatry.* 2009;11(6):316-321.

48. Vogt WB, Joyce G, Xia J, Dirani R, Wan G, Goldman DP. Medicaid cost control measures aimed at second-generation antipsychotics led to less use of all antipsychotics. *Health Af. f*2011;30(12):2346-2354.

49. Minsky S, Vega W, Miskimen T, Gara M, Escobar J. Diagnostic patterns in Latino, African American, and European American psychiatric patients. *Arch Gen Psychiatry.* 2003;60(6):637-644.

50. Neighbors HW, Trierweiler SJ, Ford BC, Muroff JR. Racial differences in DSM diagnosis using a semi-structured instrument: the importance of clinical judgment in the diagnosis of African Americans. *J Health Soc Behav.* 2003;44(3):237-256.

51. Lindsley CW. 2012 trends and statistics for prescription medications in the United States: CNS therapeutics continue to hold leading positions. *ACS Chem Neurosci.* 2013;4(8):1133-1135.

52. Ward A, Quon P, Abouzaid S, Haber N, Ahmed S, Kim E. Cardiometabolic consequences of therapy for chronic schizophrenia using second-generation antipsychotic agents in a medicaid population: clinical and economic evaluation. *P T.* 2013;38(2):109-115.

53. O'Day K, Rajagopalan K, Meyer K, Pikalov A, Loebel A. Long-term cost-effectiveness of atypical antipsychotics in the treatment of adults with schizophrenia in the US. *Clinicoecon Outcomes Res.* 2013;5:459-470.

54. Goldberg RW, Seybolt DC, Lehman A. Reliable self-report of health service use by individuals with serious mental illness. *Psychiatr Serv.* 2002;53(7):879-881.