University of Tennessee Health Science Center
UTHSC Digital Commons

Theses and Dissertations (ETD)

College of Graduate Health Sciences

12-2016

Medication Nonadherence, Health Care Utilization, and SafeMed Care Transitions Model Impact in Super-Utilizers

Satya Surbhi

University of Tennessee Health Science Center

Follow this and additional works at: <https://dc.uthsc.edu/dissertations>

Part of the [Health and Medical Administration Commons](#), [Health Services Administration Commons](#), and the [Health Services Research Commons](#)

Recommended Citation

Surbhi, Satya (<http://orcid.org/Saty-a-Su-rbhi>), "Medication Nonadherence, Health Care Utilization, and SafeMed Care Transitions Model Impact in Super-Utilizers" (2016). *Theses and Dissertations (ETD)*. Paper 412. <http://dx.doi.org/10.21007/etd.cghs.2016.0422>.

This Dissertation is brought to you for free and open access by the College of Graduate Health Sciences at UTHSC Digital Commons. It has been accepted for inclusion in Theses and Dissertations (ETD) by an authorized administrator of UTHSC Digital Commons. For more information, please contact jwelch30@uthsc.edu.

Medication Nonadherence, Health Care Utilization, and SafeMed Care Transitions Model Impact in Super-Utilizers

Abstract

BACKGROUND: Super-utilizers are individuals with disproportionately high inpatient and emergency department (ED) use, and mostly have multiple chronic conditions and use multiple concurrent medications. They place a substantial burden on the U.S. healthcare system and have become the focus of policy initiatives aimed at reducing their disproportionate inpatient and ED use. Medication management is critical for these patients since nonadherence to essential chronic medications is associated with poor health outcomes, and higher health care utilization and costs. **OBJECTIVES:** This dissertation employed a three empirical research papers approach to study the following aims: (1) the prevalence and patterns of medication nonadherence to essential chronic medications in Medicare super-utilizers with chronic conditions, and to identify the factors associated with medication nonadherence, with special emphasis on factors including mental illness and use of opioid medications, (2) examine associations between medication nonadherence, and inpatient and ED use, and to evaluate other risk factors associated with health care utilization in Medicare super-utilizers with chronic conditions, and (3) examine the impact of the SafeMed Program, a care transitions program with a focus on medication management, on medication use and adherence among publicly insured super-utilizers with chronic conditions. **METHODS:** This dissertation was based on patients eligible for the SafeMed Program, a care transitions program with a focus on medication management. The SafeMed Program targeted publicly insured super-utilizers with chronic conditions who were admitted to three hospitals that were part of a non-profit hospital system in Memphis, TN. The study sample included Medicare or TennCare insured adults who met the SafeMed Program eligibility criteria, had continuous medication coverage, and filled at least one of the drug classes used to treat hypertension, congestive heart failure, coronary artery disease, diabetes mellitus, chronic obstructive pulmonary disease (COPD), or asthma. Papers 1 and 2 were retrospective panel data analyses of the 2-year baseline data for Medicare Part D beneficiaries meeting the SafeMed Program eligibility criteria. Association between various factors and medication nonadherence was examined using random effects models with a binary distribution. Association between medication nonadherence and inpatient and ED utilization was examined using fixed effects negative binomial analyses. Paper 3 used a prospective quasi-experimental study design to examine the effectiveness of the SafeMed Program on medication use and adherence among SafeMed participants compared with patients in a control group using a difference in differences (DID) approach. **RESULTS:** Paper 1 demonstrated that the proportion of patients who were nonadherent to their essential chronic disease medications ranged from 45.7% to 58.4%, with the highest rate for COPD/Asthma medications (54.3% to 64.4%). In the multivariate analysis examining predictors of medication nonadherence, we found that compared with patients who did not use any opioid medication in the previous period, patients using >4 opioid medications had higher odds of medication nonadherence. Other risk factors for nonadherence included age <65 years, dual beneficiaries receiving low income subsidy, and higher number of unique prescribers. Factors associated with lower odds of nonadherence included number of different medications filled and >1 physician office visits in the previous period. When examining the associations between medication nonadherence, and inpatient and ED use in Paper 2, we found that among elderly Medicare beneficiaries, nonadherence was significantly associated with a 57% increase in inpatient hospitalizations, and among non-elderly Medicare beneficiaries, nonadherence was significantly associated with 41% increase in inpatient stays and 25% increase in ED visits. Similar associations were found across all therapy classes examined (diabetes, cardiovascular, and COPD/asthma) in both age groups. However, nonadherence to diabetes and COPD/asthma drugs was not significantly associated with ED visits. Among other factors, mental illness, substance use disorder, non-Hispanic blacks and dual low-income subsidy status were associated with higher inpatient and ED use. Finally, the DID analyses in paper 3 showed that SafeMed Program did not improve medication adherence in vulnerable super-

utilizers with chronic conditions. However, for some sub-group populations including Medicare only beneficiaries, patients >65 years of age, and patients with lower number of comorbidities, the intervention may have ensured that the decline in the probability of being adherent was not as low as it would have been in the absence of the intervention. Additionally, for patients diagnosed with COPD/asthma and diabetes, there were positive medication use trends in favor of enrollees, however, these associations were not statistically significant. CONCLUSIONS: This study is the first to our knowledge to demonstrate the magnitude and importance of medication nonadherence in vulnerable super-utilizers with chronic conditions. The study findings show that medication nonadherence is a significant problem among super-utilizers with chronic conditions and is associated with high inpatient and ED utilization. Furthermore, the findings suggest that medication management interventions during care transitions may not be sufficient for these high-risk patients and other alternative strategies such as addressing social risk factors, and removing cost barriers may be needed to improve adherence, especially among low-income dual beneficiaries, Medicaid enrollees, and patients with higher comorbidity.

Document Type

Dissertation

Degree Name

Doctor of Philosophy (PhD)

Program

Health Outcomes and Policy Research

Research Advisor

James E. Bailey, M.D., M.P.H.

Keywords

Care Transitions, Difference-in-Differences, Medication Nonadherence, Multiple Chronic Conditions, SafeMed Program, Super-Utilizers

Subject Categories

Health and Medical Administration | Health Services Administration | Health Services Research | Medicine and Health Sciences | Public Health

Comments

One year embargo expires December 2017.

**Medication Nonadherence, Health Care Utilization, and SafeMed Care Transitions
Model Impact in Super-Utilizers**

A Dissertation
Presented for
The Graduate Studies Council
The University of Tennessee
Health Science Center

In Partial Fulfillment
Of the Requirements for the Degree
Doctor of Philosophy
From The University of Tennessee

By
Satya Surbhi
December 2016

Copyright © 2016 by Satya Surbhi.
All rights reserved.

DEDICATION

To my parents Akhilesh and Meena.

To my husband Kiraat.

To my brother Bipul.

ACKNOWLEDGEMENTS

I would like to thank my mentor, Dr. Jim Bailey, for his guidance and encouragement that has helped me to successfully complete my dissertation. I would also like to extend my sincere gratitude to my committee members, Dr. Ilana Graetz, Dr. Justin Gatwood, Dr. Jim Wan, and Mr. George Relyea for their intellectual insights, constructive criticism, and invaluable time and contribution towards my research. I would also like to thank the SafeMed team and my colleagues, especially Jill Nault, Bonnie Binkley, and Celia Ridley. I am grateful for the financial support I received to pursue this dissertation from the Pharmaceutical Research and Manufacturers of America (PhRMA).

Finally, I would like to thank my parents, my brother, and my extended family for always being there for me. Dear Mummy and Papa, thank you for supporting me and believing in me. I would not be here without you. In the end, I want to thank my husband Kiraat, who has been a constant source of support and encouragement. I am truly thankful for having you in my life.

ABSTRACT

BACKGROUND: Super-utilizers are individuals with disproportionately high inpatient and emergency department (ED) use, and mostly have multiple chronic conditions and use multiple concurrent medications. They place a substantial burden on the U.S. healthcare system and have become the focus of policy initiatives aimed at reducing their disproportionate inpatient and ED use. Medication management is critical for these patients since nonadherence to essential chronic medications is associated with poor health outcomes, and higher health care utilization and costs.

OBJECTIVES: This dissertation employed a three empirical research papers approach to study the following aims: (1) the prevalence and patterns of medication nonadherence to essential chronic medications in Medicare super-utilizers with chronic conditions, and to identify the factors associated with medication nonadherence, with special emphasis on factors including mental illness and use of opioid medications, (2) examine associations between medication nonadherence, and inpatient and ED use, and to evaluate other risk factors associated with health care utilization in Medicare super-utilizers with chronic conditions, and (3) examine the impact of the SafeMed Program, a care transitions program with a focus on medication management, on medication use and adherence among publicly insured super-utilizers with chronic conditions.

METHODS: This dissertation was based on patients eligible for the SafeMed Program, a care transitions program with a focus on medication management. The SafeMed Program targeted publicly insured super-utilizers with chronic conditions who were admitted to three hospitals that were part of a non-profit hospital system in Memphis, TN. The study sample included Medicare or TennCare insured adults who met the SafeMed Program eligibility criteria, had continuous medication coverage, and filled at least one of the drug classes used to treat hypertension, congestive heart failure, coronary artery disease, diabetes mellitus, chronic obstructive pulmonary disease (COPD), or asthma. Papers 1 and 2 were retrospective panel data analyses of the 2-year baseline data for Medicare Part D beneficiaries meeting the SafeMed Program eligibility criteria. Association between various factors and medication nonadherence was examined using random effects models with a binary distribution. Association between medication nonadherence and inpatient and ED utilization was examined using fixed effects negative binomial analyses. Paper 3 used a prospective quasi-experimental study design to examine the effectiveness of the SafeMed Program on medication use and adherence among SafeMed participants compared with patients in a control group using a difference in differences (DID) approach.

RESULTS: Paper 1 demonstrated that the proportion of patients who were nonadherent to their essential chronic disease medications ranged from 45.7% to 58.4%, with the highest rate for COPD/Asthma medications (54.3% to 64.4%). In the multivariate analysis examining predictors of medication nonadherence, we found that compared with patients who did not use any opioid medication in the previous period, patients using ≥ 4 opioid medications had higher odds of medication nonadherence. Other risk factors for

nonadherence included age <65 years, dual beneficiaries receiving low income subsidy, and higher number of unique prescribers. Factors associated with lower odds of nonadherence included number of different medications filled and ≥ 1 physician office visits in the previous period.

When examining the associations between medication nonadherence, and inpatient and ED use in Paper 2, we found that among elderly Medicare beneficiaries, nonadherence was significantly associated with a 57% increase in inpatient hospitalizations, and among non-elderly Medicare beneficiaries, nonadherence was significantly associated with 41% increase in inpatient stays and 25% increase in ED visits. Similar associations were found across all therapy classes examined (diabetes, cardiovascular, and COPD/asthma) in both age groups. However, nonadherence to diabetes and COPD/asthma drugs was not significantly associated with ED visits. Among other factors, mental illness, substance use disorder, non-Hispanic blacks and dual low-income subsidy status were associated with higher inpatient and ED use.

Finally, the DID analyses in paper 3 showed that SafeMed Program did not improve medication adherence in vulnerable super-utilizers with chronic conditions. However, for some sub-group populations including Medicare only beneficiaries, patients ≥ 65 years of age, and patients with lower number of comorbidities, the intervention may have ensured that the decline in the probability of being adherent was not as low as it would have been in the absence of the intervention. Additionally, for patients diagnosed with COPD/asthma and diabetes, there were positive medication use trends in favor of enrollees, however, these associations were not statistically significant.

CONCLUSIONS: This study is the first to our knowledge to demonstrate the magnitude and importance of medication nonadherence in vulnerable super-utilizers with chronic conditions. The study findings show that medication nonadherence is a significant problem among super-utilizers with chronic conditions and is associated with high inpatient and ED utilization. Furthermore, the findings suggest that medication management interventions during care transitions may not be sufficient for these high-risk patients and other alternative strategies such as addressing social risk factors, and removing cost barriers may be needed to improve adherence, especially among low-income dual beneficiaries, Medicaid enrollees, and patients with higher comorbidity.

TABLE OF CONTENTS

CHAPTER 1. INTRODUCTION	1
MEDICATION ADHERENCE	1
Methods to Measure Adherence	2
Barriers to Medication Adherence	4
Association of Adherence with Health Outcomes and Costs	4
Interventions to Improve Adherence.....	5
INTEREST AND EVIDENCE IN CARE TRANSITIONS.....	6
INTERVENTIONS IMPACTING MEDICATION MANAGEMENT DURING CARE TRANSITIONS.....	7
SUPER-UTILIZERS	8
SAFEMED PROGRAM: A CARE TRANSITIONS PROGRAM WITH A FOCUS ON MEDICATION MANAGEMENT	8
CONCEPTUAL FRAMEWORK.....	9
STUDY SIGNIFICANCE	11
RESEARCH AIMS.....	12
Aim 1	12
Aim 2	12
Aim 3	12
CHAPTER 2. PREDICTORS OF MEDICATION NONADHERENCE IN SUPER-UTILIZERS WITH CHRONIC CONDITIONS.....	14
BACKGROUND	14
METHODS	15
Design and Setting	15
Study Population.....	15
Study Outcomes	16
Independent Variables.....	17
Statistical Analysis.....	18
RESULTS	18
Main Analysis	18
Sensitivity Analysis	24
DISCUSSION	27
CONCLUSION.....	29
CHAPTER 3. ASSOCIATION BETWEEN MEDICATION NONADHERENCE AND INPATIENT AND EMERGENCY DEPARTMENT USE IN SUPER- UTILIZERS WITH CHRONIC CONDITIONS	30
BACKGROUND	30
METHODS	31
Design and Setting	31
Study Population.....	31
Outcome Variables.....	32
Independent Variables.....	32

Medication nonadherence	32
Other covariates	33
Statistical Analysis	34
RESULTS	34
DISCUSSION	42
CONCLUSION	44
 CHAPTER 4. EFFECT OF A CARE TRANSITIONS PROGRAM ON MEDICATION USE AND ADHERENCE AMONG SUPER-UTILIZERS WITH CHRONIC CONDITIONS	 45
BACKGROUND	45
METHODS	46
Design and Setting	46
Population	46
Program Description	47
Outcome Variables.....	48
Medication adherence	48
Medication use	49
Independent Variables.....	49
Statistical Analysis	49
RESULTS	50
DISCUSSION	54
CONCLUSION.....	61
 CHAPTER 5. CONCLUSION	 62
SUMMARY OF FINDINGS	62
IMPLICATIONS FOR PRACTICE AND POLICY	63
IMPLICATIONS FOR FUTURE RESEARCH	65
 LIST OF REFERENCES	 67
 APPENDIX A. SUPPLEMENTAL MATERIALS FOR CHAPTER 2.....	 77
 APPENDIX B. SUPPLEMENTAL MATERIALS FOR CHAPTER 3	 81
 APPENDIX C. SUPPLEMENTAL MATERIALS FOR CHAPTER 4.....	 85
 VITA.....	 86

LIST OF TABLES

Table 2-1.	Characteristics of the Study Sample in Each 6-Month Patient-Period (N=1,092)	19
Table 2-2.	Medication Nonadherence to Essential Chronic Disease Medications by Therapy Class	21
Table 2-3.	Bivariate Associations with Medication Nonadherence (N=2,828 Patient-Periods)	22
Table 2-4.	Multivariate Association with Medication Nonadherence (N=2,828 Patient-Periods)	23
Table 2-5.	Multivariate Association with Medication Nonadherence Among Medicare Beneficiaries ≥ 65 Years of Age (N=1,676 Patient-Periods)	25
Table 2-6.	Multivariate Association with Medication Nonadherence Among Medicare Beneficiaries < 65 Years of Age (N=1,152 Patient-Periods)	26
Table 3-1.	Characteristics of SafeMed Eligible Patients in Each 6-Month Patient-Period (N=1,092)	35
Table 3-2.	Multivariable Results for Inpatient Stays and Emergency Department Visits by Therapy Class Using Fixed Effects Model	38
Table 3-3.	Multivariable Results for Inpatient Stays and Emergency Department Visits Among Medicare Beneficiaries ≥ 65 years	40
Table 3-4.	Multivariable Results for Inpatient Stays and Emergency Department Visits Among Medicare Beneficiaries < 65 years	41
Table 4-1.	Baseline Characteristics of the Study Population	51
Table 4-2.	Multivariate Difference-in-Differences Analysis Comparing Medication Adherence Between SafeMed Intervention Group and Control Group (by Therapy Class)	53
Table 4-3.	Multivariate Difference-in-Differences Analysis Comparing Medication Adherence Between SafeMed Intervention Group and Control Group (by Subgroups)	55
Table A-1.	The International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] Codes (Inclusion Criteria and Comorbidities) ...	77
Table A-2.	Medication Nonadherence to Essential Chronic Disease Medication by Therapy Class	78

Table A-3.	Multivariate Associations with Medication Nonadherence Using Alternative Proportion of Days Covered (PDC) Definition (N=2,999 Patient-Periods)	79
Table A-4.	Multivariate Associations with Medication Nonadherence Using Alternative PDC Criteria of ≥ 1 Medication Fill (N=3,062 Patient-Periods).....	80
Table B-1.	Multivariable Results for Inpatient Stays and ED Visits Among Medicare Beneficiaries ≥ 65 years Using Random Effects Models (N=1,757 patient-periods)	81
Table B-2.	Multivariable Results for Inpatient Stays and ED Visits Among Medicare Beneficiaries < 65 years Using Random Effects Models (N=1,242 patient-periods)	82
Table B-3.	Multivariable Results for Inpatient Stays and Emergency Department Visits Among Medicare Beneficiaries ≥ 65 years Using ≥ 1 Medication Fill Criteria	83
Table B-4.	Multivariable Results for Inpatient Stays and ED Visits Among Medicare Beneficiaries < 65 years Using $\geq$ Medication Fill Criteria	84
Table C-1.	Key SafeMed Care Transitions Interventions at Different Time Points	85

LIST OF FIGURES

Figure 1-1. Conceptual Framework Based on Anderson Behavioral Model of Health Services Utilization	10
Figure 3-1. Proportion of Days Covered (PDC) During Each 6-Month Period	37
Figure 4-1. Average Proportion of Days Covered in the Pre- and Post-Intervention Period	52
Figure 4-2. Multivariate Difference-in-Differences Analysis for ≥ 1 Oral Diabetes Medication Fill in Patients Diagnosed with Diabetes (N=634)	56
Figure 4-3. Multivariate Difference-in-Differences Analysis for ≥ 1 Long-Term Controller Medication Fill in Patients Diagnosed with COPD or Asthma (N=582)	57
Figure 4-4. Multivariate Difference-in-Differences Analysis for ≥ 1 ACE/ARB Fill in Patients Diagnosed with CHF (N=634)	58

LIST OF ABBREVIATIONS

ACA	Affordable Care Act
ACE	Angiotensin-converting enzyme inhibitors
ADE	Adverse drug events
ARB	Angiotensin II receptor blockers
CAD	Coronary artery disease
CHF	Congestive heart failure
CMR	Comprehensive medication review
CMS	Centers for Medicare and Medicaid Services
COPD	Chronic obstructive pulmonary disease
CVD	Cardiovascular disease
DID	Difference in differences
DRG	Diagnosis-related group
ED	Emergency department
ESRD	End-stage renal disease
FPL	Federal poverty level
IRR	Incidence Rate Ratio
LABA	Long-acting beta-agonists
LICS	Low-income cost sharing subsidy
MCC	Multiple chronic conditions
MEDPAR	Medical Provider Analysis and Review
MTM	Medication therapy management

OR	Odds Ratio
PDC	Proportion of days covered

CHAPTER 1. INTRODUCTION

MEDICATION ADHERENCE

Medication adherence has been defined as the active, voluntary, and collaborative involvement of the patient in a mutually acceptable course of behavior to produce a therapeutic result.¹ It usually refers to the extent to which patients take medications as prescribed by their health care provider.² This form of patient behavior comprises of two main concepts—adherence and persistence. Adherence refers to the intensity of the therapy, whereas persistence refers to the overall duration of the therapy.¹ Consistent and long-term use of essential chronic disease medications is critical for the treatment of chronic conditions such as diabetes, hypertension, cardiovascular disease (CVD), and chronic lung disease. Nonadherence to essential medications is a major barrier to achieving optimal therapeutic goals and is associated with poor clinical outcomes, and higher health care utilization and costs.³⁻⁶ Studies have shown that poor adherence to pharmacotherapy contributes to 33% to 69% of all medication-related hospitalizations and leads to expenses of approximately \$100 billion a year.⁷ Given the magnitude and importance of medication adherence, assessing adherence has become an essential component for clinical trials. Additionally, the National Committee for Quality Assurance and Centers for Medicare and Medicaid Services (CMS) have included medication adherence as a quality measure to evaluate healthcare plans.⁸

Medication nonadherence is a significant problem during the vulnerable period of care transitions, especially among patients with multiple chronic conditions (MCC) and complex medication regimen.^{9,10} There are two forms of nonadherence that may occur, primary nonadherence and secondary nonadherence. Primary nonadherence is defined as patient's delay or failure to fill a new prescription, while secondary nonadherence—a more widely studied phenomenon—is defined as filling a prescription but not taking it as directed by the physicians.¹¹ Research has shown that nearly 22% of prescription medications are never filled¹¹ and approximately 50% of all prescription medications for chronic disease are not taken as directed by the provider.¹² In the past, assessing primary nonadherence was difficult because it required cumbersome review of office notes and paper prescriptions. However, the recent increase in electronic prescribing systems has enabled researchers to assess primary nonadherence by linking patient's prescription data with the pharmacy fill data. Secondary nonadherence, on the other hand, has been widely studied by researchers and can be captured by most of the adherence measures including patient-reported questionnaires or pharmacy administrative claims data. Studies examining primary and secondary nonadherence after hospital discharge have mainly focused on new medication users or patients who received new prescriptions during hospital discharge.

A substantial body of evidence suggests that patients belonging to low socioeconomic strata are particularly at a higher risk for primary nonadherence.^{11,13,14} Fisher and colleagues found that patients residing in low-income ZIP code areas were more likely to not fill their new prescriptions.¹¹ Additionally, in our previous study we

found that more than 50% of vulnerable patients with MCC and polypharmacy (taking multiple medications concurrently for disease management), and those residing in medically underserved area, did not have all essential chronic and acute medications within three days of hospital discharge.¹³ In another study by Kripalani and colleagues, who evaluated medication reconciliation problems among inner-city patients after hospital discharge, found that only 40% patients filled their medications on the day of their discharge, 20% filled them within 1-2 days, 18% waited for 3-9 days, and 22% did not fill them until 12 days after discharge.¹⁴ These studies highlight the importance of examining primary nonadherence to essential chronic and acute medications in vulnerable low-income populations and addressing any financial barriers which may be playing a role in their non-adherent behavior.

Studies examining secondary nonadherence have found that the rates of adherence drop progressively after hospital discharge. Newby and colleagues found that only 21% of patients with coronary artery disease were adherent to all essential cardiovascular medications over a 6-month period after hospital discharge.¹⁵ Ho and colleagues found that among patients discharged with aspirin, β -blockers, and statins, nearly 34% of patients stopped taking at least one medication and 12% stopped taking all three medications within one month of discharge.¹⁶ Along with the issue of medication nonadherence, vulnerable patients with MCC and those experiencing frequent transitions of care are at far greater risk for drug therapy problems and adverse drug events (ADE). Following hospital discharge, nearly 81% of the hospitalized patients experience drug therapy problems,¹³ 14% to 75% of patients experience medication discrepancies,^{13,17,18} and 11% to 30% of patients experience ADE of which about half are considered preventable or ameliorable.^{19,20} Taken together, these study findings suggest that medication management is critical during the vulnerable period of care transitions, especially among patients who are at risk of drug therapy problems and medication nonadherence.

Methods to Measure Adherence

There are several ways to measure adherence, which have been broadly classified as direct and indirect measures of adherence. Direct methods include directly observed therapy, measuring drug or metabolite concentration in body fluids, or measuring of biological markers in the blood that has been added to the drug formulation. Indirect measures of adherence include patient questionnaires and self-reports, pill counts, rates of prescription refills, electronic medication monitors, measuring physiologic markers, and asking patients to maintain diaries. The advantage of using direct methods is that it is possible to assess directly whether the patient has consumed medications or not, or whether the correct dose of medication has been taken or not. With indirect methods that assess adherence using patient responses or analyzing their pharmacy claims data, it is not possible to know whether the patient adheres to the agreed upon dosage and timing of the medication regimen. The choice of the adherence measure depends on the availability of the data and cost. Although direct methods have been considered more reliable and

accurate than indirect methods, these methods are expensive, tedious, and not practical for routine clinical use.^{7,21}

Among indirect methods, patient questionnaires such as Morisky medication adherence scale has been used in many studies and has produced reliable results for patients with hypertension and diabetes;²² however, the accuracy and validity of this method remains uncertain in patients with multiple chronic conditions using multiple concurrent medications.¹³ Adherence to Refills and Medication Scale (ARMS) is another patient-reported measure that can be used for chronic disease population and is a reliable medication adherence scale for patients with low literacy.²³ However, the drawback of using most patient-reported adherence measures is that they provide a subjective way to measure adherence and patients may obfuscate and provide desired answers, and also subject to recall bias. Additionally, patient-reported adherence measures are susceptible to misrepresentation by the person collecting the data. Measuring adherence using pharmacy administrative data has gained importance recently and has become one of the most commonly used methods in the literature. Availability of pharmacy administrative data has enhanced our ability to measure adherence by understanding patients' prescription refill patterns and behaviors that are necessary to achieve desirable treatment outcomes. Moreover, this method provides an objective method to assess adherence. Using this method, most observational studies and randomized clinical trials use a standard cut-off value of 80% and classify patients as adherent if they have medications on hand available for at least 80% of the total duration of time.¹ Moreover, studies have established the clinical significance of defining the optimal adherence threshold of 80% or above.^{1,7}

Rates of refilling prescriptions is an accurate method to measure adherence in a closed pharmacy system (e.g., continuous Medicare Part D enrollment). However, the disadvantages of using this method are that it cannot capture primary nonadherence and may not accurately capture medication use beyond the medication fill. Additionally, pharmacy administrative claims data is widely used to assess adherence for a single drug class. However, measuring adherence for patients with MCC is difficult since patients use multiple concurrent medications. Choudhry and colleagues conducted a study to propose methods for measuring adherence to multiple medications.²¹ The study found variations in adherent rates depending on the way adherence was defined. And the study concluded that the choice of method depends on the reason why adherence is being measured. The interval-based proportion of days covered (PDC) is one of the standardized methods proposed in this study to measure adherence to concurrent medications. The interval-based PDC is defined as medication possession during the interval from the index date to the end of the period, that is, number of days of medication supplied throughout the period (numerator) divided by number of days in the period (denominator). This method can be applied in following three distinct ways: 1) measuring average PDC for each patient based on the number of drug classes used by the patient, 2) measuring number of days during the period in which patients had at least one of the prescribed medications for a chronic condition, and 3) examining whether patients had a PDC of 80% or more for each medication they were using for a chronic condition. Different methods produce varying adherence estimates, and measuring average PDC (method #1) seems more

reliable since it produces intermediate adherence estimates when compared with the other two methods. Requiring patients to have a PDC of $\geq 80\%$ for all medications may categorize more patients as nonadherent, while requiring patients to be adherent to at least one or their medications may categorize more patients as adherent.²¹

Barriers to Medication Adherence

Barriers to medication adherence are multifactorial. The World Health Organization (WHO) has classified barriers to medication adherence into five broad categories: 1) patient-related factors, 2) patient conditions, 3) therapy related factors, 4) socioeconomic factors, and 5) health system related factors.¹ Patient factors include age, gender, and race and ethnicity (minority race in particular). Patient conditions that are chronic in nature and require long-term therapy have been found to be associated with nonadherence. For therapy-related factors, patients having polypharmacy and complex therapy or patients experiencing side effects are more likely to have poor adherence. Among socioeconomic factors, lower education level, low income, and low health literacy are major barriers. Health system factors also play an important role in medication nonadherence. Some of the health care system-related barriers include having high cost of medications, copays, restricted formularies, or switching to another formulary.

Review of existing literature demonstrates that the most important factors associated with medication nonadherence include young age, black race, medication copay, mental illness, multiple comorbidities, and therapy complexity, among others.^{3,7,24-29} System-level factors such as inadequate post-discharge treatment plan, lack of patient counseling, discharge summaries lacking discharge medications, and failure to monitor patient's drug therapy are associated with nonadherence and other drug therapy problems during care transitions.^{18-20,30-34} Makaryus and colleagues found that less than 50% of patients were able to list their discharge medications and even fewer could recount their purpose.³⁵ In our previous study, we found that drug therapy problems and post-discharge medication discrepancies were common among super-utilizing patients with MCC and polypharmacy. The major causes of medication discrepancies were higher number of comorbidities, difficulty in picking up and paying for medications, and transportation.¹³ Additionally, Kripalani and colleagues found that medication costs and transportation served as major barriers to proper medication use after hospital discharge among inner-city patients.¹⁴ A comprehensive patient-centered approach addressing contributors to medication nonadherence and other drug therapy problems both at the patient- and system-level is needed to target effective interventions for vulnerable populations.

Association of Adherence with Health Outcomes and Costs

Studies have demonstrated the positive impact of appropriate adherence on clinical outcomes. For instance, Bailey and colleagues found that among TennCare beneficiaries, a 15% increase in antihypertensive medication refill adherence was

associated with an 8% decreased hazard of stroke and a 7% decreased hazards of death.³ Ho and colleagues conducted a retrospective cohort study of patients with diabetes and found that nonadherent patients had significantly increased risk for all-cause hospitalization and all-cause mortality.³⁶ Another observational study by Ho and colleagues among a cohort of patients with coronary artery disease showed that nonadherence to cardioprotective medications (beta blockers, statins, and/or angiotensin-converting enzyme inhibitors) was associated with increased risks for cardiovascular mortality and cardiovascular hospitalization.³⁷

Studies have also demonstrated the impact of medication adherence on health care utilization and costs. Sokol and colleagues analyzed a cohort of patients with four chronic conditions (diabetes, hypertension, hypercholesterolemia, and congestive heart failure) and found that high medication adherence was significantly associated with lower hospitalization and lower non-medication medical costs, yielding a net reduction in the overall healthcare costs.³⁸ Roebuck and colleagues evaluated patients with congestive heart failure, hypertension, diabetes, and dyslipidemia and found that although improved medication adherence increased pharmacy costs, it also produced substantial medical savings by reducing hospitalizations and emergency department (ED) use.⁵ Jha and colleagues examined a national sample of diabetes patients and found that improved adherence to diabetes medications was associated with lower hospitalization and ED visits. Furthermore, the study projected that improved adherence to diabetes medications could avert 699,000 ED visits and 341,000 hospitalizations annually, generating savings of \$4.7 billion.⁴ Similar findings were observed by studies conducted on Medicare beneficiaries. Simoni-Wastila and colleagues found that Medicare patients with chronic obstructive pulmonary disease (COPD) who were adherent to their chronic medications experienced fewer hospitalizations.⁶ And in a sample of Medicare patients with myocardial infarction, Zhang and colleagues found that higher adherence with β -blockers, statins, and ACEIs/ARBs medications was associated with lower readmission rates.³⁹ Findings from these studies reinforce the importance of taking medications as prescribed by the provider to optimize patient health outcomes and reduce health care utilization and costs. Previous studies based on Medicare population examining the association between medication adherence and utilization were largely represented by elderly Medicare beneficiaries and did not target vulnerable patients with high rates of multimorbidity and high health care utilization.

Interventions to Improve Adherence

Multimodal interventions focusing on multiple barriers of medication adherence have mostly shown improvements in medication adherence and reduced health care utilization. For instance, the Ashville projects that combined expanded medication therapy management (MTM) and disease management services, showed improved clinical outcomes and reduced overall costs in studies targeting commercially insured patients with diabetes, hypertension/dyslipidemia, or asthma.⁴⁰⁻⁴² Similarly, Pringle and colleagues evaluated the impact of a large-scale, pharmacy-based intervention on five chronic medication classes and found that, compared to the control group, the

intervention group had improved adherence for all medication classes.⁴³ Zillich and colleagues evaluated the effect of a program combining specialized medication packaging and phone MTM on medication adherence, health care utilization, and costs, among Medicaid patients. The study findings showed a significant improvement in medication adherence in the program cohort compared to controls; however, the effect on health care utilization and health care costs did not vary between the two groups.⁴⁴ Additionally, Martin and colleagues examined the effectiveness of community-based, multimedia interventions on medication adherence among low-income rural residents with hypertension and found that medication adherence did not differ significantly from individuals in the control group.⁴⁵

INTEREST AND EVIDENCE IN CARE TRANSITIONS

Care transitions is described as a process when patient's care shifts from being provided in one setting to another, for instance moving from a hospital to a patient's home.⁴⁶ Patients with complex care needs often require care at different settings. During care transitions, these patients often experience difficulties in managing their care and face problems of care fragmentation. Managing care transitions is important since inadequate management contributes to \$25 to \$45 billion in wasteful spending mainly through avoidable complications and unnecessary health care utilization.⁴⁶ The famous report by the Institute of Medicine, *Crossing the Quality Chasm*, highlighted this issue and reported that upon hospital discharge, patients receive little information on self-management and medication side effects causing unnecessary readmissions. For instance, 75% of the hospital readmissions among Medicare population are considered potentially preventable, resulting in \$12 billion in unnecessary Medicare spending each year.⁴⁶

Several care transitions models have been developed and evaluated. The Care Transitions Intervention developed by Eric Coleman utilized nurses and social workers to promote development of patient's skills in four key self-care areas including managing medications, timely follow-up care, identifying and responding to 'red-flags' (onset of a fever or worsening of a condition), and having a patient-centered record owned by the patient to simplify information transfer. The program evaluation demonstrated a 30% reduction in 30-day hospital readmissions, 17% reduction in 180-day hospital readmission, and reduced average cost per patient by 17%. Another care transitions model that has been evaluated is the Naylor model developed by Mary Naylor and colleagues. The intervention targeted high-risk, high-cost elderly patients and was provided for a longer period. The program evaluation reduced readmissions by 36% and costs by 39% per patient during 12 months following hospitalization. This program not only provided interventions in the hospital setting but also extended it to the community setting by incorporating regular home visits. However, care transitions models developed so far have not primarily focused on identifying and resolving medication-related issues during care transitions. There is a lack of evidence regarding the effectiveness of medication management interventions during care transitions, especially among vulnerable high-risk patients with chronic conditions and polypharmacy.

INTERVENTIONS IMPACTING MEDICATION MANAGEMENT DURING CARE TRANSITIONS

Given the increased interest in care transitions and widespread recognition that drug therapy problems and medication nonadherence play a major role in readmissions, care transitions interventions with a focus on medication management are being increasingly explored to reduce drug therapy problems and improve medication adherence. Pharmacists can play a central role in care transitions models focused on medication management. Pharmacist-led care transitions interventions that have focused on comprehensive discharge planning with an emphasis medication reconciliation and phone follow-ups have generally been successful in identifying drug therapy problems and reducing disease exacerbations and hospitalizations.^{17,47-52} For instance, in our prior study based on SafeMed participants with MCC, polypharmacy, and high health care utilization, we found that the Pharmacist-led interventions as part of a care transitions program successfully resolved 50% of patients' medication-related issues, resulting in substantial estimated cost savings.¹³ Schnipper and colleagues found that pharmacist-provided interventions for patients discharged home from the general medicine service was associated with a lower rate of preventable ADE. However, there was no significant effect of these interventions on overall ADE or total health care utilization.¹⁷ Similarly, Ho and colleagues found that among patients with acute coronary syndrome, multifaceted pharmacist-led interventions increased adherence to cardioprotective agents one year following hospital discharge. However, the intervention did not have any positive effect on blood pressure and low-density lipoprotein cholesterol levels.⁴⁹ A review of studies by Kaboli and colleagues examining the effects of pharmacist interventions on processes and outcomes in hospitalized adults, demonstrated improvement in quality, safety, and efficiency of care.⁵³ In a sample of patients discharged from the hospital to the nursing home, Boockvar and colleagues found that pharmacist-conducted medication reconciliation and care coordination with physicians reduced medication discrepancies in these patients.⁵² Similarly, Dudas and colleagues found that among patients discharged from hospital to home, pharmacist-facilitated discharge process was associated with increased patient satisfaction, resolution of medication-related problems and lower ED visits.⁵⁰ And in another study by Phatak and colleagues conducted on patients using high-risk medications or multiple medications, the pharmacist services provided during care transitions reduced readmissions and ED visits.⁵¹

There are few studies which did not find any positive effect of care transitions based pharmacist-provided medication management interventions. For instance, Kripalani and colleagues found that among patients hospitalized with acute coronary syndromes or acute decompensated heart failure, the hospital-based pharmacist-led interventions did not significantly reduce medication errors after hospital discharge.¹⁹ Additionally, Walker and colleagues found that pharmacist intervention during hospital discharge did not significantly reduce readmissions or ED visits in patients who were at high risk for medication-related adverse events.⁵⁴ Although most studies described above have shown positive effects of medication management interventions provided during care transitions, its effectiveness in vulnerable patient populations with chronic conditions and among those experiencing frequent hospitalizations remains unclear.

SUPER-UTILIZERS

Super-utilizing patients are those who have high health care costs from recurring, preventable inpatient or ED visits. They often face complex medical and social issues⁵⁵ and are particularly at risk for drug therapy problems and medication nonadherence during care transitions from hospital to the community setting.^{13,18} A decade ago Dr. Jeffrey Brenner, a physician from Camden, NJ, had identified that a small group of patients accounted for a bulk of health care costs.⁵⁵ Since then the interest in super-utilizers has increased among policymakers, health systems, and researchers. Super-utilizers represent only 3 to 10% of Medicare and Medicaid population, but are responsible for 30 to 50% of the health care spending.⁵⁶ They often face complex medical and social issues including mental health illnesses and substance abuse and frequently report chronic pain.⁵⁶⁻⁵⁸ A previous study found that 82% of super-utilizers had MCC and 41% had a serious mental health diagnosis.⁵⁶ Another study found that nearly 46% patients reported not having a regular primary care provider, and nearly 48% reported having severe pain during hospitalization.⁵⁷ Additionally, Medicaid super-utilizers are more likely to have comorbid conditions, behavioral health, and substance abuse conditions when compared to Medicare super-utilizers. A study found that among top high spending Medicaid super-utilizers, nearly 83% had ≥ 3 chronic conditions and about 60% had ≥ 5 conditions.^{56,59} Because of frequent transitions of care, super-utilizers are at high risk for drug therapy problems and medication discrepancies which may cause poor adherence. Thus, medication management is critical among high-risk super-utilizing patients to achieving optimal therapeutic goals. Despite increased focus on reducing the disproportionate health care utilization and costs among super-utilizer, there are very few published studies examining these outcomes among the vulnerable super-utilizing patient population. And, to our knowledge, no study has focused on the issue of medication nonadherence in the super-utilizing population.

SAFEMED PROGRAM: A CARE TRANSITIONS PROGRAM WITH A FOCUS ON MEDICATION MANAGEMENT

The SafeMed Program was a Centers for Medicare and Medicaid Services (CMS) Health Care Innovations Award (HCIA) funded care transitions program with a focus on medication management.⁶⁰ The program included comprehensive targeted interventions to improve adherence to safe and effective medications among publicly insured (Medicare, Medicaid, or dually eligible), super-utilizers who were admitted to three hospitals that were part of a non-profit hospital system in Memphis, TN from February 1, 2013 to May 1, 2015. The program enrollment occurred during an inpatient admission or an observation stay, after which the patients agreeing to participate were provided the various intervention services for a minimum of 45 days. A diverse team of health care providers, including pharmacists, pharmacy technicians, and nurse practitioners, among others, worked in collaboration with physicians to prevent, identify, and resolve any drug-related issues, which may lead to low medication adherence and suboptimal medication therapy.

Pharmacists along with pharmacy technicians worked together to improve the care transitions process of patients from the inpatient hospital setting to the community setting by providing medication management services. Pharmacist-led interventions as part of the SafeMed Program included: comprehensive medication review (CMR), targeted medication therapy management (MTM), enhanced discharge planning, home visits, phone follow-ups, medication reconciliation during discharge and post-discharge, and care coordination with patient's physicians. The SafeMed model differs from earlier care transitions models by focusing explicitly on high risk super-utilizers of inpatient and emergency services rather than all hospitalized patients targeted by hospital-focused care transitions models such as Project Boost,⁶¹ the Bridge Program,⁶² and Project RED.⁶³ And unlike other super-utilizer focused care transitions models such as the Camden Coalition,⁶⁴ the Coleman Care Transitions Program,^{9,65} and the Naylor Transitional Care Model,⁶⁶ SafeMed focused on proven medication therapy management approaches^{19,42} using program pharmacists and pharmacy technicians as key team members.

CONCEPTUAL FRAMEWORK

The present study uses the Andersen's Behavioral Model of Health Services Utilization to demonstrate associations between risk factors, medication nonadherence, and inpatient and ED utilization. This model defines the utilization of health services as a function of (1) predisposing, (2) enabling, and (3) need factors.⁶⁷ Predisposing factors refer to the individual's characteristics that are present before the illness. These factors include the demographic characteristics of age and sex, social factors including occupation, education, ethnicity, and social relationships, and health beliefs (attitudes, values, knowledge related to health services). Enabling characteristics refer to financing and organizational factors. Financial factors include income and wealth that can be used to pay for health services or health insurance status. Organizational factors refer to whether an individual has a regular source of care and nature of that source. Health policies also fall into the category of enabling factors. Need characteristics refer to a patient's need to seek health care services. At an individual level, need factors can be differentiated as perceived need for health services or evaluated need.

Although, this model was originally developed to predict health services utilization, it has been used to predict medication adherence. For instance, Murray and colleagues used this model to examine the associations between environmental factors, patient characteristics (predisposing, enabling, and need factors), and medication adherence to predict utilization outcomes.⁶⁸ Another study by De Smet and colleagues used Andersen's Behavioral Model to examine self-reported adherence to asthma medications and found that better adherence was associated with greater perceived asthma severity, longer asthma duration, stronger beliefs in the benefits of treatment, among others.⁶⁹ The conceptual framework for this study is shown in **Figure 1-1**. In this study, we propose that the predisposing, enabling, and need factors predict medication nonadherence, and all these factors along with medication nonadherence predict inpatient and ED utilization. In this study, the predisposing factors include age, gender, and race.

Figure 1-1. Conceptual Framework Based on Anderson Behavioral Model of Health Services Utilization

Modified with permission. Andersen RM. Revisiting the behavioral model and access to medical care: does it matter? *Journal of health and social behavior*. Mar 1995;36(1):1-10.

Note: In our study the predisposing factors include age, gender, and race. The enabling factors include dual low-income cost sharing subsidy status, ≥ 1 physician office visits, number of unique prescribers, and number of unique pharmacies. The need factors include Charlson comorbidity index, mental illness, tobacco use disorder, opioid medications filled, and number of unique medications filled.

The enabling factors include dual low-income cost sharing subsidy status, ≥ 1 physician office visits, number of unique prescribers, and number of unique pharmacies. The need factors include Charlson comorbidity index, mental illness, tobacco use disorder, opioid medications filled, and number of unique medications filled.

STUDY SIGNIFICANCE

With the implementation of Hospital Readmissions Reduction Program by the Affordable Care Act (ACA), hospitals are being penalized by Medicare for readmissions occurring within a month of discharge for conditions including acute myocardial infarction and heart failure. This has spurred interest in super-utilizers populations. Super-utilizers place a substantial burden on the healthcare system and have become the focus of policy initiatives aimed at reducing their disproportionate inpatient and ED visits. Hospitals and payers are important stakeholders interested in reducing avoidable use of inpatient and ED services among high-risk super-utilizers. Many care transitions models are increasingly explored, with varying target populations and focusing on different risk factors causing avoidable readmissions and ED use. Medication management is a critical component for these high-risk patients since they are at high risk for drug therapy problems and medication discrepancies, which may result in poor adherence and thereby result in high health care utilization and costs. Given the clinical importance of medication nonadherence, it is imperative to understand the magnitude of this issue in super-utilizers with chronic conditions.

Numerous studies have examined the risk factors for medication nonadherence in different populations and its association with health care utilization, however, to our knowledge, such associations have not been established in vulnerable super-utilizers with chronic conditions. Additionally, given the increased focus on reducing the disproportionate inpatient and ED use in this patient population, it is important to understand whether nonadherence to essential chronic medications contributes to their high inpatient and ED use. Moreover, considering the high prevalence of mental illness and chronic pain in the high-risk super-utilizing population, it is critical to examine whether mental illness and opioid medication use are associated with nonadherence and health care utilizations in this vulnerable population. Finally, demonstrating the impact of an innovative care transitions program on medication adherence will be critical in highlighting the central importance of medication management in improving transitions of care—that care transitions programs focusing on medication management can improve medication use and adherence among vulnerable super-utilizers who can benefit the most from such interventions. The study findings may facilitate the adoption of such care transitions programs that are targeted towards vulnerable populations and may have the potential to impact changes in the future health care delivery, to move in the direction of a more patient-centered care transitions program with a focus on medication management.

RESEARCH AIMS

Using Medicare and Tennessee Medicaid data on super-utilizers with chronic conditions, this dissertation aims to investigate the predictors of medication nonadherence, association between nonadherence and high inpatient and ED utilization, and the impact of the SafeMed Program on medication use and adherence.

Aim 1

To examine the prevalence and patterns of medication nonadherence to essential chronic medications, and factors associated with medication nonadherence, with special emphasis on factors including mental illness and use of opioid medications

- Are demographic, socioeconomic, clinical, therapy complexity, and physician office visits associated with overall nonadherence to essential chronic medications?
- Are mental illness and opioid medication use associated with overall nonadherence to chronic essential medications?

Aim 2

To examine the associations between medication nonadherence, inpatient and emergency department use. Additionally, to examine if other risk factors including mental illness and opioid medication use, are associated with inpatient and ED use

- *Hypothesis 2a:* Medication nonadherence to essential chronic medications (overall and therapy specific nonadherence) is associated with high inpatient and ED use in Medicare beneficiaries <65 years of age
- *Hypothesis 2b:* Medication nonadherence to essential chronic medications (overall and therapy specific nonadherence) is associated with high inpatient and ED visits in Medicare beneficiaries ≥ 65 years of age
- Are mental illness, opioid medication use, and other factors associated with high inpatient and emergency department use?

Aim 3

To examine the impact of the SafeMed Program on medication use and medication adherence

- *Hypothesis 3a:* SafeMed Program is associated with an increase in medication adherence (overall and therapy specific adherence) among the treatment group compared to the control group
- *Hypothesis 3b:* SafeMed Program is associated with an increase in condition-

specific medication utilization in the treatment group compared to the control group

- *Hypothesis 3c:* Does the impact of SafeMed Program on medication adherence vary by age, type of public health insurance, and number of comorbidities?

CHAPTER 2. PREDICTORS OF MEDICATION NONADHERENCE IN SUPER-UTILIZERS WITH CHRONIC CONDITIONS

BACKGROUND

The disproportionately high health care utilization and resulting colossal Medicare spending among a small fraction of Medicare beneficiaries is well established.^{56,70,71} Nearly 50% of the health care spending is incurred by 5% of the Medicare population.⁵⁸ These high-cost health care users are commonly referred to as “super-utilizers”.⁷¹ They often have complex health and social issues and have high rates of multiple chronic conditions (MCC) including mental health disorders.^{56,58} Substantial research shows that patients with MCC and polypharmacy are at high risk of medication nonadherence. The therapeutic regimen for patients with MCC is complex, often involving multiple concurrent medications, which puts them at greater risk of drug-drug interactions and makes these patients less likely to be adherent to their therapy.⁷²⁻⁷⁴ In addition, patients who experience frequent transitions of care are particularly at higher risk of drug therapy problems and medication discrepancies, which may contribute to low medication adherence. For instance, after hospital discharge nearly 14% to 75% of patients experience medication discrepancies,^{13,17,18} 11% experience adverse drug events (ADE),²⁰ and 23% to 48% do not take their medications as directed.^{14,17} Medication management is critical for super-utilizing patients since nonadherence to medications is associated with poor health outcomes, and higher hospital admissions and costs.^{5,38}

The World Health Organization has reported that nearly 50% of patients in developed countries do not take their medications as directed by physicians.¹² The reasons for medication nonadherence are multifactorial, including patient, condition, therapy-related, socioeconomic, and health system-related factors.¹ Review of existing literature demonstrates that the most important factors associated medication nonadherence include young age, black race, medication copay, mental illness, multiple comorbidities, and therapy complexity, among others.^{3,7,24-29} However, to our knowledge no research has examined the factors associated with medication nonadherence among super-utilizers with chronic conditions. Moreover, emerging evidence on super-utilizers indicates they have a high prevalence of mental illness and substance use disorder, and frequently report chronic pain.^{56,57,75} For instance, Johnson and colleagues found that among publicly insured and uninsured super-utilizers, nearly 41% had a serious mental health diagnosis.⁵⁶ In another study conducted on super-utilizers, Harris and colleagues found that nearly 48% of patients reported severe pain (>7 on a 10-point scale).⁵⁷ Considering the high prevalence of severe pain in super-utilizing patients, we anticipate that the use of opioid medications would be high in this population. Therefore, it is imperative to examine whether factors such as mental illness and opioid medication use are associated with medication nonadherence in this high-risk population.

Therefore, this study examines, using Medicare administrative claims data, the prevalence and patterns of medication nonadherence to essential chronic medications in super-utilizers with chronic conditions, and the factors associated with medication

nonadherence, with special emphasis on factors including mental illness and use of opioid medications.

METHODS

Design and Setting

SafeMed Program is a Centers for Medicare and Medicaid Services (CMS) Health Care Innovations Award funded care transitions program with a focus on medication management.⁷⁶ The SafeMed Program targeted super-utilizers between February 2013 and May 2015 who were admitted to three hospitals that were part of a non-profit hospital system in Memphis, TN. The present study is a retrospective panel analysis of the 2-year baseline data for Medicare Part D beneficiaries meeting the SafeMed Program eligibility criteria during the enrollment period from February 2013 to December 2014. The study used Medicare beneficiary eligibility, inpatient, outpatient, professional, and Part D event files data to document the sociodemographic, clinical, therapy complexity, and health services utilization factors associated with medication nonadherence. This study included SafeMed eligible patients because they were diagnosed with chronic conditions (hypertension, diabetes mellitus, congestive heart failure (CHF), coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD), or asthma) that have been identified as ambulatory care-sensitive conditions for which outpatient care improvements such as improving medication adherence, can reduce inpatient utilization.⁵⁷ Since medication adherence is a dynamic process that changes over time, the two-year data for each patient was divided into four 6-month patient-periods. The panel design helped us to examine patterns of medication nonadherence in the baseline period before the intervention, and the association of time-varying and time-invariant factors with medication nonadherence among Medicare super-utilizers.

Study Population

The study included Medicare beneficiaries who were deemed eligible for the SafeMed Program during a portion of the enrollment period between February 2013 and December 2014. The SafeMed Program eligibility was determined during an inpatient admission or an observation stay (index admission). SafeMed Program eligibility was based on the following inclusion criteria: 1) adults aged 18 years or older with continuous Medicare enrollment, 2) ≥ 2 hospital admissions in the past six months OR 1 hospital admission and ≥ 2 emergency department (ED) visits in the six months prior to the index admission, and 3) diagnosis of ≥ 1 of the following chronic conditions: hypertension, CHF, CAD, diabetes mellitus, asthma, or COPD. The International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM codes] for the chronic conditions are listed in **Appendix A, Table A-1**.

Patients were excluded from the SafeMed Program if the primary reason for index admission was related to cancer, pregnancy, or a surgical procedure for an acute problem following the approach of Jencks and colleagues recognizing that health care utilization for these conditions is less likely to be affected by outpatient chronic disease care or medication management.⁷⁷ Patients were also excluded if they had diagnoses of active psychosis, drug abuse, substance abuse or suicidal ideation during the index admission, or if they were discharged to a skilled nursing facility or hospice care because of evidence suggesting that these patient populations may be less amenable to outpatient intervention.⁵⁷ The ICD-9-CM codes and diagnosis-related group (DRG) codes for the exclusion criteria are listed in a previous paper by Harris and colleagues.⁵⁷

Of the 1,714 Medicare patients meeting SafeMed inclusion and exclusion criteria above, the final sample included the 1,092 (63.7%) who were continuously eligible for Medicare Part D during the 2-year evaluation period and who had filled at least one of the seventeen drug classes during the 2-year baseline evaluation period. These drug classes included angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARB), statins, antiplatelet agents, beta-blockers, calcium channel blockers, diuretics, alpha-1 blockers, central alpha-2 agonists, direct vasodilators, sulfonylureas, biguanides, thiazolidinediones, meglitinides, dipeptidyl peptidase-4 inhibitors, anticholinergic inhalers, inhaled corticosteroids alone or in combination with long-acting beta-agonists (LABA), and other COPD/asthma medications (theophylline and leukotriene modifiers).

Study Outcomes

The study's outcome was repeated measures of medication nonadherence measured as interval-based proportion of days covered (PDC).²¹ PDC was measured based on total number of days supplied for each drug class divided by the observation time interval for each 6-month period. Drugs that belonged to the same therapeutic class (example, amlodipine, and nifedipine in the calcium channel blockers) were considered interchangeable. Additionally, based on the evidence-based guideline, ACE inhibitors and ARB were considered a single class for this study.⁷⁸ Antiplatelet agents did not include aspirin because aspirin is usually purchased without a prescription (over-the-counter) and are not included in Part D claims data. Moreover, we did not include insulin since the days' supply information on this drug class is not accurate.⁷⁹ Interval-based PDC was measured if patients had ≥ 2 medication fills for any of the seventeen drug classes during a 6-month period. Using this approach, the numerator was defined as the number of days of medication supplied between the first and last prescription in a period and the denominator was defined as the number of days during the interval from the index date, which was the first day of the medication fill in a 6-month period, to the last day of that period. The average PDC measure was calculated at the patient-level by adding the PDC for each drug class and then dividing by the number of drug class used by the patient. Patients were then classified as nonadherent if they had PDC < 80% over the 6-month period. Adherence was also measured based on therapy-specific medication adherence classifications, which included diabetes, cardiovascular, and COPD/asthma

medications. Additionally, as a sensitivity analysis, we measured adherence by changing the fill criteria of ≥ 2 medication fills for a drug class to ≥ 1 medication fill.

Recognizing that the above definition for measuring PDC might overestimate adherence, another sensitivity analysis was conducted using an alternative PDC definition—patients were followed continuously from the time they had ≥ 2 fills during a 6-month period for a drug class, to the last 6-month period. We modified the denominator by using the first day of medication fill as index date only if patients had ≥ 2 fills for a drug class for the first time in a period. If patients filled ≥ 2 medications for a drug class in the previous period, we considered the denominator as 180 days. Additionally, we subtracted the inpatient days from the denominator. For the numerator, if the days' supply extended into the next period, it contributed to both periods.

Independent Variables

Sociodemographic variables were assessed using Medicare eligibility and prescription drug event files. Age, gender, and race/ethnicity were measured at baseline. Other sociodemographic factors measured for each 6-month period included whether patients were fully or partially eligible as dual beneficiaries in ≥ 1 months and whether patients received low-income cost sharing subsidy (LICS) for the index drug classes. The income threshold to be eligible for Tennessee Medicaid (TennCare) is 105% of the federal poverty level (FPL), while the income threshold for receiving LICS is higher—150% of the FPL. We combined these factors to create a variable with three groups (non-dual non-LICS, non-dual LICS, and dual LICS).

Clinical factors that were assessed at baseline included information on whether beneficiaries qualified for Medicare because of end-stage renal disease (ESRD) and whether beneficiaries had any disability. Disability was not included in the bivariate and multivariate models since everyone < 65 years of age was also disabled. The ICD-9 diagnosis codes present on at least one Medicare inpatient, outpatient, or Part B claim were used to identify patients in each 6-month period who had qualifying chronic conditions or comorbidities. Overall comorbidity was measured using the University of Manitoba SAS Macro for Charlson comorbidity index (mean).⁸⁰ Additionally, the SafeMed Program's qualifying chronic conditions included: diabetes, hypertension, CHF, CAD, COPD, and asthma. We only included Charlson comorbidity index in the bivariate and multivariate models as a comorbidity measure, since it includes the qualifying conditions and ESRD. In addition to this, we assessed mental illness (defined as a diagnosis of depression or anxiety or ≥ 1 anxiolytic or antidepressant fills) and tobacco use disorder. The ICD-9-CM codes for anxiety, depression, and tobacco use disorder are listed in **Appendix A, Table A-1**.

Therapeutic complexity and health services utilization factors were assessed for each 6-month period, using prescription drug event and Part B claims files. Therapeutic complexity-related factors included the number of unique medications filled, opioid

medications filled (0, 1, 2-3, or ≥ 4 fills), number of unique prescribers, and number of unique pharmacies. Health services utilization factors included ≥ 1 physician office visits.

Statistical Analysis

Descriptive analyses were conducted to show the characteristics of super-utilizers and medication nonadherence rates in each 6-month period. For bivariate and multivariate analyses, we pooled observations from the four 6-month periods. The unit of analysis for the bivariate and multivariate models was patient-period. Chi-square tests and t-tests were conducted as part of the bivariate statistics. We used random effects model with a binary distribution to obtain associations between independent variables and medication nonadherence. The model included lagged effects of comorbidities, therapy complexity, and physician office visits. As a subgroup analysis, we estimated separate multivariate models for each age group (i.e., <65 and ≥ 65 years) to understand associations specific to these Medicare age groups. Data cleaning was performed using SAS 9.4 and all data analyses were conducted using STATA 13. Variables in the multivariate models with $P < 0.05$ were considered significant.

RESULTS

Characteristics of the study population ($N=1,092$) in each 6-month evaluation period is shown in **Table 2-1**. The mean age of the study population was 65.1 years, and, 43.0% were <65 years of age. The study population was predominantly female (58.8%), non-Hispanic Black (68.6), dual eligible (63.7%), and received LICS (68.7%). In the fourth period, patients had a mean of 3.1 inpatient stays and 1.7 ED visits. Additionally, in the same period, 97.2% of the study patients had ≥ 2 chronic conditions, 57.0% were diagnosed with depression/anxiety or had filled ≥ 1 antidepressants or anxiolytics, and 69.0% had filled ≥ 1 opioid medications. These proportions were higher in the fourth period than previous periods.

Rates of nonadherence to essential chronic disease medications are shown in **Table 2-2**. We found that 40.4% of patients were nonadherent to their diabetes medications, 48.2% to their cardiovascular medications, and 54.3% to their COPD/asthma medications. Nonadherence rates for cardiovascular and COPD/asthma medications were higher in the fourth period than previous periods. When examining overall nonadherence rate, we found that 45.7% of patients were nonadherent to their essential chronic medications.

Main Analysis

Bivariate associations with medication nonadherence are shown in **Table 2-3**. In the multivariate analysis (**Table 2-4**), we found that patients who filled ≥ 4 opioid medications in the previous period had higher odds of medication nonadherence

Table 2-1. Characteristics of the Study Sample in Each 6-Month Patient-Period (N=1,092)

Characteristics	Period 1 N (%)	Period 2 N (%)	Period 3 N (%)	Period 4 N (%)
Age				
<65 years	468 (42.9)	-	-	-
≥65 years	624 (57.1)			
mean age (SD)	65.1 (14.5)			
Female	642 (58.8)	-	-	-
Race/Ethnicity				
Non-Hispanic White	326 (29.9)	-	-	-
Non-Hispanic Black	749 (68.6)			
Other	17 (1.6)			
Eligibility status				
Disabled	407 (37.3)	-	-	-
End-stage renal disease	324 (29.7)	-	-	-
Dual eligible	696 (63.7)	694 (63.6)	697 (63.8)	692 (63.4)
Receiving low-income cost sharing subsidy	750 (68.7)	790 (72.3)	791 (72.4)	803 (73.5)
Qualifying Chronic Conditions				
Diagnosis of Hypertension	852 (78.0)	950 (87.0)	1,028 (94.1)	1086 (99.5)
Diagnosis of Diabetes	571 (52.3)	638 (58.4)	696 (63.7)	784 (71.8)
Diagnosis of Congestive heart failure	338 (31.0)	467 (42.8)	603 (55.2)	799 (73.2)
Diagnosis of Coronary artery disease	368 (33.7)	481 (44.1)	590 (54.0)	785 (71.9)
Diagnosis of Asthma	134 (12.3)	199 (18.2)	262 (24.0)	377 (34.5)
Diagnosis of Chronic obstructive pulmonary disease	246 (22.7)	343 (31.4)	448 (41.0)	583 (53.4)
Number of qualifying chronic conditions				
≤1 chronic conditions	335 (30.82)	226 (20.7)	131 (12.0)	31 (2.8)
2 chronic conditions	262 (24.0)	236 (21.6)	204 (18.7)	115 (10.5)
3 chronic conditions	247 (22.6)	244 (22.3)	250 (23.0)	211 (19.3)
4 or more chronic conditions	246 (22.5)	386 (35.3)	507 (46.4)	735 (67.2)

Table 2-1. Continued

Characteristics	Period 1 N (%)	Period 2 N (%)	Period 3 N (%)	Period 4 N (%)
Comorbidity				
Charlson comorbidity index, mean (SD)	3.2 (2.7)	4.2 (3.1)	5.2 (3.3)	6.9 (3.2)
Mental illness*	389 (35.6)	460 (42.1)	533 (48.8)	622 (57.0)
Tobacco use disorder	106 (9.7)	163 (14.9)	266 (24.4)	351 (32.1)
Therapy complexity				
No. of unique medications filled, mean (SD)	11.9 (6.2)	12.3 (6.4)	12.5 (6.5)	14.9 (6.3)
No. of unique prescribers	4.4 (2.9)	4.6 (3.0)	4.7 (3.0)	5.8 (3.1)
No. of unique pharmacies	1.8 (1.3)	1.8 (1.3)	1.9 (1.3)	2.1 (1.4)
No. of opioids filled, mean (SD)	2.6 (4.0)	2.7 (4.0)	2.7 (3.9)	3.2 (4.1)
0 opioid filled	499 (45.7)	479 (43.9)	480 (44.0)	337 (31.0)
1 opioid filled	147 (13.5)	165 (15.1)	157 (14.4)	187 (17.1)
2-3 opioid filled	159 (14.6)	143 (13.1)	151 (13.8)	211 (19.3)
≥4 opioid filled	287 (26.3)	305 (27.9)	304 (27.8)	357 (32.7)
Health services utilization				
≥1 physician office visits [±]	900 (82.4)	903 (82.7)	909 (83.2)	915 (83.8)
No. of inpatient stays, mean (SD)	0.8 (1.4)	0.8 (1.4)	0.7 (1.4)	3.1 (0.9)
No. of emergency department visits, mean (SD)	0.8 (2.1)	0.8 (2.2)	0.9 (2.2)	1.7 (2.6)

[±]Physician office visits were identified using Part B claims and were defined as “location, other than a hospital, skilled nursing facility (SNF), military treatment facility, community health center, State or local public health clinic, or intermediate care facility (ICF), where the health professional routinely provides health examinations, diagnosis, and treatment of illness or injury on an ambulatory basis.”

*Mental illness was defined as ≥1 antidepressants or anxiolytics fill or diagnosis of depression/anxiety.

Table 2-2. Medication Nonadherence to Essential Chronic Disease Medications by Therapy Class

Therapy Class	Percent Nonadherent (PDC<80%)
1. Diabetes medications	
Period 1 (n=250)	41.2%
Period 2 (n=240)	40.8%
Period 3 (n=232)	38.8%
Period 4 (n=194)	40.7%
Overall (n=916 patient-periods)	40.4%
2. Cardiovascular medications	
Period 1 (n=933)	40.2%
Period 2 (n=942)	44.5%
Period 3 (n=932)	41.0%
Period 4 (n=976)	47.4%
Overall (n=3,763 patient-periods)	48.2%
3. COPD/Asthma medications*	
Period 1 (n=169)	54.4%
Period 2 (n=166)	53.6%
Period 3 (n=169)	49.7%
Period 4 (n=183)	59.6%
Overall (n=687 patient-periods)	54.3%
Diabetes, cardiovascular, and COPD/Asthma meds combined	
Period 1 (n=961)	43.2%
Period 2 (n=971)	45.9%
Period 3 (n=961)	42.6%
Period 4 (n=994)	50.9%
Overall (n=3,892 patient-periods)	45.7%

COPD: chronic obstructive pulmonary disease.

*COPD/Asthma medications included controller medications (anticholinergic inhalers, inhaled corticosteroids alone or in combination with long-acting beta-agonists (LABA), and other COPD/asthma medications (theophylline and leukotriene modifiers).

Table 2-3. Bivariate Associations with Medication Nonadherence (N=2,828 Patient-Periods)

Characteristics	Adherence N (%)	Nonadherence N (%)	P Value
Age			
<65 years	512 (33.5)	640 (49.3)	
≥65 years	1,018 (66.5)	658 (50.7)	<0.001
Female	932 (60.9)	780 (60.1)	0.656
Race			
Non-Hispanic White/other	538 (35.2)	365 (28.1)	
Non-Hispanic Black	992 (64.8)	933 (71.9)	<0.001
Eligibility status			
Non-dual and non-LIS	472 (30.9)	279 (21.5)	
Non-dual LIS	151 (9.9)	132 (10.2)	
Dual LIS	907 (59.3)	887 (68.3)	<0.001
Comorbidity			
Charlson comorbidity index, mean (SD)	4.3 (3.1)	4.6 (3.2)	0.030
Diagnosis of tobacco abuse disorder	282 (18.4)	258 (19.9)	0.330
Mental illness*	635 (41.5)	521 (40.1)	0.462
Therapy complexity			
No. of unique medications filled, mean (SD)	12.9 (5.9)	13.3 (6.3)	0.174
Opioid Medication Use			
0 opioid medication filled	720 (47.1)	503 (38.8)	<0.001
1 opioid medication filled	215 (14.1)	195 (15.0)	
2-3 opioid medications filled	227 (14.8)	167 (12.9)	
≥4 opioids medications filled	368 (24.1)	433 (33.4)	
No. of unique prescribers	4.5 (2.8)	5.1 (3.2)	<0.001
No. of unique pharmacies	1.8 (1.1)	2.0 (1.4)	<0.001
Health care utilization			
≥1 physician office visits	1,333 (87.1)	1,070 (82.4)	0.001

Significant at P<0.05. The bivariate tests included lagged effects of comorbidity, therapy complexity-related, and health care utilization factors.

*Mental illness was defined as >1 antidepressants or anxiolytics fill or diagnosis of depression/anxiety.

Table 2-4. Multivariate Association with Medication Nonadherence (N=2,828 Patient-Periods)

Characteristics	Nonadherence Odds Ratio (95% CI)	P Value
<65 years	2.15 (1.54-2.99)	<0.001
Female	1.01 (0.75-1.38)	0.931
Non-Hispanic black	1.17 (0.84-1.63)	0.343
Non-dual Non-LICS (Ref)		
Non-dual LICS	1.10 (0.66-1.83)	0.708
Dual LICS	1.47 (1.02-2.13)	0.039
Comorbidity		
Charlson comorbidity index	1.02 (0.98-1.07)	0.330
Mental illness*	0.79 (0.58-1.08)	0.140
Diagnosis of tobacco abuse disorder	0.82 (0.58-1.16)	0.264
Medication related factors		
No. of unique medications filled	0.96 (0.93-0.98)	0.006
Opioid Medication Use		
0 opioid medication filled (Ref)		
1 opioid medication filled	1.30 (0.93-1.82)	0.128
2-3 opioid medications filled	1.02 (0.71-1.46)	0.914
≥4 opioid medications filled	1.94 (1.34-2.82)	<0.001
No. of unique prescribers	1.09 (1.03-1.15)	0.003
No. of unique pharmacies	1.02 (0.92-1.14)	0.671
Health care utilization		
≥1 physician office visits	0.57 (0.40-0.81)	0.002

Significant at $P < 0.05$. The model included lagged effects of comorbidity, therapy complexity-related, and health care utilization factors.

*Mental illness was defined as ≥1 antidepressants or anxiolytics fill or diagnosis of depression/anxiety.

compared to patients with no opioid fill (odds ratio (OR), 1.94; 95% confidence interval (CI), 1.34-2.82; $P<0.001$). Compared to patients with no mental illness, those with mental illness had lower odds of nonadherence, however this association was not statistically significant (OR, 0.79; CI, 0.58-1.08; $P=0.140$). Among sociodemographic factors, patients 22-64 years of age were more likely to be nonadherent than patients ≥ 65 years (OR: 2.15; CI: 1.54-2.99; $P<0.001$), and dual beneficiaries who received LICS were more likely to be nonadherent than non-dual beneficiaries with no LICS CI, 1.02-2.13; $P=0.039$). Among therapy complexity-related factors, patients who had higher number of unique prescribers were more likely to be nonadherent (OR, 1.09; CI, 1.03-1.15; $P=0.003$), whereas patients who filled higher number of different medications were less likely to be nonadherent (OR, 0.96; CI, 0.93-0.98; $P=0.006$). Finally, we found that patients who had ≥ 1 physician office visits in the previous period were less likely to be nonadherent to their essential chronic medications (OR, 0.57; CI, 0.40-0.81; $P=0.002$).

Table 2-5 shows the multivariate associations among Medicare beneficiaries ≥ 65 years of age. Risk factors for nonadherence in this age group included ≥ 4 opioid medications filled in the previous period and higher number of unique prescribers. Additionally, we found that ≥ 1 physician office visits in the previous period was protective against nonadherence. **Table 2-6** shows the multivariate associations among Medicare beneficiaries < 65 years of age. Risk factors for nonadherence included ≥ 4 opioid medications filled in the previous period and dual LICS status. Higher number of unique medications filled was found to be protective against nonadherence.

Sensitivity Analysis

Our main adherence definition—based on patients who had at least ≥ 2 fills in a period—may underestimate nonadherence because it did not include patients who had only one fill or did not fill their medications in subsequent periods. Using the alternative PDC definition that assumes continuous chronic disease drug class use once begun (≥ 2 fills for a drug class in a period), proportion of patients who were nonadherent was about 13% higher (58.4%) (**Appendix A, Table A-2**). The multivariate model using this alternate PDC calculation demonstrated similar findings in terms of direction and statistical significance to our main analysis in terms of age, dual LICS status, number of different medications filled, unique prescribers, and physician office visits. However, there were a few differences: comorbidity index was found to be significantly associated with nonadherence and the association between opioid medication fill and nonadherence was no longer statistically significant (**Appendix A, Table A-3**). Additionally, in the sensitivity analysis using the alternative PDC criteria of ≥ 1 medication fill for our main PDC definition (**Appendix A, Table A-4**), the study findings were similar in terms of significance and directionality to our main multivariate analysis.

Table 2-5. Multivariate Association with Medication Nonadherence Among Medicare Beneficiaries ≥ 65 Years of Age (N=1,676 Patient-Periods)

Characteristics	Nonadherence Odds Ratio (95% CI)	P Value
Female	1.15 (0.77-1.71)	0.494
Non-Hispanic black	1.09 (0.71-1.68)	0.684
Non-dual Non-LICS (Ref)		
Non-dual LICS	0.90 (0.48-1.72)	0.759
Dual LICS	1.29 (0.84-1.97)	0.242
Comorbidity		
Charlson comorbidity index	1.03 (0.97-1.10)	0.330
Mental illness*	0.73 (0.48-1.11)	0.143
Diagnosis of tobacco abuse disorder	0.78 (0.45-1.35)	0.373
Medication related factors		
No. of unique medications filled	0.96 (0.91-1.02)	0.155
Opioid Medication Use		
0 opioid medication filled (Ref)		
1 opioid medication filled	1.30 (0.85-2.00)	0.228
2-3 opioid medications filled	1.04 (0.66-1.63)	0.876
≥ 4 opioid medications filled	1.89 (1.14-3.12)	0.013
No. of unique prescribers	1.14 (1.04-1.24)	0.004
No. of unique pharmacies	0.95 (0.80-1.13)	0.588
Health care utilization		
≥ 1 physician office visits	0.50 (0.31-0.80)	0.004

Significant at $P < 0.05$. The model included lagged effects of comorbidity, therapy complexity-related, and health care utilization factors.

*Mental illness was defined as ≥ 1 antidepressants or anxiolytics fill or diagnosis of depression/anxiety.

Table 2-6. Multivariate Association with Medication Nonadherence Among Medicare Beneficiaries <65 Years of Age (N=1,152 Patient-Periods)

Characteristics	Nonadherence Odds Ratio (95% CI)	P Value
Female	0.90 (0.57-1.43)	0.648
Non-Hispanic black	1.34 (0.78-2.30)	0.296
Non-dual Non-LICS (Ref)		
Non-dual LICS	0.99 (0.80-4.92)	0.139
Dual LICS	2.58 (1.18-5.61)	0.017
Comorbidity		
Charlson comorbidity index	0.71 (0.41-1.23)	0.221
Mental illness*	0.86 (0.54-1.36)	0.522
Diagnosis of tobacco abuse disorder	0.83 (0.54-1.28)	0.397
Medication related factors		
No. of unique medications filled	0.95 (0.90-0.99)	0.035
Opioid Medication Use		
0 opioid medication filled (Ref)		
1 opioid medication filled	1.16 (0.68-1.96)	0.583
2-3 opioid medications filled	0.85 (0.49-1.47)	0.570
≥4 opioid medications filled	1.83 (1.08-3.11)	0.025
No. of unique prescribers	1.03 (0.96-1.10)	0.370
No. of unique pharmacies	1.09 (0.95-1.26)	0.205
Health care utilization		
≥1 physician office visits	0.71 (0.41-1.23)	0.221

Significant at $P < 0.05$. The model included lagged effects of comorbidity, therapy complexity-related, and health care utilization factors.

*Mental illness was defined as ≥1 antidepressants or anxiolytics fill or diagnosis of depression/anxiety.

DISCUSSION

This study is the first to focus specifically on the prevalence and factors associated with medication nonadherence in super-utilizers with chronic conditions. We found high rates of medication nonadherence among super-utilizers with chronic conditions. Specifically, we found that the overall nonadherence rate for essential chronic disease medications ranged from 45.7% to 58.4%, with the highest rate for COPD/Asthma medications (54.3% to 64.4%). The high rates of nonadherence found in this study are similar to those previously found in patients using diabetes, cardiovascular, and COPD/asthma medications.^{3,15,81-83} However, this study extends these findings to super-utilizing Medicare population and provides important information to the super-utilizer literature. We not only found high rates of nonadherence among super-utilizers but also saw an increase in the nonadherence rates in the final 6-month period when patients had more frequent hospitalizations and ED visits. The study findings suggest that medication nonadherence is a significant problem among super-utilizers with chronic conditions, and greater efforts may be needed to address this issue.

Our study shows that most super-utilizers have high rates of mental illness and opioid use. During the final 6-month evaluation period, 57% were diagnosed with depression or anxiety or had filled antidepressants or anxiolytics, and 69% had filled opioid medications. A substantial amount of opioid utilization is likely driven by the high prevalence of chronic pain in the SafeMed population as documented in a previous study.⁵⁷ To our knowledge this is the first study to document the association between opioid medication fill and medication nonadherence among super-utilizers and provides evidence of high opioids use as a risk factor for medication nonadherence. These findings highlight the barrier to achieving optimal adherence in super-utilizers due to high opioid use and the need for effective strategies to address medication nonadherence among opioid-consuming super-utilizers. Our results for depression/anxiety were not consistent with the previous studies which found these conditions to be associated with nonadherence.^{24,84-87} We did not find any significant association of anxiety/depression or filling anxiolytic/antidepressants with nonadherence to essential chronic medications in the main analysis.

This study provides insight into the characteristics of super-utilizers who are at higher risk of medication nonadherence. In this study, non-elderly Medicare beneficiaries represented 43% of the study population, approximately 92% of whom received LICS, and 80% were both dual-eligible and LICS recipients. Unlike other studies based on Medicare data that have shown better or similar medication adherence for duals and those receiving LICS compared to non-dual non-LICS beneficiaries,^{88,89} we found lower adherence for duals receiving LICS. This is probably because our study population, unlike those of previous studies, had high representation of younger dual eligible beneficiaries, who had on average higher comorbidity index values and opioid medication use than patients >65 years of age. Moreover, previous studies conducted on different populations have shown that young age is associated with lower medication adherence.^{1,3} Our study findings show that medication cost subsidies are not enough to achieve optimal adherence in these high-risk patients, especially for non-elderly

Medicare beneficiaries. The highly statistically significant and large effect size of the association between age and medication nonadherence demonstrates the need for better targeting of the non-elderly Medicare group with medication management interventions. Our sub-group analysis shows that the factors associated with nonadherence vary across age groups. Examining associations separately in the two age groups may help researchers to better target these high utilizing patient populations with medication management interventions.

The study found that higher physician office visits were associated with significant higher medication adherence, consistent with the findings of other studies.^{3,5} The statistically strong association between physician office visits and lower nonadherence suggests the importance of making routine visits to providers who can play a significant role in helping patients to adhere to their essential chronic medications. This finding may also be an indicator for more health conscious patients who are more likely to visit their providers.

Of note, increased number of different medications filled was associated with lower odds of nonadherence. Other studies evaluating this relationship have reported mixed results. For instance, Bailey and colleagues found that among Tennessee's Medicaid patients with hypertension, the number of hypertensive drug classes filled was associated with lower odds of nonadherence.³ Similarly, Choudhry and colleagues found that in patients who were prescribed a cardiovascular medication, those with a large number of concurrent medications were more likely to be adherent.⁷³ However, Chapman and colleagues found that patients consuming a higher number of other medications had lower adherence to lipid lowering and antihypertensive medications.⁹⁰ Filling a higher number of concurrent medications may represent behavioral characteristics of patients who are more likely to use a higher number of medications and also adhere to their therapy. When examining other therapy complexity-related factors, we found that a higher number of unique prescribers was associated with higher odds of nonadherence. This finding was consistent with the finding of Choudhry and colleagues who also found higher number of prescribers being associated with poor adherence.⁷³

This study has important implications. The literature on super-utilizers is sparse and mainly focuses on describing the population and their hospitalization patterns.^{56,57} To our knowledge, this study is the first to focus on the issue of medication nonadherence in super-utilizers with chronic conditions. The risk factors identified in this study may enable accountable care organizations and managed care organizations identify super-utilizing populations in need of medication management interventions. Managing medication-related adverse events and improving medication adherence among vulnerable super-utilizers is critical for hospitals and payers, since 75% of the hospital readmissions among Medicare population are considered potentially preventable, resulting in \$12 billion in unnecessary Medicare spending each year and subjecting hospitals to readmission penalties.⁴⁶ Our findings suggest that super-utilizers using ≥ 4 opioid medications are at particular risk for nonadherence and may merit targeted medication management interventions to support essential chronic disease medication adherence. Given the magnitude and clinical importance of medication nonadherence in

this population, a more collaborative and holistic approach may be needed to improve adherence in this high-risk population, who experience frequent care transitions exposing them to higher drug therapy problems and medication discrepancies. Medication management interventions conducted on other populations have demonstrated mixed results,^{17,19,44,45} and care transitions programs targeting super-utilizers have not primarily focused on medication management.^{65,91} For instance, Pringle and colleagues evaluated the impact of a large-scale, pharmacy-based intervention on five chronic medication classes among Medicare, Medicaid, or commercial patients and found that, compared to the control group, the intervention group had improved adherence for all medication classes.⁴³ However, Kripalani and colleagues, who examined the effect of pharmacist interventions on clinically important medical errors after hospital discharge among Medicare, Medicaid, or private pay patients, did not find any positive effect of these interventions on medication errors.¹⁹ Our results suggest the potential for novel care transitions programs aimed at improving medication adherence.

Our study is also subject to several limitations. First, the study used administrative data and had to rely on the variables that were available in the database. Medicare claims data does not capture some of the important variables such as health literacy, social support, satisfaction with health care, and other healthcare system factors that may impact medication adherence in vulnerable super-utilizers. Second, although pharmacy fill data is widely used to assess medication adherence, we cannot be certain that patients who fill medications are also using them appropriately. To address limitations of using claims based PDC, we calculated PDC using two different definitions, which allowed for checking the reliability of our main findings. Using these approaches, the overall nonadherence rate ranged from 45.7% to 58.4% and most of the findings of multivariate models remained similar. Given that the main approach could overestimate adherence and the alternative methods could underestimate adherence, we suspect that the population estimates for nonadherence of these super-utilizers could lie somewhere between the nonadherence ranges reported in this study. Third, the PDC measure for calculating adherence is an indirect method and may not accurately capture medication use and is likely to be biased for inhalation products that are prescribed for Asthma and COPD. Finally, since this study is based on super-utilizers living in Memphis, TN, the study findings may only be generalizable to similar populations and similar settings across the country.

CONCLUSION

In summary, the overall medication nonadherence rate for essential chronic disease medications was high among super-utilizers, especially in patients using COPD/Asthma medications. Previously identified factors—including physician office visits, a higher number of medications—were found to protect against nonadherence, while young age, dual LICS status, and higher number of unique prescribers predicted nonadherence. Of note, opioid medication use was identified as a novel and significant risk factor for essential medication nonadherence in super-utilizers with chronic conditions.

CHAPTER 3. ASSOCIATION BETWEEN MEDICATION NONADHERENCE AND INPATIENT AND EMERGENCY DEPARTMENT USE IN SUPER-UTILIZERS WITH CHRONIC CONDITIONS

BACKGROUND

Consistent and long-term use of prescription medications is critical for the treatment of chronic conditions, such as heart disease, diabetes, hypertension, and chronic lung disease. Nonadherence to needed drugs could be a major barrier to achieving optimal treatment goals, especially among high-risk patient populations. Super-utilizers represent one such vulnerable patient population — patients with disproportionately high inpatient and emergency department (ED) use, who have multiple chronic conditions (MCC) and use multiple concurrent medications to treat these conditions.^{13,55,56} The cost of caring for super-utilizers is high, with estimates showing that they represent only 3 to 5% of the U.S. population, but account for 30 to 50% or more of total spending.^{56,70} Additionally, these super-utilizing patients experience frequent transitions of care and are particularly vulnerable to experiencing drug therapy problems, medication discrepancies, and medication nonadherence at each care transition.^{13,19}

Previous studies using longitudinal data have shown improved medication adherence to be associated with lower inpatient and ED use. Roebuck and colleagues found that improved medication adherence was associated with lower hospitalization and ED use in patients with congestive heart failure, hypertension, diabetes, or dyslipidemia.⁵ Another study by Jha and colleagues also found lower hospitalization or ED rates associated with improved adherence to diabetes medications.⁴ Despite widespread recognition that medication nonadherence plays a significant role in hospitalizations, such associations have not been established for super-utilizers with chronic conditions. Given the increased focus on reducing the disproportionate health care utilization and costs in this patient population, it is important to understand whether nonadherence to essential chronic medications contributes to their high inpatient and ED use.

High rates of mental illness and chronic pain have been reported among super-utilizing patient populations.⁵⁶⁻⁵⁸ Additionally, evidence from our previous study on Medicare super-utilizers demonstrates that along with the high prevalence of medication nonadherence and mental illness, these patients have higher rates of opioid medication use (Chapter 2). However, little is known whether these factors are associated with high inpatient and ED use. A recent study found that opioid use is common after hospitalization among Medicare beneficiaries.⁹² However, it is not clear whether recent opioid use has any association with high health care utilization. Using longitudinal Medicare administrative data, we examined the association between medication nonadherence and inpatients and ED use in a cohort of Medicare super-utilizers with chronic conditions. Additionally, we also evaluated if other risk factors, including mental illness and opioid medication use, are associated with inpatient and ED utilization in this vulnerable high-risk population.

METHODS

Design and Setting

SafeMed Program is a Centers for Medicare and Medicaid Services (CMS) Health Care Innovations Award funded care transitions program with a focus on medication management.⁶⁰ The program targeted super-utilizers from medically underserved areas admitted to a non-profit hospital system in Memphis, TN from February 2013 to May 2015. Using Medicare administrative data, we conducted a retrospective panel data analysis of the 2-year baseline data for Medicare Part D beneficiaries meeting the SafeMed Program eligibility criteria during the enrollment period from February 1, 2013 to December 31, 2014. The study included SafeMed eligible patients because they were diagnosed with chronic conditions (hypertension, diabetes mellitus, congestive heart failure (CHF), coronary artery disease (CAD), diabetes mellitus, asthma, or chronic obstructive pulmonary disease (COPD)) that have been identified as ambulatory care-sensitive conditions for which outpatient care improvements can reduce inpatient utilization.⁵⁷ The two-year baseline data for each patient was divided into four 6-month patient-periods, the last 6-month period being the qualifying period for the SafeMed Program. Previous studies on super-utilizers have shown that super-utilizer status is not consistent, and it changes over time.^{56,57} The panel design enabled us to examine the changes in medication adherence and health care utilization over the 2-year period prior to the intervention and to understand whether the time-varying factor, medication nonadherence, was associated with inpatient and ED utilization.

Study Population

This study included Medicare beneficiaries who were eligible for the SafeMed Program during a portion of the enrollment period between February 2013 and December 2014. Patients were enrolled in the SafeMed Program during an inpatient admission or an observation stay (index hospitalization). SafeMed Program eligibility was based on the following inclusion criteria: 1) adults aged 18 years or older with continuous Medicare enrollment, 2) ≥ 2 hospital admissions in the past six months OR 1 inpatient admission and ≥ 2 ED visits in the past six months prior to the index admission, and 3) diagnosis of ≥ 1 of the following chronic conditions: hypertension, CHF, CAD, diabetes mellitus, asthma, or COPD.

Additionally, patients were excluded from the SafeMed Program if the primary reason for index admission was related to cancer, pregnancy, or a surgical procedure for an acute problem following the approach of Jencks and colleagues recognizing that utilization for these conditions is less likely to be affected by outpatient chronic disease care or medication management.⁷⁷ Patients were also excluded if they had diagnoses of active psychosis, drug abuse, substance abuse or suicidal ideation during the index admission, or if they were discharged to a skilled nursing facility or hospice care because

of evidence suggesting that high utilization in these patient populations may be less amenable to outpatient intervention.⁵⁷

Of the 1,714 Medicare patients meeting SafeMed inclusion and exclusion criteria above, the final sample included the 1,092 (63.7%) who were continuously eligible for Medicare Part D during the 2-year evaluation period and who had filled at least one of the seventeen drug classes during the 2-year baseline evaluation period: These drug classes included angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARB), statins, antiplatelet agents, beta-blockers, calcium channel blockers, diuretics, alpha-1 blockers, central alpha-2 agonists, direct vasodilators, sulfonylureas, biguanides, thiazolidinediones, meglitinides, dipeptidyl peptidase-4 inhibitors, anticholinergic inhalers, inhaled corticosteroids alone or in combination with long-acting beta-agonists (LABA), and other COPD/asthma medications (theophylline and leukotriene modifiers).

Outcome Variables

This study included two outcomes: 1) total number of inpatient and observation stays and 2) total number of ED visits, measured for each 6-month period. Data on inpatient stays was obtained using MEDPAR (Medical Provider Analysis and Review) data files. Additionally, data on observation stays and ED visits were obtained using Medicare outpatient revenue center data files (revenue center codes for ED visits: 0450-0459, 0981; revenue center codes for observation stays: 0762). We excluded observation stays and ED visits that resulted in an inpatient admission.

Independent Variables

Medication nonadherence

The Medicare Part D drug event data was used to assess medication nonadherence. Medication nonadherence was measured as interval-based proportion of days covered (PDC).²¹ PDC was measured based on total number of days' supply for each drug class divided by the observation time interval for each 6-month period. We measured PDC for the drug classes mentioned above. Drugs that belonged to the same therapeutic class (example, amlodipine, and nifedipine in the calcium channel blockers) were considered interchangeable. Based on the evidence-based guideline, ACE inhibitors and ARB were considered a single class for this study.⁷⁸ Antiplatelet agents did not include aspirin because aspirin is usually purchased without a prescription (over-the-counter) and is not included in Part D claims data. Moreover, we did not include insulin since the days' supply information on this drug class is not accurate.⁷⁹

Using interval-based PDC approach, patients were followed continuously from the time they had ≥ 2 fills during a 6-month period for a drug class, to the last 6-month period. The numerator was defined as the number of days of medication supply between

the first and last prescription in a period, and the denominator was defined as the number of days during the interval from the index date to the last day of that period. For the numerator, if the days' supply extended into the next period, it contributed to both periods. For the denominator, we used the first day of medication fill as index date only if patients had ≥ 2 fill for a drug class for the first time in a period. If patients filled ≥ 2 medications for a drug class in any of the previous periods, we considered denominator as 180 days. Additionally, we subtracted the inpatient days from the denominator. The average PDC measure was calculated at the patient-level by adding the PDC for each drug class and then dividing by the number of drug class used by the patient. Patients were then classified as nonadherent if they had $PDC < 80\%$ over the 6-month period. Adherence was also measured based on therapy-specific medication adherence classifications, which included diabetes, cardiovascular, and COPD/asthma medications. Additionally, as a sensitivity analysis, we measured adherence by changing the fill criteria of ≥ 2 medication fills for a drug class to ≥ 1 medication fill.

Other covariates

In addition to the primary adherence variable, we assessed mental illness, substance use disorder, and opioid medication use for each 6-month period. We identified patients with mental illness if they had a diagnosis of depression or anxiety (at least 1 diagnosis claim present in Medicare inpatient, outpatient, or Part B claims) or ≥ 1 anxiolytic or antidepressant fill. Opioid medication use was based on number of opioid medication fill (0 fill, 1 fill, 2-3 fills, >3 fills). Additionally, we identified patients with substance use disorder if they had a diagnosis of tobacco use disorder.

Sociodemographic variables were assessed using Medicare beneficiary summary files. Factors assessed at baseline included age, gender, race/ethnicity, disability status, and end-stage renal disease (ESRD) status. Disability was not included in the multivariate models since everyone <65 years of age was also disabled. Additionally, ESRD was not included in the models since Charlson comorbidity index includes ESRD. Other sociodemographic factors measured for each 6-month period included whether patients were fully or partially eligible as dual beneficiaries in ≥ 1 month and whether patients received low-income cost sharing subsidy (LICS) for the index drug classes. Since the income threshold for receiving LICS is higher than to be eligible for Tennessee Medicaid, we combined them to create a variable with 3 mutually exclusive groups (non-dual non-LICS, non-dual LICS, and dual LICS).

To control for the presence of other diseases, we used the ICD-9 diagnosis codes present on at least 1 Medicare inpatient, outpatient, or Part B claim, to identify patients in each 6-month period having comorbidities. Overall comorbidity was measured using the University of Manitoba SAS Macro for Charlson comorbidity index.⁸⁰ Other control variables assessed for each 6-month period included ≥ 1 physician office visits, number of unique medications filled, and number of unique prescribers.

Statistical Analysis

For multivariate analyses, we pooled observations from the four 6-month periods. The unit of analysis was patient-period. The viability of using a random effects model or a fixed effects model was tested using the Hausman specification test.⁹³ For both outcomes, the null hypothesis was rejected ($P<0.01$) indicating that a fixed effects model would be superior to account for potential endogeneity that arises if an unobserved characteristic is related to both the independent variables and the outcome. One such bias is known as ‘healthy user effect’—people who are adherent to their medications also engage in health-enhancing behavior and are different from nonadherent individuals.⁹⁴ Thus, we used fixed effects negative binomial model at the patient level to control for this potential problem. We estimated separate models for each age group (i.e., <65 and ≥ 65 years) to understand associations specific to these Medicare age groups. We included lagged effects of all independent factors in the models.

In addition to the main models, we also conducted multivariate fixed effects analyses to examine the association between medication nonadherence and inpatient and ED utilization across different therapy classes—diabetes, cardiovascular, and COPD/asthma medication class. Additionally, to investigate the association between time-invariant factors including race, dual LICS status and inpatient and ED utilization, we conducted a random effects model. As sensitivity analyses, we ran models by changing the adherence measure criteria of ≥ 2 medication fills to ≥ 1 fill. All data analyses were conducted using SAS 9.4 and STATA 13. Variables in the multivariate models with $P<0.05$ were considered significant.

RESULTS

Characteristics of the study subjects ($N=1,092$) in each 6-month evaluation period are shown in **Table 3-1**. The mean age for the study population was 65.1, and 43.0% were <65 years of age. The study subjects were predominantly female (58.8%), non-Hispanic black (68.6), dual eligible (63.7%), and received LICS (68.7%). In the fourth period, which was the qualifying period for the SafeMed Program, patients had a mean of 3.1 (0.9) inpatient stays and 1.7 (2.6) ED visits, which was higher than previous periods. Additionally, in the same period, 97.2% of patients had ≥ 2 chronic conditions, 57.0% had mental illness, and 69.0% filled ≥ 1 opioid medications. The patterns of medication adherence among the study subjects during each 6-month evaluation period is shown in **Figure 3-1**. The mean PDC for patients decreased progressively from period 1 to period 4; mean PDC was 80.3% in period 1 and declined to 63.0% in period 4. Using the 80% PDC cutoff, we found overall nonadherence rates for all essential drug classes in the four periods to be 43.2%, 56.1%, 65.5%, and 72.8%, respectively (data not shown).

Table 3-2 displays results for the multivariate associations between medication nonadherence and inpatient stays and ED visits by therapy class, using fixed effects negative binomial models. For the three therapy classes displayed — diabetes, cardiovascular, and COPD/asthma — the adjusted models indicated that the incidence of

Table 3-1. Characteristics of SafeMed Eligible Patients in Each 6-Month Patient-Period (N=1,092)

Characteristics	Period 1 N (%)	Period 2 N (%)	Period 3 N (%)	Period 4 N (%)
Age				
<65 years	468 (42.9)	-	-	-
≥65 years	624 (57.1)			
mean age (SD)	65.1 (14.5)			
Female	642 (58.8)	-	-	-
Race/Ethnicity				
Non-Hispanic white	326 (29.9)	-	-	-
Non-Hispanic black	749 (68.6)			
Other	17 (1.6)			
Eligibility status				
Disabled	407 (37.3)	-	-	-
End-stage renal disease	324 (29.7)	-	-	-
Dual eligible	696 (63.7)	694 (63.6)	697 (63.8)	692 (63.4)
Receiving low-income cost sharing subsidy	750 (68.7)	790 (72.3)	791 (72.4)	803 (73.5)
Qualifying Chronic Conditions				
Diagnosis of Hypertension	852 (78.0)	950 (87.0)	1,028 (94.1)	1,086 (99.5)
Diagnosis of Diabetes	571 (52.3)	638 (58.4)	696 (63.7)	784 (71.8)
Diagnosis of Congestive heart failure	338 (31.0)	467 (42.8)	603 (55.2)	799 (73.2)
Diagnosis of Coronary artery disease	368 (33.7)	481 (44.1)	590 (54.0)	785 (71.9)
Diagnosis of Asthma	134 (12.3)	199 (18.2)	262 (24.0)	377 (34.5)
Diagnosis of Chronic obstructive pulmonary disease	246 (22.7)	343 (31.4)	448 (41.0)	583 (53.4)
Number of qualifying chronic conditions				
≤1 chronic conditions	335 (30.82)	226 (20.7)	131 (12.0)	31 (2.8)
2 chronic conditions	262 (24.0)	236 (21.6)	204 (18.7)	115 (10.5)
3 chronic conditions	247 (22.6)	244 (22.3)	250 (23.0)	211 (19.3)
4 or more chronic conditions	246 (22.5)	386 (35.3)	507 (46.4)	735 (67.2)

Table 3-1. Continued

Characteristics	Period 1 N (%)	Period 2 N (%)	Period 3 N (%)	Period 4 N (%)
Comorbidity				
Charlson comorbidity index, mean (SD)	3.2 (2.7)	4.2 (3.1)	5.2 (3.3)	6.9 (3.2)
Mental illness*	389 (35.6)	460 (42.1)	533 (48.8)	622 (57.0)
Tobacco use disorder	106 (9.7)	163 (14.9)	266 (24.4)	351 (32.1)
Therapy complexity				
No. of unique index drug classes filled, mean (SD)	3.9 (2.1)	4.0 (2.1)	3.9 (2.1)	4.3 (2.0)
No. of opioids filled, mean (SD)	2.6 (4.0)	2.7 (4.0)	2.7 (3.9)	3.2 (4.1)
0 opioid filled	499 (45.7)	479 (43.9)	480 (44.0)	337 (31.0)
1 opioid filled	147 (13.5)	165 (15.1)	157 (14.4)	187 (17.1)
2-3 opioid filled	159 (14.6)	143 (13.1)	151 (13.8)	211 (19.3)
≥4 opioid filled	287 (26.3)	305 (27.9)	304 (27.8)	357 (32.7)
Health services utilization				
≥1 physician office visits	900 (82.4)	903 (82.7)	909 (83.2)	915 (83.8)
No. of inpatient stays, mean (SD)	0.8 (1.4)	0.8 (1.4)	0.7 (1.4)	3.1 (0.9)
No. of emergency department visits, mean (SD)	0.8 (2.1)	0.8 (2.2)	0.9 (2.2)	1.7 (2.6)
Super-utilizers	168 (15.4)	187 (17.1)	155 (14.2)	1,192 (100.0)

Physician office visits were identified using Part B claims and were defined as “location, other than a hospital, skilled nursing facility (SNF), military treatment facility, community health center, State or local public health clinic, or intermediate care facility (ICF), where the health professional routinely provides health examinations, diagnosis, and treatment of illness or injury on an ambulatory basis.” *Mental illness was defined as >1 antidepressants or anxiolytics fill or diagnosis of depression/anxiety. Super-utilizers defined as ≥3 inpatient admissions OR ≥2 inpatient admissions and ≥2 emergency department visits in 6 months.

Figure 3-1. Proportion of Days Covered (PDC) During Each 6-Month Period

Table 3-2. Multivariable Results for Inpatient Stays and Emergency Department Visits by Therapy Class Using Fixed Effects Model

Therapy Class	Inpatient Stays		ED Visits	
	IRR (95% CI)	P Value	IRR (95% CI)	P Value
Diabetes Medications				
Nonadherence (overall sample)	1.22 (1.02-1.45)	0.026	1.17 (0.95-1.45)	0.132
Nonadherence (<65 years)	0.97 (0.72-1.30)	0.823	1.23 (0.86-1.75)	0.256
Nonadherence (≥65 years)	1.38 (1.11-1.72)	0.004	1.16 (0.89-1.52)	0.266
Cardiovascular Disease Medications				
Nonadherence (overall sample)	1.42 (1.25-1.61)	<0.001	1.14 (0.99-1.31)	0.070
Nonadherence (<65 years)	1.35 (1.13-1.62)	0.001	1.23 (1.02-1.49)	0.033
Nonadherence (≥65 years)	1.42 (1.19-1.69)	<0.001	1.05 (0.86-1.29)	0.622
COPD or Asthma Medications				
Nonadherence (overall sample)	1.35 (1.00-1.82)	0.048	1.24 (0.87-1.75)	0.237
Nonadherence (<65 years)	1.07 (0.66-1.73)	0.781	1.21 (0.77-1.91)	0.403
Nonadherence (≥65 years)	1.48 (1.01-2.18)	0.047	1.11 (0.65-1.89)	0.712

Significant at $P < 0.05$. IRR: Incidence Rate Ratio. ED Visits: Emergency department visits. COPD: Chronic Obstructive Pulmonary Disease.

We used fixed effects negative binomial models at patient level. The adjusted models included lagged effects of medication nonadherence, Charlson comorbidity index, mental illness, opioid medication filled, number of medications filled, number of different prescribers, and ≥ 1 physician office visits.

Mental illness was defined as ≥ 1 antidepressants or anxiolytics fill or diagnosis of depression/anxiety.

Diabetes Medications: Sample for inpatient stays - nonadherence (overall): 855 patient-periods, nonadherence (<65 years): 312 patient-periods, nonadherence (≥65 years): 543 patient-periods.

Sample for ED visits – nonadherence (overall): 624 patient-periods, nonadherence (<65 years): 251 patient-periods, nonadherence (≥65 years): 373 patient-periods.

Cardiovascular Disease Medications: Sample for inpatient stays – nonadherence (overall): 2,893 patient-periods, nonadherence (<65 years): 1,177 patient-periods, nonadherence (≥65 years): 1,716 patient-periods.

Sample for ED visits – nonadherence (overall): 2,133 patient-periods, nonadherence (<65 years): 945 patient-periods, nonadherence (≥65 years): 1,188 patient-periods.

COPD or Asthma Medications: Sample for inpatient stays – nonadherence (overall): 513 patient-periods, nonadherence (<65 years): 209 patient-periods, nonadherence (≥65 years): 304 patient-periods.

Sample for ED visits – nonadherence (overall): 359 patient-periods, nonadherence (<65 years): 158 patient-periods, nonadherence (≥65 years): 201 patient-periods.

inpatient stays was higher for nonadherent patients ($P<0.05$) compared with adherent patients. In the overall sample, the number of inpatient stays were 22% higher in patients not adherent to their diabetes medications (Incidence Rate Ratio (IRR), 1.22; Confidence Interval (CI), 1.02-1.45; $P=0.026$), 42% higher in patients who were nonadherent to their cardiovascular disease medications (IRR, 1.42; CI, 1.25-1.61; $P<0.001$), and 35% higher in patients not adherent to their COPD/asthma medications (IRR, 1.35; CI, 1.00-1.82; $P=0.048$). Additionally, the adjusted analyses for ED visits showed that in the overall sample, nonadherence to essential chronic medications was not significantly associated with ED visits ($P<0.05$). When examining the results stratified by age, we found that the association between nonadherence to CVD medications and inpatient admissions was significant for both age groups. Whereas for diabetes and COPD/asthma therapy classes, the association with inpatient admissions was significant only among elderly Medicare beneficiaries. Additionally, the association between nonadherence to CVD medications and ED visits was significant for non-elderly Medicare patients.

Table 3-3 shows the multivariate associations among Medicare beneficiaries ≥ 65 years of age. Patients who were nonadherent to their essential chronic medications had 57% higher inpatient stays (IRR, 1.57; CI, 1.33-1.87; $P<0.001$) compared with adherent patients. The association between medication nonadherence and ED visits was not statistically significant. Among other factors, mental illness was associated with 54% higher inpatient stays (IRR, 1.54; CI, 1.20-1.98; $P=0.001$) and 46% higher ED visits (IRR, 1.46; CI, 1.11-1.93; $P=0.007$). Opioid medication fills in the previous period were protective against inpatient and ED utilization among elderly Medicare beneficiaries, however, these associations were not statistically significant.

Table 3-4 displays the same results among Medicare beneficiaries <65 years of age. Patients who were nonadherent to their essential chronic medications had 41% higher inpatient stays (IRR, 1.41; CI, 1.17-1.69; $P<0.001$) and 25% higher ED visits (IRR, 1.25; CI, 1.04-1.51; $P=0.020$) compared with adherent patients. Mental illness was not significantly associated inpatient and ED use, while tobacco use disorder was significantly associated with higher inpatient utilization (IRR, 1.61; CI, 1.17-2.22; $P=0.003$). Additionally, among non-elderly Medicare beneficiaries, opioid medication use in the previous period was not significantly associated with inpatient and ED use.

When examining the association between race and dual-LICS status with inpatient and ED visits (**Appendix B, Tables B-1 and B-2**), random effects models showed that among elderly Medicare beneficiaries, non-Hispanic blacks had significantly higher ED use, and dual eligible beneficiaries with LICS had significantly higher inpatient and ED utilization. Similarly, among non-elderly Medicare beneficiaries, dual beneficiaries with LICS had significantly higher ED utilization. In sensitivity analyses using the alternative PDC criteria of ≥ 1 medication fill, our results were similar in terms of significance and directionality to our main analyses (**Appendix B, Tables B-3 and B-4**).

Table 3-3. Multivariable Results for Inpatient Stays and Emergency Department Visits Among Medicare Beneficiaries ≥ 65 years

Characteristics	Inpatient Stays		ED Visits	
	IRR (95% CI)	P Value	IRR (95% CI)	P Value
Overall medication nonadherence	1.57 (1.33-1.87)	<0.001	1.11 (0.91-1.34)	0.308
Comorbidity				
Charlson comorbidity index	1.23 (1.17-1.28)	<0.001	1.16 (1.09-1.23)	<0.001
Mental illness	1.54 (1.20-1.98)	0.001	1.46 (1.11-1.93)	0.007
Tobacco use disorder	1.29 (0.90-1.84)	0.166	0.79 (0.50-1.25)	0.309
Opioid medication filled				
0 opioid fill (ref)	--	--	--	--
1 opioid fill	0.96 (0.77-1.20)	0.726	0.92 (0.72-1.17)	0.487
2-3 opioid fill	0.86 (0.66-1.11)	0.248	0.90 (0.68-1.18)	0.448
>3 opioid fill	0.87 (0.64-1.18)	0.380	0.77 (0.54-1.11)	0.161
Number of unique medications filled	1.02 (0.99-1.05)	0.136	0.97 (0.94-1.07)	0.106
Number of unique prescribers	0.97 (0.92-1.02)	0.176	0.98 (0.93-1.04)	0.512
≥ 1 physician office visit	0.91 (0.67-1.23)	0.532	1.64 (1.00-2.69)	0.051

Significant at $P < 0.05$. IRR: Incidence Rate Ratio. ED visits: Emergency department visits.

We used fixed effects negative binomial models at patient level. The models included lagged effects of all the above factors.

Overall medication nonadherence measured at patient-level was based on eighteen index drug classes.

Mental illness is defined as ≥ 1 antidepressants or anxiolytics fill or diagnosis of depression/anxiety.

The multivariable model with inpatient stays as outcome included 1,742 patient-periods.

The multivariable model with ED visits as outcome included 1,203 patient-periods.

Table 3-4. Multivariable Results for Inpatient Stays and Emergency Department Visits Among Medicare Beneficiaries <65 years

Characteristics	Inpatient Stays		ED Visits	
	IRR (95% CI)	P Value	IRR (95% CI)	P Value
Overall medication nonadherence	1.41 (1.17-1.69)	<0.001	1.25 (1.04-1.51)	0.020
Comorbidity				
Charlson comorbidity index	1.18 (1.13-1.23)	<0.001	1.11 (1.05-1.16)	<0.001
Mental illness	1.14 (0.86-1.50)	0.358	1.18 (0.88-1.58)	0.277
Tobacco use disorder	1.61 (1.17-2.22)	0.003	1.30 (0.92-1.82)	0.135
Opioid medication filled				
0 opioid fill (ref)	--	--	--	--
1 opioid fill	0.81 (0.63-1.06)	0.124	0.93 (0.70-1.24)	0.614
2-3 opioid fill	0.83 (0.63-1.09)	0.182	0.98 (0.72-1.31)	0.873
>3 opioid fill	0.96 (0.69-1.33)	0.801	1.25 (0.87-1.79)	0.230
Number of unique medications filled	1.01 (0.98-1.04)	0.518	1.02 (0.99-1.04)	0.263
Number of unique prescribers	0.98 (0.95-1.02)	0.365	0.98 (0.95-1.02)	0.315
≥1 physician office visit	0.90 (0.67-1.20)	0.454	0.97 (0.67-1.40)	0.857

Significant at $P < 0.05$. IRR: Incidence Rate Ratio. ED visits: Emergency department visits

We used fixed effects negative binomial models at patient level. The models included lagged effects of all the above factors.

Overall medication nonadherence measured at patient-level was based on eighteen index drug classes.

Mental illness is defined as ≥1 antidepressants or anxiolytics fill or diagnosis of depression/anxiety.

The multivariable model with inpatient stays as outcome included 1,227 patient-periods.

The multivariable model with emergency department visits as outcome included 986 patient-periods.

DISCUSSION

This study is the first, to our knowledge, to examine the relationship between nonadherence, and other important factors with health care utilization in super-utilizers with chronic conditions. In our sample of super-utilizing Medicare population with chronic conditions, we found higher incidences of inpatient hospitalizations and ED visits among beneficiaries who were not adherent to their essential chronic medications. Specifically, we found that among elderly Medicare beneficiaries, nonadherence was significantly associated with a 57% increase in inpatient hospitalizations, and among younger beneficiaries, nonadherence was associated with 41% increase in inpatient stays and 25% increase in ED visits. Similar associations were found across all therapy classes examined (diabetes, cardiovascular, and COPD/asthma) in both age groups. However, nonadherence to diabetes and COPD/asthma drugs was not significantly associated with ED visits. Furthermore, we found that while the effects of nonadherence on inpatient stays were seen in both age groups, the effects of nonadherence on ED visits were more pronounced for younger Medicare patients. These findings suggest that nonelderly Medicare beneficiaries may be at increased risk for nonadherence which may further be associated with higher ED use. Targeted medication management interventions for younger Medicare beneficiaries may potentially help in lowering their ED visits.

Our results provide important insights into associations between medication nonadherence and hospitalizations and are consistent with prior research on Medicare population which showed nonadherence to be associated with higher incidence of hospitalizations. Simoni-Wastila and colleagues found that Medicare patients with COPD who were adherent to their chronic medications experienced fewer hospitalizations.⁶ And in a sample of Medicare patients with myocardial infarction, Zhang and colleagues found that higher adherence with β -blockers, statins, and ACEIs/ARBs medications was associated with lower readmission rates.³⁹ However, unlike previous studies based on Medicare population, this study focused specifically on super-utilizing Medicare patients with chronic conditions. Moreover, our study population was disproportionately represented by dual beneficiaries <65 years of age, who had on average higher comorbidities and were more likely to be nonadherent to their essential chronic medications than elderly patients. Given these differences, examining associations separately in the two age groups may help researchers to better target these high utilizing patient populations with medication management interventions. Our work extends these findings to these vulnerable patients and suggests that improving medication adherence—a patient behavioral factor very amenable to change—may be critical in reducing inpatient and ED utilization among Medicare super-utilizers with chronic conditions and complex pharmacotherapy regimens.

This analysis reinforced our previous findings that the super-utilizer status is dynamic and changes with time.^{56,57} We found that of 1,092 patients who met the super-utilizers criteria in the fourth period (qualifying period for the SafeMed Program), only about 14% of them were super-utilizers in all previous periods (**Table 3-1**). The higher rates of inpatient and ED utilization and lower rates of medication adherence in the last 6-month period compared to the first three periods, indicate a sudden change in adherence

and utilization in the final period. Providing early medication management interventions to potential high-risk super-utilizers may improve adherence thereby lowering their inpatient and ED utilization.

Similar to previous findings in super-utilizing population, we found high rates of mental illness and substance use disorder in super-utilizers^{56,58} — about 57% were diagnosed with depression or anxiety or had filled antidepressants or anxiolytics and 32% were diagnosed with substance use disorder, in the fourth period. In our adjusted models, we found mental illness as a risk factor for higher utilization among elderly, and substance use disorder as a risk factor for higher inpatient utilization among younger patients. These findings may help to identify and classify high-risk super-utilizers who need targeted medication management interventions along with mental health and social support.

This study makes a significant contribution to the body of empirical literature on super-utilizers by demonstrating high opioid use in this population. Specifically, we found that about 69% had filled ≥ 1 opioid medications in the fourth period. A substantial amount of opioid utilization is likely driven by the high prevalence of chronic pain in the super-utilizers as documented in a previous study.⁵⁷ In our adjusted models, although insignificant, we found that super-utilizers with recent opioids use make less use of ED and inpatient services, especially among elderly Medicare patients. A recent study found that opioid use is common after hospitalization among Medicare beneficiaries.⁹² Future studies should investigate the reasons behind this finding as this can shed some light on the patterns of high opioid use in this population.

Among other factors, non-Hispanic blacks and dual beneficiaries receiving LICs were at risk for higher utilization. These findings are consistent with previous studies conducted on Medicare patients.^{95,96} For instance, Joynt and colleagues examined racial disparities in readmissions among elderly Medicare beneficiaries and found that black patients were more likely to be readmitted after hospitalization for myocardial infarction, congestive heart failure, and pneumonia.⁹⁶ Furthermore, it has been well established that dual beneficiaries have higher utilization and account for disproportionate share of Medicare spending. Our findings highlight the vulnerability of these groups and the need for greater attention.

This study has important implications for policy makers and institutions involved in improving the quality of care and reducing health care costs for super-utilizers. Our study findings suggest that improving medication adherence may be critical in reducing inpatient and ED use. Given these findings, hospitals, managed care organizations, and payers should engage in programs aimed at improving medication adherence in super-utilizing population. Successful medication management interventions have used multiple strategies, including pharmacist-provided medication therapy management, specialized medication packaging, motivational strategies, and telemonitoring, among others.^{1,40,43,44} However, targeting interventions to patients with multiple chronic conditions, complex medication regimens, and high health care utilization, needs a comprehensive multimodal approach that can address patient and system-level barriers to achieving optimal

medication adherence. In our prior work, we found that during care transitions processes from the hospital to the community setting, super-utilizers were at high risk for drug therapy problems and medication discrepancies, which may result in poor adherence.¹³ This cyclical process of nonadherence leading to increased frequency of hospitalizations, causing drug therapy problems and medication discrepancies in super-utilizers, can have detrimental effects on their health outcomes. Our findings showing high prevalence of mental illness, substance use disorder, and opioid medication use have highlighted the importance of monitoring for signs of opioid abuse, and having a strong social support and mental health facilities for vulnerable super-utilizing populations who have complex medical and social needs. Patients with complex behavioral health issues could benefit from greater coordination of health care providers and health care systems and having access to high-quality mental health services.

Our study is also subject to several limitations. First, although pharmacy fill data is widely used to assess medication adherence, we cannot be certain that patients who fill medications are also using them appropriately. Second, many patients may have been long-term users of essential chronic medications, and we may have missed a few if they did not have any medication fill during the 2-year evaluation period. Third, the PDC measure for calculating adherence is an indirect method and may not accurately capture medication use and is likely to be biased for inhalation products that are prescribed for Asthma and COPD. Fourth, since this study is based on super-utilizers living in Memphis, TN, the study findings may only be generalizable to similar populations and similar settings across the country. Finally, although our fixed-effects models addressed potential endogeneity, we cannot conclude with certainty that these associations were causal.

CONCLUSION

In summary, medication nonadherence was associated with increased incidence of hospitalizations and ED use, both overall and across diabetes, cardiovascular, and COPD/asthma therapy classes. Additionally, the effects of nonadherence on ED visits were more pronounced for younger Medicare beneficiaries. Among other important factors, mental illness, tobacco use disorder, non-Hispanic black race, and dual eligible beneficiaries with low-income subsidy predicted higher inpatient and ED use.

CHAPTER 4. EFFECT OF A CARE TRANSITIONS PROGRAM ON MEDICATION USE AND ADHERENCE AMONG SUPER-UTILIZERS WITH CHRONIC CONDITIONS

BACKGROUND

Super-utilizers are patients who have high health care costs from recurring, preventable inpatient or emergency department (ED) visits. A decade ago Dr. Jeffrey Brenner, a physician from Camden, NJ, had identified that a small group of patients accounted for a bulk of health care costs.⁵⁵ Since then the interest in super-utilizers has increased among policymakers, health systems, and researchers. Super-utilizers represent only 3 to 10% of Medicare and Medicaid population, but are responsible for 30 to 50% of the health care spending.⁵⁶ They often face complex medical and social issues including multiple chronic conditions (MCC), mental health illnesses, substance abuse, issues with transportation, low health literacy, and low social support, among others.⁵⁶⁻⁵⁸ During care transitions processes, super-utilizers often experience difficulty in medication management; medication discrepancies and drug therapy problems being key factors in making these care transitions complex.^{13,18,97} Managing medication-related adverse events and improving medication adherence among super-utilizers may be critical for hospitals and payers since improving adherence to essential chronic medications is crucial for reducing preventable hospital readmissions.^{4,5,39} Given the widespread recognition that drug therapy problems and medication nonadherence play a major role in readmissions, care transitions models with a focus on medication management are being increasingly explored to reduce drug therapy problems and improve medication adherence.^{17,19,54}

Pharmacists can play a central role in care transitions models focused on medication management. To date, studies evaluating the impact of pharmacist-led interventions on medication errors, medication adherence, and health care utilization after hospital discharge have shown mixed results.^{17,19,49,54,98,99} For example, Kripalani and colleagues found that among patients hospitalized with acute coronary syndromes or acute decompensated heart failure, the pharmacist-led interventions did not significantly reduce medication errors after hospital discharge.¹⁹ Schnipper and colleagues found that pharmacist-provided interventions for patients discharged home from the general medicine service was associated with a lower rate of preventable adverse drug events (ADE). However, there was no significant effect of these interventions on overall ADE or total health care utilization.¹⁷ Another study by Ho and colleagues found that among patients with acute coronary syndrome, multifaceted pharmacist-led interventions increased adherence to cardioprotective agents one year following hospital discharge. Nonetheless, the intervention did not have any positive effect on blood pressure and low-density lipoprotein cholesterol levels.⁴⁹ Except for the study by Ho and colleagues, the interventions were mainly provided in the hospital setting. Moreover, despite increased interest in super-utilizers and increased focus on reducing their disproportionate health care utilization and costs, there is a lack of evidence on whether pharmacist-led intensive

medication management interventions as part of a care transitions program can improve medication use and adherence in super-utilizers with chronic conditions.

This study was an evaluation of the SafeMed Program, an innovative care transitions program targeting super-utilizers with a major focus on medication management.⁶⁰ Pharmacist-led interventions as part of the SafeMed Program included the following: comprehensive medication review (CMR), targeted medication therapy management (MTM), enhanced discharge planning, home visits, phone follow-ups, medication reconciliation during discharge and post-discharge, and care coordination with patient's physicians.¹³ The objective of this study was to examine the impact of the SafeMed Program on medication utilization and adherence among a vulnerable, publicly insured, super-utilizing cohort of patients admitted to a local hospital system in Memphis, TN. The study findings may have a positive impact by highlighting the importance of innovative care transitions medication management interventions that can improve adherence among vulnerable super-utilizers, who can benefit the most from such interventions.

METHODS

Design and Setting

This study used a quasi-experimental study design to examine the effectiveness of the SafeMed Program on medication adherence among SafeMed participants compared with patients in a control group using difference in differences (DID) approach. The SafeMed program targeted publicly insured super-utilizers with chronic conditions from medically underserved areas admitted to a non-profit hospital system in Memphis, TN from February 1, 2013 to May 1, 2015.⁶⁰ We analyzed Medicare and Tennessee Medicaid claims data for this study. We had Tennessee Medicaid claims data for beneficiaries meeting the SafeMed Program eligibility criteria for the entire program duration—from February 1, 2013 to May 1, 2015. However, since the Medicare Part D data files were incomplete at the time of this study, we used Medicare claims data only for the period from February 1, 2013 to June 30, 2014. The program enrollment occurred during an inpatient admission or an observation stay (index admission), after which the patients who agreed to participate in the SafeMed Program were provided the various medication management interventions for a minimum of 45 days following hospital discharge. For this study evaluation, program participants and controls were followed for 6-month post index discharge and 6 months prior to their index admission.

Population

The SafeMed Program eligibility was based on the following inclusion criteria: 1) adults aged 18 years or older with continuous Medicare or Medicaid enrollment, 2) ≥ 2 hospital admissions in the past six months OR 1 inpatient admission and ≥ 2 emergency

department (ED) visits in the six months prior to the index admission, and 3) diagnosis of ≥ 1 of the following chronic conditions: hypertension, congestive heart failure (CHF), coronary artery disease (CAD), diabetes mellitus, asthma, or chronic obstructive pulmonary disease (COPD) in the baseline period. The International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] codes for the inclusion criteria are listed in **Appendix A, Table A-1**.

Patients were excluded from the SafeMed Program if the primary reason for index admission was related to cancer, pregnancy, or a surgical procedure for an acute problem following the approach of Jencks and colleagues recognizing that utilization for these conditions is less likely to be affected by outpatient chronic disease care or medication management.⁷⁷ Patients were also excluded if they had diagnoses of active psychosis, drug abuse, substance abuse or suicidal ideation during the index admission, or if they were discharged to a skilled nursing facility or hospice care because of evidence suggesting that high utilization in these patient populations may be less amenable to outpatient intervention.⁵⁷ The ICD-9-CM codes and diagnosis-related group (DRG) codes for the exclusion criteria are listed in a previous paper by Harris and colleagues.⁵⁷

The control group included patients deemed eligible for the SafeMed Program based on the eligibility criteria listed above, but who either: 1) declined to participate in the program when they were offered the chance to participate, or 2) were discharged from the hospital before the SafeMed staff had an opportunity to screen them and offer participation, or 3) met basic SafeMed eligibility requirements based on a daily eligibility report generated by the hospital system. We used Medicare and Medicaid claims data to confirm further their eligibility based on the inclusion and exclusion criteria.

Of the 1,778 eligible patients meeting SafeMed inclusion and exclusion criteria above, the final sample included the 1,122 (63.1%) who were continuously eligible for Medicare Part D or had drug coverage from Medicaid and filled at least one of seventeen drug classes during both pre-and post-periods. These drug classes included angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARB), statins, antiplatelet agents, beta-blockers, calcium channel blockers, diuretics, alpha-1 blockers, central alpha-2 agonists, direct vasodilators, sulfonylureas, biguanides, thiazolidinediones, meglitinides, dipeptidyl peptidase-4 inhibitors, anticholinergic inhalers, inhaled corticosteroids alone or in combination with long-acting beta-agonists (LABA), and other COPD/asthma medications (theophylline and leukotriene modifiers).

Program Description

The program used a diverse team of health care providers, including pharmacists and pharmacy technicians as key team members. The SafeMed medication management team, including two program pharmacists and two certified pharmacy technicians, worked together to provide medication management services to SafeMed enrollees. As previously described, patient enrollment occurred during an inpatient admission or an observation stay, during which the SafeMed enrollees received an inpatient CMR from

the pharmacists. SafeMed pharmacists reviewed the drug profile with patients or their caregivers to identify any drug therapy problems. They made appropriate recommendations and worked closely with the physicians and alerted them of the identified drug therapy problems. Additionally, as part of the discharge planning, pharmacists provided and discussed a personalized patient-friendly medication list with patients, explained the purpose of each medication, dosing instructions, and potential side effects. The role of the pharmacy technician was to identify any potential drug therapy problems during home visits and phone follow-ups, who then coordinated with the pharmacist to resolve any medication-related issues.

Medication reconciliation, which involved comparing patient's discharge medication orders to all the medications that the patient had been taking, was performed by pharmacy technicians during the first and second home visits that happened within 3 days and 3 weeks of discharge, respectively. This ensured that any omissions, duplications, potential drug interactions, or any potential dosing errors and adverse events were identified and reported to the pharmacist. During home visits, pharmacy technicians also educated patients on drug disposal, filling pill boxes, and self-management guidelines. A minimum of two phone follow-ups were performed during the second and the fourth week of discharge. During each phone follow-up, pharmacy technicians identified barriers to using any prescribed medications and potential drug therapy problems. Pharmacists then followed-up with patients who were identified as having drug therapy problems and provided targeted MTM by phone and outpatient CMR to further resolve any medication-related issues and to improve the overall effectiveness of their medication regimen. Follow-up outpatient CMR was provided to patients during the fifth week of the SafeMed Program, after the completion of home visits and phone follow-ups by pharmacy technicians. The overall interventions including pharmacist-led medication management interventions provided at different time points have been shown in **Appendix C, Table C-1.**⁷⁶

Outcome Variables

Medication adherence

Medication adherence was measured using the interval-based proportion of days covered (PDC), defined as the percentage of days during the observation period during which the participants or controls had their recommended prescribed medications on hand. PDC was expressed as percentage capped at 100% and was calculated for the 6-month baseline period and the 6-month evaluation period. We measured PDC for the seventeen drug classes mentioned above. Drugs that belonged to the same therapeutic class (example, amlodipine, and nifedipine in the calcium channel blockers) were considered interchangeable. Additionally, based on the evidence-based guideline, ACE inhibitors and ARB were considered a single class for this study.⁷⁸ Antiplatelet agents did not include aspirins because aspirins are usually purchased without a prescription (over-the-counter) and are not included in Part D claims data. Moreover, we did not include insulin since the days' supply information on this drug class is not accurate.⁷⁹

Using this approach, the numerator was defined as the number of days of medication supplied between the first and last prescription in a period and the denominator was defined as the number of days during the interval from the index date, which was the first day of the medication fill in a given 6-month period, to the last day of that period. Any duration of inpatient hospitalization was subtracted from the PDC denominator. The average PDC measure was calculated at the patient-level by adding the PDC for each drug class and then dividing by the number of drug class used by the patient. We then classified patients as adherent if they had PDC of at least 80% over the follow-up and pre-intervention period. The main outcome variable was the overall binary adherence classification. Adherence was also measured based on therapy-specific medication adherence classifications, which included diabetes, cardiovascular, and COPD/asthma medications. Additionally, PDC was measured in the patient sample stratified by age, insurance type and number of comorbidities.

Medication use

We also examined whether the intervention had any positive effect on medication use based on a patient's diagnosis. Following were the medication use measures: 1) patients diagnosed with diabetes using any oral diabetes medications, 2) patients diagnosed with COPD or asthma using any long-term controller medications, and 3) patients diagnosed with CHF using any ACE/ARB medications.

Independent Variables

The main independent variables included a binary indicator of whether patients received the SafeMed intervention (1=Participant, 0=Control) and a binary indicator of time (1=post-intervention period, 0=pre-intervention period). Additionally, the multivariate models controlled for the following covariates: age, gender, race, and insurance, measured at the index admission. Covariates assessed for the 6-month baseline period included diagnosis of depression or anxiety, and disease burden measured using the University of Manitoba SAS Macro for Charlson comorbidity index.⁸⁰

Statistical Analysis

Propensity score matching was conducted to account for the observed differences between the intervention and the control group. The propensity score, which was estimated using a logistic regression model, was defined as the patient's probability of receiving the SafeMed intervention versus no intervention and was conditional on the measured baseline covariates that included age, gender, race, insurance, qualifying chronic conditions, Charlson comorbidity index, and anxiety/depression. Propensity score matching paired each participant of the intervention group to 2 controls within calipers of 0.01 units on the propensity score scale.¹⁰⁰ All analyses were conducted on propensity score-matched samples. Baseline differences between study participants and controls were estimated using chi-square tests and t-tests analyses. For multivariate analyses, we

used logistic regression with DID approach to estimate changes in average probability of adherence or medication use from the pre-intervention period to post-intervention period that differed from concurrent changes in the control group, after controlling for confounding variables. While DID models with only one pre-intervention and one post-intervention observation cannot control for differences in time trends in the SafeMed enrollees and controls, it does allow us to control for permanent unobserved differences between the groups. All data analyses were conducted using SAS 9.4 and STATA 13. Variables in the multivariate models with $P < 0.05$ were considered significant.

RESULTS

Table 4-1 provides the baseline characteristics for the SafeMed enrollees and controls before and after applying propensity score matching. Before propensity score matching, enrollees ($N=152$) and controls ($N=970$) were different on several measures. Compared with controls, the enrollees were more likely to be younger (52.2 vs. 59.7, $P < 0.001$), black (77% vs. 68.7%, $P < 0.001$), and Medicaid only beneficiaries (52% vs. 32.7%, $P < 0.001$). Additionally, compared with controls, enrollees were more likely to have diabetes (71.1% vs. 61.2%, $P = 0.020$), asthma (42.1% vs. 29.5%, $P = 0.002$), COPD (58.6% vs. 43.2%, $P = 0.004$), and lower mean Charlson comorbidity index (4.4 vs. 4.8, $P = 0.042$). After applying propensity score matching, although the sample size reduced from 1,122 to 456, the intervention ($N=152$) and the control group ($N=304$) were similar across all sociodemographic and clinical factors.

The patterns of mean PDC among the enrollees and controls during pre- and post-intervention periods is shown in **Figure 4-1**. The mean PDC was lower in enrollees than controls in both pre- and post-intervention periods. Additionally, the mean PDC for enrollees and controls decreased progressively from the pre- to the post-intervention period. Among enrollees, the mean PDC was 63.8% in the pre-intervention period and declined to 61.8% in the post-intervention period. Similarly, among controls, the mean PDC was 70.5% in the pre-intervention period and declined to 65.6% in the post-intervention period. The proportion of adherent patients ($PDC \geq 80\%$) among enrollees declined from 34.2% in the pre-intervention period to 25.0% in the post-intervention period, while among controls, this proportion declined from 41.1% to 32.6% (results not shown).

Table 4-2 shows the DID results for overall medication adherence and therapy-specific adherence. In the 6-month period following SafeMed index discharge, overall adherence decreased in both enrollees and controls. Although the magnitude of decline in adherence was greater among controls than enrollees, this difference was not statistically significant. DID estimate for overall adherence was +5 percentage points (DID: 0.05; Confidence Interval (CI), -0.28, 0.39). Similar patterns were observed for diabetes drug class where the DID estimate was +38 percentage points, but the results were not statistically significant (DID: 0.38; CI, -0.94, 1.69). For COPD/asthma medication class, following the SafeMed intervention, adherence increased in enrollees, whereas decreased

Table 4-1. Baseline Characteristics of the Study Population

Characteristic	Before Matching			After Matching		
	Enrollees N=152	Controls N=970	P Value	Enrollees N=152	Controls N=304	P Value
Age, mean (SD)	52.2 (13.7)	59.7 (15.2)	<0.001	55.2 (13.7)	56.0 (15.2)	0.580
Age $\geq$ 65	34 (22.5)	359 (37.1)	<0.001	39 (25.7)	87 (28.6)	0.505
Female sex	97 (63.8)	585 (60.3)	0.410	97 (63.8)	186 (61.2)	0.585
Race						
Non-Hispanic White	16 (10.5)	241 (24.9)	<0.001	16 (10.5)	27 (8.9)	0.793
Black	117 (77.0)	666 (68.7)		117 (77.0)	242 (79.6)	
Hispanic/Others	19 (12.5)	63 (6.5)		19 (12.5)	35 (11.5)	
Insurance						
Medicare Only	18 (11.8)	217 (22.4)	<0.001	18 (11.8)	41 (13.5)	0.198
Medicaid Only	79 (52.0)	317 (32.7)		79 (52.0)	131 (43.1)	
Dual Eligible	55 (36.2)	436 (45.0)		55 (36.2)	132 (43.4)	
Qualifying chronic conditions						
Diabetes	108 (71.1)	594 (61.2)	0.020	108 (71.1)	209 (68.8)	0.615
Hypertension	147 (96.7)	945 (97.4)	0.613	147 (96.7)	293 (96.4)	0.857
Congestive heart failure	104 (68.4)	606 (62.5)	0.157	104 (68.4)	213 (70.1)	0.719
Coronary artery disease	83 (54.6)	509 (52.5)	0.625	83 (54.6)	156 (51.3)	0.507
Asthma	64 (42.1)	286 (29.5)	0.002	64 (42.1)	111 (36.5)	0.247
COPD	89 (58.6)	419 (43.2)	0.004	83 (54.6)	156 (51.3)	0.507
Anxiety or Depression	39 (25.7)	312 (32.2)	0.108	39 (25.7)	85 (28.0)	0.602
Charlson comorbidity index, mean (SD)	4.4 (2.2)	4.8 (2.7)	0.042	4.4 (2.2)	4.4 (2.3)	0.965
Total amount paid by Medicare or TennCare, mean (SD)	340.9 (509.7)	288.7 (522.3)	0.251	340.9 (509.7)	325.6 (617.8)	0.792

Figure 4-1. Average Proportion of Days Covered in the Pre- and Post-Intervention Period

Table 4-2. Multivariate Difference-in-Differences Analysis Comparing Medication Adherence Between SafeMed Intervention Group and Control Group (by Therapy Class)

Drug Class	Pre-Intervention Period				Post-Intervention Period				Difference in Differences	95% CI
	SafeMed Group (T)	Control Group (C)	Difference (T-C)	95% CI	SafeMed Group (T)	Control Group (C)	Difference (T-C)	95% CI		
All Drug Classes	0.58	0.80	-0.22	-0.50,0.05	0.36	0.53	-0.17	-0.36,0.02	0.05	-0.28,0.39
Diabetes	0.98	1.63	-0.65	-0.71,0.42	0.75	1.02	-0.27	-1.04,0.51	0.38	-0.94,1.69
CVD	0.73	0.81	-0.08	-0.40,0.23	0.50	0.63	-0.13	-0.36,0.11	-0.04	-0.40,0.32
COPD/Asthma	0.36	0.94	-0.58	-1.10,-0.05	0.45	0.74	-0.29	-0.75,0.16	0.28	-0.40,0.96

Significant at $P < .05$

Adherence estimates are probability-scale predictions, adjusted for age, race, gender, insurance, Charlson comorbidity index, and anxiety or depression.

CVD: Cardiovascular disease

All drug classes: N=912

Diabetes drug class (oral diabetes medications): N=192

CVD drug class: N=870

COPD/asthma drug class (long-term controller medications): N=270

in controls. However, this positive effect of the intervention was not statistically significant (DID: 0.28; CI, -0.40, 0.96).

Table 4-3 shows the DID results among various sub-group populations. We found similar adherence trends across all sub-group populations. Following the SafeMed intervention, there was a decline in overall adherence in both enrollees and controls. For patients ≥ 65 years of age, Medicare only, and those with < 4 comorbidities, there was a greater decline in overall adherence among controls, which is indicated by positive DID estimates. However, for patients < 65 years of age, Medicaid only, dual eligibles, and those with ≥ 4 comorbidities, there was a greater decline in overall adherence among enrollees, which is indicated by negative DID estimates. None of the DID estimates were statistically significant.

Figure 4-2 shows DID results for ≥ 1 diabetes medication fill among patients diagnosed with diabetes. Following intervention, the probability of filling ≥ 1 oral diabetes medications increased only among enrollees, which is indicated by a positive DID estimate (DID: 0.19; CI: -0.05, 0.42). Similarly, among patients diagnosed with COPD or asthma, the probability of using ≥ 1 long-term controller medication increased among enrollees—indicated by a positive DID estimate (DID: 0.38; CI: -0.30, 1.05) (**Figure 4-3**). However, among patients diagnosed with CHF, after intervention the probability of filling ≥ 1 COPD/asthma medications decreased among enrollees—indicated by a negative DID estimate (DID: -0.86; CI: -1.93, 0.21) (**Figure 4-4**).

DISCUSSION

In this quasi-experimental study, we found that medication adherence was sub-optimal among SafeMed enrollees and controls, and it decreased further from the pre-intervention period to the post-intervention period. Combining the study findings from the analyses conducted on the 2-year baseline Medicare data (Chapter 2 and Chapter 3), this study shows a further decreasing trend in adherence over time among super-utilizers. Overall, the pharmacist-led medication management interventions as part of the SafeMed Program did not improve medication adherence in vulnerable super-utilizers with chronic conditions. However, for some sub-group populations, the intervention may have ensured that the decline in the probability of being adherent was not as low as it would have been in the absence of the intervention. Furthermore, although statistically insignificant, the SafeMed intervention had a positive impact on the use of COPD/asthma controller medications and oral diabetes medications.

Considering the lack of statistical significance in the findings from this quasi-experimental study, an important question that arises is why did this the intervention not bring about significant improvements in enrollees' medication-related outcomes? As care transitions programs for super-utilizers are becoming more popular, it is important to understand whether medication management interventions as part of care transitions programs are successful in improving medication adherence among super-utilizers who are at a greater risk of experiencing drug therapy problems. The low rates of medication

Table 4-3. Multivariate Difference-in-Differences Analysis Comparing Medication Adherence Between SafeMed Intervention Group and Control Group (by Subgroups)

Measure	Pre-Intervention Period				Post-Intervention Period				Difference in Differences	95% CI
	SafeMed Group (T)	Control Group (C)	Difference (T-C)	95% CI	SafeMed Group (T)	Control Group (C)	Difference (T-C)	95% CI		
Age<65 years	0.49	0.62	-0.13	-0.40,0.14	0.27	0.49	-0.22	-0.41,-0.03	-0.09	-0.42,0.24
Age≥65 years	0.91	1.52	-0.60	-1.64,0.43	0.68	0.64	0.04	-0.50,0.57	0.64	-0.50,1.78
Medicare Only	0.64	1.41	-0.78	-1.8,0.30	0.50	0.46	0.04	-0.55,0.62	0.81	-0.34,1.96
Medicaid Only	0.45	0.47	-0.01	-0.29,0.26	0.22	0.30	-0.07	-0.26,0.11	-0.06	-0.37,0.25
Dual Eligible	0.66	0.95	-0.29	-0.79,0.22	0.51	0.83	-0.31	-0.73,0.10	-0.03	-0.62,0.57
<4 Charlson	0.38	0.65	-0.27	-0.62,0.08	0.19	0.30	-0.12	-0.32,0.09	0.16	-0.21,0.52
Comorbidity Index ≥4 Charlson	0.68	0.87	-0.19	-0.57,0.19	0.47	0.70	-0.23	-0.52,0.07	-0.04	-0.48,0.41
Comorbidity Index										

Significant at $P < .05$

Adherence estimates are probability-scale predictions, adjusted for age, race, gender, insurance, Charlson comorbidity index, and anxiety or depression.

Sample for Age <65 years: N=660

Sample for Age ≥65 years: N=252

Sample for Medicare Only: N=118

Sample for TennCare Only: N=420

Sample for Dual Eligible: N=374

Sample for <4 Charson comorbidity index: N=338

Sample for ≥4 Charson comorbidity index: N=574

Figure 4-2. Multivariate Difference-in-Differences Analysis for ≥ 1 Oral Diabetes Medication Fill in Patients Diagnosed with Diabetes (N=634)

Note: Significant at $P < .05$. Adherence estimates are probability-scale predictions, adjusted for age, race, gender, insurance, Charlson comorbidity index, and anxiety or depression.

Figure 4-3. Multivariate Difference-in-Differences Analysis for ≥ 1 Long-Term Controller Medication Fill in Patients Diagnosed with COPD or Asthma (N=582)

Note: Significant at $P < .05$. Adherence estimates are probability-scale predictions, adjusted for age, race, gender, insurance, Charlson comorbidity index, and anxiety or depression.

Figure 4-4. Multivariate Difference-in-Differences Analysis for ≥ 1 ACE/ARB Fill in Patients Diagnosed with CHF (N=634)

Note: Significant at $P < .05$. Adherence estimates are probability-scale predictions, adjusted for age, race, gender, insurance, Charlson comorbidity index, and anxiety or depression.

adherence, even after intensive discharge preparation, planning, education, and care coordination services through the pharmacist-led medication management interventions, suggests that intensive investment in medication management interventions in this vulnerable population may not be sufficient. The study findings indicate that especially among patients <65 years of age, dual eligible beneficiaries, Medicaid beneficiaries, and those with multimorbidity, positive outcomes from interventions influencing patient behavior are difficult to achieve. Medication management interventions alone may not work for these high-risk patients and there may be other important barriers that need to be addressed to improve medication adherence in these high-risk sub-group populations.

Drug costs are one such factor that may contribute to sub-optimal medication adherence in super-utilizers, specifically among Medicaid and dual eligibles. Choudhry and colleagues found that eliminating out-of-pocket costs improved medication adherence in patients discharged after myocardial infarction.¹⁰¹ In our prior work on super-utilizers, patients experiencing high rates of medication discrepancies reported one of the major contributors to post-discharge medication discrepancies being difficulty in paying for medications.¹³ Furthermore, in our previous study (Chapter 2), we found lower adherence for dual eligible beneficiaries receiving low-income subsidy. These are strong indications that current medication cost subsidy amounts may not be sufficient to achieve optimal adherence, and cost and affordability continue to remain significant barriers among this high-risk patient population. Additional barriers to post-discharge medication discrepancies reported by SafeMed enrollees in our previous study included transportation and unavailability of needed prescription drugs before discharge.¹³ Future interventions and their evaluations should explore alternative approaches to increasing access to essential medications, especially for Medicaid and dual eligible beneficiaries, such as providing bedside delivery, or providing essential medications at zero out-of-pocket costs for patients. At policy-level, increasing days' supply for essential chronic medications may help in improving adherence in this high-risk population.

Results of studies evaluating the impact of pharmacist-led interventions during care transitions on medication-related outcomes have been mixed.^{17,19,49,54,98,102} Consistent with our results, few studies examining the impact of care transitions programs on medication-related outcomes did not find any significant effect on medication-related outcomes. For instance, Kripalani and colleagues did not find any positive effect of pharmacist-led interventions on post discharge medication errors in patients with acute coronary syndromes or acute decompensated heart failure.¹⁹ Additionally, in a sample of patients discharged to home and at high risk for medication-related problems, Walker and colleagues found that although pharmacist interventions improved quality of patient's discharge by identifying medication discrepancies, there was no effect on hospital readmissions and ED visits.⁵⁴ A direct comparison with their findings is limited by the fact that our study focused explicitly on high-risk super-utilizing patients residing in medically underserved areas. Moreover, our interventions were not only provided during hospital discharge but also extended beyond hospital discharge into the community. Ho and colleagues, who targeted patients from the Department of Veteran Affairs, found a positive impact of the post-discharge pharmacist-led interventions on adherence measured over a period of 1 year.⁴⁹ The different patient

populations and variations in program components and time frame for measuring adherence may account for differences in results. Our study findings suggest that super-utilizers are a complex patient population to intervene and extending medication management services even to their homes may face significant challenges in improving their adherence to needed life-saving medications.

Our results have important implications for health care systems striving to improve medication adherence and overall quality of care for vulnerable super-utilizers. Our analysis showed that adherence was suboptimal among super-utilizers and it declined over time. Furthermore, the study suggests that certain patient populations such as elderly Medicare beneficiaries and patients with lower comorbidities may be more amenable to medication management interventions. However, we found that despite providing intensive medication management interventions by a team of pharmacists and pharmacy technicians, there was no positive effect on medication adherence. This indicates that traditional medication management interventions during care transitions may not be enough for these patients and other alternative strategies such as addressing social risk factors and removing cost barriers may be needed to improve adherence in this population. Moreover, our work represents a real-world scenario where the SafeMed staff faced challenges in contacting and scheduling home visits and phone follow-ups with patients during the early implementation phase of the program. Initially we could not provide interventions to many patients. However, after extensive program improvement efforts, there was a significant improvement in the intervention completion rates.⁶⁰ Providing interventions to high-risk patient population is challenging and it is difficult to achieve full program potential as anticipated in a real-world setting.

The negative effect of these medication management interventions on adherence could be partly due to limitations of this study. One of the major limitations of this study is the small sample size. Because of the incomplete Medicare Part D data on enrollees and controls who became eligible from July 1, 2014 to May 1, 2015, the study findings should be interpreted with caution. In future, we aim to reanalyze data for this study using complete data for our Medicare-eligible enrollees and controls. Additionally, a key question that arises is to what extent the negative findings are generalizable to other settings? Because this study specifically focused on publicly insured super-utilizers living in a medically underserved area with multimorbidity, it may only be generalizable to a similar setting and a similar population. And, the efficacy of this intervention may differ in less vulnerable populations. Furthermore, non-randomized studies may produce selection bias; however, this study used propensity score matching, which minimized the selection bias and unobserved confounding was minimized because of the quasi-experimental study design. Additionally, the follow-up period for this study was 6 months, which limits examination of long-term effects of the SafeMed program on medication adherence. Finally, the PDC measure for calculating adherence was an indirect method and may not accurately capture medication use and is likely to be biased for inhalation products that are prescribed for asthma and COPD.

CONCLUSION

In conclusion, the rates of medication adherence among super-utilizers with chronic conditions were suboptimal, and adherence declined from the pre- to the post-intervention period. Overall we found that medication management interventions as part of the SafeMed Program did not improve adherence in enrollees compared to controls. However, for patients diagnosed with COPD/asthma and diabetes, there were positive medication use trends in favor of enrollees. The study findings suggest that intensive medication management interventions provided beyond hospital discharge may not be enough to achieving optimal adherence in super-utilizers with chronic conditions, especially among Medicaid and dual eligible beneficiaries. Future studies are needed to test alternative strategies focused on increasing access to essential chronic medications in this vulnerable population.

CHAPTER 5. CONCLUSION

SUMMARY OF FINDINGS

Our retrospective panel data analysis of the 2-year data showed that the proportion of patients who were nonadherent to their essential chronic disease medications ranged from 45.7% to 58.4%, with the highest rate for COPD/Asthma medications (54.3% to 64.4%). Nonadherence rates for cardiovascular and COPD/asthma medications were higher in the fourth period than previous periods. Additionally, of 1,092 patients who met the super-utilizers criteria in the fourth period (qualifying period for the SafeMed Program), only about 14% of them were super-utilizers in all previous periods. The baseline characteristics demonstrated that majority of super-utilizers were female, non-Hispanic black, dual eligible beneficiaries, and received low-income cost sharing subsidy (LICS). Furthermore, the study subjects had high rates of mental illness, substance use disorder, and opioid medication use. During the final 6-month period, 57% of the study subjects were diagnosed with depression or anxiety or had filled antidepressants or anxiolytics, 32% were diagnosed with tobacco use disorder, and 69% had filled opioid medications. The multivariate analysis showed that all three major factors—the predisposing, enabling, and need factors were associated with medication nonadherence. The risk factors for medication nonadherence included age <65 years as a predisposing factor, dual beneficiaries receiving LICS and higher number of unique prescribers as enabling factors, and ≥ 4 opioid medications filled in the previous period as a need factor. Mental illness was not significantly associated with medication nonadherence in the multivariate analysis. Factors associated with lower odds of nonadherence included number of different medications filled as a need factor and ≥ 1 physician office visits in the previous period as an enabling factor.

When examining the associations between medication nonadherence, and inpatient and ED use, as part of the second aim of this dissertation, we found higher incidences of inpatient hospitalizations and ED visits among beneficiaries who were not adherent to their essential chronic medications. Specifically, we found that among elderly Medicare beneficiaries, nonadherence was significantly associated with a 57% increase in inpatient hospitalizations, and among non-elderly Medicare beneficiaries, nonadherence was significantly associated with 41% increase in inpatient stays and 25% increase in ED visits. Similar associations were found across all therapy classes examined (diabetes, cardiovascular, and COPD/asthma) in both age groups. However, nonadherence to diabetes and COPD/asthma drugs was not significantly associated with ED visits. Furthermore, we found that while the effects of nonadherence on inpatient stays were seen in both age groups, the effects of nonadherence on ED visits were more pronounced for younger Medicare patients. The study findings were consistent with prior research on Medicare population which showed nonadherence to be associated with higher incidence of hospitalizations.^{6,39} However, unlike previous studies based on Medicare population, this study focused specifically on super-utilizing Medicare patients with chronic conditions and polypharmacy. Moreover, our study population was disproportionately represented by dual beneficiaries <65 years of age, who had on average higher

comorbidities and were more likely to be nonadherent to their essential chronic medications than elderly patients. Given these differences, examining associations separately in the two age groups may help researchers to target these high utilizing patient populations better with medication management interventions.

Based on Andersen behavioral model of health services utilization, we found that all three major categories—predisposing, enabling, and need factors were associated with higher inpatient and ED utilization. Among need factors, mental illness was a risk factor for higher utilization among elderly and substance use disorder was a risk factor for higher inpatient utilization among non-elderly Medicare patients. Additionally, the predisposing risk factor included non-Hispanic black race and the enabling risk factor included dual LICS status.

Finally, as part of the third aim, this study examined the impact of the SafeMed Program on medication utilization and adherence among study participants compared with propensity-matched controls. The study found that the proportion of adherent patients ($PDC \geq 80\%$) among enrollees declined from 34.2% in the pre-intervention period to 25.0% in the post-intervention period, while among controls, this proportion declined from 41.1% to 32.6%. Thus, medication adherence was suboptimal among SafeMed enrollees and controls, and it decreased further from the pre-intervention period to the post-intervention period. Combining the study findings from the analyses conducted on the 2-year baseline Medicare data (Chapter 2 and Chapter 3), this study shows a further decreasing trend in adherence over time among super-utilizers. The multivariate analyses demonstrated that the pharmacist-led medication management interventions as part of the SafeMed Program did not improve medication adherence in vulnerable super-utilizers with chronic conditions. However, for some sub-group populations including Medicare only beneficiaries, patients ≥ 65 years of age, and patients with a lower number of comorbidities, the intervention may have ensured that the decline in the probability of being adherent was not as low as it would have been in the absence of the intervention. Furthermore, although statistically insignificant, the SafeMed intervention had a positive impact on the use of COPD/asthma controller medications and oral diabetes medications.

IMPLICATIONS FOR PRACTICE AND POLICY

This study has important implications for policy makers and institutions striving to improve the quality of care and reducing health care utilization and costs for super-utilizers with chronic conditions. The literature on super-utilizers is sparse and mainly focuses on describing the population and their hospitalization patterns.^{56,57} This study is the first to our knowledge to demonstrate the magnitude and importance of medication nonadherence in vulnerable super-utilizers with chronic conditions. We not only found high rates of nonadherence among super-utilizers but also saw an increase in the nonadherence rates when patients had more frequent hospitalizations and ED visits. The study findings suggest that medication nonadherence is a significant problem among super-utilizers, and greater efforts may be needed to address this issue.

The predisposing, enabling, and need-related risk factors for nonadherence identified in this study may enable hospitals, accountable care organizations and managed care organizations identify super-utilizing populations in need of medication management interventions. Managing medication-related adverse events and improving medication adherence among vulnerable super-utilizers is critical for hospitals and payers since 75% of the hospital readmissions among Medicare population are considered potentially preventable, resulting in \$12 billion in unnecessary Medicare spending each year and subjecting hospitals to readmission penalties.⁴⁶ The study suggests that non-elderly Medicare patients, dual beneficiaries receiving low-income subsidy, and patients using a higher number of opioid medications are at greater risk for nonadherence. These high-risk patient populations may merit targeted interventions to support essential chronic disease medication adherence. Despite receiving low-income subsidy, dual beneficiaries were less likely to adhere to their therapy. This indicates that for super-utilizing low-income dual beneficiaries, subsidies may not be sufficient to achieve optimal adherence, and cost remains a significant barrier to achieving optimal adherence. Additionally, highly statistically significant and large effect size of the association between age and medication nonadherence demonstrates the need for better targeting of the non-elderly Medicare group with medication management interventions. The study findings suggest the importance of making routine visits to providers who can play a significant role in helping patients to adhere to their essential chronic medications. And, it also highlights the importance of reducing prescribing complexity in this high-risk patient population, which may result in suboptimal adherence.

Our study findings further demonstrate that improving medication adherence—a patient behavioral factor very amenable to change—may be critical in reducing inpatient and ED use among Medicare super-utilizers with chronic conditions. In our previous study, we found that during care transitions processes from the hospital to the community setting, super-utilizers were at high risk for drug therapy problems and medication discrepancies, which may result in suboptimal adherence.¹³ This cyclical process of nonadherence leading to increased frequency of hospitalizations, causing drug therapy problems and medication discrepancies in super-utilizers, can have detrimental effects on their health outcomes. Given these findings, hospitals, managed care organizations, and payers should engage in programs aimed at resolving drug therapy problems and improving medication adherence in super-utilizing populations. By examining associations for inpatient and ED use separately among non-elderly and elderly Medicare beneficiaries, this study indicates that there are variations in effects within these groups. For instance, mental illness was a risk factor for higher inpatient and ED utilization among elderly, while substance use disorder was a risk factor for higher inpatient utilization among younger patients. The study findings suggest that the two patient groups may have different barriers and varying social and medical needs, which are essential to be taken into consideration when designing interventions for these vulnerable patients. Additionally, our findings highlight the vulnerability of non-Hispanic blacks and low-income dual eligible beneficiaries who are at a higher risk for inpatient and ED utilization. Policy makers need to pay greater attention to the needs of these patient populations.

Our study findings have important implications for health care systems striving to improve medication adherence and overall quality of care for vulnerable super-utilizers. The study found that despite providing intensive medication management interventions by a team of pharmacists and pharmacy technicians, there was no positive effect on medication adherence. However, for some sub-group populations (Medicare only, elderly Medicare patients, and patients with lower comorbidity), the intervention may have ensured that the decline in the probability of being adherent was not as low as it would have been in the absence of the intervention. Furthermore, although statistically insignificant, the SafeMed intervention had a positive impact on the use of COPD/asthma controller medications and oral diabetes medications. These findings indicate that traditional medication management interventions during care transitions may not be sufficient for these high-risk patients and other alternative strategies such as addressing social risk factors, and removing cost barriers may be needed to improve adherence, especially among low-income dual beneficiaries, Medicaid enrollees, and patients with higher comorbidity.

Finally, our findings showing a high prevalence of mental illness, substance use disorder, and opioid medication use have highlighted the importance of monitoring for signs of opioid abuse, and having a strong social support and mental health facilities for vulnerable super-utilizing populations who have complex medical and social needs. Patients with complex behavioral health issues could benefit from greater coordination of health care providers and health care systems and having access to high-quality mental health services.

IMPLICATIONS FOR FUTURE RESEARCH

We found that the pharmacist-led medication management interventions as part of the SafeMed Program did not improve medication adherence in vulnerable super-utilizers with chronic conditions. Drug costs are one such factor that may contribute to suboptimal medication adherence in super-utilizers, specifically among low-income Medicaid and dual eligible beneficiaries. In our previous study (Chapter 2, Chapter 3), we found lower adherence and higher inpatient and ED utilization for dual eligible beneficiaries receiving low-income subsidies. These are strong indications that current medication cost subsidy amounts may not be sufficient to achieve optimal adherence and reduce utilization, and cost and affordability continue to remain significant barriers among this high-risk patient population. Additional barriers to post-discharge medication discrepancies reported by SafeMed enrollees in our previous study included transportation and unavailability of needed prescription drugs before discharge.¹³ Future interventions and their evaluations should explore alternative approaches to increasing access to essential medications, especially for low-income Medicaid and dual eligible beneficiaries, such as using hospital outpatient pharmacies to fill medications, providing bedside delivery, providing essential medications at zero out-of-pocket costs for patients, or increasing days' supply for essential chronic disease medications.

We used Medicare claims data to examine the factors associated with medication nonadherence (Aim 1) and the association between nonadherence and health care utilization (Aim 2). The follow-up of this study would analyze these aims using TennCare claims data to provide a comprehensive picture of the predictors of nonadherence and the association between nonadherence and health care utilization in the vulnerable TennCare population. Additionally, one of the major limitations of the study examining the impact of the SafeMed Program on medication use and adherence was small sample size. Because of the incomplete Medicare Part D data on enrollees and controls who became eligible from July 1, 2014 to May 1, 2015, the study findings should be interpreted with caution. In future, we aim to reanalyze data for this study using complete data for Medicare-eligible enrollees and controls. Finally, costs associated with medication nonadherence among super-utilizers are an important outcome and may be of more interest to policymakers. The follow-up to this study would examine the costs, including total costs and costs specific to health care services from the payer perspective.

LIST OF REFERENCES

1. Ho PM, Bryson CL, Rumsfeld JS. Medication adherence: its importance in cardiovascular outcomes. *Circulation*. Jun 16 2009;119(23):3028-3035.
2. Hess LM, Raebel MA, Conner DA, Malone DC. Measurement of adherence in pharmacy administrative databases: a proposal for standard definitions and preferred measures. *The Annals of pharmacotherapy*. Jul-Aug 2006;40(7-8):1280-1288.
3. Bailey JE, Hajjar M, Shoib B, Tang J, Ray MM, Wan JY. Risk factors associated with antihypertensive medication nonadherence in a statewide Medicaid population. *The American journal of the medical sciences*. Nov 2014;348(5):410-415.
4. Jha AK, Aubert RE, Yao J, Teagarden JR, Epstein RS. Greater adherence to diabetes drugs is linked to less hospital use and could save nearly \$5 billion annually. *Health affairs*. Aug 2012;31(8):1836-1846.
5. Roebuck MC, Liberman JN, Gemmill-Toyama M, Brennan TA. Medication adherence leads to lower health care use and costs despite increased drug spending. *Health affairs*. Jan 2011;30(1):91-99.
6. Simoni-Wastila L, Wei YJ, Qian J, et al. Association of chronic obstructive pulmonary disease maintenance medication adherence with all-cause hospitalization and spending in a Medicare population. *The American journal of geriatric pharmacotherapy*. Jun 2012;10(3):201-210.
7. Osterberg L, Blaschke T. Adherence to medication. *The New England journal of medicine*. Aug 4 2005;353(5):487-497.
8. PQA Measures Used By CMS in the Star Ratings. Pharmacy Quality Alliance Website. <http://pqaalliance.org/measures/cms.asp>. Accessed October 1, 2016.
9. Coleman EA. Falling through the cracks: challenges and opportunities for improving transitional care for persons with continuous complex care needs. *Journal of the American Geriatrics Society*. Apr 2003;51(4):549-555.
10. Forster AJ, Murff HJ, Peterson JF, Gandhi TK, Bates DW. The incidence and severity of adverse events affecting patients after discharge from the hospital. *Annals of internal medicine*. Feb 4 2003;138(3):161-167.
11. Fischer MA, Choudhry NK, Brill G, et al. Trouble getting started: predictors of primary medication nonadherence. *The American journal of medicine*. Nov 2011;124(11):1081 e1089-1022.

12. Brown MT, Bussell JK. Medication adherence: WHO cares? *Mayo Clinic proceedings*. Apr 2011;86(4):304-314.
13. Surbhi S, Munshi KD, Bell PC, Bailey JE. Drug therapy problems and medication discrepancies during care transitions in super-utilizers. *Journal of the American Pharmacists Association : JAPhA*. Oct 6 2016.
14. Kripalani S, Henderson LE, Jacobson TA, Vaccarino V. Medication use among inner-city patients after hospital discharge: patient-reported barriers and solutions. *Mayo Clinic proceedings*. May 2008;83(5):529-535.
15. Newby LK, LaPointe NM, Chen AY, et al. Long-term adherence to evidence-based secondary prevention therapies in coronary artery disease. *Circulation*. Jan 17 2006;113(2):203-212.
16. Ho PM, Spertus JA, Masoudi FA, et al. Impact of medication therapy discontinuation on mortality after myocardial infarction. *Archives of internal medicine*. Sep 25 2006;166(17):1842-1847.
17. Schnipper JL, Kirwin JL, Cotugno MC, et al. Role of pharmacist counseling in preventing adverse drug events after hospitalization. *Archives of internal medicine*. Mar 13 2006;166(5):565-571.
18. Coleman EA, Smith JD, Raha D, Min SJ. Posthospital medication discrepancies: prevalence and contributing factors. *Archives of internal medicine*. Sep 12 2005;165(16):1842-1847.
19. Kripalani S, Roumie CL, Dalal AK, et al. Effect of a pharmacist intervention on clinically important medication errors after hospital discharge: a randomized trial. *Annals of internal medicine*. Jul 3 2012;157(1):1-10.
20. Forster AJ, Murff HJ, Peterson JF, Gandhi TK, Bates DW. Adverse drug events occurring following hospital discharge. *Journal of general internal medicine*. Apr 2005;20(4):317-323.
21. Choudhry NK, Shrank WH, Levin RL, et al. Measuring concurrent adherence to multiple related medications. *The American journal of managed care*. Jul 2009;15(7):457-464.
22. Morisky DE, Ang A, Krousel-Wood M, Ward HJ. Predictive validity of a medication adherence measure in an outpatient setting. *Journal of clinical hypertension*. May 2008;10(5):348-354.
23. Kripalani S, Risser J, Gatti ME, Jacobson TA. Development and evaluation of the Adherence to Refills and Medications Scale (ARMS) among low-literacy patients

- with chronic disease. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research*. Jan-Feb 2009;12(1):118-123.
24. Gehi A, Haas D, Pipkin S, Whooley MA. Depression and medication adherence in outpatients with coronary heart disease: findings from the Heart and Soul Study. *Archives of internal medicine*. Nov 28 2005;165(21):2508-2513.
 25. Doshi JA, Zhu J, Lee BY, Kimmel SE, Volpp KG. Impact of a prescription copayment increase on lipid-lowering medication adherence in veterans. *Circulation*. Jan 27 2009;119(3):390-397.
 26. Charles H, Good CB, Hanusa BH, Chang CC, Whittle J. Racial differences in adherence to cardiac medications. *Journal of the National Medical Association*. Jan 2003;95(1):17-27.
 27. Taira DA, Wong KS, Frech-Tamas F, Chung RS. Copayment level and compliance with antihypertensive medication: analysis and policy implications for managed care. *The American journal of managed care*. Nov 2006;12(11):678-683.
 28. Hsu J, Price M, Huang J, et al. Unintended consequences of caps on Medicare drug benefits. *The New England journal of medicine*. Jun 1 2006;354(22):2349-2359.
 29. Gazmararian JA, Kripalani S, Miller MJ, Echt KV, Ren J, Rask K. Factors associated with medication refill adherence in cardiovascular-related diseases: a focus on health literacy. *Journal of general internal medicine*. Dec 2006;21(12):1215-1221.
 30. Davis TC, Wolf MS, Bass PF, 3rd, et al. Literacy and misunderstanding prescription drug labels. *Annals of internal medicine*. Dec 19 2006;145(12):887-894.
 31. Gandhi TK, Weingart SN, Borus J, et al. Adverse drug events in ambulatory care. *The New England journal of medicine*. Apr 17 2003;348(16):1556-1564.
 32. Coleman EA, Mahoney E, Parry C. Assessing the quality of preparation for posthospital care from the patient's perspective: the care transitions measure. *Medical care*. Mar 2005;43(3):246-255.
 33. Calkins DR, Davis RB, Reiley P, et al. Patient-physician communication at hospital discharge and patients' understanding of the postdischarge treatment plan. *Archives of internal medicine*. May 12 1997;157(9):1026-1030.
 34. Kripalani S, LeFevre F, Phillips CO, Williams MV, Basaviah P, Baker DW. Deficits in communication and information transfer between hospital-based and

- primary care physicians: implications for patient safety and continuity of care. *Jama*. Feb 28 2007;297(8):831-841.
35. Makaryus AN, Friedman EA. Patients' understanding of their treatment plans and diagnosis at discharge. *Mayo Clinic proceedings*. Aug 2005;80(8):991-994.
 36. Ho PM, Rumsfeld JS, Masoudi FA, et al. Effect of medication nonadherence on hospitalization and mortality among patients with diabetes mellitus. *Archives of internal medicine*. Sep 25 2006;166(17):1836-1841.
 37. Ho PM, Magid DJ, Shetterly SM, et al. Medication nonadherence is associated with a broad range of adverse outcomes in patients with coronary artery disease. *American heart journal*. Apr 2008;155(4):772-779.
 38. Sokol MC, McGuigan KA, Verbrugge RR, Epstein RS. Impact of medication adherence on hospitalization risk and healthcare cost. *Medical care*. Jun 2005;43(6):521-530.
 39. Zhang Y, Kaplan CM, Baik SH, Chang CC, Lave JR. Medication adherence and readmission after myocardial infarction in the Medicare population. *The American journal of managed care*. 2014;20(11):e498-505.
 40. Bunting BA, Smith BH, Sutherland SE. The Asheville Project: clinical and economic outcomes of a community-based long-term medication therapy management program for hypertension and dyslipidemia. *Journal of the American Pharmacists Association : JAPhA*. Jan-Feb 2008;48(1):23-31.
 41. Bunting BA, Cranor CW. The Asheville Project: long-term clinical, humanistic, and economic outcomes of a community-based medication therapy management program for asthma. *Journal of the American Pharmacists Association : JAPhA*. Mar-Apr 2006;46(2):133-147.
 42. Cranor CW, Bunting BA, Christensen DB. The asheville project: long-term clinical and economic outcomes of a community pharmacy diabetes care program. *Journal of the American Pharmacists Association : JAPhA*. Mar 2003;43(2):173-184.
 43. Pringle JL, Boyer A, Conklin MH, McCullough JW, Aldridge A. The Pennsylvania Project: pharmacist intervention improved medication adherence and reduced health care costs. *Health affairs*. Aug 2014;33(8):1444-1452.
 44. Zillich AJ, Jaynes HA, Snyder ME, et al. Evaluation of specialized medication packaging combined with medication therapy management: adherence, outcomes, and costs among Medicaid patients. *Medical care*. Jun 2012;50(6):485-493.

45. Martin MY, Kim YI, Kratt P, et al. Medication adherence among rural, low-income hypertensive adults: a randomized trial of a multimedia community-based intervention. *American journal of health promotion : AJHP*. Jul-Aug 2011;25(6):372-378.
46. Improving Care Transitions. Better coordination of patient transfers among care sites and the community could save money and improve the quality of care. Health Policy Brief. Health Affairs. September 13, 2012. http://healthaffairs.org/healthpolicybriefs/brief_pdfs/healthpolicybrief_76.pdf. Accessed October 1, 2016.
47. Kalista T, Lemay V, Cohen L. Postdischarge community pharmacist-provided home services for patients after hospitalization for heart failure. *Journal of the American Pharmacists Association : JAPhA*. Jul-Aug 2015;55(4):438-442.
48. Kilcup M, Schultz D, Carlson J, Wilson B. Postdischarge pharmacist medication reconciliation: impact on readmission rates and financial savings. *Journal of the American Pharmacists Association : JAPhA*. Jan-Feb 2013;53(1):78-84.
49. Ho PM, Lambert-Kerzner A, Carey EP, et al. Multifaceted intervention to improve medication adherence and secondary prevention measures after acute coronary syndrome hospital discharge: a randomized clinical trial. *JAMA internal medicine*. Feb 1 2014;174(2):186-193.
50. Dudas V, Bookwalter T, Kerr KM, Pantilat SZ. The impact of follow-up telephone calls to patients after hospitalization. *The American journal of medicine*. Dec 21 2001;111(9B):26S-30S.
51. Phatak A, Prusi R, Ward B, et al. Impact of pharmacist involvement in the transitional care of high-risk patients through medication reconciliation, medication education, and postdischarge call-backs (IPITCH Study). *Journal of hospital medicine*. Jan 2016;11(1):39-44.
52. Boockvar KS, Carlson LaCorte H, Giambanco V, Fridman B, Siu A. Medication reconciliation for reducing drug-discrepancy adverse events. *The American journal of geriatric pharmacotherapy*. Sep 2006;4(3):236-243.
53. Kaboli PJ, Hoth AB, McClimon BJ, Schnipper JL. Clinical pharmacists and inpatient medical care: a systematic review. *Archives of internal medicine*. May 8 2006;166(9):955-964.
54. Walker PC, Bernstein SJ, Jones JN, et al. Impact of a pharmacist-facilitated hospital discharge program: a quasi-experimental study. *Archives of internal medicine*. Nov 23 2009;169(21):2003-2010.

55. Better care for super-utilizers. Robert Wood Johnson Foundation.
<http://www.rwjf.org/en/library/collections/super-utilizers.html>. Accessed October 1, 2016.
56. Johnson TL, Rinehart DJ, Durfee J, et al. For many patients who use large amounts of health care services, the need is intense yet temporary. *Health affairs*. Aug 2015;34(8):1312-1319.
57. Harris LJ, Graetz I, Podila PS, Wan J, Waters TM, Bailey JE. Characteristics of Hospital and Emergency Care Super-utilizers with Multiple Chronic Conditions. *The Journal of emergency medicine*. Apr 2016;50(4):e203-214.
58. Jiang HJ, Weiss AJ, Barrett ML, Sheng M. Characteristics of Hospital Stays for Super-Utilizers by Payer, 2012: Statistical Brief #190. *Healthcare Cost and Utilization Project (HCUP) Statistical Briefs*. Rockville (MD)2015.
59. Regenstein M, Andres E. Reducing hospital readmissions among medicaid patients: a review of the literature. *Quality management in health care*. Oct-Dec 2014;23(4):203-225.
60. Bailey JE, Surbhi S, Bell PC, Jones AM, Rashed S, Ugwueke MO. SafeMed: Using pharmacy technicians in a novel role as community health workers to improve transitions of care. *Journal of the American Pharmacists Association : JAPhA*. Jan 2016;56(1):73-81.
61. Williams MV, Li J, Hansen LO, et al. Project BOOST implementation: lessons learned. *Southern medical journal*. Jul 2014;107(7):455-465.
62. Integrating Care Across Settings: The Illinois Transitional Care Consortium's Bridge Model. American Society on Aging Website.
<http://www.asaging.org/blog/integrating-care-across-settings-illinois-transitional-care-consortium%E2%80%99s-bridge-model>. Accessed October 1, 2016.
63. Gans D, Hadler MW, Chen X, et al. Cost Analysis and Policy Implications of a Pediatric Palliative Care Program. *Journal of pain and symptom management*. Sep 2016;52(3):329-335.
64. Kaufman S, Ali N, DeFiglio V, Craig K, Brenner J. Early efforts to target and enroll high-risk diabetic patients into urban community-based programs. *Health promotion practice*. Nov 2014;15(2 Suppl):62S-70S.
65. Coleman EA, Parry C, Chalmers S, Min SJ. The care transitions intervention: results of a randomized controlled trial. *Archives of internal medicine*. Sep 25 2006;166(17):1822-1828.

66. Naylor MD, Brooten DA, Campbell RL, Maislin G, McCauley KM, Schwartz JS. Transitional care of older adults hospitalized with heart failure: a randomized, controlled trial. *Journal of the American Geriatrics Society*. May 2004;52(5):675-684.
67. Andersen RM. Revisiting the behavioral model and access to medical care: does it matter? *Journal of health and social behavior*. Mar 1995;36(1):1-10.
68. Murray MD, Morrow DG, Weiner M, et al. A conceptual framework to study medication adherence in older adults. *The American journal of geriatric pharmacotherapy*. Mar 2004;2(1):36-43.
69. De Smet BD, Erickson SR, Kirking DM. Self-reported adherence in patients with asthma. *The Annals of pharmacotherapy*. Mar 2006;40(3):414-420.
70. Riley GF. Long-term trends in the concentration of Medicare spending. *Health affairs*. May-Jun 2007;26(3):808-816.
71. Gawande AA. The hot spotters: can we lower medical costs by giving the neediest patients better care? *New Yorker*. 2011 Jan 4.
72. Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. *Clinical therapeutics*. Aug 2001;23(8):1296-1310.
73. Choudhry NK, Fischer MA, Avorn J, et al. The implications of therapeutic complexity on adherence to cardiovascular medications. *Archives of internal medicine*. May 9 2011;171(9):814-822.
74. Qato DM, Wilder J, Schumm LP, Gillet V, Alexander GC. Changes in Prescription and Over-the-Counter Medication and Dietary Supplement Use Among Older Adults in the United States, 2005 vs 2011. *JAMA internal medicine*. Apr 1 2016;176(4):473-482.
75. Super-Utilizer Summit Common Themes from Innovative Complex Care Management Programs. 2013. http://www.chcs.org/media/FINAL_Super-Utilizer_Report.pdf. Accessed October 1, 2016.
76. Bailey JE, Binkley B. Using SafeMed model for transitions of care approach. Increasing engagement and adherence for complex patients. https://www.stepsforward.org/Static/images/modules/34/downloadable/Using_SafeMed_Model_for_Transitions_of_Care_Approach.pdf. Accessed October 1, 2016.

77. Jencks SF, Williams MV, Coleman EA. Rehospitalizations among patients in the Medicare fee-for-service program. *The New England journal of medicine*. Apr 2 2009;360(14):1418-1428.
78. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *Jama*. Feb 5 2014;311(5):507-520.
79. Frequently Asked Questions about PQA Measure Development and Measures. <http://pqaalliance.org/measures/faqs.asp>. Accessed October 1, 2016.
80. Concept: Charlson Comorbidity Index. Pharmacy Quality Alliance Website. Manitoba Centre for Health Policy. University of Manitoba Website. <http://mchp-appserv.cpe.umanitoba.ca/viewConcept.php?conceptID=1098>. Accessed April, 30, 2016.
81. Jackevicius CA, Mamdani M, Tu JV. Adherence with statin therapy in elderly patients with and without acute coronary syndromes. *Jama*. Jul 24-31 2002;288(4):462-467.
82. Cramer JA. A systematic review of adherence with medications for diabetes. *Diabetes care*. May 2004;27(5):1218-1224.
83. Restrepo RD, Alvarez MT, Wittnebel LD, et al. Medication adherence issues in patients treated for COPD. *International journal of chronic obstructive pulmonary disease*. 2008;3(3):371-384.
84. Rieckmann N, Gerin W, Kronish IM, et al. Course of depressive symptoms and medication adherence after acute coronary syndromes: an electronic medication monitoring study. *Journal of the American College of Cardiology*. Dec 5 2006;48(11):2218-2222.
85. Bane C, Hughes CM, McElnay JC. The impact of depressive symptoms and psychosocial factors on medication adherence in cardiovascular disease. *Patient education and counseling*. Feb 2006;60(2):187-193.
86. DiMatteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence. *Archives of internal medicine*. Jul 24 2000;160(14):2101-2107.
87. Martin LR, Williams SL, Haskard KB, Dimatteo MR. The challenge of patient adherence. *Therapeutics and clinical risk management*. Sep 2005;1(3):189-199.

88. Yala SM, Duru OK, Ettner SL, Turk N, Mangione CM, Brown AF. Patterns of prescription drug expenditures and medication adherence among medicare part D beneficiaries with and without the low-income supplement. *BMC health services research*. 2014;14:665.
89. Stuart B, Yin X, Davidoff A, et al. Impact of Part D low-income subsidies on medication patterns for Medicare beneficiaries with diabetes. *Medical care*. Nov 2012;50(11):913-919.
90. Chapman RH, Benner JS, Petrilla AA, et al. Predictors of adherence with antihypertensive and lipid-lowering therapy. *Archives of internal medicine*. May 23 2005;165(10):1147-1152.
91. Naylor MD, Sochalski JA. Scaling up: bringing the transitional care model into the mainstream. *Issue brief*. Nov 2010;103:1-12.
92. Jena AB, Goldman D, Karaca-Mandic P. Hospital Prescribing of Opioids to Medicare Beneficiaries. *JAMA internal medicine*. Jul 1 2016;176(7):990-997.
93. Torres-Reyna O. Panel Data Analysis Fixed and Random Effects using Stata (v. 4.2). December, 2007. <https://www.princeton.edu/~otorres/Panel101.pdf>. Accessed October 1, 2016.
94. Shrank WH, Patrick AR, Brookhart MA. Healthy user and related biases in observational studies of preventive interventions: a primer for physicians. *Journal of general internal medicine*. May 2011;26(5):546-550.
95. Rathore SS, Foody JM, Wang Y, et al. Race, quality of care, and outcomes of elderly patients hospitalized with heart failure. *Jama*. May 21 2003;289(19):2517-2524.
96. Joynt KE, Orav EJ, Jha AK. Thirty-day readmission rates for Medicare beneficiaries by race and site of care. *Jama*. Feb 16 2011;305(7):675-681.
97. Kripalani S, Jackson AT, Schnipper JL, Coleman EA. Promoting effective transitions of care at hospital discharge: a review of key issues for hospitalists. *Journal of hospital medicine*. Sep 2007;2(5):314-323.
98. Gil M, Mikaitis DK, Shier G, Johnson TJ, Sims S. Impact of a combined pharmacist and social worker program to reduce hospital readmissions. *Journal of managed care pharmacy : JMCP*. Sep 2013;19(7):558-563.
99. Polinski JM, Moore JM, Kyrychenko P, et al. An Insurer's Care Transition Program Emphasizes Medication Reconciliation, Reduces Readmissions And Costs. *Health affairs*. Jul 1 2016;35(7):1222-1229.

100. Parsons LS. Performing a 1:N Case-Control Match on Propensity Score. <http://www2.sas.com/proceedings/sugi29/165-29.pdf>. Accessed September 12, 2016.
101. Choudhry NK, Avorn J, Glynn RJ, et al. Full coverage for preventive medications after myocardial infarction. *The New England journal of medicine*. Dec 1 2011;365(22):2088-2097.
102. Kirkham HS, Clark BL, Paynter J, Lewis GH, Duncan I. The effect of a collaborative pharmacist-hospital care transition program on the likelihood of 30-day readmission. *American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists*. May 1 2014;71(9):739-745.

APPENDIX A. SUPPLEMENTAL MATERIALS FOR CHAPTER 2

Table A-1. The International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] Codes (Inclusion Criteria and Comorbidities)

Categories	ICD-9-CM Codes
Qualifying Chronic Conditions	
Hypertension	'36211','4010','4011','4019','40200','40201','40210','40211','40290','40291','40300','40301','40310','40311','40390','40391','40400','40401','40402','40403','40410','40411','40412','40413','40490','40491','40492','40493','40501','40509','40511','40519','40591','40599','4372'
Congestive heart failure	'39891','40201','40211','40291','40401','40403','40411','40413','40491','40493','4254','4255','4257','4258','4259','4280','4281','42820','42821','42822','42823','42830','42831','42832','42833','42840','42841','42842','42843','4289'
Coronary artery disease	'41000','41001','41002','41010','41011','41012','41020','41021','41022','41030','41031','41032','41040','41041','41042','41050','41051','41052','41060','41061','41062','41070','41071','41072','41080','41081','41082','41090','41091','41092','4110','4111','41181','41189','412','4130','4131','4139','41400','41401','41402','41403','41404','41405','41406','41407','41412','4142','4143','4148','4149','42979'
Diabetes mellitus	'24900','24901','24910','24911','24920','24921','24930','24931','24940','24941','24950','24951','24960','24961','24970','24971','24980','24981','24990','24991','25000','25001','25002','25003','25010','25011','25011','25012','25013','25020','2502','25022','25023','25030','25031','25032','25033','25040','25041','25042','25043','25050','25051','25052','25053','25060','25061','25062','25063','25070','25071','25072','25073','25080','25081','25082','25083','25090','25091','25092','25093','3572','36201','36202','36641'
Asthma	'49300','49301','49302','49310','49311','49312','49320','49321','49322','49381','49382','49390','49391','49392'
Chronic obstructive pulmonary disease	'490','4910','4911','49120','49121','49122','4918','4919','4920','4928','4940','4941','496'
Comorbidities	
Anxiety or depression	'29384','30000','30001','30002','30009','30010','30020','30021','30022','30023','30029','3003','3005','30089','3009','3080','3081','3082','3083','3084','3089','3091','3130','3131','31321','31322','3133','31382','31383','29383','29620','29621','2962','29623','29624','29625','29626','29630','29631','29632','29633','29634','29635','29636','3004','311'
Tobacco use disorder	'3051'

Table A-2. Medication Nonadherence to Essential Chronic Disease Medication by Therapy Class

Therapy Class	Percent Nonadherent (PDC <80%)
1. Diabetes medications	
Period 1 (n=250)	41.2%
Period 2 (n=269)	48.7%
Period 3 (n=298)	58.4%
Period 4 (n=300)	67.3%
Overall (n=1,117 patient-periods)	53.3%
2. Cardiovascular medications	
Period 1 (n=933)	40.2%
Period 2 (n=987)	53.1%
Period 3 (n=1,010)	60.8%
Period 4 (n=1,045)	66.0%
Overall (n=3,955 patient-periods)	54.2%
3. COPD/Asthma medications	
Period 1 (n=169)	54.4%
Period 2 (n=191)	63.4%
Period 3 (n=216)	66.7%
Period 4 (n=258)	74.8%
Overall (n=834 patient-periods)	64.4%
Diabetes, cardiovascular, and COPD/Asthma meds combined	
Period 1 (n=961)	43.2%
Period 2 (n=1,011)	56.1%
Period 3 (n=1,031)	65.5%
Period 4 (n=1,060)	72.8%
Overall (n=4,043 patient-periods)	58.4%

COPD: chronic obstructive pulmonary disease.

COPD/Asthma medications included controller medications (anticholinergic inhalers, inhaled corticosteroids alone or in combination with long-acting beta-agonists (LABA), and other COPD/asthma medications (theophylline and leukotriene modifiers).

Table A-3. Multivariate Associations with Medication Nonadherence Using Alternative Proportion of Days Covered (PDC) Definition (N=2,999 Patient-Periods)

Characteristics	Nonadherence	
	Odds Ratio (95% CI)	P Value
<65 years	2.14 (1.47-3.11)	<0.001
Female	1.32 (0.94-1.85)	0.114
Non-Hispanic Black	1.03 (0.71-1.51)	0.863
Non-dual LIS	1.59 (0.88-2.86)	0.121
Dual LIS	1.62 (1.07-2.44)	0.021
Comorbidity		
Charlson comorbidity index	1.14 (1.07-1.20)	<0.001
Diagnosis of tobacco abuse disorder	1.03 (0.70-1.52)	0.867
Mental illness*	1.00 (0.71-1.41)	0.987
Medication related factors		
No. of unique medications filled	0.93 (0.89-0.96)	<0.001
Opioid Medication Use		
0 opioid medication filled (Ref)		
1 opioid medication filled	1.21 (0.85-1.74)	0.288
2-3 opioid medications filled	1.21 (0.83-1.78)	0.326
≥4 opioid medications filled	1.57 (0.94-2.08)	0.101
Number of unique prescribers	1.09 (1.03-1.16)	0.005
Number of unique pharmacies	1.08 (0.95-1.21)	0.235
Health care utilization		
≥1 physician office visits	0.66 (0.45-0.98)	0.037

Significant at $P < 0.05$. The model included lagged effects of comorbidity, therapy complexity-related, and health care utilization factors.

*Mental illness was defined as ≥1 antidepressants or anxiolytics fill or diagnosis of depression/anxiety.

Table A-4. Multivariate Associations with Medication Nonadherence Using Alternative PDC Criteria of ≥ 1 Medication Fill (N=3,062 Patient-Periods)

Characteristics	Nonadherence	
	Odds Ratio (95% CI)	P Value
<65 years	1.61 (1.23-2.10)	<0.001
Female	1.16 (0.90-1.49)	0.242
Non-Hispanic black	1.03 (0.78-1.37)	0.830
Non-dual LIS	1.43 (0.95-2.17)	0.089
Dual LIS	1.46 (1.08-1.98)	0.014
Comorbidity		
Charlson comorbidity index	1.00 (0.96-1.04)	0.905
Diagnosis of tobacco abuse disorder	0.96 (0.69-1.34)	0.828
Mental illness	0.76 (0.59-0.99)	0.040
Medication related factors		
Unique other medications filled	0.96 (0.94-0.99)	0.003
Opioid Medication Use		
0 opioid medication filled (Ref)		
1 opioid medication filled	1.23 (0.91-1.67)	0.177
2-3 opioid medications filled	1.17 (0.85-1.60)	0.344
≥ 4 opioid medications filled	1.62 (1.19-2.20)	0.002
Unique prescribers	1.09 (1.04-1.15)	<0.001
Unique pharmacies	1.04 (0.95-1.15)	0.363
Health care utilization		
≥ 1 physician office visits	0.60 (0.45-0.82)	0.001

Significant at $P < 0.05$. The model included lagged effects of comorbidity, therapy complexity-related, and health care utilization factors.

*Mental illness was defined as ≥ 1 antidepressants or anxiolytics fill or diagnosis of depression/anxiety.

APPENDIX B. SUPPLEMENTAL MATERIALS FOR CHAPTER 3

Table B-1. Multivariable Results for Inpatient Stays and ED Visits Among Medicare Beneficiaries ≥ 65 years Using Random Effects Models (N=1,757 patient-periods)

Characteristics	Inpatient Stays		ED Visits	
	IRR (95% CI)	P Value	IRR (95% CI)	P Value
Overall medication nonadherence	1.37 (1.23-1.52)	<0.001	1.20 (1.04-1.39)	0.016
Female	0.98 (0.88-1.09)	0.691	1.04 (0.87-1.25)	0.660
Non-Hispanic Black	0.90 (0.79-1.01)	0.083	1.40 (1.14-1.71)	0.001
Non-Dual LICS	1.17 (0.96-1.42)	0.120	1.31 (0.96-1.79)	0.093
Dual LICS	1.13 (1.00-1.28)	0.045	1.44 (1.18-1.75)	<0.001
Comorbidity				
Charlson comorbidity index	1.08 (1.06-1.09)	<0.001	1.06 (1.03-1.09)	<0.001
Mental illness	1.16 (1.03-1.30)	0.015	1.47 (1.24-1.75)	<0.001
Tobacco abuse disorder	1.14 (0.99-1.32)	0.065	1.03 (0.82-1.29)	0.818
Opioid medication filled				
0 opioid fill (ref)				
1 opioid fill	1.02 (0.88-1.18)	0.830	1.05 (0.85-1.29)	0.661
2-3 opioid fill	0.92 (0.78-1.08)	0.331	1.08 (0.87-1.34)	0.495
>3 opioid fill	0.92 (0.80-1.06)	0.263	0.95 (0.77-1.19)	0.670
Number of unique medications filled	1.01 (1.00-1.03)	0.118	0.98 (0.95-1.00)	0.047
Number of unique prescribers	1.01 (0.98-1.03)	0.697	1.07 (1.03-1.11)	<0.001
≥ 1 physician office visits	0.91 (0.78-1.05)	0.192	4.06 (2.87-5.74)	<0.001

Significant at $P < 0.05$. IRR: Incidence Rate Ratio. ED visits: Emergency department visits.

We used random effects negative binomial models at patient level. The models included lagged effects of all the above factors.

Overall medication nonadherence measured at patient-level was based on seventeen index drug classes.

Mental illness is defined as ≥ 1 antidepressants or anxiolytics fill or diagnosis of depression/anxiety.

The multivariable model with inpatient stays as outcome included 1,227 patient-periods.

The multivariable model with ED visits as outcome included 986 patient-period.

Table B-2. Multivariable Results for Inpatient Stays and ED Visits Among Medicare Beneficiaries <65 years Using Random Effects Models (N=1,242 patient-periods)

Characteristics	Inpatient Stays		ED Visits	
	IRR (95% CI)	P Value	IRR (95% CI)	P Value
Overall medication nonadherence	1.37 (1.21-1.54)	<0.001	1.32 (1.13-1.54)	0.001
Female	1.04 (0.93-1.18)	0.489	1.04 (0.85-1.27)	0.723
Non-Hispanic Black	1.06 (0.91-1.22)	0.459	1.25 (0.98-1.58)	0.072
Non-Dual LICS	1.15 (0.89-1.49)	0.294	1.37 (0.88-2.13)	0.162
Dual LICS	1.07 (0.85-1.34)	0.559	1.51 (1.03-2.21)	0.037
Comorbidity				
Charlson comorbidity index	1.08 (1.06-1.09)	<0.001	1.06 (1.03-1.09)	<0.001
Mental illness	1.15 (1.02-1.31)	0.026	1.26 (1.05-1.53)	0.015
Tobacco abuse disorder	1.28 (1.13-1.44)	<0.001	1.30 (1.07-1.58)	0.008
Opioid medication filled				
0 opioid fill (ref)				
1 opioid fill	0.84 (0.69-1.02)	0.076	0.83 (0.64-1.06)	0.133
2-3 opioid fill	0.99 (0.83-1.19)	0.948	0.89 (0.70-1.14)	0.356
≥3 opioid fill	1.16 (0.99-1.35)	0.064	1.05 (0.83-1.32)	0.694
Number of unique medications filled	0.99 (0.98-1.01)	0.783	1.01 (0.99-1.03)	0.535
Number of unique prescribers	1.02 (1.00-1.04)	0.075	1.05 (1.03-1.08)	<0.001
≥1 physician office visits	0.80 (0.68-0.95)	0.009	1.82 (1.33-2.49)	<0.001

Significant at $P < 0.05$. IRR: Incidence Rate Ratio. ED visits: Emergency department visits.

We used random effects negative binomial models at patient level. The models included lagged effects of all the above factors.

Overall medication nonadherence measured at patient-level was based on seventeen index drug classes.

Mental illness is defined as ≥1 antidepressants or anxiolytics fill or diagnosis of depression/anxiety.

The multivariable model with inpatient stays as outcome included 1,227 patient-periods.

The multivariable model with ED visits as outcome included 986 patient-periods.

Table B-3. Multivariable Results for Inpatient Stays and Emergency Department Visits Among Medicare Beneficiaries ≥ 65 years Using ≥ 1 Medication Fill Criteria

Characteristics	Inpatient Stays		ED Visits	
	IRR (95% CI)	P Value	IRR (95% CI)	P Value
Overall medication nonadherence	1.78 (1.50-2.12)	<0.001	1.14 (0.94-1.39)	0.192
Comorbidity				
Charlson comorbidity index	1.22 (1.17-1.28)	<0.001	1.17 (1.10-1.23)	<0.001
Mental illness	1.54 (1.20-1.96)	0.001	1.46 (1.11-1.93)	0.006
Diagnosis of tobacco use disorder	1.31 (0.91-1.86)	0.145	0.69 (0.45-1.05)	0.082
Opioid medication filled				
0 opioid fill (ref)				
1 opioid fill	0.98 (0.78-1.22)	0.846	0.94 (0.73-1.20)	0.611
2-3 opioid fill	0.87 (0.67-1.12)	0.270	0.95 (0.73-1.25)	0.736
>3 opioid fill	0.89 (0.66-1.20)	0.445	0.83 (0.57-1.19)	0.306
Number of unique medications filled	1.01 (0.99-1.03)	0.461	0.97 (0.94-1.00)	0.099
Number of unique prescribers	0.97 (0.92-1.02)	0.211	0.98 (0.93-1.04)	0.537
≥ 1 physician office visit	0.95 (0.70-1.28)	0.721	1.51 (0.94-2.42)	0.086

Significant at $P < 0.05$. IRR: Incidence Rate Ratio. ED visits: Emergency department visits. We used fixed effects negative binomial models at patient level. The models included lagged effects of all the above factors.

Overall medication nonadherence measured at patient-level was based on seventeen index drug classes.

Mental illness is defined as ≥ 1 antidepressants or anxiolytics fill or diagnosis of depression/anxiety.

The multivariable model with inpatient stays as outcome included 1,792 patient-periods.

The multivariable model with ED visits as outcome included 1,250 patient-periods.

Table B-4. Multivariable Results for Inpatient Stays and ED Visits Among Medicare Beneficiaries <65 years Using ≥ Medication Fill Criteria

Characteristics	Inpatient Stays		ED Visits	
	IRR (95% CI)	P Value	IRR (95% CI)	P Value
Overall medication nonadherence	1.46 (1.21-1.76)	<0.001	1.24 (1.01-1.51)	0.038
Comorbidity				
Charlson comorbidity index	1.18 (1.13-1.23)	<0.001	1.11 (1.05-1.16)	<0.001
Mental illness	1.20 (0.92-1.56)	0.184	1.18 (0.88-1.58)	0.277
Diagnosis of tobacco use disorder	1.72 (1.26-2.34)	0.001	1.30 (0.92-1.82)	0.135
Opioid medication filled				
0 opioid fill (ref)				
1 opioid fill	0.82 (0.64-1.06)	0.124	0.90 (0.69-1.18)	0.459
2-3 opioid fill	0.87 (0.67-1.14)	0.309	0.94 (0.71-1.25)	0.674
>3 opioid fill	1.03 (0.75-1.43)	0.835	1.14 (0.81-1.62)	0.452
Number of unique medications filled	0.99 (0.96-1.01)	0.257	1.00 (0.98-1.02)	0.969
Number of unique prescribers	1.00 (0.96-1.03)	0.836	0.99 (0.96-1.03)	0.643
≥1 physician office visit	0.84 (0.64-1.10)	0.212	0.87 (0.62-1.22)	0.416

Significant at P<0.05. IRR: Incidence Rate Ratio. ED visits: Emergency department visits
We used fixed effects negative binomial models at patient level. The models included lagged effects of all the above factors.

Overall medication nonadherence measured at patient-level was based on eighteen index drug classes.

Mental illness is defined as ≥1 antidepressants or anxiolytics fill or diagnosis of depression/anxiety.

The multivariable model with inpatient stays as outcome included 1,299 patient-periods.

The multivariable model with ED visits as outcome included 1,045 patient-period.

APPENDIX C. SUPPLEMENTAL MATERIALS FOR CHAPTER 4

Table C-1. Key SafeMed Care Transitions Interventions at Different Time Points

Week	Activities	Lead staff*
	Hospital-based	
0	Real time in-hospital identification, screening and enrollment of eligible patients	NP/RN
	Introduction of SafeMed team and initial patient engagement with team and SafeMed program	SafeMed team
	Medication reconciliation and medication therapy management	Pharmacist, CPhT-CHW
	Enhanced discharge preparation, planning, education and care coordination with outpatient providers and community resources	NP/RN, Pharmacist
	Community-based	
1	1 st home visit within 72 hours of discharge	
	<ul style="list-style-type: none"> Symptom and physical assessment Medication reconciliation Medication therapy management Identify and address social needs 	LPN-CHW CPhT-CHW Pharmacist (remote) SW/LPN-CHW
2	Phone follow-up and care coordination to ensure PCP appointment within 14 days of enrollment	CPhT-CHW and LPN-CHW
3	2 nd home visit	
	<ul style="list-style-type: none"> Symptom and physical assessment Medication reconciliation Medication therapy management Identify and address social needs 	LPN-CHW CPhT-CHW Pharmacist (remote) SW/LPN-CHW
4	30-day phone follow-up	CPhT-CHW and LPN-CHW
5	In-clinic comprehensive medication review (30-45 days after enrollment)	Pharmacist (CPhT-CHW to schedule)
6	SafeMed support session: monthly peer support group and educational session open to all program participants on an ongoing basis	SafeMed team

*The following abbreviations are used for lead SafeMed staff categories: nurse practitioner (NP), registered nurse (RN), licensed practical nurse–community health worker (LPN-CHW), certified pharmacy technician–community health worker (CPhT-CHW), social worker (SW).

VITA

Satya Surbhi was born in India. She completed her undergraduate education in Pharmaceutical Sciences from Manipal University in Karnataka, India in 2007. She moved to the United States to pursue her master's degree in Pharmacy Administration at St. John's University in Jamaica, NY, which she successfully obtained in 2011. In 2012 she joined the University of Tennessee Health Science Center (UTHSC) as a doctoral student in the Health Outcomes and Policy Research program, majoring in Health Policy.

During her time at UTHSC, Satya has made several presentations, including posters, published papers in peer-reviewed journals, and been in a leadership position as a Chair of the Professional Development Committee of the Graduate Student Executive Committee, UTHSC. In her role as a Data Manager for the SafeMed program, Satya has successfully handled several responsibilities, including, training the SafeMed staff in data entry, oversight of the SafeMed patient data and hospitalization data quality, periodic analyses of the SafeMed data for examining process measures for the dashboard run charts and quarterly reports, and coordinating with the SafeMed measurement team in obtaining Medicare and Medicaid claims data and designing the final SafeMed data analysis plan. In September 2015, she received a Pre-Doctoral fellowship award from the Pharmaceutical Research and Manufacturers of America (PhRMA) to pursue her dissertation topic. From November, 2016, Satya will start her postdoctoral fellowship in the Department of Medicine-Division of General Internal Medicine, under Dr. Jim Bailey, Professor in the Department of General Internal Medicine.