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Concurrent Adherence To Multiple Chronic Disease Medications: Examining The Behavior And Issues Concerning Its Measurement

Ram Sankar Basak
University of Mississippi

CONCURRENT ADHERENCE TO MULTIPLE CHRONIC DISEASE MEDICATIONS: EXAMINING THE BEHAVIOR AND ISSUES CONCERNING ITS MEASUREMENT

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RAM SANKAR BASAK

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ABSTRACT

Objectives

The objectives were to 1) examine adherence to multiple medications prescribed for a chronic disease (intra-disease multiple medication adherence) and that of multiple chronic diseases (inter-disease multiple medication adherence); 2) determine appropriate measurement paradigm from different intra-disease multiple medication adherence measurement approaches; 3) identify optimal cut-point for a dichotomized composite measure.

Methods

A retrospective study design was used. The subjects came from the MarketScan® Commercial Claims and Encounters data 2002-2003 and filled both sulfonylurea (SU) and thiazolidinedione (TZD). Adherence was measured by proportion of days covered (PDC) over each period of 30 or 90 days and cumulatively. Random components from multivariate multilevel models were analyzed to examine multiple medication adherence relationships, including associations of evolutions of adherence. Survival analysis was performed on any-cause or diabetes-related emergency services (ER) utilization. Concordance statistics were computed to compare different measurement approaches.

Results

Intra-disease multiple medication analysis demonstrated strong and significant ($p<0.05$) relationships between overall adherence estimates for SU and TZD and changes in adherence estimates over time. Patients who were receiving lipid or hypertension medications, or both in addition to SU and TZD showed strong and significant ($p<0.05$) relationships between overall adherence to cross-disease medications or cross-disease adherence slope estimates. However, such results were not observed in diabetic subjects who were prescribed nitrates for angina.

Each of six composite measures of intra-disease multiple medication adherence significantly predicted hazard (hazard ratio <1.0) of all-cause or any diabetes-related ER utilization. Although each concordance statistic was significant ($p<0.05$), there were no differences among concordance statistics produced by these measurement approaches. The average and all approach showed some superiority. The optimality of cut-point for categorizing adherence based on a composite measure of intra-disease multiple medication adherence ranged from 75-85%.

Conclusion

The study population demonstrated good but not optimal levels of adherence to multiple chronic disease medications. Factors that affect adherence to individual medications appear to be related and should be targeted for intervention. Efficacy of a composite measure of intra-disease multiple medications may depend on intervention goals. Further research needs to identify a composite measurement approach that demonstrates superiority in predictive and discriminatory power consistently.

DEDICATION

This dissertation is dedicated to my late father, my mother, and Shri Shri Lokenath Bramhachari.

LIST OF ABBREVIATIONS AND SYMBOLS

ACEI ..... Angiotensin I Converting Enzyme Inhibitors
AH..... Antihypertensive Medications
AHT ..... Antihypertensive Therapy
ANG..... Antianginal Medications
ARB ..... Angiotensin II Receptor Blockers
CCB..... Calcium Channel Blockers
CCI..... Charlson Comorbidity Index
CSM ..... Common Sense Model of Self-Regulation
DV..... Dependent Variable
ER ..... Emergency Room Services Utilization
ICD..... International Classification of Diseases
LP ..... Medications for hyperlipidemia
LIP..... Medications for hyperlipidemia
MPR ..... Medication Possession Ratio
NDC ..... National Drug Codes
OAD..... Oral Antidiabetic Medications
QTR..... Quarter
PDC..... Proportion of Days Covered
SU ..... Sulfonylurea
TZD..... Thiazolidinedione

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TABLE OF CONTENTS

LSIT OF TABLES

LSIT OF FIGURES

CHAPTER 1

INTRODUCTION

Chronic Diseases and Its Implication

The disease-related pharmaceutical market landscape has been evolving for the last few decades. This evolution is characterized primarily by marked changes in incidence and prevalence, and thus importance, of chronic diseases. According to the Centers for Disease Control and Prevention (CDC), chronic diseases such as cancer, diabetes, heart disorders, stroke, and arthritis are among the most common, expensive, and preventable of all health problems in the U.S. The number of patients with at least one chronic disease is growing in America and projected to rise to 164 million by 2025 (Wu and Green, 2000). Chronic diseases have associated with them significant implications. For example, seven out of 10 deaths annually among Americans occur from chronic diseases; heart disease, cancer, and stroke account for more than 50% of all deaths each year (Kung et al., 2008). Moreover, chronic disease patients are likely to consume health care resources frequently because of the nature of care they require.

Chronic comorbidities

It is undeniable that the situation facing the healthcare system today is dire because of the increasing prevalence of chronic diseases in the U.S. population. However, the chronic disease crisis looms even larger for tomorrow. It is imperative that chronic diseases be managed

appropriately. Additionally, the challenge associated with the management of chronic disease is compounded because many of these patients experience two or more chronic diseases simultaneously (multiple comorbidities). In fact, a consistent pattern has been found currently such that many individuals present to the healthcare system with multiple coexisting diseases (Starfield, 2006). In the U.S., the number of patients with multiple comorbidities has been estimated to increase from 60 million in 2000 to 81 million by 2020 (Mollica and Gillespie, 2003). This growth in comorbidities is not confined to any specific segment of population or geographic region. The National Center for Health Statistics (NCHS) reported that 7% of adults of 45–54 years of age, 30% of low income adults of 55–64 years of age, and 37% of adults of 75 years of age and over had three or more chronic conditions in 2005 (NCHS, 2007). Moreover, not all chronic disease necessarily have symptoms associated with them and they may remain undiagnosed. Approximately 10% and 8% of U.S. adults of 20–64 years of age were reported to have undiagnosed high cholesterol and elevated blood pressure, respectively in 1999–2004 (NCHS, 2007). Thus, it is possible that many chronic disease patients, at some point in time, may be suffering from comorbidities the number of which may exceed current estimates.

The impact of chronic disease and multiple morbidities on the U.S. healthcare system is not trivial. This is so partly because of an increase in number of the elderly population apart from some of the reasons discussed above. In the U.S., about 80% of Medicare spending is devoted to patients with four or more chronic conditions and costs increase exponentially as number of chronic conditions increases (Wolff, Starfield, and Anderson, 2002). Health care managers increasingly have had to deploy additional resources toward the management of chronic diseases and specifically, multiple comorbidities. This confluence of events has led to a growing interest on the part of researchers and practitioners in the impact of comorbidity on

health outcomes, including mortality, health-related quality of life, and quality of health care (Fortin et al., 2007; Ritchie, 2007).

Chronic Disease Treatment and Outcomes

Treatment Trend

Prescription drug utilization in the U.S. has experienced a significant change over the last decade. Lundy (2010) reported that from 1999 to 2009, the number of prescriptions dispensed increased by 39% compared to a U.S. population growth of only 9%.In addition, the average number of retail prescriptions per capita grew by approximately 25% during the same period. These findings, at a minimum, suggest that prescription medications are being utilized for the treatment of diseases at an increasing rate.

In addition to an overall increase in medication use, the pattern of medication use unfolds an interesting trend. Physicians frequently recommend multiple therapies for the treatment of chronic disease. This trend – oftentimes described by treatment intensification or therapy augmentation – is prevalent largely in chronic disease management and has been facilitated by the availability of new products and product classes. Until the early 1990s, U.S. prescribers had only two anti-diabetic drug classes (i.e., insulins and sulfonylureas (SU)) to treat hyperglycemia associated with type 2 diabetes. Several new classes of oral anti-diabetic medications (OAD) such as metformin, acarbose, thiazolidinediones (TZD) (pioglitazone and rosiglitazone)were introduced to the U.S. market from 1995 to 1999. The availability of multiple therapeutic options gave physicians the opportunity to manage diabetes in ways that directly influenced glycemic control and the underlying disease pathophysiology. The CDC estimated that 14% of adult diabetes patients were using insulin and at least one oral medication for diabetes (CDC

National Diabetes Fact Sheet 2011). Other anti-diabetic medications that were introduced relatively recently, including glucagon-like peptide-1 (GLP-1) analogues, dipeptidyl peptidase-4 (DPP-4) inhibitors, and lispro insulin are gaining in popularity and more importantly, many products including new product classes are currently under development (Nguyen et al., 2011). Thus, it is not surprising that antihyperglycemic prescription patterns in the U.S. have changed in the last decade. The trend has included an increasing use of multiple medication regimens (Cohen et al., 2003).

The practice of intensive treatment is advocated in other chronic diseases. For example, an aggressive management of hypertension has been recommended for some patients in the U.S (Leeper 2005; Mustone-Alexander, 2006). As a result, multiple medication regimens are prescribed initially or in response to poor outcomes. This practice may have provided the impetus for two-medication combination products; in fact, a combination product of three anti-hypertensive drugs exists in the market (e.g., Exforge HCT). Interestingly, the use of combination of antihypertensive therapies (i.e., use of ≥2 antihypertensive medication classes) was higher in the U.S. when compared against European countries (Wang et al., 2007). Similarly, multiple medication regimens are the treatment norm in other chronic conditions including those in which multiple classes of medications are prescribed. For example, a number of pharmacological agents are prescribed to treat the underlying causal factors, including hypertension, coronary artery disease, and dyslipidemia in patients with heart failure. Wong et al. (2011a) reported that there has been a significant change in heart failure patient characteristics over the last two decades; along with an increasing number of comorbidities, the mean number of prescription medications has grown from 4.1 to 6.4 prescriptions. Similarly, a U.K. study of patients suffering from diabetes, hypertension, and lipid disorder reported that approximately

50%, 20%, and 30% of subjects were receiving 3, 4-5, and 6 or more medications, respectively (Stack et al., 2010).

Medication Adherence and Its Implications

Appropriate medication consumption behavior is critical to chronic disease management. In general, rates of adherence to medication regimens are low in patients with chronic conditions. An estimated 33-50% of all patients do not take their medications as prescribed (Horne, 1999; Osterberg and Blaschke, 2005). Likewise, persistence with chronic disease medications is also low as many patients with chronic conditions oftentimes discontinue treatment within a few months of initiation. One study found that while adherence was approximately 80% in the first 3 months of treatment, the adherence rate to anti-hyperlidemic medications reduced to 56% within 6 months and only one in four patients showed an adherence level of 80% or more after 5 years (Benner et al., 2002). Among a large cohort of patients who were suffering from coronary artery disease, over 25% of patients discontinued their medication within 6 months and only 74% of patients were adherent to all prescribed medications just 120 days after an acute myocardial infarction (MI) (Jackevicius, Mamdani, and Tu, 2002). In spite of evidence supporting the use of pharmacotherapy, patients do not appear to demonstrate appropriate medication use behaviors.

Large-scale studies have confirmed repeatedly that pharmacological treatment can reduce adverse outcomes associated with chronic diseases. However, the reduction of the occurrence of potential adverse outcomes depends on patients' ability to follow their prescribed medication regimens. The relationships between poor adherence and desirable treatment outcomes have been examined. Various outcomes that have been studied include clinical parameters (e.g., systolic or diastolic blood pressure, HbA1c, or lipid profile) or adverse events (e.g.,

hospitalizations or emergency room visits). Patients who were highly adherent to antihypertensive therapy (AHT) were more likely to achieve blood pressure control than those with medium or low adherence (Chapman et al., 2005). Similarly, 'good' adherence to pharmacotherapy was associated with a host of positive health outcomes. A study investigating the relationship between antihypertensive therapy use and the risk of MI/stroke reported that patients who stayed with the therapy were at significantly lower risk of myocardial infarction (MI) or stroke than who did not (Charles et al., 2003). Additionally, adherence to medication regimens has been shown to reduce the risk of hospitalization or emergency room (ER) visits. Sokol et al. (2005) examined the relationship between adverse health outcomes and poor adherence in patients with diabetes, hypertension, high cholesterol, and congestive heart failure to examine the relationship between poor adherence and adverse health outcomes. In all four conditions, hospitalization rates were significantly higher for patients with low medication adherence and there were 26% and 18% reductions in hospitalization or ER visits over a 2-3 year period among diabetes patients and hypertension patients, respectively, who were adherent to treatment. A negative association between adherence and mortality has also been reported (Ho et al., 2006a; Rasmussen, Chong, and Alter, 2007; Simpson et al., 2006). For example, one-year mortality was significantly higher in patients who were taking only some of their medications compared to those adherent to all medications (Jackevicius, Li, and Tu, 2008). More importantly, similar associations, including those against all-cause mortality, hold for different medication classes (e.g., statins and β-blockers) (Rasmussen, Chong, and Alter, 2007; Wei et al., 2002).

In spite of the strong association of adherence with positive outcomes, nonadherence to medication remains a significant public health problem. A report by the World Health

Organization (WHO) states that nonadherence to medications for chronic disorders such as hypertension, dyslipidemia, and diabetes leads to reduced health benefits and serious economic consequences in terms of wasted resources including time and money (WHO, 2003). Poor medication adherence is a source of waste in health care systems or avoidable medical spending in the U.S. because it gives rise to unnecessary health risks, particularly for patients with chronic illnesses (New England Healthcare Institute (NEHI), 2009).For a typical, mid-sized employer that spends $10 million in medical claims, poor adherence is associated with avoidable healthcare expenditures of about $1 million annually (NEHI, 2009). Poor adherence or nonadherence has been shown to result in $100 billion each year in excess hospitalizations alone (Osterberg and Blaschke, 2005). In addition to poor health outcomes that translate into societal costs, overall health care costs are much higher for patients with poor adherence. The annual healthcare costs were estimated to be $8,886 for diabetes patients with high levels of adherence as compared to $16,498 for those with low levels of adherence (Sokol et al., 2005). Additionally, a 10% increase in adherence was associated with 2% and 4% decrease in total health care costs and diabetes-related medical care costs respectively (Shenolikar et al., 2006). However, the association between costs and adherence is not clear. Medication adherence was positively associated with lower disease-related medical costs in chronic conditions such as diabetes and hypercholesterolemia (Sokol et al., 2005); however, evidence contrary to what mentioned above exists also (e.g., Karve et al., 2008). Because 75% of U.S. health care spending is used for the treatment of chronic disease (CDC, 2009), the role of adherence in chronic disease management, improving the efficiency in the health care system, and achieving desired health outcomes cannot be overemphasized.

Need for the Project

Decades of research has advanced our understanding of patient adherence to medication. A range of perspectives including medicine, pharmacology, psychology, and nursing (Russell et al., 2003) have been employed to examine adherence behavior. A host of factors, both internal (e.g., personality) and external (e.g., socio-cultural), (see Cameron, 1996 for a review) have been implicated. Some of these factors offer a simplistic but, to some extent, successful model explaining patient adherence. Other approaches emphasize the complex, dynamic, and reciprocal nature of relationships among the factors affecting adherence including how patients cognitively interpret and act on their illness and associated symptoms (Bishop, 1991; Leventhal, Diefenbach, and Leventhal, 1992). In spite of these effects, several questions related to adherence remain unanswered. Specifically, there is a dearth of understanding about the consistency of adherence behavior within a disease and across diseases and the state of change of such behaviors in patients over time.

Multiple therapies are often prescribed for patients suffering from chronic diseases. Indeed, treatment intensification is advocated and advised earlier in the patient's treatment for a chronic condition (Grant et al., 2011). Thus, multiple medication regimens may occur because of multiple medications intended to treat a single disease or because of the need to treat comorbidities. While treatment intensification and treatment of comorbidities have become the norm, new issues arise as a result of such practices. Further examination of intra-disease and inter-disease multiple medication adherence are warranted. Another important issue is the measurement of intra-disease multiple medication adherence, including the selection of right measure. These issues seem relevant and merit empirical exploration.

Study Aims:

The present study has several aims. The hypotheses and objectives associated with these aims are discussed in Chapter 2. Specifically, this study:

1. examined adherence to multiple medications prescribed for the treatment of a chronic disease (intra-disease multiple medication adherence behavior);
2. examined adherence to multiple medications prescribed for the treatment of different but related chronic diseases (inter-disease multiple medication adherence behavior);
3. proposed a composite measure for the estimation of adherence to multiple medications prescribed for the treatment of a chronic disease;
4. compared the existing methods and the proposed method of estimating adherence to multiple medications prescribed for the treatment of a chronic disease;
5. calibrated the intra-disease multiple medication adherence measurement approaches including the composite measure.

Significance

The rising prevalence of chronic disease, including diabetes, hypertension, and hyperlipidemia is a recognized public health concern. For patients on intensified treatment regimens or multiple medications, the concern is increased due to the risk of adverse consequences associated with inadequately controlled or uncontrolled disease. The practice of prescribing multiple medications for a chronic disorder has increased recently and is expected to continue in the future due to the aging U.S. population, increase in knowledge of disease, and the availability of newer classes of medications. Although chronic disease patients may be managed with a single fixed-dose combination medication, this option is not always available for all

patients. Thus, the importance of understanding multiple medication adherence within a disease or across diseases is and remains an important issue facing the healthcare system. It is believed that this information on multiple medication adherence may act as trigger to providers and will guide clinicians, pharmacists, healthcare managers, and policy makers to formulate strategies to improve medication adherence and design interventions to promote health behaviors. As various suggestions (e.g., synchronization and scheduling) (Agarwal et al., 2009) have been made to improve medication adherence, the applicability of these strategies will be strengthened by the knowledge about intra-disease and inter-disease multiple medication adherence behavior. Indeed, profiling patients based on adherence patterns will help with designing subsequent interventions.

Assessing or measuring medication adherence is the first step in order to understand nonadherence and lay the groundwork for interventions for improving adherence (Morisky et al., 2008). Although many measures of adherence exist (see McCaffrey, 2011 for a review), most were developed to evaluate adherence to individual medications or medication classes. Thus, an examination of these measures in situations where patients are prescribed multiple medications for a disease is important. In a market where implementation of quality initiatives and performance-based incentives are increasingly advocated and emphasized (Lee, 2007), the question about measuring multiple medication adherence occupies a central position. The lack of informed thought, as it is now, is going to constrain the appropriate assessment of adherence to multiple medications and hamper the quality of patient care. Moreover, the effect of metric choice must be known in order to provide guidance and consistency in the adherence literature. In particular, an empirical rationale about measure choice while examining multiple medication adherence is needed for practitioners, researchers, and policy makers alike.

CHAPTER 2

LITERATURE REVIEW

Adherence Research

Adherence to medication has been a focus of much research for, at least, the last five decades. Apart from a nearly uncountable number of primary studies that have been conducted on adherence/compliance, the number of reviews and meta-analyses of studies on the same topic is not small. The breadth and depth of past research on adherence is extremely large and a thorough discussion is beyond the scope and objective of this chapter. It is well known that many factors affect adherence. Researchers have attempted to categorize these factors into different dimensions deemed to be most important. For example, the WHO (2003) describes five sets of factors as being influential on medication-taking behaviors of patients. These are socioeconomic, patient-related, therapy-related, condition-related, and healthcare team-related factors of adherence. However, there is little consensus regarding the optimal categorization of factors that influence adherence.

Adherence to Chronic Disease

Given the prevalence and overarching impact of chronic diseases, adherence to chronic disease medications has been extensively investigated empirically. In general, these studies are conducted within a disease category such as diabetes (Adams et al., 2008), hypertension (Morrell et al. 1997), dyslipidemia (Huser, Evans, Berger, and 2005), heart failure (Dunlay et al., 2011),

ischemia (Carney et al., 1998), myocardial infarction (Maio et al., 2011), stroke (Khan et al., 2010), and so on. While some studies focused on a single class of medications or a single product within a disease (e.g., Kogut et al., 2004; Pladevall et al., 2004; Shenolikar et al., 2006), others focused on multiple medications, including multiple therapeutic classes within a disease (e.g., Alvarez Guisasola et al., 2008; Dunlay et al., 2011; Guillausseau, 2003) or on a single medication across diseases (e.g., Thavendiranathan et al., 2006).

On average, there is not much difference in adherence estimates among different chronic disease categories. A meta-analysis concluded that adherence rates, measured by 12-month medication possession ratio (MPR), in antihypertensive, anti-diabetic, and anti-hyperlipidemic medication(LIP) categories varied between 67% and 76% and were not significantly different (Cramer et al., 2008). However, it is not uncommon to find individual studies reporting lower rates of adherence to pharmacotherapy. For example, one U.S. study reported that the average antihypertensive adherence was 49% among elderly patients initiating therapy (Monane et al., 1996). Likewise, a systematic review of studies reported that adherence rates in diabetes varied widely among oral agent-only (36%-87%) versus concomitant or insulin-only (54%-81%) regimens (Lee et al., 2006). Adherence within a disease may vary depending on therapeutic class or subclass. For example, Wogen et al. (2003) compared adherence rates of amlodipine, lisinopril, or valsartan. These medications belong to three different pharmaceutical subclasses calcium-channel blocker (CCB), angiotensin-converting enzyme inhibitor (ACEI), and angiotensin receptor blocker (ARB), respectively and were found to exhibit significantly different average MPRs (75% for valsartan, 67% for amlodipine, and 65% for lisinopril). Other studies have examined different measurement approaches to examine adherence. One such method is analyzing dichotomized adherence rates. Dunlay et al. (2011) investigated 6-month

adherence rate among community dwelling heart failure patients; proportions of patients who had poor adherence based on medication possession (proportion of days covered (PDC)< 80%) to β-blockers, ACEIs/ARBs, and statins were 19%, 19%, and 13%, respectively. Monane et al. (1996) reported only 23% of hypertension patients showed adherence levels of 80% or greater measured over a year.

Alternatively, studies have examined persistence with therapy or duration with therapy before discontinuation. Unlike adherence rates, persistence rates were somewhat similar for different product categories. An analysis of 139 studies that focused on diabetes, hypertension, dyslipidemia, and other cardiovascular diseases revealed that only 63% of patients continued with their medication for one year (Cramer et al., 2008). Persistence appears to have strong relationship with time; in general, persistence decreases over time. A systematic review reported that treatment persistence with OAD ranged from 16 to 80% in patients who continued their treatment for 6-24 months and discontinuation time ranged from 83-300 days (Cramer, 2004). Approximately 10-30% of type 2 diabetes patients enrolled in a Medicaid population were found to withdraw from SU regimens within one year of diagnosis (Sclar et al., 1999). Persistence fell less sharply from 97% at 1 year to 82% at 4.5 years for patients with established hypertension compared to that of 78% and 46% over the same period for those with newly diagnosed disease (Caro et al., 1999). Persistence with anti-hyperlipidemic medications is lower in primary prevention than in secondary prevention. Perreault et al. (2005) observed that persistence with statin fell from 71% after 6 months of treatment to 45% after 3 years in the secondary prevention cohort, while the corresponding values in the primary prevention cohort were 65% and 35% respectively. Ho et al. (2006b) evaluated the early discontinuation of β-blockers, aspirin, and statins among acute myocardial infarction patients. One month after treatment initiation, the

authors reported, 12.1%, 3.7%, and 17.9% of patients discontinued all three drugs, two out of three drugs, and one drug, respectively, while approximately 66% of patients continued taking all three medications. Likewise, persistence to medications has been examined across disease states. In elderly patients (≥ 65 years) the two-year adherence rate (measured as medication being dispensed at least every 120 days) to statin treatment was about 40% in patients with a recent diagnosis of acute coronary syndromes (ACS), 36.1% in patients having chronic coronary heart disease (CHD), and 25.4% in primary prevention patients (Jackevicius, Mamdani, and Tu, 2002). Interestingly, the average persistence rate across the studies conducted in Europe was 61.7% over an average observation period of 17 months, while that of the U.S. studies was 51.1% observed over a mean period of 21 months (Cramer et al., 2008). Hudson, Richard, and Pilote (2007) investigated the patterns of prescription and discontinuation of anti-platelet agents, β-blockers, ACE inhibitors and/or ARBs, and statins in all post-AMI (acute myocardial infarction) patients; the rates of discontinuation increased significantly during follow-up and had a parabolic shape with the youngest and oldest patients having the highest rates.

Medication adherence in different chronic conditions has been studied together within a sample (i.e., within a single study). Usually, these studies have shown modest variation in adherence across different chronic disease categories. For example, Briesacher et al. (2008) compared drug adherence rates among patients with hypercholesterolemia, hypertension, hypothyroidism, seizure disorders, and type 2 diabetes mellitus (T2D) in a commercially insured population. Approximately 72% of subjects with hypertension achieved adherence rates of 80% or better compared with 68.4%, 65.4%, 60.8%, or 54.6% for those with hypothyroidism, type 2 diabetes, seizure disorders, and hypercholesterolemia, respectively. Khanna et al. (2012) compared population adherence rates in a Medicaid population across different diseases,

including diabetes, hypertension, and dyslipidemia. On average, adherence rates were poor in the population such that approximately 35-42% patients showed adherence rate ≥ 80%.

Adherence and Demography

Medication adherence is a function of several factors, including individual characteristics. Early research on determinants of adherence focused primarily on demographic factors, not to say that such studies are not carried out any more. Indeed, many investigations were conducted within specific demographic segments such as age (e.g., Benner et al., 2002), gender (e.g., Khan et al., 2010), and race (e.g., Adams et al., 2008). In the classic review by Sacket and Haynes (1976), no clear relationship emerged between adherence and demography, including gender, race, ethnicity, education, marital status, and income. Many studies included specific age groups that ranged from a relatively young group of patients of 20-49 years (Okano et al., 1997) to elderly cohort aged 65 years or older (Monane et al., 1997). Patient age has been found to predict adherence more consistently than other demographic characteristics. Yet, some studies reported positive association of adherence to medication (e.g., AHTs or OADs) and age (Ren et al., 2002; Venturini et al., 1999) while other studies failed to do so (Coons et al., 1994; Evangelista et al., 2003). The relationship between age and adherence, however, may not be linear. Morrell et al. (1997) reported that the younger old, (e.g., 60-70 years), demonstrated the highest levels of adherence to AHTs, whereas the adherence levels of those over 75 years were the lowest. Indeed, the study concludes, adherence was problematic for those over 75 years. In light of such finding, it appears that the differential impact of age on medication adherence may be affected by some other factors. Park (1999) argued such effects may be mediated by cognitive changes or other age-related factors.

Adherence: Trait and Intention

Researchers have searched for stable characteristics that affect adherence. Dispositional characteristics that affect general behaviors have been examined. Specifically, associations have been examined between personality factors and adherence to medications in chronic diseases, including diabetes and hyperlipidemia (Axelsson et al., 2009; Christensen and Smith, 1995; Stilley et al., 2004). Past research has shown that conscientiousness, a personality trait reflecting methodical and industrious behavior, is associated with treatment adherence (Christensen and Smith, 1995; Stilley et al., 2004). However, the associations with personality traits have not been supported consistently. Using a medication events monitoring system (MEMS), Insel, Reminger, and Hsiao (2006) investigated the association between personality and adherence in older community dwelling adults who were using chronic medications, including AHT and LIP. The study found no association with conscientiousness but it did found negative associations with other personality factors, namely self-reliance and independence. Recently, an observational study found that no personality traits except neuroticism were associated with medication nonadherence over 6 years of follow-up in a sample of elderly patients receiving an alternative (herbal) medication (Jerant et al., 2011). It is possible that these characteristics work in conjunction with other factors. For example, the interaction between conscientiousness and health beliefs was found to predict adherence among hemodialysis patients (Wiebe and Christensen, 1997). Thus, the influence of personality factors may be less clear or conditional on other variables. In addition, with evidence showing that there may be marked inter-individual and intra-individual variation in adherence to different medications or different aspects of treatment over time (Cleary et al., 1995; Kruse and Weber, 1990), defining patients by stable characteristics, which could be speculated to constitute ‘compliant patient’ or ‘noncompliant

patient' is not practically sensible or theoretically tenable. At most, as suggested by Horne (1998), they can influence some but not others and this has led to exploration of the interaction of patients with their disease and treatment.

A patient may make decision, consciously or subconsciously, about adherence to medications. It has been argued that such decision-making is related broadly to distinct types of medication nonadherence – intentional nonadherence and unintentional nonadherence – and potentially contribute to observed patterns of adherence behaviors (Clifford, Barber, and Horne, 2008; Johnson 2002; Morisky, Green, and Levine, 1986; Stack et al., 2010). While intentional nonadherence describes an active process in which the patient makes a conscious decision about deviating from a medication regimen, unintentional nonadherence represents a passive process in which the patient may deviate from appropriately following the treatment regimen because of carelessness or forgetfulness (Morisky, Green, and Levine, 1986). Past research has examined these mechanisms empirically in chronic care management. Using a self-report measure, Lowry et al. (2005) examined adherence to antihypertensive medications among veterans and found that approximately 9% of the study subjects reported intentional nonadherence and 31% reported unintentional nonadherence. Stack et al. (2010) measured self-reported intentional and unintentional nonadherence to differing numbers of medicines prescribed in type 2 diabetes patients and found no difference in intentional nonadherence. Among patients receiving OADs, AHTs, and statins; the authors noted, while intentional nonadherence to statin significantly increased with number of medicines prescribed, unintentional nonadherence was higher for some medicines than for others (e.g., OAD adherence < AHT or statin). Similarly, Wroe (2002) found that different reasons or beliefs with regard to utility were associated with intentional adherence as opposed to unintentional adherence among asthma patients. Other researchers examined a

number of other factors including complexity, type, and knowledge of medication regimens and presence of co-morbid conditions (Barr et al., 2002; Horne, 1998; Lehane and McCarthy, 2007) to explore the unintentional nonadherence. Thus, it appears that varying levels of both the intentional and the unintentional dimensions of medication taking may occur simultaneously. It is recommended that simultaneous examination of the intentional and unintentional dimensions of nonadherence be considered for the sake of comprehensive understanding of the factors of nonadherence (Lehane and McCarthy, 2007; Johnson, 2002), although these dimensions may have varied motivational or psychosocial factors associated with them.

Psychological Factors in Adherence: Health and Disease Beliefs and Attitudes

Several theoretical models in social psychology have been adapted to explain variations in adherence to treatment. These theories can be broadly categorized into two groups: Social Cognition Models (SCM) and Self-regulatory Theory. The social cognitive perspectives focus on attitudes and beliefs or expectancies as major determinants of health behavior (Conner and Norman, 1996). They assume that patients undertake cost/benefit analyses as a motivating factor to act. Subjective weighting of the benefits, barriers, and consequences of behaviors provide the motivation for actions. Several theoretical models fall under this group(e.g., the Health Belief Model (HBM), the Theory of Reasoned Action (TRA), the Theory of Planned Behavior (TPB), and the Social Learning Theory). The HBM has been utilized in studies of medication adherence across several diseases including hypertension (Cronin, 1986) and diabetes (Brownlee-Duffeck et al., 1987). The TRA and TPB constructs have been useful in predicting adherence to prescription medications (Miller, Wikoff, and Hiatt, 1992; Reid and Christen, 1988). The concept of locus of control - more specifically, multidimensional health locus of control (HLC)

(Wallston, Wallston, and Devellis, 1978) - has been applied in the health care context. The HLC beliefs provide inconclusive or inconsistent evidence and remain fairly weak predictors of adherence behavior (see Horne and Weinman, 1998 for a discussion). Disease-specific HLC beliefs have also been advanced. The use of condition-specific HLC measures appears to improve the utility of the framework. For instance, disease-specific locus of control measures have been associated with adherence to diabetes care and hypertension (Bradley et al., 1990; Kohlman et al., 1993; Stanton, 1987). Several studies have combined constructs from different theories were combined to examine patients' adherence behavior. For example, Reid et al. (1985) used the HBM and the TRA to examine intention to comply with antihypertensive regimens. Efficacy beliefs (e.g., outcome efficacy and self-efficacy) and HBM constructs were examined among patients who were compliant or noncompliant to tuberculosis treatment (Barnhoorn and Adriaanse, 1992) or for predicting adherence with an over-the-counter acne medication (Flanders and McNamara, 1984). Wang et al. (2002) used health beliefs based on the TRA and LOC beliefs to examine medication nonadherence in hypertension patients.

Although Social Cognitive Models have been extensively used, they are not devoid of criticism. Rationality of health-related behavior, a fundamental premise of SCMs, is questioned. Indeed, some health behaviors appear to be habitual or routine and may not always be characterized by rational decision-making. Moreover, the dynamic nature of health behavior is often ignored. In an attempt to explain the dynamic relationships among cognitions, motivations, and behaviors, Leventhal and colleagues developed the Self Regulatory Model (SRM) - a self-regulatory framework for understanding illness perceptions (Leventhal, Diefenbach, and Leventhal, 1992; Leventhal et al., 1997). The fundamental premise of the SRM is that patients are active problem solvers who respond to illness in a dynamic and specific fashion based on

their interpretation and evaluation of illness and its symptoms (more discussion follows). The role of illness representation in explaining adherence decisions have been examined empirically and illness representations (i.e., patient's own beliefs about illness) were associated with treatment adherence among chronic disease patients (Bane, Hughes, and McElnay, 2006; Gonder-Frederick and Cox, 1991; Meyer et al., 1985).

Patient-Provider Interaction and Associated Impacts on Adherence

Chronic disease care requires a long-standing interaction between a patient and a health care provider. Thus, the patient-provider relationship is important for the success of chronic diseases management. Researchers have recognized factors that characterize the quality of patient-provider interactions as important determinants of medication adherence. Interaction quality, including the state of collaboration between a provider and a patient, behaviors and attitudes of healthcare professionals, and amount of time spent with patients in a supportive environment discussing medications or diseases (Arbuthnott and Sharpe, 2009; Cameron, 1996; Kiortsis et al., 2000) have been examined for their effect on medication adherence. A specific aspect of the patient-physician interaction that has been extensively investigated is the role of communication. A meta-analysis of 106 studies found a positive relationship between physician communication and adherence (Zolnierek and Dimatteo, 2009). Piette et al. (2003) examined dimensions of communication; both general communication and diabetes-specific communication were correlated independently with patients' self-reported adherence to hypoglycemic medications. Thus, it is believed that an appropriate collaborative relationship between a patient and a provider may improve medication adherence. As may be expected, one of the basic communication goals is to improve patient's knowledge about various aspects of

disease or treatment. Numerous studies have been conducted to examine the effects of knowledge of disease and medication on adherence. Although there is some conflicting evidence, in general, a positive correlation has been found between knowledge and adherence to chronic disease medications (Cuspidi et al., 2001; McDonald, Garg, and Haynes, 2002). In addition, patient-centered, communication-driven interventions, such as disease management programs, are thought to facilitate the management of chronic care and help patients in their effort to self-care. In fact, disease management has been implemented to educate chronic disorder patients and support self-management skills and reported to improve adherence to treatment recommendations (Fitzner et al., 2005; Thiebaud et al., 2008). Indeed, disease management is widely recommended for patients on multiple medications.

Adherence and Treatment Intensification

Adherence to medication assumes importance because of its profound role in achieving desired therapeutic benefits. In other words, that nonadherence to medications may potentially lead to adverse consequences is of great public health concern and reasons for such concerns have been discussed in the previous chapter. Thus, adherence enhancement occupies a central role in chronic disease management in that it helps achieve treatment goals. Another potential way to achieve treatment goals is through intensification of therapy. Specifically, therapy intensification (TI) can occur through an increase in dosage of a medication that is already being consumed by the patient for a disease, an addition of a medication or multiple medications to the patient's prescribed regimen intended for the disease, or switching to a new class of medication (Rodoni et al., 2006; Schmittdiel et al., 2008). As such, the relationship between adherence and treatment intensity is important for research purposes due to its clinical implications. A survey

of physicians reported that those who intensified therapy in patients with type 2 diabetes were more likely to consider issues such as patient adherence and medication costs (Grant et al., 2009). Some researchers have addressed whether physicians are likely to increase therapy depending on patient adherence (Grant, Singer, and Meigs, 2005; Heisler et al., 2008). Nonadherence was not related to the subsequent addition of a second drug in diabetes patients (Kogut et al., 2004). Others suggest that there may be an interaction between adherence and disease. Poor adherence was reported to inhibit intensification of diabetes therapy but not that for antihypertensive medications in diabetes patients (Voorham et al., 2011). The extent of lack of therapy intensification among adherent patients has also been investigated. Among diabetes patients with no evidence of poor adherence, the lack of treatment intensification was found in 30% , 47%, and 36% of patients for hyperglycemia, hyperlipidemia, and hypertension treatment, respectively (Schmittdiel et al., 2008). On the contrary, Grant et al. (2007) reported that diabetes patients with poor adherence were less likely to have their regimen increased and time to intensification was negatively associated with adherence in poorly controlled patients. Researchers have examined the relationship between TI and adherence in achieving desired control over time. Rose et al. (2009) observed that treatment intensification was associated with improvement in blood pressure regardless of the patient's level of adherence. However, other researchers have concluded that achieving desired treatment goals is a function of a combination of intensification and adherence; therapy intensification must be coupled with interventions to improve medication adherence (Ho et al., 2008). Although no consensus exists regarding the role of adherence in intensification of therapy, it can be posited at a minimum that the full benefit of therapy intensification cannot be realized without adequate adherence.

Adherence to Multiple Chronic Disease Medications

It has been well established that underutilization of medications is a major problem in health care. In general, studies on medication utilization focus on a single therapeutic class of medications. A meta-analysis undertaken to examine studies related to adherence to diabetes, hypertension, and dyslipidemia medications concluded that over 80% of the 139 studies that were reviewed investigated only one therapeutic class (Cramer et al 2008). Although a few studies exist that have compared adherence rates across different disease categories in a single study (e.g., Khanna et al., 2012), they did not analyze simultaneous adherence to multiple medication regimens. This approach (i.e., considering adherence within a single disease category) is not much insightful because it is well known that the presence of multiple chronic comorbidities is now more of a norm than an exception. Moreover, this approach is not consistent with the recommendation of aggressive treatment of comorbidities.

Only a few published studies have examined concomitant adherence to medications prescribed for multiple chronic diseases. Chapman et al. (2005) investigated patterns and predictors of simultaneous adherence to newly initiated antihypertensive and anti-hyperlipidemic therapies. Using a dichotomized measure of adherence, the researchers concluded that 44.7% and 35.8% of the patients were adherent with both antihypertensive (AH) and anti-hyperlipidemic (LIP) medications at 3 and 12 months after medication initiation respectively; however, at each time, approximately an additional 25%-29% of the subjects demonstrated PDC $\geq$ 80% to either AHT or LIP. Concomitant medication consumption behavior has been examined, although less explicitly, in other disease conditions. For example, patients receiving long-term dialysis demonstrated higher adherence to antihypertensive and calcitriol therapies than their phosphate binder regimens (Cleary et al., 1995). Preferential or selective adherence

was shown to be prevalent in kidney transplant patients. A cross-sectional study of kidney transplant patients compared adherence rates over a month for nonimmunosuppressive medications (i.e., AHT, LIP, and anti-diabetic agents) and immunosuppressive medications; more patients were reported to be selectively more adherent to immunosuppressive medications and nonadherent in the former therapeutic category were more likely to have diabetes (Terebelo and Markell, 2010). A study was conducted to examine medication use in patients who were discharged from hospital after acute myocardial infarction with prescriptions for aspirin, statin, and β-blockers; while 34% of the patients discontinued at least one medication, 12% stopped all three medications within a month of hospital discharge (Ho et al,. 2006b). A small study with diabetes patients who had asthma reported that the pattern of diabetes and asthma medications had a similar dispensation interval among 52% of the patients (Krigsman, Nilsson, and Ring, 2007). However, the refill adherence rate for diabetes medication was higher than that for asthma medication with no correlation between adherence levels. Adherence to medication for one disease has been examined as predictor of adherence for another disease. Diabetes medication adherence, for instance, was associated positively with odds of being adherent to statin medication in a university employee population (Kumar and Holiday-Goodman, 2010). Simultaneous adherence across therapeutic classes has been examined among patients with psychiatric as well as physical comorbidities. A study with patients who were using medications for schizophrenia, diabetes, and hypertension examined differential medication adherence (Piette et al., 2007). Intra-patient adherence rates as measured by MPR across therapeutic classes, the authors noted, were correlated modestly; while the correlation of MPRs for hypertension and diabetes was the highest, there were weak but significant correlations between MPR for antipsychotic medications and MPR for each of the two physical conditions. MPR for

antipsychotic medications explained only 13% and 16% of the variance in that for antihypertensive and hypoglycemic medications, respectively. In addition, patients were more likely to show poor adherence for antihyperglycemic and antihypertensive therapies than for antipsychotic therapy (Piette et al., 2007).

Relatively few studies have examined selective adherence over a long period of time. Indeed, such research is insightful in that it has the ability to guide in understanding changes within an individual. Nichol et al. (2009) examined the transition probabilities of patients receiving both LIP and AHT therapies among different adherence categories (i.e., fully adherent, partially adherent ($0.2 \leq PDC < 0.8$), and nonadherent) over a period of six years. The study reported that patients showing full adherence to both medications at the beginning were more likely to maintain their adherence status and patients who were partially adherent to one and fully adherent to the other were more likely to elevate to the adherent status for both medications. The results of the study are interesting in that they suggest the presence of an adherence trait. However, other variables (e.g., comorbidity profile, beliefs, etc.) that were not evaluated may explain further the results. The study found an association between type of medication and transition to nonadherence. Interestingly, this finding is also supported by another study despite methodological differences. Grant et al. (2003) interviewed diabetic patients to examine 7-day adherence to multiple medications; patients with overall suboptimal adherence appeared to have issues with one specific medication and similar observation was made in patients who showed suboptimal adherence and were consuming three or more anti-diabetic medicines although no association with number of medications was found.

Adherence and Burden of Consuming Multiple Medications

From the above discussion, it is apparent that chronic disease patients are likely to experience multiple medication regimens. As such, the burden may occur because of multiple chronic diseases, aggressive treatment (e.g., therapeutic intensification), or a combination thereof. The relationship between number of medications being taken and adherence has been the focus of many studies including those of concomitant adherence. Chapman et al. (2005) observed a negative relationship between number of other prescription medications taken in the year before initiating concomitant antihypertensive and anti-hyperlipidemic medications and the likelihood of adherence with concomitant therapy. Similar relationships have been observed by other studies examining joint adherence (Benner et al., 2009; Terebelo and Markell, 2010). Interestingly, Benner et al. (2009) noted a significant curvilinear relationship indicating a decline in change in adherence to concomitant AHT and LIP with increase in number of prescriptions. The relationship within the context of adherence to a single medication or a class of medications has also been examined. For example, statin adherence in an elderly population was negatively associated with number of total prescriptions for other medications (Benner et al., 2002; Jackevicius, Mamdani, and Tu, 2002). However, evidence contradicting the relationship as discussed above also exists. Grant et al. (2004) examined the impact of concurrent medication use on statin adherence and refill persistence; number of concurrent medications, including statin, measured at initiation of statin therapy as well as at last recorded fill of statin was positively associated with statin adherence and persistence. In a study of predictors of suboptimal adherence in diabetes patients, Grant et al. (2003) observed that total number of medications prescribed was not associated with self-reported medication adherence measured over seven days. Similarly, Piette et al. (2007) found that number of drug classes was associated

with a slight decrease in odds of being nonadherent. The relationship may vary by disease. Briesacher et al. (2008) found that add-on drug therapies enhanced adherence among subjects with hypertension, type 2 diabetes, hypothyroidism but not with hyperlipidemia; although burden was generally small, the association of comorbidity with adherence varied across disease. Thus, the relationship between the burden of prescription medications and adherence appears to be intriguing. Patients' overall comorbidity profile and medication beliefs may be the potential reasons for the discrepancy. However, methodological issues (e.g., method to sum up all prescriptions) may also explain such results.

Measurement of Adherence

Precise and appropriate measurement of medication use behavior has been an important topic in the realm of adherence research. Adherence/compliance and persistence are commonly chosen to present medication utilization patterns although terminology, definitions, and methods of assessment vary widely in the published literature. Several different ways to measure adherence exist (see Fairman and Motheral, 2000 for a review). A review of studies of patient adherence with cardiovascular medications and anti-diabetic medications showed that administrative claims data were used in the greatest number of studies, followed by questionnaires, MEMS, 'other' sources, and pill counts (Cramer et al., 2008). Retrospective pharmacy and medical claims data, although not devoid of limitations, offer several advantages, including relative efficiency. A set of diverse measures of medication adherence (e.g., MPR, discontinuations, refill adherence, medication gaps, etc.) have been used in studies using claims data; interestingly, variations in operational definition were observed within subgroups (see Andrade et al., 2006; Vik, Maxwell, and Hogan, 2004 for a review). In recent years, there has

been an increase in the trend in use of continuous measures of adherence that are based on days' worth of medication dispensed or related measures and this trend seems be driven by the propensity to analyze longitudinal observations using pharmacy claims data (Cramer et al., 2008).

Comparison of Adherence Measurement

Given that several operationalizations of adherence exist, the interpretation of research findings, if required, becomes difficult. In addition, the disparate use of adherence measures creates challenges to researchers about the appropriateness of measures to be used in adherence studies. As such, the task of selecting an appropriate measure is critical. Fortunately, some efforts have been made to compare different measures of adherence. Hansen et al. (2009) assessed the agreement among different adherence measurement methods – patient self-report, pharmacy refills, and electronic adherence measures and compared the sensitivity and specificity of different cut-off points for classifying nonadherence in a sample of hypertensive or heart failure patients. Hess et al. (2006) compared 11 measures of refill adherence that include Continuous Measure of Medication Acquisition (CMA); Continuous Multiple Interval Measure of Oversupply (CMOS), MPR, Medication Refill Adherence (MRA), Continuous Measure of Medication Gaps (CMG), Continuous Single Interval Measure of Medication Acquisition (CSA), PDC, Refill Compliance Rate (RCR), Medication Possession Ratio, modified (MPRm), Dates Between Fills Adherence Rate (DBR), and Compliance Rate (CR); while six measures(CMA, CMOS, MPR, MRA, CMG, and PDC) provided similar values, the others yielded higher values. Karve et al. (2008; 2009) compared the abilities of eight different measures of adherence to predict all-cause or disease specific hospitalization in a state Medicaid population; PDC and

MPR emerged as the best predictors of hospitalization in different disease cohorts such as diabetes, hypertension, hyperlipidemia, and congestive heart failure.

A practice that is common in the adherence literature is the dichotomization of continuous adherence estimates to categorize patients as adherent or nonadherent. Most often, the 80% cut-point is used to classify a patient as adherent or nonadherent. However, different cut-points for an operational definition of adherence have been used in past studies; such differences exist not only across studies that employed different methods but also across studies that used the same method. Maenpaa et al. (1987) defined good adherence as consuming 85% by pill count in a study of adherence in heart disease patients. Irvine et al. (1999) classified cardiac patients as poorly adherent when they had an average pill count below the 20th percentile of the pill count distribution in which the 20th percentile point represents those taking lesser than 66% of doses dispensed. Granger et al. (2005) used a complex method of estimation of adherence; the proportion of time patients took more than 80% of their study medication by pill count was determined first and then those demonstrating proportion of time greater than 80% were classified as adherent. In a study of ambulatory patients with stable coronary heart disease, nonadherence was defined as self-reported consumption of medications 75% of the time or less (Gehi et al., 2007). There are many examples of similar variations in the literature (see Vik, Maxwell, and Hogan, 2004).

Apart from using different thresholds for categorization, differences in number of categories also exist. Some studies had grouped patients into multiple categories based on adherence. For example, Bramely et al. (2006) examined the relationship between adherence and blood pressure control in patients with essential hypertension and categorized patients into three adherence groups: high (80%-100%), medium (50%-79%), and low (< 50%). In a study

exploring the relationship between drug adherence and mortality, adherence estimates, measured by PDC, were subdivided a priori into three categories: high (≥ 80%), intermediate (40%-79%), and low (< 40%) (Rasmussen, Chong, and Alter, 2007). Likewise, Nichol et al. (2009) used three adherence categories while examining adherence rates in patients who were prescribed concomitant AHT and LIP; however, different labels were used with different cut-points: fully adherent (PDC ≥ 0.8), partially adherent (0.2 ≤ PDC < 0.8), and nonadherent (PDC < 0.2). Furthermore, other researchers have used four categories to classify adherence to chronic medications (Mason et al., 2011).

Classifying patients into different categories according to their adherence behavior may be appropriate when it is consistent with the goal of research. In fact, categorization offers efficiency from the perspective of healthcare providers, including practicing pharmacists. However, the practice is not without limitations. Given a lack of uniform method, it becomes difficult to compare results, if needed. Oftentimes, the rationale behind such classification schema decisions is not explicitly stated; however, some researchers perform sensitivity analysis to examine the susceptibility of results to different classification schema. Recently, Karve et al. (2009) attempted to validate the optimality of cut-points for adherence measure for classifying patients as adherent or nonadherent. Using retrospective claims data for patients in five disease cohorts, the authors observed that the optimal cut-point of the PDC measure that predicted disease-specific hospitalization varied from 0.58 to 0.85 depending on disease. However, the predictive power of the study models was only modest as was evident from weak c-statistics. In addition, by excluding patients who were prescribed two or more drug classes for a disease the study limited its applicability in that the result may not be generalizable to patients on concurrently advised multiple medication regimens.

Measurement of Adherence to Multiple Medication Regimens

Measurement of adherence to multiple medications has been and remains a complex issue. The level of complexity may vary in situations in which the issue of measurement of adherence arises: multiple medication regimens for a single disease (i.e., therapy intensification/augmentation) and multiple medication regimens used to treat two or more diseases. Although adherence to multiple medications has been examined in few studies, the question of measurement has not been discussed explicitly. Indeed, this issue has not received the critical deliberation that it deserves. Currently, there is no consensus or published guideline for measuring adherence to multiple medications. Quite understandably, a set of varied practices exists.

Several approaches are followed for the measurement of adherence to multiple medications concurrently consumed for a single disease. These include 1) average of adherence (PDC) to each medication (henceforth, termed as 'average'), 2) adherent only if ≥ 80% PDC, measured separately for each medication, on each concurrent medication (termed as 'all'), and 3) adherent if ≥ 80% PDC measured as proportion of days when at least one medication was available, i.e., a patient is adherent on a day if he possesses at least one medication on the day, (termed as 'at least one') (see Choudhry et al., 2009 for further illustration). These estimation approaches are further complicated depending on the definition of individual intervals, i.e., denominators of adherence measures. Specifically, the interval of individual medications can be based on the entire observation period or prescription period for each drug. However, because medications are to be continued, the prescription period-based interval may not be important for most chronic disease medications except for situations when physician-recommended switches

occur. Several studies can be cited in which adherence to multiple medications was computed based on one of these approaches or some variants of them. Khanna et al. (2012) adopted the 'at least one' approach in the study of adherence to medications although the objective was not to examine multiple medication adherence. Yu, Yu, and Nichol (2010) averaged adherence of multiple medications for diabetes. Studies focusing on adherence to multi-disease medications adopted one of the above approaches. Piette et al. (2007) employed a weighted average, analogous to the average measure, in the calculation of intra-disease adherence to two medications; weight was based on the adjustment (of days supply needed) made in the denominator of the MPR estimator and weighted average MPR was then dichotomized. A similar method was employed by Schmittdiel et al. (2008) in which each drug class adherence, measured by CMG, was combined into a single estimate for all drugs for a chronic disorder; the summary measure was computed by weighting the estimate for each class by the number of days from the first to last fill in the observation period and then the single estimate was dichotomized. It is not surprising that different measurement methods result in different estimates, at least in some cases. For example, Choudhry et al. (2009) reported concurrent medication adherence estimates that ranged from 35% to 95% depending on different measurement approaches followed in patients receiving oral hypoglycemic agents. Martin et al. (2009) used a restricted definition of PDC for quarters in which multiple medications were recommended such that a patient was considered adherent on a day when he possessed all medications concurrently recommended and categorized as adherent if he had 80% or higher PDC as estimated by the method during the observation period (herein, termed as 'both'). It can be noted here that this definition ('both') will not yield any estimate greater than that of the all approach as described above. For example, if a patient is prescribed two medications concurrently and he is adherent to

the first medication for the first 16 days (80%) of a 20-day period but possesses the second medication for the last 16 days, then he will be categorized as adherent according to the 'all' measure (80% on each) but not according to the 'both' method (60%). Because of such complexities of estimation of multiple medication adherence, patients taking two or more medications for a disease are typically excluded from subsequent analyses (e.g., Karve et al., 2008; 2009; Piette et al., 2007).

As discussed above, few studies have examined joint adherence to medications for multiple conditions. While classifying patients as adherent or nonadherent based on joint adherence behavior, researchers have followed a dichotomized adherence measurement approach that is, in principle, identical to the both approach (e.g., Chapman et al., 2005). In other words, patients were considered adherent with concomitant therapy if 80% or more days are simultaneously covered by each therapy. In contrast, Nichol et al. (2009) defined fully adherent to concomitant antihypertensive therapy and anti-hyperlipidemic medications as those demonstrating ≥ 80% adherence (PDC) on each medication where adherence was estimated separately for each medication (the 'all' approach). Other researchers adopted an average-based approach for estimating overall adherence to multiple medications prescribed for different diseases. Ho et al. (2006a) examined the relationship between mortality and overall adherence to multiple medications in a cohort of diabetes patients who were prescribed one or more classes of medications that included oral hypoglycemics, antihypertensives, and statins; for patients who were prescribed medications from multiple categories, a summary PDC measure was calculated as the average of PDC of any one or more categories of medications. The study might have applied the same principle while estimating adherence to multiple medications intended to treat a single disease although it was not explicitly explained. Interestingly, different approaches were

adopted simultaneously for estimating adherence to multiple medications – one for a disease and another for two different diseases. In the case of estimating adherence to medications for a disease, Benner et al. (2009) noted, a patient was considered covered if he was adherent with at least one AH medication on a given day; for different diseases, however, patients with a PDC of ≥ 80% for both AHT and LIP were considered adherent.

Limitations of Research Related to Adherence to Multiple Medications

Adherence to Multiple Medications

Patients for whom intensified treatment regimen is advised may be at high risk for experiencing adverse consequences if the disease is not adequately controlled. However, studies on adherence have focused largely on understanding consumption of any single medication prescribed for a disease or collective consumption patterns in which all medications for a disease are considered together. In addition, failing to establish adherence as a universal trait characteristic (Horne, 1998) leaves us with a critical knowledge gap about whether individual adherence patterns of a multiple medication regimen for a disease duplicate or closely follow one another. In other words, what happens to adherence behavior for each medication in patients on multiple medications for a single disease? What is the relationship between adherence values estimated for different medications taken concurrently for a single disease? While the roles of illness perceptions (Leventhal et al., 1997) may suggest concurrent adherence, the burden of taking more medications may attenuate adherence although the effect of prescription burden on adherence is not consistent. Thus, further research is needed to explore adherence to multiple medications taken concurrently for a disease or intra-disease multiple medication adherence. Specifically, there is much to learn about the covariation of adherence behavior, including the

extent of covariation, effect of demography on covariation, and relationships between individual change patterns over time.

Similarly, there is a dearth of empirical knowledge about covariation in adherence among medications prescribed for multiple diseases (i.e., inter-disease multiple medication adherence) in patients suffering from multiple chronic diseases simultaneously and where fixed combination (single) dosage are not available. Although there have been some attempts to examine cross disease adherence behaviors (e.g., Chapman et al., 2005; Stack et al., 2010), several issues, including those raised above, however, remain to be solved. While some studies do not answer long term association or change in trends regarding joint adherence behaviors because of the study design (cross-sectional), others are limited to specific populations (e.g., newly initiated therapy, mental disorder, etc.). It is known that some patients suffer simultaneously from more than two chronic diseases some of which are more symptomatic than others. In addition, an overarching situation arises when therapy intensification occurs in some of these diseases. It is not known how inter-disease and intra-disease adherence covariations emerge, if any, in complex therapeutic situations in patients having multiple morbidities.

Measurement of Adherence to Multiple Medications

Assessing adherence accurately is crucial for many reasons including identifying opportunities for intervention. Although many measures of adherence exist, these measures were developed specifically for the measurement of adherence to individual medications or medication classes. The applicability of these measures in a multiple medications situations is not known. Thus, there is a global need to revisit the issue of measuring adherence to multiple medications. Currently, the operationalization of joint adherence to multiple medications is

borrowed from the definition of adherence to a single drug. That is, a patient is adherent if he or she is ≥ 80% (in general) on all or some medications simultaneously taken for a disease. Empirical work is required to determine the optimality of cut-points or threshold when researchers choose to use nominal measure of intra-disease multiple medication adherence, including those in which an average-based estimate is dichotomized. Another important issue, particularly because of the absence of evidence for optimal thresholds for joint adherence, is the selection of a method (e.g., 'all', 'average', 'at least any' etc.) that results in the best prediction of outcomes. In other words, benchmarking the measurement practices within the domain of intra-disease multiple medication adherence has not yet happened.

Intra-disease multiple medication adherence entails a situation that is conceptually distinct form that of single drug adherence. The situation occurs because of prescriptions of two different chemical entities intended to treat the same disease. In other words, the issue is to devise a measure that represents clinically meaningful summary adherence by virtue of its focus on the disease and treatment outcomes but not on individual medication adherence estimates. In their pursuit to improve quality of care, several organizations (e.g., the National Committee for Quality Assurance (NCQA), the Agency for Healthcare Research and Quality (AHRQ), and the Pharmacy Quality Alliance (PQA)) emphasize the need for developing measures including healthcare quality indicators. As a result, there exist composite measures of clinical quality indicators (e.g., Shwartz et al., 2008). However, the development of appropriate composite measures for joint adherence is still lacking. In summary, the issue of appropriately operationalization of the measure of multiple medication adherence is very consistent with contemporary thoughts in the measurement literature (e.g., Reeves et al., 2007; Shwartz et al., 2008) but has not been addressed yet.

CONCEPTUALIZATION

Adherence to Multiple Medications

Adherence to Multiple Medications Taken for a Single Disease

Chronic disease management requires at least continual and effective pharmacotherapeutic intervention. The patient remains always at the center of and is a crucial partner in disease control efforts that take place in social and physical environments. Despite the advancement of knowledge and the availability of advanced pharmacotherapies, significant barriers to treatment appear to reside in the psychological and behavioral domains (Rosenstock, 1985).

Health psychologists have advanced different theoretical approaches in their attempt to understand various determinants of health behavior, including adherence to medications. One of such approaches emphasizes on the dynamic, iterative, and reciprocal nature of such behaviors and adopts a system theory view that is oftentimes governed by goals or feedback processes (Bishop, 1991). Fundamental to this approach is the understanding of how patients assess and interpret their illness. According to the Common Sense Model of Self-Regulation (CSM) (Leventhal, Brissette, and Levethal, 2003), adherence behavior represents an effort on the patient's end to cope with a disease that results from cognitive and emotional appraisals of illness. The theory postulates that a patient is likely to exhibit adherence behavior if adherence makes sense within his concept of the illness, taking into account his experience with the illness and medications, potential outcomes of adherence behavior, and individual beliefs about the illness. Indeed, as changes in cognitive pathways are accompanied by befitting coping attempts, medication adherence will be affected accordingly. The CSM has been further extended to

incorporate medication beliefs into the cognitive mechanisms of the CSM (Horne, 2003). The extended framework contends that medication adherence is related to specific beliefs about beneficial effects (necessity beliefs) and worries about detrimental effects (concern beliefs) of medications. In addition, the extended framework includes two general beliefs: general harm beliefs – general mistrust about medications and general overuse beliefs, which describe a patient's concern that physicians prescribe too many medications. This framework has been applied to medication adherence in different chronic diseases (diabetes and cardiovascular diseases) (Bane, Hughes, and McElnay, 2006; Tibaldi et al., 2009). It should be noted here that there is a distinction (see Helman, 1981 for a discussion) between illness and disease. However, the propositions advanced by the framework seem to make sense regardless of such distinctions, as adherence behavior is largely patient driven and based on a determination of health status or perception of illness. Empirical evidence from studies (BaneHughes, and McElnay, 2006; Tibaldi et al., 2009) suggest that specific necessity and concern beliefs consistently predict intentional medication adherence and are indeed better predictor than general beliefs. Allen LaPointe et al. (2010) reported a significant association between nonpersistent use of anti-hyperlipidemic medications and decrease in perceived necessity of cardiac medications. Schuz and colleagues (2011) applied the framework in a longitudinal study to examine the role of beliefs about medication 'as a whole' without regard to specific illnesses. Elderly patients' necessity beliefs about medication were associated with intentional nonadherence and general overuse beliefs with unintentional nonadherence. Interestingly, a positive association between number of medications and adherence was found after controlling for past adherence. However, these findings are difficult to interpret adherence because of a lack of focus on illness in the study. Specifically, adherence may be driven by beliefs in individual medications or subsumed

under overall illness beliefs to seek protections from the illness. The later argument is consistent with illness perceptions under the CSM and may be relevant for understanding intra-disease multiple medication adherence. In other words, it may be that cognitive perceptions or representations of medications along with that of the disease play a pivotal role in adherence behavior and affect adherence behavior to multiple medications prescribed for a disease. Again, this argument is founded on a cogent theoretical rationale that is based on the role of illness representation in adherence behavior (Leventhal, Difenbach, and Leventhal, 1992).

Empirically, self-regulatory perspective or illness representation has been applied to examine adherence in multiple chronic disease categories (e.g., hypertension, diabetes) (Meyer, Leventhal, and Gutmann, 1985; Gonder-Frederick and Cox, 1991). It is important to note that it is unlikely for a patient to understand the necessity of individual medications within a disease category. However, it is not unlikely to have distinct concerns (e.g., side effects) for individual medications. As such, these concerns may be addressed appropriately (e.g., therapy modification, counseling, subsidence of symptoms gradually etc.) at the provider level during subsequent pharmacy or clinic visits. If addressed, it may rather enhance patient convictions about the medications. In addition, empirical findings suggest that compared to necessity, concern beliefs play a minor role in affecting adherence (Schuz et al., 2011). This argument about adherence to multiple medications for a disease rests on the premise of patients' knowledge of the indications of their prescription medications. Only 13% of patients in a primary care practice reported not knowing the indication of at least one of their prescription medications, which constituted 6.3% of all prescription medications that were studied (Persell et al., 2004). A small survey at an academic primary care clinic reported that patients identified a correct indication for nearly 80% of their medications (Marks et al., 2010). While impressive, it

is important to note that the extent of understanding may vary for different diseases. For example, lack of knowledge was only 3% for diabetes medications (5% for oral anti-diabetic medicines and none for insulin) and most prevalent for cardiovascular medications with 11% in hypertensive and anti-hyperlipidemic medications (Persell et al., 2004). Another study conducted among dialysis patients reported that a significantly larger number of patients knew the indication for their antihypertensive drugs and calcitriol than for their phosphate binder (Cleary et al., 1995).

Several other variables, including demography, have been examined as determinants of adherence. However, as discussed previously, conclusive evidence relating demography to adherence does not exist. It is not an exception even when the studies that used the self-regulatory framework are considered. For example, Wroe (2002) reported unintentional nonadherence was less strongly associated with decision balance, and more so with demography, age in particular. In contrast, Schuz et al. (2011) found no association of demography with adherence while Horne and Weinman (1999) reported only age affecting adherence. At a minimum, it can be posited that illness and medication beliefs may have an independent effect on joint adherence behavior that cannot be explained by other factors. Indeed, adherence may be primarily driven by illness perceptions. Therefore, the following hypotheses are presented with regard to adherence to multiple medications taken for a disease:

H1: Overall, there will be a positive covariation between adherence behaviors related to two medications taken concurrently for the same chronic disease.

H1a: Overall, the covariation of adherence between behaviors related to two medications taken concurrently for the same chronic disease will persist after controlling for gender.

H1b: Overall, the covariation of adherence between adherence behaviors related to two medications taken concurrently for the same chronic disease will persist after controlling for age.

H 2: In general, patients will demonstrate a positive relationship between changes in adherence behaviors related to two medications taken concurrently for the same chronic disease over a period. In other words, the slope of adherence to each medication over time will be positively related ('association of the evolutions').

H2a: The 'association of the evolutions' will persist after controlling for gender.

H2b: The 'association of the evolutions' will persist after controlling for age.

Adherence to Multiple Medications Taken for Concordant Diseases

Many patients suffer from multiple chronic diseases. Chronic disease patients have a higher propensity to suffer from multiple morbidities. For instance, according to the Medical Expenditure Panel Survey, most adult diabetics have at least one comorbid chronic disorder (Druss, 2001). Other studies reported that as many as 40% of diabetics had more than two chronic diseases (Maddigan, Feeny, and Johnson, 2005; Wolff, Starfield, and Anderson, 2002). However, not all chronic comorbidities are necessarily similar in terms of having underlying relationships among them. Piette and Kerr (2006) provided a useful yet broad typology for classifying chronic conditions. They outlined three general dimensions or features of comorbid conditions: clinically dominant comorbid conditions, concordance of conditions, and symptomatic/asymptomatic conditions. Most relevant for the purpose of this study is the concordance feature. As defined by Piette and Kerr (2006), concordant diseases are those that "represent parts of the same overall pathophysiologic risk profile and are more likely to be the focus of the same disease and self-management plan" (p. 727). In contrast, discordant comorbidities do not directly share either pathogenesis or management characteristics. For

example, hypertension, coronary artery disease, and diabetes are considered concordant while diabetes and cancer or irritable bowel syndrome would be defined as discordant conditions. Moreover, it is thought that concordant diseases are likely to be managed by a single provider. Clinical practice guidelines help shape the management of chronic concordant comorbidities. For example, diabetes guidelines oftentimes make specific recommendations for the management of concordant conditions such as hyperlipidemia and hypertension (Boyd et al., 2005). In other cases, treatment management plans for concordant diseases follow specific patterns. For example, treatment of hypertension and dyslipidemia may be initiated together or within a short interval of each other. These patterns (e.g., treatment synchronization) may have a positive influence on adherence (Agarwal et al., 2009).

Patients may hold different beliefs about illnesses and associated medications. Medication use for individual medications may vary because of differential perceived risks and benefits attributed to each medication (McHorney and Gadkari, 2010). Similarly, illness perceptions may or may not vary depending on disease. For instance, it was reported that while perceptions of diabetes were different from hyperlipidemia and hypertension, the latter two demonstrated similarity on many components of illness perceptions (Stack et al., 2008; 2011); however, self-reported intentional nonadherence did not vary between OADs, AHT, and statins (Stack et al., 2010). Such a relationship between adherence and beliefs is counterintuitive. Methodological issues and a lack of distinction between dimensions (e.g., intentional) of adherence may explain some difference. It may also be such that even if perceptions (e.g., necessity) vary across some diseases, patients may still demonstrate adherence to all (e.g., varying degrees of necessity for all) but strengths of associations between medication use may be attenuated. Thus, a latent influence may be conceived that ties along concordant chronic disease

care. While Nichol et al. (2009) reported the likelihood of transition to full adherent status over time of those who showed selective adherence to one drug but not the other, Ho et al. (2006b) reported that some patients chose to continue with only one therapy or more. These results provide mixed evidence for associations of adherence across medication categories.

Patients may possibly exhibit different behaviors across diseases when one of disease is symptomatic in nature. Inferences derived from perceived symptoms play a very important role in patient-driven management of chronic diseases (Gonder-Frederick and Cox, 1991). Although, in general, adherence to treatment regimens tends to be lower in patients whose illnesses are asymptomatic, contrary evidence also exists. Symptom status did not predict adherence among ischemia patients (Carney et al., 1998). Haynes, Taylor, and Sackett (1979) concluded that the association between symptoms and adherence was not very consistent. However, recognition, interpretation, and inferences made about symptoms may influence behavior in every aspect of medical decision-making and disease management. Piette and Kerr (2006) argued that physicians might view managing bothersome symptoms as greater concerns for patients and focus on treating symptoms to improve patients' functioning and quality of life as well as prevent poor long-term outcomes.

Different factors are likely to affect adherence behavior across different concordant diseases. Some factors (e.g., medication-specific beliefs) may not favor associations of adherence across such diseases. Another factor that has been examined in studies of adherence is prescription burden; however, the relationship is not very clear (Benner et al., 2002; Grant et al., 2004). In contrast, treatment focus or clinician priority related to concordant disease management during clinical encounters, if any, may alter patient perceptions about respective medications or illness leading to associations. It is contended that there will be, at least weak,

associations of adherence across concordant diseases. Therefore, the following hypotheses were proposed:

H 3a: For patients suffering from multiple concordant chronic diseases, there will be a significant covariation of adherence behaviors related to medications taken concurrently for an index chronic disease and another asymptomatic chronic disease.

H 3a1: For patients suffering from multiple concordant chronic diseases, there will be a significant covariation of adherence behaviors related to medications taken concurrently for an index chronic and another asymptomatic chronic disease regardless of disease.

H 3b: For patients suffering from multiple concordant chronic diseases, there will be a significant covariation of adherence behaviors related to medications taken concurrently for an index chronic disease and another asymptomatic chronic disease even when number of chronic diseases increases.

H 3c: For patients suffering from multiple concordant chronic diseases, there will be a significant covariation of adherence behaviors related to medications taken concurrently for an index chronic disease and another symptomatic chronic disease.

Measurement of Intra-disease Multiple Medication Adherence

While deliberating on the issue of intra-disease multiple medication adherence, an issue that remains is the determination or development of an appropriate composite measure of adherence. Currently, several approaches are used for measuring joint adherence. These measurement approaches are grounded in the definition of adherence to a single drug. That is, a patient is adherent only if he is 80% (in general) or more on all simultaneously taken medications intended to treat a disease or some other variant of this approach. Another way to measure multiple medication adherence is averaging individual medication adherence estimates of all simultaneously taken medications intended to treat a disease. An assumption made by these approaches is that all medications are created equal. This assumption is questionable for several

reasons. First, some medications are more "forgiving" – a drug attribute, which dictates that the duration of action significantly exceeds the dosing interval – of poor adherence compared to others (Urquhart, 1998). Thus, the impact of nonadherence is likely to differ based on this characteristic. This, of course, needs to be emphasized that even the most forgiving medication cannot be effective if not taken for a long time. Second, physicians intensify therapy with a purpose such as controlling different biomarkers representing different pathways (e.g., fasting serum insulin or glucose) or aggressively controlling a single end-point (e.g., blood pressure). The mechanistic approach of drug action dictates that there are differential effects of medications on individual disease markers (de Winter et al., 2006). Indeed, medication consumption affects one intermediary outcome or more that are considered to cause observable outcomes such as hospitalizations or death. It is sensible to think of medications in terms of preventing such outcomes. This thought is consistent with clinical practice that oftentimes emphasizes achieving targeted intermediary outcomes (e.g., HbA1c). Finally, pathophysiology of chronic disease is not yet fully understood. However, it is generally accepted that chronic disease may progress at a certain rate and individual medications are likely to have different impact on that rate. For example, de Winter et al. (2006) compared disease progression rates representing change in β-cell function and change in insulin sensitivity over time in patients receiving gliclazide, metformin, and pioglitazone; apart from differential symptomatic short-term effects, different disease progression rates for each parameter were observed among these treatment groups. In fact, drug treatment for a chronic disease only slows down the process, which will continue to progress at a specific rate. For example, it was found that even when patients' adherence with diabetic medications was nearly 100%, the disease was found to progress over time (Charbonnel et al., 2004; de Winter et al., 2006). Thus, the overall impact of noncompliance may be further

complicated when the effect, likely to be different for individual medications, on disease progression rate is considered. Although these effects cannot be accurately captured without pharmacokinetic-pharmacodynamic (PK-PD) modeling, potentially differential effects should be considered in some way while conceptualizing a summary measure of joint adherence. One plausible way is to derive weights based on a medication's comparative effectiveness with respect to some outcome. Precisely, the weight represents adherence driven efficacy, conceptually analogous to what is termed as 'use-effectiveness' by Hughs and Walley (2003), as it is practically very difficult or infeasible to tease out pure efficacy from the impact of adherence. Thus, weights can be determined by estimating the impact of adherence on intermediate clinical markers, composite outcomes such as QALY, or adverse consequences, including hospitalization. Furthermore, weights may be based on short-term or long-term outcomes as deemed appropriate.

Over the last few years, there has been an increasing emphasis on developing composite measures of quality indicators. This wave has been seen in the domain of hospital and clinical quality indicators. However, the definition of composite indicators varies across studies. While some researchers define composite measure as weight-based average (Geppert, 2011; Shwartz et al., 2008), others define it as dichotomized measure (Reeves et al., 2007). Geppert et al. (2011) operationalized a complex formula of AHRQ quality indicator (QI) composite measure as weighted average of risk-adjusted ratio and the reference population ratio from which weight is determined empirically. In contrast, Reeves et al. (2007) defined 'all or none', conceptually equivalent to 'all' or 'both' measures as described previously, as composite measure. In this study, the composite measure was defined in the spirit of Geppert et al. (2011). The proposed new measure representing composite adherence is defined below. The formula is presented for

two medications; however, it can be extended to accommodate more medications. This is an empirical regression weight-based composite average measure, henceforth termed as 'composite' measure. By definition, the composite measure allows for the benefits of individual medications based on partial adherence, if any.

$$\mathrm{Adh}_{\mathrm{com}} = \frac{\mathrm{W}_1.\,\mathrm{A}_1 + \mathrm{W}_2.\,\mathrm{A}_2}{\mathrm{W}_1 + \mathrm{W}_2}$$

where $\mathrm{Adh}_{\mathrm{com}}$ = empirical regression weight-based composite adherence estimate,

Adh_i = estimated adherence to drug *i* ,

w_i = outcome-based regression weight for drug *i*;

- Assuming all drugs do NOT have equal effectiveness/ efficacy
- Assuming a joint additive effect
- Assuming trivial effects of disease progression and disease status at baseline

As stated before, apart from developing a summary measure, there is a need to determine which one constitutes an appropriate method among several measurement approaches for intra-disease multiple medication adherence. In other words, the performance of these measurement approaches must be compared in order to select the most appropriate measure. In most studies, adherence measures are dichotomized including categorization of an average-based measure (e.g., Piette et al., 2007) although wide variability occurs. From the perspective of calibration, such approaches for categorization suffer from limitations and make some assumptions that do not appear to be grounded theoretically or empirically. Therefore, the following objectives will be examined:

1. To examine the effectiveness of the composite measure,

2. To compare the performance of the existing measurement approaches with the composite measure,
3. To determine the optimal cut-point of the composite measure,
4. To determine the optimal cut-point of the average measure and other continuous measures.

CHAPTER 3

METHODOLOGY

This chapter will discuss the methodology used to examine the study hypotheses and objectives. The study has two major focuses: adherence behavior to multiple medications and multiple medication adherence measurement. The methodology addressing the hypotheses and objectives associated with these two substantive areas are organized separately whenever appropriate. In addition, the data analysis plan to examine the hypotheses and objectives are discussed.

The study was approved by Thompson Reuters and compliant with the protocol specified in the Data User Agreement (DUA) between the company and The University of Mississippi. The study was compliant with the Health Insurance Portability and Accountability Act (U.S. Department of Health and Human Services). In addition, approval was obtained from the Institutional Review Board (IRB) at The University of Mississippi.

Research Design

A longitudinal observational study design was employed for this study. Using retrospective administrative claims data, study subjects were identified. Medication and health service utilization of these patients were determined as described below. However, for the comparative validation and calibration of the measurement approaches a prospective study design was conducted utilizing the same data source.

Description of Data Source

This study utilized the MarketScan® Commercial Claims and Encounters database (MCCED) for 2002 and 2003 from Thomson Reuters (Healthcare) Inc. The MCCED is a large and comprehensive relational database that represents millions of individuals and consists of medical and prescription claims of private sector employees and their dependents. This multi-source database is constructed through submissions of health insurance data. Collectively, the database incorporates data from a large number of payers, including commercial insurance companies, Blue Cross and Blue Shield plans, and third-party administrators (TPAs). The fully-integrated data can track patient information across sites, types of providers, all claims types including medical/surgical and outpatient pharmaceutical claims, and over a number of years. Rigorous validation methods, as stated by the company, ensure the completeness, accuracy, and reliability of data. The data appear robust and reflect a continuum of care provided to patients that allows analysis of utilization patterns and the subsequent outcomes associated with medical care and medication use.

The Commercial Claims and Encounters Database has the following structure:

1. Annual Enrollment file
2. Aggregated Populations file
3. Medical/surgical Claims files:
    - Inpatient Admissions file
    - Inpatient Services file

- Facility Header file

4. Outpatient Services file
5. Outpatient Pharmaceutical Claims file

The enrollment files include information about demography (e.g., age, gender, geographic region of residence), plan, and enrollment history. The prescription claims files include national drug codes (NDC), therapeutic class, dates of purchase, quantities of medication dispensed, days' supplies, refill indicator, and plan and cost related information. The Inpatient Admissions files contain records that summarize information about a hospital admission. These files are constructed after identifying all of the encounters or claims (service records) associated with an admission (e.g., claims from hospital, physician and/ or surgeon, and independent labs). Information in the Inpatient Admission claims files includes hospital stays, including length of stay, date of admission or discharge, diagnosis (ICD-9) and procedure codes (CPT-4 or HCPCS), diagnosis related group (DRG), and provider type. The Inpatient Services files contain the individual facility and professional encounters and services associated with the inpatient admission record. An identifier that exists in both the Inpatient Admissions and the Inpatient Services files identifies the individual service records that come from each admission record. The outpatient services claims files include services that were rendered in a doctor's office, hospital outpatient facility, emergency room, or other outpatient facility. Some of the information, aggregated to the level of each outpatient visit, are diagnosis codes, treatment procedures, place of outpatient service (e.g., emergency room, office). A few claims in the outpatient claims files may represent inpatient services because the claim could not be incorporated into an inpatient admission (e.g., no room and board charge was found); generally, place of service is coded as inpatient. For the study, the Enrollment files, Inpatient Admission

files, Inpatient Services files, Outpatients Services files, and Outpatient Pharmaceutical claims files were utilized to create a longitudinal panel of observations for each subject.

Disease State Selection

Primary Disease Context of the Study

In recent years, physicians have been found to prescribe multiple medications concurrently for the treatment of a single disease. Such multiple medication regimens occur in many diseases, including hypertension, diabetes, heart failure, and so on. Thus, a number of diseases are available, in which the objectives of this research can be studied empirically. In fact, two or more diseases can be selected for empirical work. For the sake of parsimony, however, only one disease was selected. Diabetes was chosen as the primary disease state. Such a selection was deemed appropriate for several reasons.

Diabetes has been and continues to be a concern in the U.S. The recently published National Diabetes Fact Sheet 2011 estimated that the number of diabetes patients including those undiagnosed was at 25.6 million or 11.3% of all people in the age group of 20 years or older. The report revealed that diagnosed and undiagnosed diabetes patients comprised 13.7% of individuals who were 45-64 years old and 26.9% of 60 years or older in 2010. In addition, according to the fact sheet, 1.9 million new cases of diabetes were diagnosed in people aged 20 years and older in 2010; the extent of newly diagnosed cases varied by age group. Among diagnosed new cases in 2010, over one million patients were between 45 and 64 years old (CDC National Diabetes Fact Sheet 2011). However, a great concern implied in the report could be that the number of patients estimated to have pre-diabetes (i.e., serum glucose levels higher than normal but not yet high enough to be classified as diabetes) was reported to be 79 million in

2010. Pre-diabetes was also reported to affect patients across all ages. Not all pre-diabetes individuals develop diabetes but a large proportion do over time. Estimates provided by different studies widely vary depending on methods and definitions (e.g., impaired glucose tolerance vs. impaired fasting glucose levels, population, follow-up time) (see Nichols, Hillier, and Brown, 2007 for a discussion). The Diabetes Prevention Program revealed that 11 cases per 100 person-years progressed from pre-diabetes to type 2 diabetes over about three years of follow-up and many people with pre-diabetes develop type 2 diabetes within 10 years (Knowler et al., 2009).

Diabetes patients often suffer from a number of comorbidities. CDC estimates that 67% of adults aged 20 years or older with self-reported diabetes in 2005–2008 had high blood pressure or used prescription medications for hypertension. Mykkanen et al. (1993) reported that 70% of the adults with type 2 diabetes also had hypertension or hyperlipidemia. As such, many diabetes patients are prescribed multiple medicines to improve metabolic control, serum glucose and cholesterol level, and blood pressure (Morris, 2001; Rosenstock, 2001). Indeed, intensive disease management is often advocated for diabetes patients. The American Diabetes Association (2004) recommends aggressive management of hypertension in adult diabetes patients and the use of multiple (two or more at proper doses) medications to achieve blood pressure targets. Improper or poor management of diabetes has been associated with deaths and several secondary complications, including heart disease, stroke, kidney disease, blindness, and amputation. Diabetes was the seventh leading cause of death in 2007 and the risk for stroke is 2 to 4 times higher among people with diabetes (CDC National Diabetes Fact Sheet 2011). Understandably, the cost of diabetes is enormous. The total cost of diagnosed diabetes in the

United States in 2007 was estimated to be $174 billion, including $116 billion for direct medical costs (CDC National Diabetes Fact Sheet 2011).

Apart from adverse outcomes that may be attributed to the fact that patients fail to achieve treatment goals (Saydah et al., 2004), the treatment pattern in diabetes has undergone a significant change over the last couple of years. Specifically, the trend of using multiple medication regimens has increased considerably. Nau, Garber, and Herman (2004) examined the use of multiple medication therapies in a managed care population and reported that the percentage of diabetes patients who were receiving multiple medications for diabetes increased to 43% in 2001 from 27% in 1997. Similarly, Alexander et al. (2008) found that the average number of diabetes medications per treated patient increased from 1.14 in 1994 to 1.63 in 2007 and monotherapy declined by approximately 40%. This trend could be attributable partly to pharmaceutical innovation. A number of new medication classes (e.g., TZD, DPP-4 inhibitors) have been introduced over the past two decades. More importantly, a number of new medication classes are in the development pipeline (Nguyen et al., 2011) and expected to be introduced to the U.S. market in the future. Thus, it does not appear likely that multiple medication regimens use for the treatment of diabetes will decrease in the future. Conversely, the continuing trend of more aggressive pharmacotherapeutic management coupled with the availability of innovative therapies makes multiple medication therapies more likely in diabetes. Thus, diabetes appears to be an appropriate disease category for examining the effect of polypharmacy on adherence and polypharmacy adherence on health outcomes.

Selection of Concordant Diseases

Effective disease management for patients with multiple medications or chronic conditions may pose an overwhelming challenge to providers and patients alike. Piette and Kerr (2006) provided a useful and intuitive framework that might facilitate such efforts. The authors provided several examples to outline the concordant-discordant as well as the symptomatic-asymptomatic framework. Although the orthogonality of boundaries may be blurred, it is undeniable that some examples make more intuitive sense than do others. Following the authors' proposition, hypertension, dyslipidemia, and diabetes are considered concordant asymptomatic diseases whereas angina is considered symptomatic. Applying the principle, angina can also be considered concordant with the aforementioned diseases.

Identification of Study Subjects

Selection of Multiple Medication Regimens within the Primary Disease

As was presented previously, the major focus of the study lies on those patients who have been prescribed multiple medications for a disease (i.e., diabetes). Several classes of medications are available for the treatment of diabetes, including sulfonylureas (SU), metformin, insulins, thiazolidinediones (TZD), alpha-glucosidase inhibitors, meglitinide, glucagon-like peptide-1 (GLP-1) analogues, and dipeptidyl peptidase-4 (DPP-4) inhibitors. Diabetic patients who are prescribed multiple medications may receive two or more classes of medications described above. Thus, a number of different combinations exist and some combinations of medications occur more frequently than do others. For example, insulin and metformin are oftentimes prescribed together. TZDs are added often to metformin or SU. For this study, patients who were prescribed TZDs and SUs concurrently were included. These two classes are

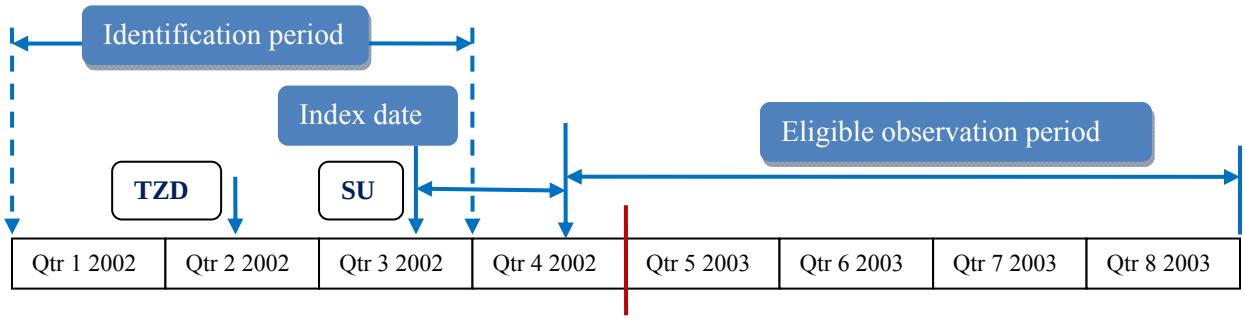
frequently used but not, usually, as fixed-dose combinations. Although insulins are frequently used, adherence to insulin is difficult to measure from administrative claims data. Metformin is widely used but oftentimes prescribed as fixed-dose combination product that restricts its variability in usage. Other medications (e.g., DPP-4 inhibitors) are relatively new and their usage patterns are still evolving.

Selection of Medications for Concordant Diseases

Two asymptomatic diseases concordant with diabetes were considered in this study: dyslipidemia and hypertension. Commonly used medications for the treatment of dyslipidemia include fibrates and statins. Other classes include bile acid sequestrants **(**cholestyramine, colesevelam, and colestipol), niacin, and ezetimibe. Two classes of anti-hyperlipidemic medications are seldom prescribed together and medications under the other classes are prescribed generally as adjunct to statins. In instances where patients were found to be on more than one medication, statin adherence was considered for the sake of simplicity of calculation of adherence. Many medications are available and indicated for the treatment of hypertension. Angiotensin II receptor blockers (ARB) or Angiotensin I converting enzyme inhibitors (ACEI), generally in combination with a thiazide diuretic, are considered as initial therapy for diabetic hypertensive patients while β-blockers and calcium channel blockers (CCB) are add-on therapies (Whaley-Connell and Sowers, 2005). As such, these five classes of AHTs were considered. Moreover, such an approach is consistent with a previously published study of adherence to medications among diabetes patients suffering from multiple comorbidities (Stack et al., 2010). An attempt was made to confirm diagnoses of hypertension (ICD-9 codes 401 - 405) from medical services records. Unlike dyslipidemia and hypertension, angina is symptomatic and

concordant with diabetes. While many medication classes including antihypertensives are prescribed for angina pectoris, nitrates are the core pharmacotherapeutic treatment for angina (Parker and Parker, 1998). In addition, past adherence/persistence research has examined nitrates for the treatment of angina (Grant et al., 2004; Kardas, 2004; Poluzzi et al., 2006). Only di-nitrate, mono-nitrate and nitroglycerin (not sublingual) tablets and capsules were considered as these medications are expected to be consumed at regular intervals (at least once daily). In addition, an effort was made to confirm from medical services utilization data whether they had any diagnosis of angina. Consistent with past research, the ICD-9 codes 413.x (angina pectoris), 414.0, 414.8, 414.9 (ischemic heart disease), and 786.5 (chest pain) were selected to operationalize "ICD angina" such that it includes all conditions most likely representing chronic angina (Pakhomov et al., 2007). Medications, including those for diabetes, were selected based on literature (Parker and Parker, 1998; Wang, 2006) (Appendix A).

Figure 3.1: Illustration of Subject Identification to Examine Adherence



Selection of Subjects and Observation Periods

For this study, the identification of subjects occurred from January 1, 2002 through September 30, 2002 (Figure 3.1). Patients who filled at least one prescription for each medication (i.e., SU and TZD) were identified from the prescription claims records. Such a

filling pattern would provide an indication that the patient was prescribed both medications. Furthermore, the earliest (or later of two initial fills) fill date indicating that patient was prescribed both medications served as the index date. For example, if a patient filled a prescription for a SU on March 23, 2002 and a prescription for a TZD on September 29, 2002, the index date for the patient would be September 29, 2002. Because of their complementary mechanisms of action, it was assumed that physicians were unlikely to replace one medication with the other even when the latest fill date for one and the earliest fill date for the other occur at widely-apart temporal distance. However, the order of prescription was not considered for this project. The observation period started 90 days after the index date. The 90-day limit was chosen to allow for any physician-driven therapy modification. Thus, the latest date on which an observation can start for a patient was January 1, 2003 and continued through December 31, 2003. It can be noted here that subjects were likely to have variable observation periods depending on respective index dates.

Primary Inclusion Criteria

Subjects identified thus far were considered for inclusion in the study if they met a set of additional requirements. First, subjects were required to be 18 years or older on the index date. Second, they must have been continuously enrolled in MCCED with pharmacy and medical benefits for at least 15 months starting from their respective index date. The 15-month period included 90 days (approximately, 3 months) of pre-observation period and 12 months of observation period. It can be noted here that the choice of the duration is consistent with the literature. A review of studies on adherence with AHT, OAD, and LIP reported that the mean duration of studies were 30, 18, and 15 months for LIP, OAD, and AHT, respectively (Cramer et

al., 2008). Anti-diabetic prescription trends using the data source suggested that a large proportion of these diabetes patients were prescribed the combination of SU and TZD before January 1, 2002 (Cohen et al., 2003). Thus, many patients who continued to fill during the pre-index period had been filling the scripts for at least a year. In addition, it was required to ensure that failing to refill was not driven by physician decisions. In other words, the lack of filling was not due to a decision to modify therapy on the part of the prescriber. Especially for those new to treatment, early modification of therapy is likely to occur because of many issues (e.g., side effects) within a first few months of treatment. Third, patients must not have records of filling other anti-diabetic medications including insulin after the respective index date and during the study period; however, patients were included if they filled a prescription for insulin or other anti-diabetic medicines than SU and TZD only after the minimum 15-month period. In such cases, patients were not followed after they had started such fills. In other words, the period in which only the two study medications were filled were considered for analysis for these patients. Because anti-diabetic therapies are to be continued life long, this criterion together with some others as described above would, as best as can be determined, ensure that any lack of filling is because of nonadherence and not because of physician-driven treatment modifications. Finally, study subjects who were less than 65 years at all time during the observation period were selected. Elderly (≥ 65 years) patients suffer from multiple diseases including diabetes - the disease of interest for the study. Because of their age, oftentimes a disease might have advanced to a point when clinician might find it a clinical necessity to prescribe multiple medications for the disease. However, prescription drug coverage of all elderly may not be uniformly captured in the database (i.e., MCCED). In addition, Medicare beneficiaries' inpatient and outpatient medical services utilization might not be completely captured in this commercial claims database

and such information is very critical for examining the measurement-related objectives. Those patients who met all the above criteria constituted the general pool of eligible subjects. It is noted here that additional criteria are required to be met prior to examining some hypotheses and objectives and are discussed in appropriate sections below.

Inclusion Criteria for Examining Inter-disease Medication Adherence

Subjects for examining inter-disease medication adherence were selected from those identified as described above by imposing additional requirements. Dyslipidemia, hypertension, and angina were considered as concordant diseases in conjunction with diabetes. Statins or fibrates were considered for dyslipidemia, any of ACEI, ARB, CCB, diuretics, and β-blockers for hypertension, and nitrates (oral nitroglycerin, di-nitrates, and mono-nitrates) for ischemia. Patients were required to show at least two fills for medications for the respective diseases. For example, patients with diabetes and dyslipidemia must be filling statins or fibrates in addition to a SU and a TZD; patients with diabetes, dyslipidemia, and hypertension must fill any AHT as described above and any anti-hyperlipidemic medications in addition to a SU and a TZD. A similar process was followed for patients on angina medications. The two fills criterion for concordant disease medications was consistent with that of intra-disease (diabetes) medications adherence. In addition, having the subjects demonstrate that they had filled concordant disease medications before the observation period started ensured at least one year of observation. Again, this was consistent with intra-disease medications adherence criteria.

Inclusion Criteria for Examining Measurement Approaches

Patients who were included for examining intra-disease multiple medication adherence constituted the general pool of patients. In addition, subjects were excluded from analysis if they had experienced within the first 90 days of observation any adverse outcome events (i.e., hospitalization or ER visits) against which measures were to be compared. This step was adopted to avoid measurement problems and potential confounding. A similar exclusion criterion was used while examining the effect of adherence on health outcomes in diabetes patients (Yu, Yu, and Nichol, 2010).

Variables and Measurement

Periods of Observation

The observation period for each patient was divided into several quarters or 90-day periods. Each patient was observed for at least four quarters. Duration of three months as the unit of observation was chosen because some patients might obtain their prescription medications from mail-order pharmacies and received 90 days' worth of medication supply. In addition, such a time period is, to an extent, consistent with reality such that chronic disease patients may visit a pharmacy or a physician once in three months. Whenever a patient entered the study, the first quarter for the patient is started. Thus, first quarters for different patients may represent different calendar time points.

The selected patients were followed until one of the following events happened: 1) disenrollment; 2) patients started filling insulins or any other OADs than SUs and TZDs; or 3)

the end of the year 2003. An additional criterion was imposed for comparing the measurement approaches. Subjects were followed until the event occurred.

Measurement of Adherence

Various measures of adherence can be computed using administrative claims data. These measures use different formulas to estimate adherence (see Hess et al., 2006 for a discussion). Mathematically, these formulas are closely related and yield similar values. Past research has attempted to compare the values estimated by different measures. Karve et al. (2008) compared the predictive validity of eight different measures that are generally used in studies that utilize administrative claims data. The authors concluded that PDC provided the most conservative estimate of adherence. Similarly, Hess et al. (2006) examined several measures and reached a similar conclusion. Martin et al. (2009) compared adherence estimates measured by PDC, MPR, and truncated MPR (MPRt) in psychiatric disorder patients, including those who were prescribed multiple therapies because of therapeutic duplication; the authors recommended using PDC as measure of adherence. Interestingly, the authors discussed a variant of PDC (i.e., the both approach) that can be considered a conservative estimate of adherence when applied in the (intra-disease) multiple medications context such as this study. Considering only the overlapped period, the 'both' approach inherently assumes that effects of simultaneously-prescribed medications occur only when taken together. It is very likely that best plausible outcomes can be achieved if consumed together as deemed by prescribers. Nonetheless, effects of individual medications cannot be, in general, denied regardless of whether one is taken or both are taken concurrently. PDC appears to demonstrate better or equivalent predictive ability of outcomes when compared against other measures suitable for use in research with claims data. For

example, PDC showed the highest c-statistic reflecting its superior ability of health care utilization in patients suffering from diabetes (Karve et al., 2008).

Table 3.1: Intra-disease Multiple Medication Adherence Measurement Approaches

Measure	Operational Definition
Composite	$\left[w1.\frac{DayswithSUinQtri}{DaysinQtri} + w2.\frac{DayswithTZDinQtri}{DaysinQtri}\right]/(w1+w2)$
Average*	$\left[\frac{DayswithSUinQtri}{DaysinQtri} + \frac{DayswithTZDinQtri}{DaysinQtri}\right]/2$
At least one*	$Adherentif\left[\frac{DaysinQtriwith \geq 1\ medicationavailable}{DaysinQtri}\right] \geq 80\%$
Max**	$\left[\frac{DaysinQtriwith \geq 1\ medicationavailable}{DaysinQtri}\right]$
Both	$Adherentif\left[\frac{DaysinQtriwithbothmedicationsavailable}{DaysinQtri}\right] \geq 80\%$
Min***	$\left[\frac{DaysinQtriwithbothmedicationsavailable}{DaysinQtri}\right]$
All*	$Adherentif\left[\frac{DayswithSUinQtri}{DaysinQtri}\ \text{X}\ 100\%\right] \geq 80\%\ and\left[\frac{DayswithTZDinQtri}{DaysinQtri}\ \text{X}\ 100\%\right] \geq 80\%$

Note: Qtr: quarter; SU: sulfonylureas; TZD: thiazolidinediones; w1 and w2: weights;
* adapted from Choudhry et al., 2009;
** and *** continuous estimate of the 'at least one' and 'both' approaches respectively

For this study, adherence was measured as PDC and estimated based on days supply for each patient for each class of medications in each quarter. As noted above, days supply data were available in the pharmacy claims data. The value of the days' supply was truncated in case the supply extended beyond the observation period. Thus, for some patients who were found to

be suffering from multiple chronic diseases, more than two PDC were calculated in some quarters. Any switches between different therapeutic agents (molecules) were not carried forward but that between equivalent agents (e.g., different brands of the same molecule) were carried forward. For instance, if a patient was switched from glyburide to glipizide, then glyburide on hand, if any, on the day of filling of glipizide was not carried forward for calculating PDC for SU. While the assumption in case of the former was that the physician modified the therapy for some reasons and the patient was not supposed to consume those extra medications on hand, the assumption in the latter (i.e., between brands) was that the patient continued taking the medication from previous refills as part of the same regimen. Similarly, in case of dosage modification, adjustments were made based on recommendations occurring at a later point in time.

Anticipating the plausibility of multiple medications prescribed for hypertension, an a priori method was adopted for calculating adherence to antihypertensives after considering several alternative options. One possibility was to consider each PDC separately. However, it could add complexity to statistical analysis and cause potential modeling problems because of an increase in number of DVs. Second, it was possible to estimate PDC in a manner analogous to the both approach. If a therapy augmentation for AHT occurs after observation starts, adherence estimates can be weighted by days' supply. However, it would be difficult to distinguish nonadherence episodes from physician-driven switch or discontinuation for some reasons (e.g., side effects). In such cases, it would further underestimate adherence of these patients. Therefore, it was decided that adherence to multiple antihypertensive medications would be measured based on the 'at least one' approach, i.e., proportion of days covered by at least one AH therapy. This is essentially a single medication adherence estimation approach. This was

thought appropriate because it consistently measured adherence for all hypertension patients regardless of numbers of AH medications.

Four different measurement approaches exist in the literature for estimating adherence in situations of multiple medications use for a single disease. In addition, a composite measure was conceived and empirically tested. Three of these measurement methods (average-based, composite, and all) utilized the values of PDC estimated individually for each medication for diabetes. Although the other two methods (i.e., at least one and both) of PDC estimates are generally dichotomized for analysis, they can be used as continuous measures as well (termed here as 'max' and 'min' respectively) following the operational definition described in Table 3.1. These seven PDC estimates of adherence to multiple medications were computed for each patient for each quarter for intra-disease adherence measurement comparisons.

Measurement of Outcome Variable

The outcome variable was meant to assess the potential impact of nonadherence to medications. The outcome was used for assessing comparative performance of the various measures of intra-disease multiple medications adherence. In other words, the variable was used only for examining issues related to the measurement of combined adherence. Several clinical outcomes are available of which one may be chosen for the effectiveness of diabetes treatment. HbA1c, fasting serum insulin level, fasting plasma glucose (FPG), and post-prandial blood glucose (PPG) are frequently used for monitoring patients for clinical purposes. However, these variables cannot be measured from administrative claims data. Several variables have been used as proxy measures for clinical effectiveness in research related to adherence. Some of them are quality adjusted life years (QALY) (Martinez et al., 2008) and health service utilization such as

hospital service utilization or ER visits (Balkrishnan et al., 2007). Two utilization outcomes are generally assessed in studies on adherence to diabetes medication: 1) diabetes-related health services utilization (DSU), and 2) all-cause health services utilization (Balkrishnan et al., 2007; Karve et al., 2008; Sokol et al., 2005). Outcomes frequently encountered by diabetes patients can also be considered. Smith and Maynard (2004) reported cardiovascular hospitalizations, primarily coronary in origin, accounted for approximately 50% of all hospitalizations in persons with diabetes within VA and non-VA medical care systems. Lau and Nau (2004) reported an increased likelihood of a diabetes-, cardiovascular-, or cerebrovascular-related hospitalization among diabetes patients with poor adherence ($\leq 80\%$). It is easy to understand such an outcome (i.e., cardio- or cerebrovascular related) lies in the middle of the conceptual continuum on which more extreme points are occupied by any-cause hospitalization and DSU. Yu, Yu, and Nichol (2010) examined the association between adherence and microvascular complications of diabetes using office-based diagnosis of complications. A number of chronic complications of diabetes and their association with medical costs have been identified (American Diabetes Association, 2002). This report considered a diverse set of clinical conditions such as cardiovascular diseases, neurological symptoms, renal complications, endocrine/metabolic complications among others. In contrast, a study conducted in Europe examined eight conditions, including myocardial infarction, heart failure, stroke, ischemic heart diseases, while estimating diabetes-related hospitalization costs (Gerdtham et al., 2009). While it may be logical to focus on macrovascular diseases, including heart attack, chest pain, coronary heart disease, heart failure, and stroke, as they are among major complications in diabetes patients (Deshpande, Harris-Hayes, and Schootman, 2008), diabetes-specific outcomes encompassed in past research has varied from

being very specific to very broad. Even within specific events, the focus has been laid on microvascular complications or macrovascular events.

Diagnoses of microvascular complications (DSU) and macrovascular events appeared as suitable outcome measures for this project. Cohen et al. (2003) reported that approximately 29% of diabetes patient population enrolled in the MarketScan database suffered from diabetes complications in 2000 at which time the number of diabetes population was growing at an approximate rate of 10%. Although, microvascular complications lie closer to medication consumption in the causal chain of medication effect, it was not selected because of possibility of difficulty in finding a sufficient number (expected to be about 5%) of outcome events in a relatively short time-frame of this study. Similarly, it was difficult to determine if a patient had a preexisting diagnosis (for exclusion purposes) if they did not make a physician's office visit within three months or even six months, which might leave even a shorter window for analysis. It is further complicated by an inherent limitation in the database that includes only two diagnosis options for outpatient services. Similarly, because of the availability of only 2 years of data it would be difficult to find enough subjects having DSU. Furthermore, any-cause inpatient hospitalizations or those occurred primarily because of medical reasons was not chosen because of anticipation of insufficient number of events required for a robust analysis.

Any-cause ER service utilization (ERSU) was chosen as the primary outcome variable to examine the measurement issues-related objectives. ERSU is defined as any ER visits occurring after at least 90 days since the beginning of observation. Existing evidence support that any-cause ER visits can be used as an indicator for quality of diabetes care (Stern et al., 2009). Although objectives in this study are different from Stern et al., yet the adaptation of the concept seemed reasonable. In addition, ERSU as outcome variable may have practical implications

given high cost of management associated with them. ERSU was identified from the outpatient services claims file used for comparing the utility of different measures. ER service utilization was identified based on the procedures followed by a previously published study (Margolis et al., 2010), which used the MarketScan data. ERSU was dummy coded where 1 indicated occurrence and 0 nonoccurrence of events.

Measurement of Covariates

As discussed previously, chronic diseases often co-occur. As such, the comorbidity profile of these patients was measured. Several measures of comorbidity exist that were developed for different purposes and applied in different population (see de Groot et al 2003 for a review). For this study, the Charlson Comorbidity Index (CCI) (Deyo, Cherkin, and Ciol, 1992) was used as the measure of comorbidity. The CCI demonstrates good reliability and validity across studies (de Groot et al., 2003). As correlations between the CCI and adherence is generally weak (Sokol et al., 2005), it is less likely to cause multicollinearity. The CCI was measured based on medical claims until the end of first quarters. Patient demographic characteristics (age and gender) were obtained from the enrollment file. Patients' age as mentioned in the annual enrollment summary file 2002 was used in the analysis. Other variables recorded for descriptive purposes include pharmacy type, insurance type, and geographic region.

Data Analysis

The study has several broad aims. Data analysis plans for these aims are organized for these aims and discussed below. Apart from hypotheses testing, descriptions of study population

and estimates of adherence for different diseases and those based on different measurement methods will be provided.

Intra-disease Multiple Medication Adherence Behavior

It can be recalled that the substantive points that were to be examined included relationship between adherence to multiple medications for a disease and that of the evolutions of adherence behaviors. These relationships are outlined by hypotheses 1 through 2b (Table 3.2). These hypotheses were tested in the longitudinal analysis framework using a multilevel approach. This analytical approach offers sophisticated modeling appropriate to the discrete-time longitudinal structure of the data and concurs with Fitz-Simon, Bennett, and Feely (2005) who argued to model random effects that incorporate intra-patient variability in prescription refill patterns.

Table 3.2: Statement of Hypotheses	
H1:	Overall, there will be a positive covariation between adherence behaviors related to two medications taken concurrently for the same chronic disease.
H1a:	Overall, the covariation of adherence between behaviors related to two medications taken concurrently for the same chronic disease will persist after controlling for gender.
H1b:	Overall, the covariation of adherence between adherence behaviors related to two medications taken concurrently for the same chronic disease will persist after controlling for age.
H 2:	In general, patients will demonstrate a positive relationship between changes in adherence behaviors related to two medications taken concurrently for the same chronic disease over a period. In other words, slope of adherence to each medication over time will be positively related ('association of the evolutions').
H2a:	The 'association of the evolutions' will persist even after controlling for gender.
H2b:	The 'association of the evolutions' will persist even after controlling for age.

H 3a:	For patients suffering from multiple concordant chronic diseases, there will be a significant covariation of adherence behaviors related to medications taken concurrently for an index chronic disease and another asymptomatic chronic disease.
H 3a1:	For patients suffering from multiple concordant chronic diseases, there will be a significant covariation of adherence behaviors related to medications taken concurrently for an index chronic and another asymptomatic chronic disease regardless of disease.
H 3b:	For patients suffering from multiple concordant chronic diseases, there will be a significant covariation of adherence behaviors related to medications taken concurrently for an index chronic disease and another asymptomatic chronic disease even when number of chronic diseases increases.
H 3c:	For patients suffering from multiple concordant chronic diseases, there will be a significant covariation of adherence behaviors related to medications taken concurrently for an index chronic disease and another symptomatic chronic disease.

The multilevel modeling approaches are one of the frequently employed statistical methods to analyze longitudinal data. Specifically, multilevel modeling has been widely used by education psychologists for years to investigate contextual effects for a variety of outcomes including educational performance, instructional effectiveness, and change in attitudes over time (Fraine, Van Damme, and Onghena, 2007; Marsh, 2007). Multilevel modeling has also been applied in the context of health and health behavior. For example, researchers have examined the association between various contextual factors and disease morbidity rates in many diseases, including asthma (Juhn, 2005), coronary heart disease (Diez-Roux et at., 1997), and cardiovascular diseases (Leyland, 2005). These approaches account for the hierarchical or clustered nature of data. Hierarchy occurs because units are grouped or clustered at different levels. Multilevel modeling considers information from all levels simultaneously and is able to assess the variation in a particular response attributable to each level (Goldstein, 1991). Certainly, for clustered data multilevel approaches may offer advantages including chance of

drawing correct inferences over traditional methods (Hox 2002; Snijder and Bosker, 1999) and allow for, most importantly, micro-level and cross-level analyses including modeling changes as a function of time.

Table 3.3: Multilevel Approach to Longitudinal Data Analysis

Unconditional Means Model

$Y_{ij} = M_{0j} + R_{ij}$, where $M_{0j}$is the mean of subject *j* and R_{ij} is deviation of Y for subject *j* at occasion *i* from the mean

$M_{0j} = M_0 + U_{0j}$, where U_{0j} is deviation of subject *j* from the population mean M_0

Alternatively, $Y_{ij} = M_0 + U_{0j} + R_{ij}$

Unconditional Growth Model

$Y_{ij} = M_{0j} + M_{1j}.\text{Time} + R_{ij}$, where $M_{0j}$and $M_{1j}$are the intercept and slope (or growth rate) of subject *j* respectively and R_{ij} is deviation of Y for subject *j*'s at occasion *i* from his or her true change trajectory

$M_{0j} = M_0 + U_{0j}$, where U_{0j} is deviation of subject *j* from the population intercept M_0

$M_{1j} = M_1 + U_{1j}$, where U_{1j} is deviation of subject *j* from the population slope M_1

Alternatively, $Y_{ij} = M_0 + M_1.\text{Time} + U_{0j} + U_{1j}.\text{Time} + R_{ij}$

Variance components can be computed for each of U_{0j}, U_{1j}, and R_{ij}

Adapted from Singer and Willet (2003)

Multilevel growth curve modeling can be extended to incorporate multiple dependent variables (DV) that are collected longitudinally. Such an approach, also known as multivariate multilevel regression modeling (Snijder and Bosker, 1999), was used to assess the hypothesized relationship between the two DVs (i.e., adherence to SU and adherence to TZD) including the

trend parameters of them. More specifically, the association of the evolutions (i.e., changes) over time was examined. In the multivariate model that was used in the study, the dependent variables were nested within the measurement occasions, which were nested, in turn, within the subjects. The multiple outcome variables were combined through proper specification at the lowest level. Thus, the dependent variables form level 1, measurement quarters form level 2, and patients form level 3.

First, the unconditional means (or, random intercept) model was fitted (Table 3.3). It can be noted here that hypothesis testing (for intra-disease medication adherence) that was followed in the study is consistent with the approach suggested by Singer and Willet (2003) who recommend fitting the unconditional (i.e., without predictors) means model followed by unconditional growth (or, random slope) model. The unconditional means model implies that a specific observed value of y (i.e., Y_{tj} or in this analysis, a person's PDC at a specific quarter) at a point *t* is a deviation from a person *j*'s true mean (i.e., Y_{0j}) and thus, the actual individual change trajectory is flat as represented by person-specific mean. In other words, under this model such deviations or level 2 residuals (as level 1 contains multiple DVs in this study) are within-person distance from respective individual means. Thus, variance component of level 2 under unconditional means model is the population variability in an average person's outcome estimates around his or her own mean. Similarly, level 3 (for this study) residuals represent between-person deviations from the population mean because a person individual mean is a deviation from the population mean (Singer and Willet, 2003). The statistical models for examining hypotheses associated with intra-disease multiple medication adherence were adapted from the literature (Fieuws and Verbeke, 2004; Snijder and Bosker, 1999) and are presented below.

Random intercept model

$Y_{htj} = M_{10}.d_1 + M_{20}.d_2 + U_{10j}.d_1 + U_{20j}.d_2 + R_{1tj}.d_1 + R_{2tj}.d_2$ ---------- (1)

Random intercept with fixed covariates model

$Y_{htj} = M_{10}.d_1 + M_{20}.d_2 + C_1.d_1.Cov + C_2.d_2.Cov + U_{10j}.d_1 + U_{20j}.d_2 + R_{1tj}.d_1 + R_{2tj}.d_2$----- (2)

Random slope model

$Y_{htj} = M_{10}.d_1 + M_{20}.d_2 + M_{11}.(t-t_0)d_1 + M_{21}.(t-t_0).d_2 + U_{10j}.d_1 + U_{20j}.d_2 + U_{11j}.(t-t_0).d_1 + U_{21j}.(t-t_0).d_2 + R_{1tj}.d_1 + R_{2tj}.d_2$---------- (3)

Random slope with fixed covariates model

$Y_{htj} = M_{10}.d_1 + M_{20}.d_2 + C_1.d_1.Cov + C_2.d_2.Cov + M_{11}.(t-t_0)d_1 + M_{21}.(t-t_0).d_2 + U_{10j}.d_1 + U_{20j}.d_2 + U_{11j}.(t-t_0).d_1 + U_{21j}.(t-t_0).d_2 + R_{1tj}.d_1 + R_{2tj}.d_2$---------- (4)

where h=1 for adherence to SU and h=2 for adherence to TZD;

d_1=1 when h=1; d_1=0 otherwise, and d_2=1 when h=2; d_2=0 otherwise;

M_{10} and M_{20} are population mean for random intercepts model (eq. 1 and 2) but population intercepts for random slope models (eq. 3 and 4);

M_{11} and M_{12} are population mean slope;

C_h (h=1,2) are coefficients for fixed covariates Cov;

U_{h0j} (h=1,2) are individual-dependent random components for j^{th} individual that affect all values Y_{htj} in the same way;

U_{h1j} (h=1,2) are individual-dependent random components indicating rate of change for j^{th} individual where t_0 is the reference point;

R_{htj} (h=1,2) are random deviations from individual mean for j^{th} individual at time t.

Random effects, not parameters in a statistical sense but latent variables (Snijder and Bosker, 1999), were the effects of interest. Under the assumption of normal distribution, there

are two major estimation methods for measuring random effects: maximum likelihood (ML) and residual (or restricted) maximum likelihood (REML). However, the REML method is useful for testing overall model fit only when two models have the same fixed parameters but differ in random effects. Random intercepts or random slopes were fitted first. Then sequentially covariates (gender and age) were introduced in each model to examine whether effects would persist after the effects of covariates were controlled. It should be noted here that while residual variance components U_{10} and U_{20} (estimated from deviations U_{10j} and U_{20j}, respectively) for eq. 1 and 2 represent between-person variability around grand mean, those for eq. 3 and 4 represent between person variability in initial estimate and U_{11} and U_{21} estimate between-person variability in rates of change. Similarly, R_1 and R_2 (estimated from deviations R_{1tj} and R_{2tj}, respectively) for eq. 1 and 2 estimate within-person variance or the pooled scatter of each individual's data around his or her individual mean and those for eq. 3 and 4 measure the scatter of each individual's values around his or her linear growth trajectory (Singer and Willet, 2003). Covariances related to level 3 (i.e., inter-individual) random components between two dependent variables (i.e.,U_{10} and U_{20} for eq. 1 and 2; U_{11} and U_{21} for eq. 3 and 4) were examined for significance. In addition, the goodness of fit test was conducted for covariate models. To examine the association of the evolutions, methods suggested by Fieuws and Verbeke (2004) were followed. The correlation between changes in adherence was given by

$$r = \frac{Covariance\ (U11\ and\ U21)}{std.dev\ (U11).std.dev\ (U21)} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (5)$$

Inter-disease Multiple Medications Adherence Behavior

The random intercept model (described by equation 1) employed for hypothesis 1 was adapted to examine hypothesis 3a through 3c. Specifically, hypertension, dyslipidemia, and angina medication adherence were added in the model in addition to diabetes medication adherence for hypothesis 3a, 3a1, and 3c, respectively, whereas adherence to anti-hyperlipidemic medications was added in the model for hypothesis 3a to test hypothesis 3b. It can be understood that the number of DVs in each of these models are either three or four. Thus, random intercept model for intra-disease adherence is extended for inter-disease adherence by addition of extra DVs. Notations are extended accordingly to incorporate additional random intercept components due to additional DVs. Covariances/correlations between these random intercepts were the effects of interest and tested for significance.

Random Intercept Model for Inter-disease Multiple Medications Adherence

$Y_{htj} = \sum M_{i0}.d_i + \sum U_{i0j}.d_i + \sum R_{itj}.d_i$, where h =1, 2 or 3; d_i=1 if i=h, otherwise d_i=0.---- (6)

Measurement of Intra-disease Medication Adherence

The new composite measure that was described in Chapter 2 is a weighted average-based measure. Conceptually, each adherence estimate can be weighted to form a formative scale of composite value based on their relative contribution to patient health or treatment outcomes. Deriving appropriate weights is critical to the success of any composite measures. Thus, important issues include but not limited to which parameters and how such weights should be derived. Some directions can be provided from the medical risk assessment literature. Several risk evaluation models have been proposed to stratify risks systematically (see Gale et al., 2009 for a review). These models estimate risk of an event based on weights of individual factors

derived from regression. For example, the EMMACE risk model predicts the risk of 30-day mortality where age, blood pressure, heart rate are weighted (Gale et al., 2009). Similarly, the TIMI risk score for the prediction of mortality in ST- elevation myocardial elevation is computed as the simple arithmetic sum of factors of mortality weighted according to the adjusted odds ratios (e.g., 1 point for $1 < OR < 2$; 2 points for $2 < OR < 2.5$ and so on) from logistic regression analysis (Morrow et al., 2000). Calvin et al. (2000) cited the RUSH model where the risk of sustaining a major cardiac complication is computed as weighted average; two medication histories (0.85 for IV nitroglycerine required on admission and 1.34 for receiving neither β-blocker nor CCB at admission) were weighted differentially. Indeed, weighting individual risk factors by odds ratio, Calvin et al. (1995) argued, does provide a reasonable approach to risk stratification for major complications.

The Cox proportional hazards model was used to derive weight estimates. This model provides a semiparametric regression technique to discriminate risk factors, including those varying with time, associated with the occurrence of events (e.g., ER visits) during a specific interval (Singer and Willet, 2003).Advantages of the Cox method to model the time until an event of interest occurs are that it makes no assumption about the shape of the underlying hazard function, but identifies determinants of risks and estimates multipliers of the baseline hazard and the relative risks(hazard ratios) associated with the risk factors(Singer and Willet, 2003). The analysis of Cox regression is based on number of events per variable (EPV), not number of patients or patient-years. Thus, a sufficient number of events is required to enable accurate estimates. A general rule of a minimum of 10-20 EPV has been advocated for Cox regression (Concato et al., 1995; Peduzzi et al., 1995) although Vittinghoff and McCulloch (2007) argued that analysis with 5-9 EPV might be comparable with 10-16 EPV in some situations. In cases of

fewer events per independent variable, resampling techniques can be used to test model validity (Akins et al., 2008). In the Cox model for weight derivation, ERSU was the outcome measure and adherence estimates were treated as time-varying covariates. Adherence measured as PDC was computed for each quarter for each medication for diabetes. Comorbidity (CCI), gender, and age were treated as fixed (i.e., time-invariant) covariates. However, as mentioned before, patients were followed until the first occurrence of event. This analysis strategy was consistent with a previous study (Yu, Yu, and Nichol, 2010) that examined the effect of adherence on health outcomes. Hazard (parameter) estimates derived from Cox regression were used subsequently as weights.

Following the effort of computation of weights, a series of analysis were performed to compare the predictive ability of medication adherence as measured by different measurement techniques available in the literature and the one proposed in this study. The seven PDC measures of adherence (see Table 3.1) were calculated for each quarter for each patient. The Cox regression analysis as described above was repeated in which ERSU was used as outcome measure and one of the seven adherence estimates was used as risk factor in different models while keeping the same covariates. Then the next step is to characterize the performance of the models in which adherence was operationalized differently or measured by different mathematical formulas. Two types of measures are used for such purposes while modeling dichotomous outcomes: calibration and discrimination (Pembina and D'Agostino, 2004). Calibration, as defined by the authors, describes how closely the probabilities predicted by the model correspond with the observed outcomes. Discrimination is a measure of a model's ability to classify subjects correctly into one of the binary outcome categories (e.g., events vs. no-events). Although calibration and discrimination may be related, good discrimination does not

automatically confer the ability of good calibration and vice versa (Pencina and D'Agostino, 2004); demonstration of a model's ability to discriminate well should be of primary importance (Harrell, Lee, and Mark, 1996).

C-statistic – equivalently, area under the Receiver Operating Characteristic (ROC) curve – computed from a logistic regression analysis determines the predictive accuracy or discrimination ability of the model and is one of the most popular measures of model discrimination for binary outcomes (Hanley and McNeil, 1982). Unlike logistic regression, the measurement of predictive accuracy in survival analysis is more complex because of censoring. Harrell, Lee, and Mark (1996) introduced c-statistic as a natural extension of the ROC curve analysis and suggested plotting the predicted probability of surviving until each time point t_j (j=1,2..) against the actual proportion of subjects surviving beyond t_j. An overall C index, conceptually based on the measure of c-statistic in logistic regression, has been proposed to describe the performance of a survival analysis model (D'Agostino and Nam, 2004; Pencina and D'Agostino, 2004). D'Agostino and colleagues outlined the steps of computation of C-index as follows. From a time-to-event model, three sets of comparison groups can be identified: those who experience event against those who do not (event vs. non-event), those developing event against those also developing event (event vs. event), and event group against those censored (event vs. censored). For the sake of computing C-index, event vs. event and event vs. non-event comparisons are considered as usable pairs; in other words, if two individuals are randomly drawn at least one must have an event while the other may or may not develop so. Given all usable pairs, the C-index is computed based on the proportion of concordance such that a subject with a lower predicted probability of event experiences event later than does another with a higher probability or vice versa. Several variants of this conceptualization (Gonen and Heller,

2005; Kremers, 2007) and implementation in statistical software exist (e.g., Liu, Forman, and Barton, 2009). The modified definition advanced by Kremers (2007) was used in the study as it is suitable for time-dependent covariates and adjusts for ties of events, if any. Unlike D'Agostino and colleagues', Kremers' definition is indexed by event times and counting occurs with respect to each event time. For example, if an individual i experiences event at time t_i, it counts all other individuals (C_i) except i not having event at t_i but with predictor score lower than that of i, those with greater score at t_i and no-event at t_i as D_i, those (P_i) with equal score but no-event at t_i, and those (i.e., ties) with event at t_i as T_i. Then C_i, D_i, P_i, and T_i represent the count of useable pairs that can be formed with individual i at time t_i and can be termed as concordant, discordant, tied in prediction, and tied in time, respectively. Concordance (or, C-index) quantifies the proportion of all useable pairs of subjects such that a subject with the higher model-predicted risk of event experiences event earlier and vice versa. Kremers' conceptualization of concordance has been used in empirical studies (Fang et al., 2011; Wong et al., 2011b) to examine the accuracy of risk predictions and implemented in SAS by the author. Concordance values and their confidence intervals estimated for models with different adherence measures were compared.

Analysis was undertaken to determine the optimal cut-off point for dichotomization of the four continuous adherence (i.e., composite, average, min, and max) measures. Unlike data dependent methods (e.g., median-split), outcome-based methods for dichotomization of continuous variables rely on statistical criteria that best separate groups with regard to the outcome. ROC curve analysis is generally used to determine the optimal threshold of continuous or ordinal variables that differentiates binary outcomes and is a popular method in diagnostic medicine (Begg et al., 2000; Hanley and McNeil, 1982; Harrell, Lee, and Mark, 1996). Unlike

in logistic regression, ROC curves appear to vary as a function of time when derived from survival analysis (Heagerty, Lumley, and Pepe, 2000). Therefore, deriving optimal threshold based on ROC curves is difficult. Moreover, time-dependent optimal threshold may not be appealing conceptually. Another approach to dichotomization is based on maximization of appropriate test statistics. In the case of censored data, several statistics that are routinely reported by statistical software can be utilized for such purposes, including log-rank test (Williams et al., 2006), concordance statistic, Wald statistic, and partial likelihood ratio statistic (Gonen and Sima, 2008; Hollander, Sauerbrei, and Schumacher, 2001). Mazumdar and Glassman (2000) outlined the steps required to derive an optimal cut-off value. This approach, known as maximally selected statistic, is based on a series of two sample tests such that models are run with each of the potential candidate cut-off values and the cut-off value for which the respective model generates the maximum test statistic (or, minimum p-value) is chosen as optimal threshold. In general, such models are run in a unavailable setting although recommendations for multivariable model also exist (Mazumdar and Glassman, 2000; Mazumdar, Smith, and Bacik, 2003). In order to manage potential inflation of type I error due to multiple tests, several approaches have been recommended. The methods to address such problems include: (1) significance level (α) adjustment (e.g., Bonferroni adjustment or some variants), (2) p-value adjustment based on mathematical functions or distribution (e.g., adjusted p-value of 0.002 is equivalent to unadjusted $p = 0.05$ while examining all values within the inner 80% distribution of the variable), and (3) cross-validation/ split sample approach (Altman et al., 1994; Faraggi and Simon, 1996; Hilsenbeck and Clark, 1996; Lausen and Schumacher, 1996; Mazumdar and Glassman, 2000; Mazumdar, Smith, and Bacik, 2003; Miller and Siegmand, 1982). In an unpublished study, Gonen and Sima (2008) contrasted the utility of five different

statistics in deriving optimal cut-point with censored data and the partial likelihood ratio statistic based method emerged as the best strategy that performed consistently. The partial likelihood ratio statistic based minimum p-value approach was employed in the study. A set of candidate values (65, 70, 75, 80, and 85) were chosen a priori. These points are somewhat consistent with existing evidence (e.g., Karve et al., 2009; Hansen et al., 2009 for a single medication adherence) and clinical expert opinion and may be useful for implementation purposes. Bonferroni-adjustment was made for p-value and such adjustment may not result in underpowered analysis because of relatively small number of tests.

Data were analyzed in SAS software, version 9.3 (SAS Institute, Inc., Cary, North Carolina). Relevant SAS codes for multilevel modeling and SAS macros were obtained from the literature and past research (Kremers 2007; Thorp, 2007).

CHAPTER 4

RESULTS

Of all subjects whose data were available in the MarketScan 2002-2003 commercial claims database, 32,400 enrollees had filled at least one prescription for a SU and TZD by September 30, 2002. After the application of study inclusion criteria, 6922 subjects were eligible for subsequent analysis. These subjects were between18 and 62 years old as of 2002, continuously enrolled for at least 15 months from their index date (i.e., earliest date indicating filling of both SU and TZD), and either did not fill any diabetes medications other than SU and TZD after the respective index date or did not begin filing other diabetes medications until at least 15 months after their index date.

Note on Study Subject Selection

All prescription claims records for 2002 and 2003 of the selected subjects were extracted. NDCs from prescription (RX) claims files were merged with their respective active ingredient (or drug) name and strength using the Multum Lexicon Drug Data Table (Cerner Multum, 2011). Some enrollees filled nonzero quantities of a NDC more than once on one day. As such, duplicate fillings occurred for both SU and TZD. Subjects associated with duplicate fillings of medications were excluded from subsequent analysis. It was observed in the dataset that some subjects had a record of filling multiple SU (e.g., Amaryl and glipizide) or multiple TZD and others filled multiple strengths of a SU or a TZD (e.g., Avandia 2 mg, 4 mg, or 8 mg). For subjects displaying prescription fillings of multiple medications or strengths of SUs or TZDs, it

was observed that some patients filled multiple classes or strengths somewhat regularly while others switched from one strength to another within a medication. It is conceivable as to why a patient might be filling multiple strengths of medications. One potential reason may be that a physician might advise his patient to take different strengths of medication at different times in order to achieve desired therapeutic outcomes (e.g., 2 mg at morning and 4 mg at night). However, it is difficult to differentiate instances of nonadherence from physician-driven medication consumption decisions in cases of lack of regular filling patterns. Similarly, in cases of patients filling multiple medications, it cannot be clearly determined whether or not a change was made because of some legitimate medical reasons such as side effects. Thus, it is not possible to determine accurately the state of adherence for a patient who filled multiple medications. Because of indeterminacy a criterion was imposed for inclusion. That is, subjects were restricted to any molecule switch and/or strength switch once only. This would ensure that if subjects switched from one strength to another of the same medication or one medication to another they would not be filling two strengths or two classes of medications simultaneously as switches of each type were constrained to once or less. Thus, these subjects will be on two diabetes medications, a SU and a TZD, at any point in time consistent with the objective of examining simultaneous medication adherence for two diabetes medications.

Demography of Study Subjects

A total of 6043 subjects were available for final analysis and constituted the general pool of study participants. The demographic characteristics of the subjects are described in Table 4.1. On average, these subjects were available for observation for over 600 days. There were 55.5%

male and the average age of the subjects was nearly 54 years. The subjects were located across different geographic regions as determined from the enrollment summary file in 2002; however, the majority of the subjects came from the South and north central regions. The subjects were enrolled in different types of health benefit plans. PPO and comprehensive type of plans were predominantly chosen ones. However, few subjects appeared to have changed their plan types over their enrollment period. Approximately, 19% subjects filled prescriptions of SU and/or TZD from both community and mail order pharmacies. However, the majority of the subjects appeared to patronize community pharmacies only when prescription fills for SU and TZD were considered jointly.

Table 4.1: Demography of the Study Subject Pool

Variable	**N**	**Mean (std. dev) /Frequency %**
Age	6043	53.86 (6.67)
Gender (male)	3356	55.54%
Geographic Region#		
Northeast	523	8.65%
North Central	2442	40.41%
South	2580	42.69%
West	488	8.08%
Plan type		
Comprehensive	1862	27.61%
EPO	161	2.39%
HMO	588	8.72%
POS	883	13.09%
PPO	2789	41.35%
POS with capitation	462	6.85%
Number of Plan type		
One type	5359	88.68%
Two or more	684	11.32%
Pharmacy Patronage*		
Community Pharmacy only	3776	62.49%

Mail-order only Either type	893 1135	14.78% 18.78%
Number of Days of Observation	6043	636.21 (79.01)
Number of Comorbidities	6043	1.06 (0.31)
Charlson Comorbidity Index (CCI)	6043	2.08 (0.42)

* Based on filling patterns for SU and TZD and other medication fills were not considered; # there were 10 subjects from unknown regions:

INTRA-DISEASE MULTIPLE MEDICATION ADHERENCE

Overall, the subjects demonstrated good levels of adherence (about 74%) for both SU and TZD and maintained consistency in adherence over time (Table 4.2). With regard to population level estimates, the adherence levels of SU measured at each quarter closely followed the adherence levels of TZD for the respective quarters. All subjects had 90-day observation periods at least until the fifth quarter but the number of available days of observation in their last quarter varied among subjects. For example, if a person was observed for seven quarters, he has six 90-day observation periods and the last (i.e., seventh) quarter with 90-days or less. For the sake of estimation of last quarter PDC, two options were available: keeping the 90-day denominator for everyone or using subject-specific variable denominators based on availability. For the last quarter, the number of available days of observation for a subject was entered in the respective denominator as a wide variety of available days of observation were found (e.g., less than 10 days to 90 days). In addition, more than 1000 subjects had a last quarter such that the number of days available for observation in the quarter was less than 30. As expected, adherence rates continuously declined, although slightly, over time until quarter 6. However, the rates increased

slightly for the last two quarters when number of patients who were available for observation continued to decrease.

Table 4.2: PDC Estimates for SU and TZD

Quarter	N	SU		TZD	
		Mean	Std. dev.	Mean	Std. dev.
1	6043	84.19	23.87	85.64	22.52
2	6043	75.00	32.78	75.79	33.13
3	6043	73.81	34.00	73.98	34.82
4	6043	72.90	35.15	72.52	36.42
5	6043	71.70	36.06	70.31	37.86
6	6043*	69.76	37.79	69.04	39.38
7	4979*	70.00	38.18	69.36	39.58
8	3752*	72.18	38.46	70.77	40.02
Weighted Average#		73.86		73.66	

* Numbers of days of observation in these quarters are not 90 days for all subjects
# Weighted by N
SU: Sulfonylureas; TZD: Thiazolidinediones

Examination of Hypotheses: Intra-disease Multiple Medication Adherence

A total of 6043 subjects were available initially for the examination of intra-disease multiple medication adherence (Hypotheses 1 through 2b. Only full-quarter observations were included in these analyses. For example, if a person had 7 full quarters of observations and one incomplete quarter, his incomplete quarter PDC was dropped when analysis was performed on the 8th quarter. The number of persons available in the 6th, 7th, and 8th quarter were 4996, 3772,

and 447, respectively. Although random intercept models were run successfully, growth models could not be run on the entire set of subjects because of computation limitations when the SAS default method for the estimation of denominator degree of freedom (ddf) was used. However, by limiting the analysis to subjects having at least 6 full quarters of observation, both models could be run successfully. Another alternative option was to choose other methods for estimation of ddf. Estimation of ddf is concerned primarily with fixed effect tests, which were not the objective of this research. SAS offers many approximate ddf estimation methods. The Kenward and Roger method (i.e., ddfm=KR on the PROC MIXED model statement) was used in this study. The Kenward and Roger method requires less memory than the default method in SAS and is thought to perform reasonably well when complicated covariance structures are present, sample sizes are moderate to small, and the design is moderately balanced (Schaalje, McBride, and Fellingham, 2001). Unconditional and conditional random intercept models and growth models using the KR method were run for examining the hypotheses. The results are summarized in Table 4.3.

Table 4.3: Multilevel Model Analysis – Intra-disease Multiple Medication Adherence

Model	Parameter	Covariance				Correlation
		Estimate	Std. error	Z value	P	
Unc. Mns	Int-SU/Int-TZD	420.71	11.7966	35.66	<.0001	0.5665
Con. Mns[1]	Int-SU/Int-TZD	394.94	11.3517	34.79	<.0001	0.5509
Con. Mns[2]	Int-SU/Int-TZD	416.79	11.7301	35.53	<.0001	0.5641
Con. Mns[3]	Int-SU/Int-TZD	391.77	11.2982	34.68	<.0001	0.5488
Unc. Grt	Slp-SU/Slp-TZD	17.4088	0.6031	28.87	<.0001	0.6209*
Con. Grt[1]	Slp-SU/Slp-TZD	17.4006	0.6030	28.86	<.0001	0.6207*
Con. Grt[2]	Slp-SU/Slp-TZD	17.4111	0.6031	28.87	<.0001	0.6209*
Con. Grt[3]	Slp-SU/Slp-TZD	17.4027	0.6031	28.86	<.0001	0.6207*

Unc. Mns: Unconditional Means model; Con. Mns: Conditional Means model; Unc. Grt: Unconditional Growth Model; Con. Grt: Conditional Growth Model;
Int: Random intercept; Slp: Random slope;
1: mean centered age as covariate; 2: gender as covariate; 3: mean centered age and gender as covariates; * Represents the association of evolutions
SU: Sulfonylureas; TZD: Thiazolidinediones

For the examination of hypothesis 1, a random intercept model was analyzed on quarter-specific PDC estimates. PDC estimates for different medications can be identified by a dummy variable indicating different medications (i.e., SU and TZD). The covariation between random intercepts of SU and TZD was estimated at 420. 71 and it was significant ($p<0.001$). Thus, H1 was supported. The corresponding correlation between random intercept for SU and that of TZD was 0.5665. For examining Hypotheses 1a and 1b, age (mean centered) and gender was entered one at a time in the above model. The effects were significant (Appendix). After controlling for age and sex, the covariations remained significant at the level of 0.001. The correlations between random intercepts of SU and TZD in the model with age and with gender were 0.5509 and 0.5641, respectively, providing support for H1a and H1b were confirmed.

Growth models were used to examine Hypotheses 2 through 2b. Two random components were added to the slopes of PDC estimates for SU and TZD. Thus, the growth models contained four random components – one component for the intercept and one for the slope for each of the two adherence estimators. For the examination of hypothesis 2, covariation between random slopes was examined. The results are described in Table 4.3. The covariation between random slopes of SU and TZD was estimated at 17.41 and it was significant ($p<0.001$). Thus, H2 was confirmed. The corresponding correlation (i.e., the association of evolutions)

between random slopes for SU and that of TZD was found to 0.62. When Hypotheses 2a and 2b, age (mean centered) and gender was entered respectively in the model specified for H2. After controlling for the effect of age and gender, the covariation remained significant at the level of 0.001. The associations of evolutions of SU and TZD in the model with age and with gender were 0.62. Thus, the results supported H2a and H2b, respectively.

INTER-DISEASE MULTIPLE MEDICATION ADHERENCE

In addition to using multiple diabetes medications, diabetes patients may use medications for the treatment of one or more different chronic disorders. Hypotheses 3a through 3c were meant to examine simultaneous adherence behaviors for medications prescribed for different additional chronic diseases. Subjects were selected from the general pool with an additional restriction that subjects must have at least four full quarters of observation beginning from the inter-disease index date. The index date for inter-disease medication adherence may be different from index date for intra-disease medication adherence. Inter-disease index date was determined by the first fill for a medication intended for the asymptomatic chronic disease of interest; the inter-disease index date could occur on or later than the index date. For example, in case of examining adherence relationships between diabetes medications and an anti-hyperlipidemic medication (asymptomatic chronic disorder), if a patient filled an anti-hyperlipidemic medication before his index date for SU and TZD, the inter-disease index date took the value of the diabetes index date. Similarly, for a patient on two diabetes medications, antihypertensives, and anti-hyperlipidemic medications the earliest date indicating the patient filled all requisite medications at least once was considered as the index date for subsequent analysis. Four inter-disease index

dates were computed for a patient who was eligible for inclusion in all analyses associated with Hypotheses 3a through 3c. Only those patients who demonstrated at least one prescription fill for chronic disease of interest and had at least four quarters of observation following respective inter-disease index dates were included in hypotheses testing.

Table 4.4: Demography of the Inter-disease Multiple Medication Adherence Subjects

Analysis	Variable	N*	Mean (std. dev) /Frequency (%)
SU + TZD + LIP (H3a)	Age Gender (male) Number of Days of Observation	2360	54.92 (6.02) 1387 (58.77) 609.95 (92.38)
SU + TZD + AHT (H3a1)	Age Gender (male) Number of Days of Observation	2444	53.70 (6.57) 1316(53.85) 578.57 (162.81)
SU + TZD + LIP + AHT (H3b)	Age Gender (male) Number of Days of Observation	860	54.60 (94.15) 462 (55.66) 601.87 (6.13)
SU + TZD + ANG (H3c)	Age Gender (male) Number of Days of Observation	300	56.46 (4.73) 187 (62.33) 559.92 (101.74)

* Subjects who had at least four 90-day quarters of availability starting from analysis-specific index dates
SU: Sulfonylureas; TZD: Thiazolidinediones; LIP: anti-hyperlipidemic medications; AHT: hypertension medications; ANG: Anti-anginal medications

Table 4.4 describes the demographic profile of the subjects included in inter-disease multiple medication adherence analyses. Subjects were about 55 year old and had, on average, 560 days of observation following the start of the analysis-specific (e.g., SU + TZD + AHT + LIP for H3b) index date. With regard to gender, subjects consuming multiple asymptomatic chronic disorder medications were evenly split except for those having angina in which 62% were male.

PDC Estimates for Different Chronic Diseases

The population PDC estimates for different asymptomatic chronic disorders were about 70% (Table 4.5). Subjects may have had incomplete observation periods from quarter 5 onward. The PDC denominator for any incomplete quarters was based on available days of observation. Patients receiving anti-hyperlipidemic medications had slightly lower average adherence rates on those medications than their PDC for their diabetes medications. In contrast, those subjects receiving antihypertensives showed slightly higher adherence rates when compared to their diabetes medications. Higher adherence rates for antihypertensives, although small, persisted even in subjects receiving four medications: SU, TZD, anti-hyperlipidemic medications agents, and antihypertensives. Interestingly, adherence rates to nitrates were lower substantially. Additionally, adherence rates in the last two quarters showed an increasing trend regardless of the nature of disease.

Table 4.5: PDC Estimates for Subjects on Medications for Multiple Chronic Disorders									
Model	**Param**	**Qtr 1**	**Qtr 2**	**Qtr 3**	**Qtr 4**	**Qtr 5**	**Qtr 6**	**Qtr 7**	**Qtr 8**
SU+TZD+ LIP	Mean (SU)	85.20	77.31	76.38	75.44	74.46	72.36	72.49	74.17
	Std. Dev	23.76	31.92	33.17	34.53	35.28	37.16	37.79	38.74
	Mean (TZD)	86.22	79.02	77.21	75.53	73.07	72.38	72.98	74.99
	Std. Dev	22.76	31.20	33.61	34.91	36.90	38.48	38.43	38.54
	Mean (LIP)	84.05	74.02	72.01	69.98	68.79	67.36	70.09	71.46
	Std. Dev	24.42	34.05	36.27	37.89	38.65	40.47	39.22	39.59
	N	2360	2360	2360	2360	2357	2234	1748	1233
SU+TZD+ AHT	Mean (SU)	84.47	75.76	74.87	73.92	72.23	70.58	70.32	73.55
	Std. Dev	23.85	32.36	33.42	34.46	35.59	37.50	37.97	37.80
	Mean (TZD)	85.26	76.76	74.66	73.67	71.57	70.84	70.82	71.99
	Std. Dev	23.26	32.99	34.77	35.91	37.34	38.44	38.96	39.79
	Mean (AHT)	86.07	78.72	77.56	76.71	75.45	74.82	76.31	77.58
	Std. Dev	22.71	31.34	32.40	34.06	35.12	36.21	35.05	35.70
	N	2212	2212	2212	2212	2212	2145	1734	1276
SU+TZD+ LIP+AHT	Mean (SU)	85.46	78.02	76.87	75.74	74.56	72.48	72.65	75.09
	Std. Dev	24.01	31.94	33.14	34.74	35.30	37.22	37.65	38.61
	Mean (TZD)	85.88	79.50	78.05	77.32	74.90	73.88	74.74	76.38
	Std. Dev	22.71	31.34	33.24	33.79	35.80	37.79	37.63	38.23
	Mean (LIP)	82.78	74.90	72.66	72.11	68.68	67.25	71.09	71.56
	Std. Dev	25.23	33.73	35.99	36.70	38.00	40.42	38.83	39.92
	Mean (AHT)	86.40	81.75	80.42	79.50	78.03	77.79	79.89	80.19

	Std. Dev	23.27	29.29	31.04	33.23	33.74	35.22	33.64	34.82
	N	830	830	830	830	830	775	593	408
SU+TZD+ ANG	Mean (SU)	79.84	75.53	75.41	73.37	72.13	69.57	69.36	77.01
	Std. Dev	28.94	34.27	34.89	36.34	37.38	40.27	39.47	36.87
	Mean (TZD)	80.90	71.09	69.57	70.12	68.09	69.00	69.87	71.45
	Std. Dev	29.18	37.28	38.96	38.86	39.93	40.97	40.32	42.07
	Mean (ANG)	37.99	25.76	25.73	24.69	24.43	25.38	31.41	36.05
	Std. Dev	37.07	40.48	40.12	38.38	39.10	39.50	42.38	44.80
	N	300	300	300	300	299	253	166	88

Param: Parameters; Qtr: Quarter;
Subjects may have incomplete quarters from quarter 5 onward and PDC denominator for any incomplete quarters was based on available days of observation
SU: Sulfonylureas; TZD: Thiazolidinediones; LIP: anti-hyperlipidemic medications; AHT: hypertension medications; ANG: Anti-anginal medications

Table 4.6: Number of Subjects for Inter-disease Multiple Medication Adherence

Quarter	Number of subjects with medications for multiple chronic diseases			
	SU+TZD+LIP	SU+TZD+AHT	SU+TZD+LIP+AHT	SU+TZD+ANG
1	2360	2212	830	300
2	2360	2212	830	300
3	2360	2212	830	300
4	2360	2212	830	300
5	2235	2145	776	253
6	1752	1736	594	167
7	1240	1284	410	88
8	92	87	19	6

SU: Sulfonylureas; TZD: Thiazolidinediones; LIP: anti-hyperlipidemic medications; AHT: hypertension medications; ANG: Anti-anginal medications

Examination of Hypotheses: Inter-disease Multiple Medication Adherence

Multi-level modeling analyses were used to examine Hypotheses 3a through 3c. Specifically, multivariate unconditional random intercept models were analyzed in which quarter-specific PDC estimates for each medication were analyzed. Consistent with the approach used to examine intra-disease multiple medication adherence hypotheses, a subject was included in a quarter only if he had a full quarter of observation. Random effects were modeled from data using the unstructured option in SAS and subject-specific random error was modeled using the variance component option in SAS. It is noted that number of subjects in the following analyses continued to decrease after the fourth quarter. The numbers of subjects available for each analysis in each quarter appear in Table 4.6.

Table 4.7: Multilevel Model Analysis – Inter-disease Multiple Medication Adherence

Model	Parameter	Covariance				Correlation
		Estimate	Std. error	Z value	P	
Unc. Mns [1]	Int-SU/Int-TZD	379.31	17.4716	21.71	<.0001	0.5524
Unc. Mns [1]	Int-SU/Int-LIP	376.26	18.3807	20.47	<.0001	0.6239
Unc. Mns [1]	Int-LIP/Int-TZD	467.59	19.5534	23.91	<.0001	0.5136
Unc. Mns [2]	Int-SU/Int-TZD	402.97	19.0566	21.15	<.0001	0.5524
Unc. Mns[2]	Int-SU/Int-AHT	371.98	17.8122	20.88	<.0001	0.5436
Unc. Mns[2]	Int-AHT/Int-TZD	452.80	19.4428	23.29	<.0001	0.6208
Unc. Mns [3]	Int-SU/Int-TZD	371.46	29.1893	12.73	<.0001	0.5428
Unc. Mns [3]	Int-SU/Int-LIP	318.59	27.1611	11.73	<.0001	0.4909
Unc. Mns [3]	Int-LIP/Int-TZD	410.15	28.6394	14.32	<.0001	0.6293
Unc. Mns [3]	Int-SU/Int-AHT	348.81	30.5863	11.40	<.0001	0.4753
Unc. Mns [3]	Int-AHT/Int-TZD	457.90	32.3164	14.17	<.0001	0.6213
Unc. Mns [3]	Int-LIP/Int-AHT	439.85	30.7196	14.32	<.0001	0.6294
Unc. Mns [4]	Int-SU/Int-TZD	341.21	59.4130	5.74	<.0001	0.3837
Unc. Mns [4]	Int-SU/Int-ANG	78.2794	63.7770	1.23	0.2197	0.0753

Unc. Mns [4]	Int-ANG/Int-TZD	164.53	68.0516	2.42	0.0156	0.1498

Unc. Mns: Unconditional means model; Int: Random intercept;
1: PDCs for SU, TZD, LIP; 2: PDCs for SU, TZD, AHT; 3: PDCs for SU, TZD, LIP, AHT; 4: PDCs for SU, TZD, ANG
SU: Sulfonylureas; TZD: Thiazolidinediones; LIP: anti-hyperlipidemic medications; AHT: hypertension medications; ANG: Anti-anginal medications

A total of 2360 subjects were available for analysis initially (i.e., until the fourth quarter) and the number reduced to 1240 at the seventh quarter and only 92 in the eighth quarter. The results of these analyses are summarized in Table 4.7. Covariation of random intercepts between SU and anti-hyperlipidemic medications and that of TZD and anti-hyperlipidemic medications were significant ($p<0.001$). Thus, H3a was supported. The correlation between random intercepts for diabetes medications was 0.55. The correlation between random intercepts for SU and that of anti-hyperlipidemic medications was 0.62 and that of TZD and anti-hyperlipidemic medications was 0.51.

The above analysis was repeated to examine H3a1 in which subjects were on antihypertensive medications instead of anti-hyperlipidemic medications. Initially, 2212 persons were available. Covariation of random intercepts between SU and antihypertensives and that of TZD and antihypertensive medications were significant ($p<0.001$). Thus, H3a1 was supported. The correlation between random intercepts for SU and that of antihypertensive medications was estimated at 0.54 (Table 4.7) and that of TZD and antihypertensives was 0.62.

To examine H3b, multivariate multilevel analysis was performed on subjects receiving antihypertensive medications and anti-hyperlipidemic medications in addition to two diabetes medications. Unlike the subjects in the aforementioned analyses, the subjects in the present

analysis were on at least one additional medication. All covariations between cross-disease medications were examined. Covariation of random intercepts between SU and antihypertensives and that of TZD and antihypertensive medications were significant ($p<0.001$). Covariation of random intercepts between SU and anti-hyperlipidemic medications and that of TZD and anti-hyperlipidemic medications were significant ($p<0.001$). Finally, covariation of random intercepts between anti-hyperlipidemic medications and hypertension medications were significant ($p<0.001$). Thus, H3b was supported. The correlations of random intercepts for SU and hypertension medication, for SU and cholesterol medication, for TZD and cholesterol medication, for TZD and hypertension medication, and for hypertension and cholesterol medication were estimated at 0.48, 0.49, 0.63, 0.62, and 0.63, respectively.

For the examination of H3c, in which subjects were on anti-anginal medications in addition to diabetes medications, 300 persons were available initially. The covariation of random intercepts between SU and angina medications was not significant ($p=0.075$) whereas that of TZD and angina medications was significant ($p=0.016$). Thus, H3c was partially supported. However, the correlation between random intercepts for SU and TZD was estimated at 0.38 (Table 4.7) and significant ($p<0.001$).

Table 4.8: Associations of Evolutions for Inter-disease Multiple Medication Adherence

Model	Parameter	Correlation	P
Con. Grt [1]	Slp-SU Slp -TZD	0.6437	<0.0001
Con. Grt [1]	Slp -SU/ Slp -LIP	0.6084	<0.0001
Con. Grt [1]	Slp -LIP/ Slp-TZD	0.6897	<0.0001
Con. Grt [2]	Slp -SU/ Slp -TZD	0.6390	<0.0001

Con. Grt[2]	Slp -SU/ Slp -AHT	0.7086	<0.0001
Con. Grt[2]	Slp -AHT/ Slp -TZD	0.6881	<0.0001
Con. Grt [3]	Slp -SU/ Slp -TZD	0.7283	<0.0001
Con. Grt [3]	Slp -SU/ Slp -LIP	0.7215	<0.0001
Con. Grt [3]	Slp -LIP/ Slp -TZD	0.7131	<0.0001
Con. Grt [3]	Slp -SU/ Slp -AHT	0.6280	<0.0001
Con. Grt [3]	Slp -AHT/ Slp -TZD	0.7699	<0.0001
Con. Grt [3]	Slp -LIP/ Slp -AHT	0.7123	<0.0001
Con. Grt [4]	Slp -SU/ Slp -TZD	0.5913	<0.0001
Con. Grt [4]	Slp -SU/ Slp -ANG	0.1472	0.1233
Con. Grt [4]	Slp -ANG/ Slp -TZD	0.2093	0.0406

Con. Grt.: conditional growth model with mean centered age and gender as covariates
1: PDCs for SU, TZD, LIP; 2: PDCs for SU, TZD, AHT; 3: PDCs for SU, TZD, LIP, AHT; 4: PDCs for SU, TZD, ANG
SU: Sulfonylureas; TZD: Thiazolidinediones; LIP: anti-hyperlipidemic medications; AHT: hypertension medications; ANG: Anti-anginal medications

Following the intra-disease multiple medication adherence analysis, additional analyses were undertaken to examine the relationship between random growth patterns of inter-disease medication adherence over time. Specifically, the relationships between random slopes for adherence to two medications (i.e., associations of evolutions) were examined. The results of the analyses are presented in Table 4.8. In general, associations of evolutions are strong and significant at the level of 0.001. After controlling for the effects of age and gender, such associations ranged from 0.61 to 0.76 for people who are on either anti-hyperlipidemic medications or antihypertensive medications or both in addition to two diabetes medications. However, the association of evolutions between SU and anti-anginal medications was poor and not significant ($p>0.1$) whereas that of TZD and anti-anginal medications were week (0.21) but significant ($p<0.05$). The association of evolutions of SU and TZD measured in patients taking angina medications was estimated at 0.59 and significant ($p<0.001$).

MEASUREMENT OF INTRA-DISEASE MULTIPLE MEDICATION ADHERENCE

PDC Estimates

It is known that single estimates of PDC for multiple medications can be computed using different algorithms. Table 4.9 provides quarter specific and cumulative PDC estimates as calculated by the continuous measure-based approaches. Cumulative PDC estimates were calculated by proportion of days on medications out of all days until the end of quarter or observation. Thus, subjects may or may not have a complete last quarter. Individual or population estimates of PDC varied widely depending on types of measures used. For example, population PDC estimates for the fifth quarter in which all had a 90-day observation period were 82.78%, 59.22%, and 71% based on maximum (i.e., availability of any medications on a day), minimum (i.e., availability of all medications on a day), and average approaches, respectively. Similarly, cumulative PDC estimates differed; cumulative PDC estimates for the eighth quarter with subject-specific variable observation period were 87.40%, 67.29%, 71.47% when PDC was calculated by maximum, minimum, and average based approaches, respectively. Variations in estimates based on the minimum measurement were generally more than those of the other two approaches.

Table 4.9: PDC estimates by Different Continuous Measures						
Approach	**Quarter**	**N**	**Quarter–specific**		**Cumulative**	
			Mean	**Std Dev**	**Mean**	**Std Dev**
Maximum	1	6043	93.30	14.88	93.30	14.88
	2	6043	86.73	24.86	90.02	18.07
	3	6043	85.45	26.79	88.49	19.52
	4	6043	84.39	28.51	87.47	20.62
	5	6043	82.78	30.26	86.53	21.46
	6	6043	81.40	32.19	85.76	22.09
	7	4979	81.63	32.32	86.47	21.26
	8	3752	83.05	32.19	87.40	20.49
Minimum	1	6043	76.54	28.28	76.54	28.28
	2	6043	64.06	37.26	70.30	29.88
	3	6043	62.34	38.31	67.65	30.62
	4	6043	61.03	39.48	65.99	31.15
	5	6043	59.22	40.21	64.64	31.52
	6	6043	57.40	41.54	63.52	31.80
	7	4979	57.74	41.99	64.89	31.04
	8	3752	59.90	42.75	67.29	29.97
Average	1	6043	84.92	19.33	84.92	19.33
	2	6043	75.40	27.96	75.40	27.96
	3	6043	73.90	29.36	73.90	29.36
	4	6043	72.71	30.66	72.71	30.66
	5	6043	71.00	31.88	71.00	31.88
	6	6043	69.40	33.38	69.40	33.38
	7	4979	69.68	33.55	69.68	33.55
	8	3752	71.47	33.72	71.47	33.72

Single measures of multiple medication adherence were computed based on a dichotomous scale where a cut-point of 80% was used to classify patients as adherent. There was considerable variability in estimates measured by the 'at least one' (i.e., whether or not 80% days on at least one medication), 'both' (i.e., whether or not 80% days on both medications), and 'all' (i.e., whether or not 80% days on each medication measured separately) approaches. PDC

estimates varied from 88% at quarter 1 to 78% at quarter 8 when measured by the 'at least 1' approach. Similar estimates for 'both' were from 61% to 51%, and for 'all' 63% to 52%. A detailed description of all estimates has been provided in Appendix. Thus, the both approach consistently provided lowest estimates. The all-based estimates were slightly smaller but closely followed the estimates measured by the both approach.

Table 4.10: Measure of Discrepancy

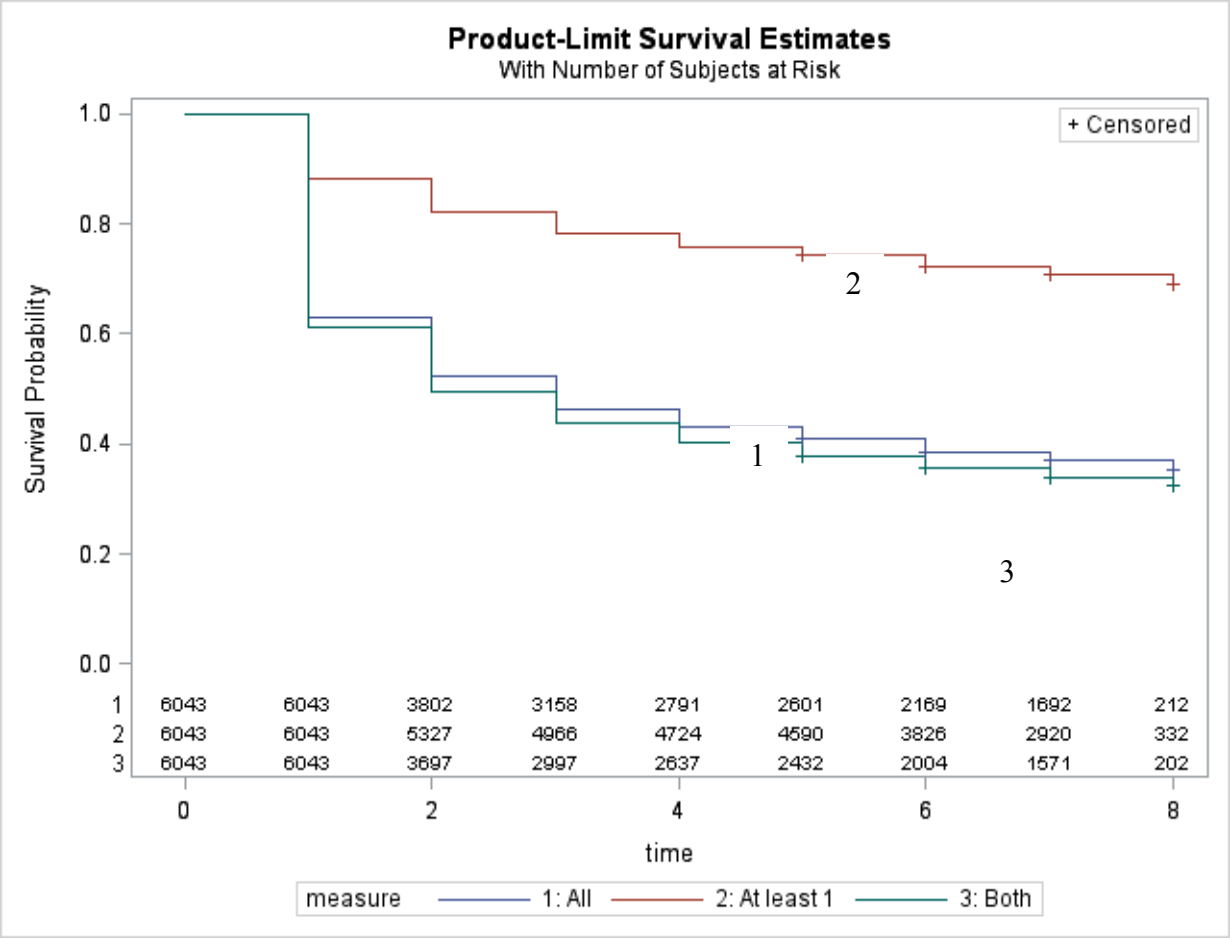
Quarter	Quarter-specific	
	N	%
1	1630	30.6
2	1778	36.71
3	1815	38.21
4	1769	37.74
5	1735	37.9
6	1697	37.71
7	1366	36.47
8	1011	34.55

Number of subjects who were rated adherent by one or two dichotomous measures but not by all three approaches.

Using dichotomous measures of adherence, a subject can be classified as adherent or nonadherent. Thus, a person can be classified as adherent by only one composite dichotomous measure, two measures, or all three. An analysis was performed to examine the discrepancy in classification provided by different dichotomy-based approaches. The analysis was run on quarter-specific PDC for subjects who were rated adherent by at least one of the approaches. Table 4.10 describes the rate of discrepancy across different quarters. It was found that at least

30% subjects were differentially classified. In other words, about one third population will be rated as adherent based on an approach but nonadherent based on another approach. Interestingly, the rates of such differential classification were even higher (35-38%) in later quarters.

Figure 4.1: Persistency Estimates as Measured by Different Categorical Single Measures



Kaplan-Meier analysis (Figure 4.1) was performed to compare how different categorical composite measures classified population persistence estimates. PDC was measured cumulatively until last full quarter of observation and patients were followed until they became

nonadherent (i.e., cumulative adherence <80%) for the first time or censored at the end of last full quarter. As can be understood, 'at least one' identified more subjects as persistent and showed a much slower decline than did the all or both approaches both of which closely followed each other. In addition, the gap widened over time. The log-rank test (adjusted) revealed that statistics produced by all three approaches were significantly ($p<0.005$) different from one another. Thus, choice of measurement approach does matter.

EFFECTIVENESS OF MEASURES OF MULTIPLE MEDICATION ADHERENCE

PDC estimates for multiple medications based on different approaches varied. Apart from six measures as above, a weighted-average measure of multiple medication adherence was conceived as part of the objectives of the study. The analyses that follow address the selection of the most effective measurement paradigm. Specifically, the analysis aims are to compare different measures and offer an optimal cut point for adherence classification.

Different outcome measures may be used for answering the substantive issue described above. Among them are emergency room (ER) visits, inpatient stays, and a combined indicator of any ER or inpatient hospitalization, whichever occurring first. Additionally, outcomes may be any cause, primarily diabetes related, or any diabetes-related utilization. Thus, it was possible to choose from nine different outcome measures. The sample of study population demonstrated high rates of censoring. It was more so for some types of events (e.g., primarily diabetes related utilization). Thus, it was necessary to pay attention to focus on the selection of an outcome that would be theoretically and practically meaningful and yet had a reasonable number of events for survival analysis to run successfully.

Table 4.11: Event Distribution Across Quarters				
Quarter	**AC_ER N (%)**	**Diab_ER N (%)**	**AC_cmb N (%)**	**Diab_cmb N (%)**
2	313 (22.06)	55 (16.92)	379 (22.47)	107 (16.77)
3	279 (19.66)	49 (15.08)	338 (20.04)	100 (15.67)
4	299 (21.07)	51 (15.69)	355 (21.04)	118 (18.5)
5	235 (16.56)	69 (21.23)	268 (15.89)	141 (22.1)
6	169 (11.91)	58 (17.85)	193 (11.44)	95 (14.89)
7	107 (7.54)	37 (11.38)	133 (7.88)	66 (10.34)
8	17 (1.2)	6 (1.85)	21 (1.24)	11 (1.72)
Total*	1419	325	1687	638

AC_ER: all cause emergency room (ER) visits; Diab_ER: any diabetes related ER; AC_cmb: all cause ER or inpatient hospitalization (IP), whichever occurring first; Diab_cmb: any diabetes related ER or IP, whichever occurring first

* Events occurring only in any fully observed quarters included

Event Distribution Analysis

A total of 1419 subjects had an all cause ER event. It is noted here that there were a few more events when all observations were considered regardless of whether or not events occurred in any fully observed period. Thus, an event that occurred during a subject's last quarter, which was shorter than 90 days, was not counted as the person was followed only until the last full quarter, which preceded the occurrence of event. Such events were not concentrated in any quarter and rather spread across quarters (Table 4.11). However, few events were observed during quarter 8. There are other event types that can be utilized to examine the issue of measurement effectiveness. Some have been presented in Table 4.11. Any diabetes related

utilization was considered conceptually meaningful and proximal to the causal relationship between event and medication use. Similarly, any diabetes related ER or inpatient hospitalization events (i.e., Diab_cmb in Table 4.11) capture those with which diabetes has been explicitly associated. These outcomes not only appear theoretically appealing but also hold practical implications. A total of 325 and 638 events were observed, respectively. However, only the former category was used in this study for unbiased and consistent analysis because the latter category may include planned inpatient admissions (e.g., surgical procedures such as CABG) for which medication adherence may not be directly related. For this study, any diabetes related ER utilization was considered in addition to any cause ER.

Measurement of PDC for Survival Analysis

For all PDC calculations associated with this dissertation study a duration of 90 days (i.e., 90-day quarter) was used. However, several issues arose that needed additional consideration with regard to the measurement of PDC. A large number of participants had an incomplete observation period in their last quarter. In the examination of multiple medication adherence, these incomplete observations (i.e., incomplete quarters) were ignored. However, the adoption of a similar strategy for survival analysis may not be appropriate. A total of 1240 subjects had a last quarter with 30 days or less and about 5500 had fewer than 90 days of observation. Moreover, events may have occurred in some of these incomplete reporting periods. As such, ignoring all incomplete 90-day quarters will result in a loss of events and, in turn, an increase in censoring, the rate of which is already somewhat high. Because of excessive censoring, the survival analysis may become underpowered. As such, it was believed that shortening of

measurement period to 30-day periods might alleviate the problem of losing events and would allow the inclusion of full-length observations. In addition, it was thought that shortening the length of measurement period of PDC would bring closer the period of event measurement, which was measured as day, to the PDC measurement period. If these periods are closer to each other then there will be less error associated with any probable overestimation of PDC, especially for PDC measured over the post-event period or any increase in post-event PDC. Another consideration is that the primary outcome measure (i.e., all cause ER) chosen for this analysis may require a short measurement period in order for capturing the effect of nonadherence. Episodes of nonadherence within a short period may lead to hyperglycemia, which may represent an underlying contributing factor for an acute event such as all cause ER. In contrast to the above period-specific temporal measurement approach, the disease progression paradigm posits that a patient's adherence behavior over a period of time would represent his propensity of having an event. Thus, the analyses for this part of the project will present the results for 30-day and 90-day PDC period-specific measures as well as cumulative monthly and cumulative quarter-specific measures. Only observations that represented a complete reporting period were included. Subjects were censored at the of their last full observation period or after an event, whichever occurred earlier.

Weighted Average Adherence Measure

Survival analysis was performed to estimate drug-specific weights (Ws) required to estimate weighted average adherence measure. By definition, the composite measure reflects the benefits of individual medications based on partial adherence, if any.

$$\mathrm{Adh}_{\mathrm{com}} = \frac{W_1 . A_1 + W_2 . A_2}{W_1 + W_2}$$

Table 4.12:Hazard Estimates for Predictors of Adverse Events

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
Age	1	-0.00160	0.00405	0.1550	0.6938	0.998
Gender (male)	1	-0.28755	0.05328	29.1282	<0.0001	0.750
CCI	1	0.35141	0.04240	68.7027	<0.0001	1.421
PDC (SU)	1	-0.00095	0.00085	1.2507	0.2634	0.999
PDC (TZD)	1	-0.00215	0.00082	6.9825	0.0082	0.998

Outcome: all cause ER; PDC is measured at each quarter

Weights were to be represented by medication-specific hazard estimates. Survival analysis was performed with all cause ER visits as the outcome. Several models were run with different PDC estimates based on the period lengths. Adherence estimates were calculated as PDC measured over a period of 30 days and 90 days for each quarter and PDC measured cumulatively at each quarter. When 90-day quarter-specific PDC was used, only PDC for TZD was significant at the level of 0.05 (Table 4.12). However, when 90-day cumulative PDC estimates were used, none of them were significant at a level of 0.05. In this instance, PDC for

SU was significant at the level of 0.01 (Table 4.13). A similar trend was observed when PDC measurement period was changed to 30 days. In other words, period-specific PDC for TZD was significant (p=0.008) (Table 4.14), but cumulative PDC for SU was significant (p=0.028) (Table 4.15).

There was no difference between parameter estimates of individual 90-day quarter-specific PDCs (Chi square 0.725, p=0.39). A similar result (p=0.97) was observed when cumulative 90-day PDCs were entered into the survival analysis. Results did not differ for PDCs, both period-specific and cumulative, measured over a 30 period. Although all individual hazard estimates were in the right direction and some were significant, there were no differences in the hazard ratios. Under this situation, weights could not be estimated that were nontrivial and different from each other. Thus, it was not possible to calculate a weighted average measure of PDC.

Table 4.13:Hazard Estimates for Predictors of Adverse Events

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
Age	1	-0.00166	0.00407	0.1668	0.6829	0.998
Gender (male)	1	-0.28968	0.05331	29.5281	<0.0001	0.749
CCI	1	0.35082	0.04243	68.3703	<0.0001	1.420
PDC (SU)	1	-0.00183	0.00110	2.7725	0.0959	0.998
PDC (TZD)	1	-0.00175	0.00109	2.5576	0.1098	0.998

Outcome: all cause ER; PDC is measured cumulatively over quarters

Table 4.14:Hazard Estimates for Predictors of Adverse Events

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
Age	1	-0.00070	0.00397	0.0315	0.8592	0.999
Gender (male)	1	-0.27109	0.05204	27.1320	<0.0001	0.763
CCI	1	0.34317	0.04279	64.3337	<0.0001	1.409
PDC (SU)	1	-0.00093	0.00073	1.5925	0.2070	0.999
PDC (TZD)	1	-0.00190	0.00072	6.9829	0.0082	0.998

Outcome: all cause ER; PDC is measured at each 30-day period

Table 4.15:Hazard Estimates for Predictors of Adverse Events

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
Age	1	-0.00042	0.00399	0.0111	0.9160	1.000
Gender (male)	1	-0.27231	0.05209	27.3289	<0.0001	0.762
CCI	1	0.34038	0.04288	63.0147	<0.0001	1.405
PDC (SU)	1	-0.00236	0.00107	4.8133	0.0282	0.998
PDC (TZD)	1	-0.00150	0.00108	1.9347	0.1642	0.998

Outcome: all cause ER; PDC is measured cumulatively over 30-day periods

Comparison of the Adherence Measures: Predictive Power

As a weighted average-based composite model could not be computed, multiple survival analyses were performed with the six different PDC estimates as described before. Analyses were run using both a univariable and a multivariable framework. The results from survival analysis with the six different PDC measures are presented in Table 4.16. Medication adherence was significantly ($p<0.001$) associated with the adverse outcomes of interest. Indeed, nonadherence to diabetes medications as measured by all different single estimates predicted hazards of adverse events. However, hazard estimates as given by different single measures of adherence widely varied. Hazard ratios for adherence, measured temporally over a 30-day period, varied from 0.784 to 0.997. Although some hazards estimates were nearly 1.0, all were statistically significant ($p<0.005$). Hazard estimates were slightly lower under the univariable analysis for adherence measured over each 30-day period by the all, at least one, and both approaches. Such differences were not observed when continuous measures of PDC were used.

As proposed, the analyses were rerun with PDC estimated at each quarter (i.e., 90 days). Adherence was associated significantly with lower hazards of all-cause ER visits. For example, the hazard of having any all-cause ER visit was 0.787 when adherence was measured over each quarter following the both approach. Measures using dichotomous approaches provided slightly lower hazard ratios when only PDC was used as the independent variable. The hazard estimates for at least one-based PDC measured over 90 days were 0.785 and 0.807 in a univariable and multivariable setting, respectively (Table 4.16). Mostly, the at least one approach among all different measures appeared to provide lower hazard estimates regardless of measurement period.

Table 4.16: Hazard Estimates for Different PDC Measurements

Measurement Period	Model	Approach	Parameter estimate	Std. Err	P	Hazard Ratio
30 days	Uni	All	-0.2536	0.05192	<.0001	0.776
		Atlst1	-0.2437	0.06193	0.0001	0.784
		Avg	-0.0033	0.00075	<.0001	0.997
		Both	-0.2538	0.05192	<.0001	0.776
		Max	-0.0027	0.00078	0.0007	0.997
		Min	-0.0025	0.0006	<.0001	0.997
	Mul	All	-0.2189	0.05253	<.0001	0.803
		Atlst1	-0.2205	0.06296	0.0005	0.802
		Avg	-0.0028	0.00077	0.0002	0.997
		Both	-0.2186	0.05254	<.0001	0.804
		Max	-0.0024	0.0008	0.0202	0.998
		Min	-0.0021	0.0006	0.0005	0.998
90 days	Uni	All	-0.2129	0.05321	<.0001	0.808
		Atlst1	-0.2421	0.06114	0.0001	0.785
		Avg	-0.0038	0.00084	<.0001	0.996
		Both	-0.2392	0.0534	<.0001	0.787
		Max	-0.0031	0.00088	0.0006	0.997
		Min	-0.003	0.00067	<.0001	0.997
	Mul	All	-0.1689	0.05399	0.0018	0.845
		Atlst1	-0.2147	0.06233	0.0006	0.807
		Avg	-0.0031	0.00086	0.0003	0.997
		Both	-0.1965	0.05417	0.0003	0.822
		Max	-0.0027	0.0009	0.0033	0.997
		Min	-0.0024	0.00068	0.0005	0.998

Outcome: all cause ER; Uni: univariable; Mul: Multivariable; PDC measured for each period

Atlst1: At least one approach; Avg: Average approach; Max: Maximum approach; Min: Minimum approach

Table 4.17: Hazard Estimates for Different Cumulative PDC Measurements

Measurement Period	Model	Approach	Parameter estimate	Std. Err	P	Hazard Ratio
30 days	Uni	All	-0.2279	0.05198	<.0001	0.796
		Atlst1	-0.1918	0.06376	0.0032	0.825
		Avg	-0.0033	0.00075	<.0001	0.997
		Both	-0.2098	0.05221	<.0001	0.811
		Max	-0.0041	0.00123	0.0011	0.996
		Min	-0.0036	0.00083	<.0001	0.996
	Mul	All	-0.1897	0.05276	0.0003	0.827
		Atlst1	-0.1638	0.06511	0.0119	0.849
		Avg	-0.0028	0.00077	0.0002	0.997
		Both	-0.169	0.05302	0.0014	0.845
		Max	-0.0036	0.00126	0.0045	0.996
		Min	-0.0028	0.00084	0.0009	0.997
90 days	Uni	All	-0.2279	0.05321	<.0001	0.796
		Atlst1	-0.1988	0.0646	0.0025	0.82
		Avg	-0.0038	0.00084	<.0001	0.996
		Both	-0.2185	0.05351	<.0001	0.804
		Max	-0.0039	0.00124	0.0022	0.996
		Min	-0.0035	0.00084	<.0001	0.996
	Mul	All	-0.1857	0.05401	0.0006	0.83
		Atlst1	-0.1658	0.06602	0.012	0.847
		Avg	-0.0031	0.00086	0.0003	0.997
		Both	-0.1725	0.05438	0.0015	0.842
		Max	-0.0033	0.00128	0.011	0.997
		Min	-0.0027	0.00086	0.0021	0.997

Outcome: all cause ER; Uni: univariable; Mul: Multivariable; PDC measured cumulatively up to a period

Atlst1: At least one approach; Avg: Average approach; Max: Maximum approach; Min: Minimum approach

In general, medication adherence is measured over a period of 6 months or greater. Cumulative PDC measurements are thought to capture patient behavior over a longer period of time than do by period-specific measures. Adherence was measured cumulatively at each 30 day period or 90-day quarter. Hazard of having an all cause event was significantly ($p < 0.05$) associated with medication adherence. Hazards estimates (Table 4.17) ranged from a low of 0.796 to almost 1 (0.997) for dichotomous measures and continuous PDC estimated cumulatively over a 30-day period or 90-day period, respectively. The all approach revealed consistently lowest hazards of having an all cause ER event regardless of whether a univariable model or multivariable model was used or a measurement period of 30 or 90 days was used.

A subset of all cause events is any diabetes related event. Analyses were repeated with diabetes-related ER as the outcome for adherence measured at each temporal period and cumulatively at each period. The hazard estimates (Appendix) for PDC measured over each 30-day period varied from 0.66 to 0.75 for the at least one, all, both approaches while continuous measures indicated a hazard slightly less, although statistically significant, than one. The corresponding results for dichotomous measures were between 0.54 and 0.71 when PDC measurement period was 90 days. The at least one approach provided the lowest hazard estimates that ranged from 0.54 to 0.69. When PDC was measured cumulatively, the hazard estimates for the three said categorical approaches ranged for 0.56 to 0.68.

Comparison of the Adherence Measures: Discriminatory Power

Nonadherence was found to be a consistent predictor of events of interest regardless of measurement approach used or measurement period considered. However, the extent of predictive power differed depending on the approach used. Analyses were performed to examine how different measurement approaches discriminated subjects having events from those not experiencing an event. Concordance statistics were computed with each PDC measurement approach. Analyses were run in both a univariable and a multivariable framework. All the approaches resulted in concordance statistics that lay very close to one another (Table 4.18). The average based approach resulted in the highest mean value of 0.5391 under the univariable setting. The mean value of other continuous measures were 0.5380 (min) and 0.5360 (max). Dichotomous approaches resulted in slightly lower c-statistics than for analyses using continuous adherence measures. Among dichotomy-based measures, the at least one approach showed the lowest mean of 0.5228. Table 4.18 reports the values and confidence intervals of all concordance statistics. Under the multivariable analysis, the mean values of all concordance statistics improved from their respective univariable estimate. Among all, the average approach showed the highest values of 0.5648 and at least one the lowest value of 0.5584. Although indicating poor discrimination, all these concordance statistics were greater than 0.50 ($p<0.05$). In addition, confidence intervals from all concordance statistics overlapped one another indicating a lack of statistical significance.

Table 4.18: Concordance Statistics for Different Adherence Measurement Approaches

Measure-ment Period	Model	Approach	All cause ER		Diabetes ER	
			C-statistic	CI	C-statistic	CI
30 days	Uni	All	0.5330	0.5201-0.5460	0.5404	0.5137-0.5672
		Atlst1	0.5224	0.5115-0.5333	0.5385	0.5146-0.5624
		Avg	0.5426	0.5282-0.5570	0.5637	0.5340-0.5933
		Both	0.5329	0.5199-0.5458	0.5410	0.5142-0.5677
		Max	0.5355	0.5225-0.5485	0.5483	0.5208-0.5757
		Min	0.5394	0.5252-0.5535	0.5572	0.5284-0.5860
	Mul	All	0.5606	0.5453-0.5759	0.5643	0.5328-0.5958
		Atlst1	0.5564	0.5411-0.5718	0.5664	0.5349-0.5979
		Avg	0.5645	0.5494-0.5796	0.5698	0.5386-0.6009
		Both	0.5602	0.5449-0.5755	0.5639	0.5322-0.5955
		Max	0.5622	0.5470-0.5774	0.5659	0.5350-0.5968
		Min	0.5627	0.5476-0.5779	0.5649	0.5340-0.5959
90 days	Uni	All	0.5290	0.5158-0.5422	0.5484	0.5212-0.5757
		Atlst1	0.5228	0.5114-0.5342	0.5614	0.5353-0.5876
		Avg	0.5391	0.5240-0.5542	0.5597	0.5270-0.5923
		Both	0.5324	0.5192-0.5455	0.5475	0.5204-0.5746
		Max	0.5360	0.5216-0.5504	0.5599	0.5288-0.5910
		Min	0.5380	0.5230-0.5531	0.5530	0.5209-0.5850
	Mul	All	0.5612	0.5456-0.5768	0.5687	0.5360-0.6014
		Atlst1	0.5584	0.5428-0.5739	0.5820	0.5494-0.6146
		Avg	0.5648	0.5493-0.5804	0.5725	0.5395-0.6054
		Both	0.5628	0.5472-0.5783	0.5679	0.5351-0.6006
		Max	0.5621	0.5465-0.5777	0.5759	0.5436-0.6082
		Min	0.5636	0.5481-0.5792	0.5663	0.5334-0.5991

C-statistic: Concordance statistic (CT from Kremers); CI: confidence interval of C-statistic; Uni: univariable; Mul: Multivariable; PDC measured at each quarter
Atlst1: At least one approach; Avg: Average approach; Max: Maximum approach; Min: Minimum approach

Table 4.19: Concordance Statistics for Different Cumulative Adherence Measurement Approaches

Measure-ment Period	Model	Approach	All cause ER		Diabetes ER	
			C-statistic	CI	C-statistic	CI
30 days	Uni	All	0.5276	0.5146-0.5406	0.5515	0.5249-0.5780
		Atlst1	0.5157	0.5053-0.5261	0.5531	0.5288-0.5775
		Avg	0.5426	0.5282-0.5570	0.5637	0.5340-0.5933
		Both	0.5253	0.5124-0.5382	0.5529	0.5268-0.5789
		Max	0.5216	0.5068-0.5364	0.5475	0.5153-0.5798
		Min	0.5338	0.5188-0.5487	0.5587	0.5278-0.5896
	Mul	All	0.5582	0.5429-0.5734	0.5690	0.5371-0.6008
		Atlst1	0.5535	0.5383-0.5687	0.5728	0.5410-0.6045
		Avg	0.5645	0.5494-0.5796	0.5698	0.5386-0.6009
		Both	0.5572	0.5419-0.5725	0.5710	0.5395-0.6025
		Max	0.5569	0.5416-0.5722	0.5646	0.5328-0.5963
		Min	0.5599	0.5446-0.5751	0.5665	0.5349-0.5982
90 days	Uni	All	0.5290	0.5157-0.5422	0.5460	0.5186-0.5733
		Atlst1	0.5169	0.5061-0.5277	0.5457	0.5208-0.5706
		Avg	0.5391	0.5240-0.5542	0.5597	0.5270-0.5923
		Both	0.5281	0.5149-0.5413	0.5489	0.5221-0.5758
		Max	0.5258	0.5107-0.5410	0.5493	0.5161-0.5825
		Min	0.5358	0.5206-0.5510	0.5542	0.5223-0.5861
	Mul	All	0.5612	0.5456-0.5767	0.5660	0.5330-0.5989
		Atlst1	0.5570	0.5415-0.5725	0.5672	0.5344-0.6000
		Avg	0.5648	0.5493-0.5804	0.5725	0.5395-0.6054
		Both	0.5607	0.5451-0.5763	0.5683	0.5356-0.6011
		Max	0.5593	0.5437-0.5749	0.5670	0.5341-0.5998
		Min	0.5626	0.5470-0.5782	0.5648	0.5320-0.5975

C-statistic: Concordance statistic (CT from Kremers); CI: confidence interval of C-statistic; Uni: univariable; Mul: Multivariable; PDC measured cumulatively at each quarter
Atlst1: At least one approach; Avg: Average approach; Max: Maximum approach; Min: Minimum approach

The concordance statistics for different measurement approaches were computed for PDC estimated over 30-day periods. The concordance statistics measured in the univariable setting ranged from 0.5426 to 0.5224 (Table 4.18) with statistic for 'average' being the largest among all. Like statistics for PDC measured over 90 days, multivariable concordance statistics for adherence estimated in each 30-day period were higher than their univariable counterpart. Again, the at least one approach resulted in lowest mean concordance statistics in both multivariable and univariable analyses. Most of 30-day mean values are slightly higher than their corresponding 90-day values.

Additional analyses were performed using the cumulative PDC measurement approach. That is, adherence measured cumulatively at a specific period (i.e., 30 or 90 days) was entered in survival analysis. For the 30-day based cumulative measures, the average and minimum approaches showed two highest concordance statistics. The univariable and multivariable mean values for the average approach were 0.5426 and 0.5645, respectively (Table 4.19) and for the minimum-based approach, the corresponding statistics were 0.5338 and 0.5599, respectively. When the 90-day measurement period was used, the estimates closely followed that of 30-day cumulative analysis. For example, concordance statistics were 0.5391 and 0.5648 in the univariable and multivariable analysis, respectively. Interestingly, the lower bounds of the at least one based approach and its continuous version (i.e., maximum) lay barely above 0.5 in the univariable analyses regardless of cumulative measurement period.

Analyses were repeated using any diabetes-related event as the outcome measure for adherence measured at each period and cumulatively at each period. Table 4.18 and Table 4.19 present the results. Concordance estimates for PDC measured over each 30-day period varied from 0.5385 (at least one) to 0. 5637 (average) under the univariable analysis and remained

literally constant in the multivariable models for all approaches (Table 4.18). When period of measurement was 90 days, concordance estimates ranged from 0.5475 (both) to 0.5646 (average) in univariable models (Table 4.18). In the multivariable analysis, the at least one had the highest estimate of 0.5820 and its continuous counterpart (minimum) has the lowest estimate of 0.5663. When cumulative measures were used, the mean concordance varied from 0.5457 to 0.5728 (Table 4.19). The average approach resulted in the highest estimate in all analyses except for the 30-day multivariable model in which the at least one approach had the highest mean concordance statistic of 0.5728 (Table 4.19). Confidence intervals of all concordance statistics were above 0.5.

Examination of Optimal Cut-points of Measures of Multiple Medication Adherence

There are three single measures of multiple medication adherence that measure adherence on a continuous scale. These are based on the average, maximum, and minimum algorithms and can be converted into categorical measures. Cut point analyses were performed on these continuous PDC measures and results from both multivariable and univariable survival analysis are presented in Table 4.20. In the case of multivariable analysis, likelihood difference contributed by PDC was considered. That is, the differences in log likelihood of a survival analysis model containing all variables (age, gender, CCI, and PDC) and that of a model with all variables except PDC were computed. Additional dichotomous PDC variables were created from the respective continuous measures by applying different cut points for dichotomization. Five cut points were chosen for dichotomization: 65, 70, 75, 80, and 85. Maximum Chi square statistics that were significant at p=0.05/15 (Bonferroni adjusted) were identified. Any values

that were above 8.6154 were considered significant at a level of p=0.05/15 (approximately, 0.003). As above, analyses were performed using cumulative and period-specific PDC measured over 90 days or 30 days.

Table 4.20: Optimality of Cut Point Analysis with Different Adherence Measures

Measure-ment	Model	Approach	PDC 65	PDC-70	PDC-75	PDC-80	PDC-85
Cumulative 90-day Quarter	Mul	Average	7.0462	3.9441	6.4148	9.3322	**11.227**
		Maximum	5.0143	3.8126	6.7254	6.125	2.7552
		Minimum	9.4119	8.4991	**14.401**	10.107	11.284
	Uni	Average	12.487	8.3871	11.314	14.915	**18.259**
		Maximum	7.1239	6.0205	**9.5342**	9.1097	5.1445
		Minimum	15.524	14.799	**22.259**	16.789	17.904
90-day Quarter	Mul	Average	8.7781	8.468	8.048	9.9933	**12.409**
		Maximum	5.9385	10.912	**12.115**	11.465	10.812
		Minimum	9.5463	9.4438	12.106	**13.223**	11.887
	Uni	Average	13.974	13.938	13.278	16.268	**19.359**
		Maximum	8.0635	14.232	**15.73**	15.037	14.893
		Minimum	15.399	15.904	19.018	**20.18**	18.44

Outcome variable: all cause ER visits; Uni: univariable; Mul: Multivariable; bold cells are maximum chi square values among respective row values and are significant at p=0.05/15. Numbers were obtained from chi square statistics from the Survival analysis

First, survival analyses were performed on all cause ER visits as outcome measure. When PDC was measured cumulatively over 90 days, maximal Chi square statistics were identified when dichotomization occurred at 85% in both multivariable and univariable analysis (Table 4.20). Thus, statistics for average-based dichotomization analyses were significant. In case of maximum and minimum algorithms, similar analyses showed that maximization occurred

at 75%. However, statistic for maximum in the multivariable model was not significant at p = 0.003. When the PDC measure was based on each quarter, the maximization of average-based dichotomization occurred at 85% in both univariable and multivariable models in which chi square statistics were significant ($p<0.003$). For the maximum based approach, maximum values were found at 75% and were significant ($p<0.003$). For minimum-based dichotomization, maximizations occurred at 80% in both multivariable and univariable models.

Table 4.21: Optimality of Cut Point Analysis with Different Adherence Measures

Measurement	Model	Approach	PDC 65	PDC-70	PDC-75	PDC-80	PDC-85
Cumulative 30-day Period	Mul	Average	5.2231	6.8647	7.6926	9.7486	**13.277**
		Maximum	6.4368	6.2179	**8.6639**	6.1458	4.0449
		Minimum	9.7597	11.011	**16.019**	10.196	9.7981
	Uni	Average	9.6211	11.914	12.568	15.195	**19.98**
		Maximum	8.6173	8.5361	**11.381**	8.7115	6.4434
		Minimum	15.754	17.486	**23.36**	16.23	15.484
30-day Period	Mul	Average	7.4047	8.8584	9.2459	8.0082	**14.139**
		Maximum	8.6901	9.8615	9.5206	11.803	**21.378**
		Minimum	11.919	11.323	15.285	17.281	**23.137**
	Uni	Average	11.925	13.673	14.375	12.927	**20.274**
		Maximum	11.286	12.559	12.184	14.786	**25.587**
		Minimum	17.648	16.832	21.398	23.857	**30.723**

Outcome variable: all cause ER visits; Uni: univariable; Mul: Multivariable; colored cells are maximum chi square values among respective row values and bold ones are significant at p=0.05/15.
Numbers were obtained from chi square statistics from the Survival analysis

Above analyses on all cause ER visit were repeated with PDC measured over a 30-day period. Table 4.21 presents the results of the analyses. When PDC was measured cumulatively

or at each period over 30 days, the maximization of the average approach based dichotomization occurred at 85% in both univariable and multivariable models. Similarly, maximizations were noted for the maximum and minimum based approaches at 85% when PDC was measured at each 30-day period in multivariable or univariable analysis. In contrast, dichotomization analysis on these two approaches demonstrated that the maximized values were found to occur at 75% when PDC was measured cumulatively.

Table 4.22: Cut Point Analysis with Different Adherence Measures

Measure-ment	Model	Approach	PDC 65	PDC-70	PDC-75	PDC-80	PDC-85
Cumulative 90-day Quarter	Mul	Average	7.070	8.521	11.783	**13.766**	11.221
		Maximum	3.455	7.464	**12.105**	12.094	9.549
		Minimum	8.885	8.712	**13.235**	11.048	9.641
	Uni	Average	10.080	10.906	14.400	**15.521**	12.066
		Maximum	9.395	11.023	18.319	**22.031**	19.952
		Minimum	8.990	8.185	**9.596**	9.3371	9.184
90-day Quarter	Mul	Average	9.698	11.381	14.956	**17.135**	14.345
		Maximum	5.114	9.860	15.038	**15.21**	12.52
		Minimum	11.613	11.419	**16.386**	13.879	12.268
	Uni	Average	12.826	13.768	17.57	**18.809**	15.045
		Maximum	11.806	13.786	21.716	**25.721**	23.724
		Minimum	11.475	10.640	**12.207**	11.887	11.704

Outcome variable: any diabetes ER visits; bold cells are maximum chi square values among respective row values and significant at p=0.05/15.
Numbers were obtained from chi square statistics from the Survival analysis

Next, optimal dichotomization analyses were performed using any diabetes related ER visits as outcome measure. When PDC was measured cumulatively over 90-day quarters,

maximal partial likelihood statistics occurred for dichotomization at 80% in both multivariable and univariable analysis (Table 4.22). Similar results were observed for PDC measured at each quarter. In case of minimum based algorithms, maximizations of partial likelihood statistics occurred when PDC was dichotomized at 75% and these results held true for both multivariable and univariable analysis. When analyses were run on the maximum based approaches, maximization of statistic occurred for PDC dichotomized at 80% except for the case of multivariable analysis with PDC measured cumulatively. In the latter case, the maximum value was found at 75%. Statistics for all the above analyses were significant ($p < 0.003$).

Table 4.23: Optimality of Cut Point Analysis with Different Adherence Measures

Measure-ment	Model	Approach	PDC 65	PDC-70	PDC-75	PDC-80	PDC-85
Cumulative 30-day Period	Mul	Average	9.4571	12.758	14.643	**15.281**	12.669
		Maximum	4.3559	6.4868	11.369	**18.242**	11.067
		Minimum	12.223	13.581	**17**	14.18	10.945
	Uni	Average	12.705	16.438	18.483	**19.145**	16.237
		Maximum	6.4359	9.0358	14.642	**22.376**	14.582
		Minimum	15.591	17.101	**20.746**	17.619	13.956
30-day Period	Mul	Average	5.4106	4.7225	4.9703	6.9607	8.245
		Maximum	4.4476	5.7976	7.1672	8.4171	8.383
		Minimum	6.2205	6.8583	5.5575	7.0427	**10.764**
	Uni	Average	7.5734	6.7659	7.0906	9.3951	**10.884**
		Maximum	6.4519	8.0648	9.6847	11.136	**11.188**
		Minimum	8.4399	9.1793	7.6826	9.4027	**13.586**

Outcome variable: any diabetes ER visits; bold cells are maximum chi square values among respective row values and significant at p=0.05/15.
Numbers were obtained from chi square statistics from the Survival analysis

The above analyses on any diabetes related ER visit were repeated with PDC measured over a 30-day period. Table 4.23 presents the results of the analyses. For PDC measured cumulatively over 30 days, the maximization of statistic for the average approach based dichotomization occurred at 80% in both univariable and multivariable models. Similarly, maximizations were observed at 80% for the maximum based approach when PDC was measured cumulatively over a 30-day period in multivariable or univariable analysis. In contrast, dichotomization analysis on the minimum approach showed the maximization at 75% in both multivariable and univariable models. When analysis was performed on PDC measured at each 30-day period, the maximization occurred at 85% in all cases except for the maximum-based multivariable analysis in which the statistic was maximized at 80% but not significant.

The above discussions on dichotomization have so far focused on the maximization of partial likelihood statistic. However, in true sense, maximization was not found to occur for some multivariable analysis. For example, in case of PDC measured cumulatively at 30-day periods, partial likelihood statistic for average based dichotomization increased monotonously (5.2231, 6.8647, 7.6926, 9.7486, and 13.277) before being maximized at 85%. Similarly, for the PDC measure based on average at every 30 days, the partial statistics increased almost monotonously (7.4047, 8.8584, 9.2459, 8.0082, and 14.139) before showing the highest value at 85%. In the latter case, all values except the first one (i.e., 65%) lie above 8.615, which is the chi square value of the Bonferroni adjusted p value of 0.05. In other cases, maximization occurred in true sense but statistics on either sides of the maximized one were significant. For example, the results from analysis on diabetes-related ER based on average-based dichotomized PDC measured cumulatively over 30 days demonstrated maximization at 75% (17) and values around 75% (12.223, 13.581, 14.18, 10.945) were significant ($p<0.0033$) as well.

Concordance Analysis between Results of Concordance Statistics and Maximization Statistics

While computing concordance statistics, analyses were run with PDC measurement approaches such as at least one and both. These two approaches had some equivalent formats in the maximization analysis. These equivalent formats occurred when corresponding continuous PDC was dichotomized at 80% (i.e., dichotomization performed on maximum and minimum based estimates). Comparisons were made between statistics obtained from concordance statistics analysis and maximization analysis. The results from analysis on all-cause ER visits were presented in Table 4.24 in which C-stat represents concordance statistic for at least one or both-based PDC and partial likelihood statistic contributed by maximum and minimum based PDC dichotomized at 80%. Perfect correspondence was noted between concordance statistic and partial likelihood statistic regardless of measurement period and multivariable or univariable analysis. In other words, when C-statistic increased, so did partial likelihood. For example, when PDC was measured cumulatively over quarters both concordance statistic and partial likelihood statistic were lower for 'at least one' than those were for the both-based approach.

Because maximization analysis was performed on 5 cut points (65% through 85% at 5% intervals), for each row (i.e., PDC measurement) in Table 4.24 contained a respective maximum statistic that could range from 75% through 85%. The maximization column in Table 4.24 reports the maximum values associated with analysis performed on all-cause ER visit. The concordance column reports whether maximum values are 80% or not. Of the 16 different ways

in which PDC were measured in the study, maximization occurred at 80% only in 2 (12.5%) cases.

Table 4.24: Concordance Analysis on Optimality of Cut-off Points

Measurement	Model	Approach	C-stat/ PL80	Max	Concordance
Cumulative 90 day	Multivar	At least one/ max 80	0.557/6.125	75%*	no
		Both/min 80	0.5607/10.107	75%	no
	Univar	At least one/max 80	0.5169/9.1097	75%	no
		Both/min 80	0.5281/16.789	75%	no
90 day	Multivar	At least one/ max 80	0.5228/11.465	75%	no
		Both/min 80	0.5324/15.037	80%	yes
	Univar	At least one/ max 80	0.5584/13.223	75%	no
		Both/min 80	0.5628/20.18	80%	yes
Cumulative 30 day	Multivar	At least one /max 80	0.5535/6.1458	75%	no
		Both/min 80	0.5572/10.196	75%	no
	Univar	At least one/ max 80	0.5157/8.7115	75%	no
		Both/min 80	0.5253/16.23	75%	no
30 day	Multivar	At least one/ max 80	0.5224/11.803	85%	no
		Both/min 80	0.5329/17.281	85%	no
	Univar	At least one/ max 80	0.5564/14.786	85%	no
		Both/min 80	0.5602/23.857	85%	no

Max: Maximization cut point; Outcome variable: All-cause ER; C-stat: Concordance statistics (CT from Kremers); PL80: partial likelihood statistic of PDC dichotomized at 80%; Multivar: multivariable model; Univar: univariable model; Max 80: dichotomization of maximum approach at 80%; Min 80: dichotomization of minimum approach at 80%
* statistic not significant at p=0.0033

Concordance analysis was performed on any diabetes related event as outcome variable. A total of six of eight of maximum-based PDC dichotomized at 80% yielded highest values among all respective maximum-based PDC measure dichotomized at different cut points (Appendix). The two that were not maximized at 80% were the ones when PDC was measured cumulatively over 90 days in a multivariable model and when PDC was measured at every 30 days in a univariable model. Thus, the at least one based approach showed high concordance with the maximization of partial likelihood statistic-based approach when analysis was run on any diabetes related event. All of both-based PDC – alternatively, minimum-based PDC dichotomized at 80% – were maximized either at 75% or at 85%.

CHAPTER 5

DISCUSSION

Using the MarketScan 2002-2003 commercial claims database, this dissertation examined intra-disease and inter-disease multiple medication adherence and issues associated with intra-disease multiple medication adherence. A number of inclusion and exclusion criteria were imposed for the selection of study subjects; such methods resulted in a smaller pool of subjects receiving two oral diabetes medications (SU and TZD) but they were thought to ensure consistency in measurement and unbiased results. On average, this pool of older adults demonstrated good levels of adherence for both SU and TZD over time although rates continued to decline over time; these findings were consistent with past research.

Intra-disease Multiple Medication Adherence

A total of 6043 subjects were available initially for examining intra-disease multiple medication adherence; however, the number of subjects declined to 4996, 3772, and 447 in the 6^{th}, 7^{th}, and 8^{th} quarter, respectively. A series of multivariate multilevel random intercept and growth models with and without covariates were undertaken to examine multiple medication adherence. It was expected that a positive covariation between adherence behaviors related to two medications taken concurrently for the same chronic disease would exist; consequently, a significant correlation of 0.57 between the random components of adherence to the two

medications was observed. The strength of the relationship persisted after controlling for age and gender. To an extent, these results can be anticipated from the patterns of population adherence estimates (Table 4.2) of the two diabetes medications under investigation. Thus, even if there were variations in adherence at different times to individual medications prescribed for a disease, the relationship between means measured at the individual level appear to be related. More precisely, factors that are affecting the overall medication adherence behaviors for two medications appear to have strong relationship. Many reasons can be speculated in support of such results, including synchronization and scheduling (Choudhry et al., 2011); however, a conceptually plausible reason may include the patient's overall disease beliefs as a driver of adherence behavior as supported by studies based on psychosocial factors affecting adherence (Stack et al., 2011). The latter may be further supported by the subgroup analysis, which included community pharmacy patrons only, that demonstrated a strong correlation between the random effects (Appendix). In general, medications obtained from community pharmacies are not refilled automatically; thus, community patrons generally make conscious decisions about getting their prescriptions filled and continuing them over time.

Multivariate growth models were run to examine the relationships between changes in an individual's adherence behaviors to two medications taken concurrently for a chronic disease. In other words, relationships between the random slopes for each medication adherence were analyzed. The correlations (i.e., the association of evolutions) between random slope for SU and that of TZD were greater than 0.62 regardless of whether or not the effects of age and gender were controlled for. Thus, it appears that factors that affect adherence behaviors for multiple medications over time are strongly related. Subgroup analysis on community patrons also replicated strong relationships as described above. It is interesting to note that correlations of

random slopes from the growth model analyses were stronger than correlations from means (i.e., random intercept) model analyses. Among a host of potential reasons, one is that underlying factors driving the growth of individual medication adherence behaviors change in a more closely coordinated manner than do those representing overall behaviors.

To a patient receiving treatment, medications may have a symbolic meaning for disease state. It is possible that when a patient is put on an additional medication for the treatment of a disease, he will start perceiving the disease more seriously. Thus, disease beliefs may be driving the state of adherence for each medication for that disease at every point in time and ensure similarities in the pattern of consumption variations. In contrast, mean model correlation estimations may be affected by differential initial states of adherence as prescriptions are likely to be not initiated simultaneously more often than not. However, the effect of statistical modeling (i.e., use of random intercept vs. growth model) cannot be ruled out when a variable such chronic medication adherence is truly time-dependent.

Inter-disease Multiple Medication Adherence

Because so many patients suffer from multiple chronic diseases, this study explored the adherence behaviors of diabetes patients for medications prescribed for other diseases in addition to adherence to two diabetes medications. In order to investigate inter-disease multiple medication adherence, diabetes patients who were prescribed two oral diabetes medications were evaluated as to their use of medications to treat hypertension, hyperlipidemia, or angina. Over 2300 patients were taking medications for either hypertension or cholesterol, 860 were on prescriptions for both hypertension and cholesterol. Additionally, many were prescribed anti-

anginal medications. It should be noted here that these numbers are not estimates of percent of diabetes patients suffering from the aforementioned chronic diseases; it is very likely that the number of diabetes patients suffering from other chronic diseases has been underestimated because of the selective medication filling-based selection criterion used in the study. The subjects for the analyses of inter-disease multiple medication adherence were observed, on average, for over one and a half years and slightly dominated by male.

As such, there were four sets of patients on which analyses related to inter-disease multiple medication adherence were performed. While the statistical modeling strategy was the same as that of the intra-disease multiple medication adherence analysis, the number response variables was 3 or 4; thus, the number of random effect correlations were always 3 or greater. Adherence rates for individual medications for all four subgroups of patients were estimated (Table 4.5) for each quarter. Adherence rates for diabetes medications of these groups of patients as presented in Table 4.5 were slightly different from actual adherence estimates of the same because different index dates for intra-disease and inter-disease medication adherence might have been used for some patients.

Diabetes Patients with One Additional Asymptomatic Chronic Disease

Chronic diseases may be related to one another based on disease patho-physiologic profile leading to concordance or lack of that with another chronic disease. There were two groups of diabetes patients who were suffering from concordant diseases and prescribed medications (hypertension or hyperlipidemia). The average quarter-specific PDC estimates for concordant disease medications trailed the corresponding PDC estimates for SU and TZD except for that of hypertension medications, which were slightly above their respective diabetes

medications estimates. However, the results for hypertension medications may have occurred because of a liberal methodology adopted for estimation (i.e., possession of any medications on a day) of PDC for hypertension medications. The average population adherence estimates for cholesterol medications were about 70% in all quarters and that for hypertension were slightly greater than 70% in all quarters.

Similar to intra-disease multiple medication adherence analyses, the multivariate multi-level models for inter-disease multiple medications adherence were run on quarter-specific PDC estimates for each medication on those subjects that had a full quarter of observation and the strategy led to decline in number of subjects in later quarters. The results of unconditional random intercept models analyses revealed strong correlations (greater than 0.5) among all medications, including those for cholesterol and hypertension. Thus, when patients suffered from multiple concordant chronic diseases, significant correlations were observed with regard to within-patient adherence to medications taken concurrently for an index chronic disease (i.e., diabetes) and another asymptomatic chronic disease regardless of disease state (i.e., hypertension or hypercholesterolemia). Interestingly, correlation estimates of inter-disease multiple medication adherence (i.e., between SU and anti-hyperlipidemic medications and between hypertension medications and TZD) were stronger than that for intra-disease correlation. It is difficult to explain such findings definitively. However, a few reasons can be speculated to have caused such results including simultaneous initiation or synchronization of refills of those specific medications. Alternatively, patients demonstrated selective medication adherence (e.g., Wogen et al. (2003) noted adherence to specific medication class; McHorney and Gadkari (2010) found differential beliefs to medications patients chose to persist compared to ones patients did not) that are tied to one medication for each disease. Additional analyses using conditional

growth models showed that there were significant correlations between random slopes of medication-specific adherence over time. Thus, it appears that a patient's changes in adherence behavior over time related to each chronic disease medication are strongly related even after controlling for age and gender. Interestingly, the results of means model analyses are replicated qualitatively in growth model analyses in that some inter-disease association of evolutions estimates were higher than their intra-disease counterparts although association of evolutions estimates were much greater than estimates of association of means. In sum, consistency and strength in relationships that were observed for inter-disease multiple medication adherence is interesting; indeed, it may provide evidence of a higher order construct affecting patients' health behavior decisions, specifically as it relates to medication consumption. This is consistent with a recent work that found that a pharmacist-provided counseling program improved adherence to target and nontarget chronic medications (Taitel et al., 2012).

Diabetes Patients with More than One Additional Asymptomatic Chronic Disease

Many diabetes patients suffer from more than one chronic disease (e.g., hypertension and hypercholesterolemia). This study found that for these patients the average adherence estimates in all quarters were consistently highest for hypertension medications and lowest for cholesterol medications. The average adherence rates for hypertension medications were about 80% in all quarters whereas other rates were suboptimal (based on the ≥80% criterion). The unconditional random intercept models were run to examine six correlations: five for cross-disease medications and one for within-disease medications. All random intercept correlations were significant and were above 0.5 except for two between SU and anti-hyperlipidemic medications (0.49) and SU and hypertension medications (0.47). Thus, when patients suffered from multiple concordant chronic diseases, significant correlations were observed with regard to within-patient adherence

to medications taken concurrently for an index chronic disease (i.e., diabetes in this case) and another asymptomatic chronic disease even when number of chronic diseases increased. Conditional growth model analyses in which age and gender were controlled for showed that there were significant correlations between random slopes of medication-specific adherence over time with the correlation between TZD and hypertension medications and that of TZD and SU being the highest (0.77) and lowest (0.6), respectively. Although these patients are a subset of the group with one asymptomatic chronic disease and not different from the later concerning their demographic profile and mean adherence estimates, such high correlations in random slopes appear interesting and need further investigation. At the present time, it can be suggested that factors affecting their adherence that may include disease or medication beliefs are strong and consistent. Alternatively, it is likely that these subjects are very health conscious and maintain healthy behaviors. It should be noted here that there were very few subjects left in the last quarter in the analysis reported above. However, the result did not differ when the 1st or 8th quarter was dropped from the analysis (Appendix).

Diabetes Patients with an Additional Symptomatic Chronic Disease

Chronic diseases may be symptomatic or asymptomatic in addition to being concordant with another chronic disease. Angina is symptomatic and considered concordant with diabetes. Angina patient selection was limited to those filling only tablet or capsule forms of nitroglycerin. Although necessary, this inclusion criterion resulted in about 300 subjects being available for analysis and this number declined sharply in the last two quarters. The average population adherence estimates for nitrates were substantially lower in all quarters in comparison with corresponding rates for diabetes medications although it showed small improvement in the last two quarters with smaller numbers of patients. Given that this group was not very different in

the overall follow up time and demographic profile from those with only asymptomatic diseases, such low rates are hard to explain and may lie in methodological artifacts (e.g., SOS prescriptions). Alternatively, low adherence may reflect by patients' decision that they can find a rescue medication (e.g., sublingual nitrates) to treat the disease when needed. The correlations of random intercepts between SU and TZD and between TZD and nitrates were statistically significant ($p<0.05$) while that for SU and nitrates was not. Thus, the relationship between adherence to concordant chronic symptomatic and asymptomatic disease medications was not clear. It is interesting to note that the correlation estimate (0.38) between random intercepts of SU and TZD is much lower than the corresponding ones observed in intra-disease or other inter-disease analyses. Similarly, there was a poor correlation (0.15; $p=0.016$) between TZD and nitrates. Like other analyses, the association of evolutions estimates were higher than random intercepts model estimates; however, the association of evolutions of SU and nitrates were not significant while that of TZD and nitrates was poor but significant (0.21; $p<0.05$) and that of SU and TZD was strong (0.59; $p<0.001$). When the models were rerun excluding the last 2 and 3 quarters, no significant changes in results were observed. Although the analyses may be constrained by smaller sample size especially in the last few quarters, it is encouraging to note that the intra-disease random intercepts and growth model correlation estimates were consistent with the results from all other analyses. Contrary to popular beliefs about higher adherence to symptomatic disease, lower adherence to angina medications was little surprising.

Measurement of Intra-disease Multiple Medication Adherence

Based on existing methods that were identified from the literature, a single composite estimate of adherence for multiple medications for a disease can be computed using six different

methods: three each for continuous and categorical measures. The means of (single) continuous PDC estimates of multiple medication adherence varied widely depending on the type of measurement used. Both average and minimum-based approaches yielded suboptimal (per ≥80% criterion) adherence rates. These differences were present when PDCs were calculated at each quarter or estimated cumulatively up to each quarter. It can be expected that variations in estimates of PDC based on a restrictive methodology (e.g., requiring patients to take both medications or minimum approach) became large and would continue to grow in populations in which overall adherence rates are lower than the population used in the study or in instances where a patient is followed for a longer time (i.e., >8 quarters).

When single measures of multiple medication adherence based on a dichotomy (i.e., adherent vs. nonadherent) with a cut-point of 80% PDC were used, similar to the results for continuous measure-based estimates, there was a considerable variability in estimates based on the approach used and adherence estimates can be considered suboptimal based on measurement method selected. The all-based estimates were slightly smaller but closely followed the estimates measured by the both approach, which provided the lowest estimates. Thus, it is understood that not every composite dichotomous measure will classify patients consistently as adherent or nonadherent unless a patient shows high adherence rates. Interestingly, it was found that the extent of discrepancy in classification of patients who were rated adherent at least by one approach could be as high as 38%. Thus, this can be concluded that such discrepancy, which is indeed high in the study population, will become more apparent if overall population adherence rates become poor or when a longer observation period is considered.

Different composite measures of PDC estimates for multiple medications were compared. In addition, a weighted average-based composite measure was conceptualized and proposed to

be compared against other composite measures. All-cause and any diabetes related ER visits were chosen to derive weights and compare the performance of measurement approaches. The decisions to choose outcome measures were based on theoretically and practically meaningful and statistical modeling rationales. In analyses related to measurement, an additional time unit (i.e., 30-day periods) of measurement was considered. This decision was partly driven by the fact that episodes of nonadherence within a short period might lead to hyperglycemia that might lead to an acute ER event. In addition, shorter measurement unit may prevent excluding subjects due to incomplete reporting periods and thus, to some extent, might alleviate the problem of high censoring rate or fewer events. Although small, the number of events was not particularly concentrated on any specific quarters except that the last quarter had the fewest events.

In order for deriving weights for the proposed weighted average-based composite measure, survival analysis was performed. Although individual hazard estimates were in the right direction, hazard estimates for both SU and TZD were not significant simultaneously. In some analyses, hazard estimates for SU were significant but not that of TZD or vice versa. Such results were repeated regardless of whether PDC was measured using 30-day periods or 90-day periods or cumulatively over those periods. As strong relationships between adherence to SU and TZD were noted consistently in the multiple medication adherence analyses, it is believed that strong multicolinearity may have caused such results. Thus, any outcome-based weights and weighted average-based composite measure of intra-disease multiple medication adherence could not be computed. Most studies in adherence do not differentiate specific medications with regard to their impact of health outcome. In the light of evidence gained in this study, the assumption that all medications have the same health impact cannot be ruled out. Indeed, this study provides evidence for averaging out adherence values for multiple medications.

Comparisons of Measures of Multiple Medication Adherence: Predictive power

A series of survival analyses were performed to compare the six different composite measures of intra-disease multiple medication adherence. All composite measures of adherence to diabetes medications significantly predicted hazards of all-cause adverse events; however, hazard estimates yielded by different composite measures varied depending on whether continuous or dichotomous measures were used. Hazards estimates of all continuous measures approached one regardless of whether or not PDC was measured at 30-day or 90-day periods or cumulatively, all were statistically significant ($p<0.005$). As such, findings that even a small improvement in adherence will result in lower hazards of adverse events are encouraging for healthcare providers for whom adherence improvement is a focus of their patient care activities. The hazard ratios of dichotomous composite measures differed on the basis of the method used to compute adherence estimate; while the at least one method showed slightly superior (i.e., lower) hazards when adherence was computed over 90-day periods, the all measure consistently revealed the lowest hazards regardless of adherence being computed cumulatively over 30-day periods or 90-day periods. Interestingly, the hazard ratios in multivariable models were slightly higher than those in the corresponding univariable models for all dichotomous measures. As age and comorbidity are strong and consistent predictors of health outcomes, the effect of adherence is less pronounced in the multivariable models.

When analysis was performed on any diabetes related ER events, a clear trend emerged. Similar to the results from all-cause analysis, hazard estimates on any diabetes-related ER visits were significant ($p<0.05$) but nearly one for all continuous composite PDC measured over 30-day periods or 90-day periods or cumulatively. In cases of dichotomous composite measures, the at least one measure consistently demonstrated the lowest estimates regardless of period specific

or cumulative PDC or the length of PDC measurement period used; hazards estimates were slightly wide apart and 90-day based measures yielded lower hazards whereas 30-day based cumulative measures showed lower hazards. Thus, the results appear to suggest that 30-day based measures show enough power if considered cumulatively whereas 90-day based measures is strong enough to predict an event in a period when patients are nonadherent. Compared to all-cause hazard ratios as estimated by composite PDC measures, all of the respective diabetes-related hazard estimates were much lower. This is intuitive in that diabetes medication adherence should be a better predictor of diabetes-related ER events than it would be for all-cause ER events. In sum, consistent with other studies (Balkrishnan et al., 2003; Sokol et al., 2005), nonadherence measured by any composite measure was a consistent predictor of adverse healthcare events regardless of adherence measurement approach or period. However, significant relationships do not state anything about a model's overall prognostic or explanatory power.

Comparison of the Adherence Measures: Discriminatory Power

One attribute of a good measure is its ability to discriminate well between groups that are different on outcome potential. In other words, a measure should have the ability of classifying subjects into appropriate groups to which they actually belong. A concordance statistic was computed for each adherence measurement approach to determine how well each method classifies subjects into groups of those having events and those having none. All the approaches resulted in statistically significant concordance statistics. With regard to all-cause analyses, the average based approach consistently demonstrated highest concordance statistics regardless of

30-day or 90-day measurement periods or cumulative period measurement. Among categorical composite measures 'all' (especially, when measured cumulatively) or 'both' showed slightly higher values than did 'at least one'. When diabetes-related outcomes were analyzed, no clear trends emerged; the average and at least one approaches appeared to perform better than others. Regardless of outcome selected, the multivariable models resulted in improved concordance statistics compared to their respective univariable model-based values. Although some performance-related trends were observed, concordance statistics generated by the different measurement methods were not statistically different from one another as reflected by their overlapping confidence intervals. In addition, the value of concordance statistics were slightly greater than 0.5 implying poor discriminatory power. However, comparable values of discriminatory index (i.e., c-statistics) were observed in a previous study of comparison of measures of adherence to a single medication or medications for a disease (Karve et al., 2009).

Examination of Optimal Cut-points of Measures of Multiple Medication Adherence

Apart from the average approach, the two other continuous composite approaches evaluated were the maximum and minimum algorithms. These two showed comparable estimates of concordance statistics while the average-based estimates were slightly better than those estimated by the minimum and maximum approach. Cut point analysis was performed on these continuous composite PDC measures. Five cut points were chosen for dichotomization: 65, 70, 75, 80, and 85. The dichotomization point that resulted in an adjusted significant maximization of likelihood statistics was examined. Analysis on all-cause ER revealed that if the average measure is dichotomized at 85% with PDC being measured at each period or

cumulatively over 90 days, the likelihood statistics maximized. For the more restrictive minimum approach, such results were observed at 75% or 80%, while it is interesting to note that the more liberal minimum approach indicated maximization at 75%. More clear trends emerged when PDC was measured over 30 days such that almost all maximization occurred at 85%. When the analyses were repeated on diabetes-related outcomes with measurement period being at 90 days or cumulative 90 days, maximization occurred at 80% for average, 75% for minimum, and 80% or 75% for maximum. When the measurement period was cumulative 30 days, above results were replicated. However, when the measurement was done at every 30 days, higher value (85%) of optimal adherence was observed. Thus, based on the study findings it can be suggested that, in general, the 80% cut-point paradigm holds in the context of multiple medication adherence; however, providers should encourage their patients to bring their adherence level slightly higher for more effective disease management and for avoiding unnecessary health events.

Several points deserve attention in light of the above discussion. In a true sense, it may not be appropriate to describe some phenomena as maximization if it had occurred at 85% as no higher values were examined. That said, as the other maximum points also lie below 85% and conventional wisdom advocating 80%, it can be suggested that increment in benefit of improving adherence will be declining sharply above 85% or maximum occurs at 85% even if higher values are examined. It was apparent that from a measurement standpoint, the optimality of cut point was related to what methods were used to measure multiple medication adherence. This makes sense because some measurements are more restrictive than others in their rationale on disease management and control process. Another interesting observation can be made from the results such that when diabetes medication adherence is used for its ability to predict global events the

bar that indicates that adverse events are unlikely should be raised. Similarly, if there is an imminent chance of event, higher standard of medication consumption behavior may be required considering that the maximization values were 85% in most 30-day period analyses. Finally, the maximization analysis provided a valuable insight. The at least one, all, and both approaches were operationalized with a cut point at 80%, which may not always be appropriate as maximization did not occur at that level for most cases. Those measurement algorithms may still be useful, but the issue of cut point may need to be revisited to generate more clear insight.

Limitations

The study has several limitations, which should be considered while the results of the study are interpreted. The study was conducted in a population that is enrolled in employer provided insurance programs. This population has several attributes that might have affected study results. For example, this population consists of relatively younger adults and, on average, is 10 years younger than the Medicare population. Age is a well-known risk factor for disease outcomes. Indeed, in this study, age has been found to be a significant predictor in all analyses. The results of this study (i.e., associations of evolutions or cut-point estimates) may or may not hold in other populations that differ with respect to age. Similarly, this population may be different from general population with regard to other socio-economic variables (e.g., income, life style, dietary habits, etc.) that may play a role in disease progression, health outcomes, and health behavior including medication adherence.

Chronic disease management, by definition, is a long term process. In this study, the mean observation time was little over one and a half years. Although not short, the observation period may not reflect long-term patient behavior or capture health outcomes that are likely to

occur as a result of poor medication adherence for a longer period of time. In fact, some patients were available for observation for less than a year for survival analysis or just a little over a year for the analysis of multiple medication adherence association. The results may not be appropriate when the goal is to study or predict long term behavior or events.

This study primarily focused on diabetes patients who were on two medications. If adherence behavior is rooted in specific medications then the study results may not be generalizable to other medications. For many patients, different medication formulations are currently prescribed concurrently for the treatment of diabetes. As both of the study medications were tablets, findings based on tablet formulation may not be applicable to other formulation types or a combination of different formulation types. Similarly, it may not be generalizable to situations where primary disease state is not diabetes. Existing evidence (Cramer et al., 2008) suggests that adherence rates may be different in difference diseases and failure to adhere to prescribed regimen may result in adverse outcomes that might occur at different times dependent on disease. If such underlying dynamics are at play, it would limit the findings of this study.

For analyzing the optimality of cut point for dichotomization of medication adherence, patient comorbidity (i.e., CCI) was calculated based on only two quarters. While it was consistent for all subjects, comorbidity may not have measured optimally by the method followed in the study. For example, if a patient does not visit a physician in six months under consideration for CCI calculation, CCI will be underestimated for the patient. Similarly, if a patient does not have any in-patient hospitalizations during the period under consideration his CCI score may likely to be underestimated compared to one having a hospitalization (e.g., increased options for reporting ICD-9 codes that may result in higher likelihood of reporting multiple diagnoses compared to ones that may occur in an outpatient setting). It is not known

what the impact would be on the study findings had CCI been measured over a year or longer. As CCI has been consistently found as a significant predictor in all analyses related to measurement issues, it is speculated that appropriate measurement of CCI would likely improve concordance statistics.

This study was able to include only a relatively small number of subjects. The inclusion and exclusion criteria that led to small sample size were based on the objective of deriving an unbiased result. In general, studies that use claims data methodology include a larger number of subjects compared to the number of subjects included in this study. However, precedence also exists in which a small sample size was used including studies on medication adherence (e.g., Balkrishnan et al., 2003). That said, a relatively smaller sample size should be recognized as a limitation, especially when it is known that millions of subjects in the US suffer from diabetes or other chronic diseases.

The outcome events that were analyzed in this study deserve a note. Two types of events were analyzed: all-cause ER visits and any diabetes-related ER visits. Other types of outcome events that are analyzed in claim-based studies include in-patient hospitalization or primary-cause events. Naturally, extending the results of measures being able to predict outcomes beyond the ones used in the study or comparing measures in any contexts of outcomes beyond these ones are limited. In addition, patients were not followed once they had an event. Thus, results cannot be extended to situations in which the goal is to identify patients susceptible to readmission or repeated adverse events.

The methodology adopted to estimate adherence could limit the results of the study. Many patients included in the study had an incomplete period of observation. Such patients (i.e., those having less than 30 days for 30-day periods or less than 90 days for 90-day quarters) were

not included while calculating period-specific adherence rates for multi-level model or survival analyses. Thus, adherence estimates or association between adherence estimates could have been different had these people been included. This problem may be further aggravated for inter-disease multiple medication adherence estimates as the number of observation periods further declined. Furthermore, if there was any significant nonlinearity in patient adherence behavior, associations of evolutions estimated in this study will not represent true estimates. As many of the subjects were not included in later time-periods, number of subjects continued to decline in later periods that may have affected the results related to survival analysis in several ways including reducing statistical power or introducing some biases.

Finally, the results should be interpreted with caution because of the statistical techniques that were used in the study. Several approaches have been proposed in the statistical literature for computing discriminatory index (i.e., concordance statistic) for a survival analysis model; however, there is a limited guidance in the literature as to which approach performs better. In addition, this question becomes further complicated for analyzing a time dependent variable and in presence of a high rate of censoring. Similar issues exist for choosing a method for determining an optimal cut point. As the method adopted in this study was based on an unpublished scholastic work and failed to demonstrate a consistent and meaningful trend in some analyses (e.g., for ‘at least one’), such limitations should be recognized while interpreting the results.

Future Research

This study opens up several opportunities for future investigation. First, although the hypothesized multiple medication adherence relationships were founded upon the Common Sense Model it was not possible to conclude about association of actual beliefs. Future research should focus on the collection of information on actual beliefs about two or more different medications and how these beliefs evolve over a period of time. Actual measures of theory-based adherence beliefs will help us further understand multiple medication adherence behavior. Second, it is important to understand the multiple medication adherence construct. If beliefs drive adherence behavior, it will be insightful to understand how beliefs are structured or nested. For example, intra-disease multiple medication adherence may be driven by beliefs in individual medications or it may be subsumed under disease beliefs. From the results of the study it can be speculated that there may be a higher order construct in which part of individual medication beliefs are nested as reflected by high correlation. In other words, disease beliefs may influence individual medication beliefs and adherence. If so, how distinct are individual medications beliefs from disease beliefs? Are there any contextual effects where one might be more important than the other? Are there different antecedents to each of these belief types? Third, as the current literature on medication adherence provides no conceptualization of multiple medication adherence, understanding of the theoretical structure of multiple medication adherence begs further attention. In the future, studies should be undertaken to understand whether or not multiple medication adherence is a complex construct and is distinct from single therapy adherence. In particular, its complexity increases further for inter-disease multiple medication adherence. Presently, it leaves us with no understanding of what roles are played by

disease beliefs and individual medication beliefs within the context of inter-disease multiple medication adherence.

Medication adherence is a complex behavior. A multitude of factors are thought to affect medication adherence. Previous studies of medication adherence have found that disease state (Briesacher et al., 2008), severity (DiMatteo, Haskard, and Williams, 2007), cormorbid conditions (Rozenfeld et al., 2008; Wogen et al., 2003), cost (Briesacher, Gurwitz, and Soumerai, 2005), and medication burden (Benner et al., 2009; Ren et al., 2002) affect medication adherence (i.e., adherence to a single medication). While comorbidity was controlled for when analyzing measurement issues, it was not included in the analyses related to intra- and inter-disease multiple medication adherence. Additional analysis (Appendix), consistent with past work (Ho et al., 2006b), shows that patients behave differently after an adverse event that affects disease state. Fourth, in the future, the effects of variables found to have significant relationships with adherence, including disease state, comorbidity, cost, and number of medications need to be investigated in the context of multiple medication adherence.

Multiple prescriptions are likely to occur more naturally in elderly than others. Fifth, in future studies of multiple medication adherence the Medicare population should be included. Especially, in light of emphasis on outcome-based reimbursement by the Centers for Medicare and Medicaid Services (CMS), as reflected by higher weight on medication adherence based measures, multiple medication adherence in the Medicare population assumes increased relevance.

Sixth, future studies should be designed such that a large number of patients can be observed for a longer duration. A few past studies of adherence have followed patients over a couple of years (e.g., Nichol et al. (2009) followed patients for 6 years), and found adherence

rates generally declining, thus, it will be interesting to know how associations of evolutions evolve over years. While increasing sample size and duration of observation will certainly increase power and have the potential to provide better concordance statistic estimates and stronger evidence of maximization (as opposed to trends that were observed for some cut-point analyses in the study), yet empirical evidence is required before any conclusion can be made.

Seventh, it may be useful to validate the results in different disease states. Past research on optimality of cut point for medication adherence has been replicated in different disease states (e.g., Karve et al., 2009); however, disease state was not related to cut-point estimates. A similar analysis related to multiple medication adherence will be useful for at least two reasons: 1) it may make results more generalizable in terms of identifying the measure demonstrating consistent and superior predictive and discriminatory power and 2) it will improve the strength of evidence. In addition, it will be enlightening to know if any clarity of and differences in cut-points emerge in such studies.

Finally, this study proposed a novel (weighted) composite measure of multiple medication adherence. Although the measure was theoretically appealing, it was not possible to test the measure empirically because of multicollinearity. Future studies should employ an appropriate methodology (e.g., analysis on split sample, matched sample analysis with one medication) such that the weighted composite measure can be compared against other measurement approaches discussed in this dissertation.

Contribution

This dissertation makes several contributions to the literature and enriches the existing knowledge base. First, this study generates baseline information on multiple medication adherence. Unlike prior studies that either looked at a single medication or did not differentiate medications for a disease, this research provides temporal adherence (population) estimates for individual medications when patients are advised two medications simultaneously for a disease. Similarly, it provides temporal adherence estimates for patients who are on multiple medications for different chronic disorders. Although adherence estimates are high for some medications, they are not at an acceptable level of appropriate adherence target and may be utilized for intervention decisions.

Second, recently efforts have been made to understand medication adherence for two distinct diseases (e.g., Chapman et al., 2005). This study is the first to extend the work by focusing on diseases that have different types of relationships. This work identifies the fact that many patients may be suffering from two or more chronic concordant symptomatic and asymptomatic diseases and attempts to estimate adherence rates for the subgroup of patients who are on multiple medications for different chronic diseases.

Third, this study extends the generalizability of past work that focused on other population (e.g., Nichol et al., 2009) examined multiple medication adherence for two diseases in the Medicaid population. Although the commercially-insured older adult population may be perceived to be adherent because of higher ability to afford costs or better access to healthcare, empirical evidence shows they may not reflect an ideal behavior.

Fourth, multiple medication adherence has strong futuristic implications given the way the science of drug development and medical treatment are evolving. This is the first study that

draws an explicit attention to intra-disease multiple medication adherence. Indeed, it strives to differentiate multiple medication adherence into distinct phenomena: intra-disease multiple medication adherence and inter-disease multiple medication adherence by comparing and contrasting these two types of adherence behaviors.

Fifth, measurement of adherence is the first step before any intervention decisions can be made. This research highlights how the selection of a measurement paradigm can result in inconsistency in classification of a patient's adherence status; it provides an estimation of inconsistency in patient classification that occurred based on the different measurement paradigms chosen. It is noted that the issue of inconsistency may become more important when the population average PDC estimates are not as high as was observed in this study.

Finally, the academic community has always wrestled over the issue of choosing an appropriate adherence measure. Past work has compared and contrasted different measurement approaches for measuring adherence (e.g., Hess et al., 2006). This work complements the previous work by generating evidence regarding the selection of an appropriate measure of intra-disease multiple medication adherence and toward formalizing an operational definition of multiple medication adherence. A categorical measure of adherence is very frequently employed by researchers. To serve the need in the context of multiple medication adherence, this work attempted to derive an optimal cut-point that was not based on the concept of adherence to a single medication.

This study has two primary methodological contributions to the field. First, many individual-level factors (e.g., attitude, intentions, self-efficacy) may not be temporally stable and time-dependent values of these factors may affect outcomes. Medication adherence is potentially one of such variables because of the possibility that changes in factors that may affect

adherence. These factors may be manifested as within-patient random variables. This research utilized the multilevel modeling technique to explicitly model intra-patient variation or random effects modeling. There are other approaches that can be utilized for multiple medication adherence. For example, latent growth curve modeling is a powerful and flexible technique to analyze the interrelationships among multiple dependent variables such as nested longitudinal adherence measures (Appendix). However, multilevel modeling offers advantages when there are incomplete observations that may have little influence on mixed models (Gao et al., 2009; Littell et al., 1996). In addition, it adopted the concept of association of evolutions from the statistics literature to introduce in the adherence research.

Second, adherence has traditionally been treated as a non-time varying variable in the literature. This research treated adherence as a time-dependent variable and thus, it emphasizes examining not only events but also the proximity of event or time to event. Such a consideration is more meaningful practically and similar to an operationalization followed in a recent published study of relationship between adherence and health outcomes (Yu, Yu, and Nichol, 2010). This dissertation work has operationalized adherence in its true sense such that values that change over time are captured adequately while examining the measurement of adherence itself.

Implications

The importance of medication adherence cannot be overstated. Any work that improves adherence or deepens the understanding of adherence holds strong implications. This study focused on patient behavior under a specific treatment pattern (i.e., use of multiple medications for better management). Within such a disease management context, it brings insight about how

medication adherence behavior evolves for patients who are advised to consume multiple prescriptions. As the practice is likely to grow in the future because of advancement in knowledge and technology, findings of the study appear to have strong implications for future disease management practice. Furthermore, these results will become more valuable because of the declining age of onset of chronic disease and increasing life expectancy both of which affect cost and management strategies.

Interventions are made to improve patient adherence. Many factors may affect the effectiveness of intervention or adherence. Although much is not known about their potential effect on multiple medication adherence, the study results suggest that there may be some higher order constructs (e.g., disease belief or trait) that may drive the joint behavior. If interventions are designed effectively around such factors, there may be a spillover effect of any success in one disease into others with respect to medication consumption. Period-specific changes in adherence demonstrated a stronger relationship in patient adherence behavior than overall mean associations. Thus, it can be suggested that interventions focused on factors that may change periodically may be more effective. Similarly, intervention decisions should be tailored to the goal of achieving a desired outcome or preventing outcome of interest. This is implied by the variability in cut-points in predicting health outcomes or predicting outcomes that may occur at differential temporal points.

Measurement of adherence to multiple medications is an important issue. This study brought to light several issues including the potential chance of misclassification and the utility of existing measurement approaches. The study results may help toward formulating a consistent operational definition of multiple medication adherence and serve to identify an appropriate and effective measurement algorithm.

Conclusion

Medication adherence is critical to managing a rising burden of chronic diseases. This research investigated medication adherence that would occur in a particular segment of patients due to the pressing need to manage the disease process more effectively or aggressively. Intra-disease multiple medication adherence and inter-disease multiple medication adherence were clearly discussed, distinguished, and defined and examined in the working older adult population that might be increasingly inflicted given onset age decreasing and life span increasing. Although this population demonstrated good adherence, the adherence rates cannot be termed optimal by a much-accepted norm of 80% based on the single medication adherence. Applying the concepts from the biostatistics literature, it was observed that there were significant relationships in the growth pattern in intra-patient adherence behavior to multiple medications intended to treat a single chronic disease or multiple chronic diseases that are related to one another with regard to the patho-physiology of disease or disease management. Consistent with existing knowledge (Steiner et al., 2009), this study found that demographic variables alone may not explain adherence well as reflected in the fact that random effect correlations remained strong after controlling for covariates. Additional analyses in a subset of patients (i.e., community patrons) supported the theoretical justifications and interpretation of results. Compared to the association of overall means, a stronger relationship between period-specific changes in adherence implies that factors that may change periodically may be stronger determinants of long-term adherence to multiple medications.

This dissertation assembled different approaches from the literature that can be applied to measure intra-disease multiple medication adherence and compared and contrasted the measurement approaches in the context. This is consistent with past scholastic work on the issue

of choosing an appropriate adherence measure. In spite of statistical power issues and methodological constraints, the study found that all measurement approaches significantly predicted outcomes and discriminated subjects. However, there were no clear trends in superiority in predictive and discriminatory power of one approach over others. That said, the average (continuous) and all (dichotomous) approaches appear to have edge over others due to some empirical support observed in the study or merely for the ease of measurement. The efficacy of a measure may also be tied to outcome of interest as differences in predictive or discriminatory power or the optimality of cut points were observed depending on outcome event (i.e., diabetes vs. all-cause ER) analyzed. Diabetes outcomes may have theoretical justification because of diabetes medication adherence being measured and more proximity to underlying causes leading to adverse events; however, it may also suffer from the lack of measurement validity because of the way a physician chooses ICD-9 codes or due to limited options of coding in the outpatient setting. In addition, other issues of substantive interest include whether or not the objective is to prevent any undue adverse events or design interventions to prevent any versus diabetes-specific events. Study findings should be interpreted and utilized with these issues in mind.

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LIST of APPENDICES

APPENDIX: LIST OF MEDICTIONS

Table D: List of Medications Used in the Study		
Disease	**Medication Class**	**Medication (Brand)**
Diabetes	Sulfonylurea (SU)	Acetohexamide, chlorpropamide, glimepiride, glipizide, glyburide, tolazamide, tolbutamide
	Thiazolidinediones (TZD)	Pioglitazone, rosiglitazone
Hypertension	Angiotensin Receptor Blockers **(**ARB)	Candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan
	Angiotensin-Converting Enzyme (ACE) inhibitors	Benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril
	Calcium Channel Blockers(CCB)	Amlodipine, diltiazem, felodipine, isradipine, nicardipine, nifedipine , nisoldipine, verapamil
	β-blockers	Acebutolol, atenolol, betaxolol, bisoprolol, carvedilol, labetolol, metoprolol, nadolol, pindolol, propranolol, sotalol
	Diuretics	Hydroclorothiazide, chlorthiazide, indapamide, methyclothiazide, metolazone, bumetanide, ethacrinic acid, furosemide, torsemide, amiloride, spironolactone, triamterene
Dislipidemia	Statins	Atorvastatin, fluvastatin, lovastatin, pravastatin, simvastatin, rosuvastatin
	Fibrates	Gemfibrozil, fenofibrate
Angina	Nitrates (oral)	Isosorbide dinitrate, isosorbide-5-mononitrate, nitroglycerin
Adapted from Parker and Parker, 1998; Wang, 2006		

APPENDIX: ADDITIONAL RESULTS

Table A1: PDC Estimates by Different Dichotomous Measures						
Approach	**Qtr**	**N**	**Quarter –specific**		**Cumulative**	
			Nonadh	**Adh**	**Nonadh**	**Adh**
At least one	1	6043	716 (11.85)	5327 (88.15)	716 (11.85)	5327 (88.15)
	2	6043	1199 (19.84)	4844 (80.16)	967 (16)	5076 (84)
	3	6043	1293 (21.4)	4750 (78.6)	1156 (19.13)	4887 (80.87)
	4	6043	1356 (22.44)	4687 (77.56)	1209 (20.01)	4834 (79.99)
	5	6043	1465 (24.24)	4578 (75.76)	1275 (21.1)	4768 (78.9)
	6	6043	1543 (25.53)	4500 (74.47)	1393 (23.05)	4650 (76.95)
	7	4979	1233 (24.76)	3746 (75.24)	1091 (21.91)	3888 (78.09)
	8	3752	826 (22.01)	2926 (77.99)	777 (20.71)	2975 (79.29)
Both	1	6043	2346 (38.82)	3697 (61.18)	2346 (38.82)	3697 (61.18)
	2	6043	2977 (49.26)	3066 (50.74)	2868 (47.46)	3175 (42.54)
	3	6043	3108 (51.43)	2935 (48.57)	3132 (51.83)	2911 (48.17)
	4	6043	3125 (51.71)	2918 (48.29)	3253 (53.83)	2790 (46.17)
	5	6043	3200 (52.95)	2843 (47.05)	3345 (55.35)	2698 (44.65)
	6	6043	3240 (53.62)	2803 (46.38)	3423 (56.64)	2620 (43.36)
	7	4979	2599 (52.2)	2380 (47.8)	2766 (55.55)	2213 (44.45)
	8	3752	1837 (48.96)	1915 (51.04)	1999 (53.28)	1753 (46.72)
All	1	6043	2241 (37.08)	3802 (62.92)	2241 (37.08)	3802 (62.92)
	2	6043	2868 (47.46)	3175 (52.54)	2681 (44.37)	3362 (55.63)
	3	6043	3004 (49.71)	3039 (50.29)	2952 (48.85)	3091 (51.15)
	4	6043	3029 (50.12)	3014 (49.88)	3037 (50.26)	3006 (49.74)
	5	6043	3112 (51.5)	2931 (48.5)	3085 (51.05)	2958 (48.95)
	6	6043	3161 (52.31)	2882 (47.69)	3201 (52.97)	2842 (47.03)
	7	4979	2549 (51.2)	2430 (48.8)	2579 (51.8)	2400 (48.2)
	8	3752	1805 (48.11)	1947 (51.89)	1847 (49.23)	1905 (50.77)

Qtr: Quarter; Nonadh: Nonadherent; Adh: Adherent (based on the 80% rule)

Table A2: Intra-disease Multiple Medication Adherence: Fixed Effects for Unconditional Growth Models

Effect	Med	Estimate	Standard Error	DF	t Value	Pr > |t|
med	SU	80.3023	0.3425	5988	234.46	<0.0001
med	TZ	81.6592	0.3389	5976	240.98	<0.0001
qtr_cont		-2.8469	0.0853	5537	-33.36	<0.0001
qtr_cont*med	SU	0.5825	0.0903	5310	6.45	<0.0001
qtr_cont*med	TZ	0	.	.	.	.

Table A3: Intra-disease Multiple Medication Adherence: Fixed Effects for Conditional Growth Models

Effect	med	Estimate	Standard Error	DF	t Value	Pr > |t|
med	SU	80.2982	0.3391	5985	236.78	<0.0001
med	TZ	81.6541	0.3351	5972	243.64	<0.0001
qtr_cont		-2.8435	0.0853	5537	-33.32	<0.0001
age_mc		0.6348	0.0495	6029	12.82	<0.0001
qtr_cont*med	SU	0.5818	0.0903	5310	6.44	<0.0001
qtr_cont*med	TZ	0	.	.	.	.
age_mc*med	SU	-0.0199	0.0511	6036	-0.39	0.6975
age_mc*med	TZ	0	.	.	.	

Table A4: Intra-disease Multiple Medication Adherence: Fixed Effects for Conditional Growth Models							
Effect	**med**	**Gender of Patient**	**Estimate**	**Standard Error**	**DF**	**t Value**	**Pr > |t|**
med	SU		79.0280	0.5036	6236	156.92	<.0001
med	TZ		79.5628	0.5034	6092	158.04	<.0001
qtr_cont			-2.8463	0.08534	5537	-33.35	<.0001
SEX		1	3.7732	0.6713	6019	5.62	<.0001
SEX		2	0	.	.	.	.
qtr_cont*med	SU		0.5824	0.09031	5310	6.45	<.0001
qtr_cont*med	TZ		0	.	.	.	.
med*SEX	SU	1	-1.4798	0.6861	6035	-2.16	0.0310
med*SEX	SU	2	0	.	.	.	.
med*SEX	TZ	1	0	.	.	.	.
med*SEX	TZ	2	0	.	.	.	.

Table A5: Intra-disease Multiple Medication Adherence: Fixed Effects for Conditional Growth Models

Effect	med	Gender of Patient	Estimate	Standard Error	DF	t Value	Pr > |t|
med	SU		79.1823	0.4982	6251	158.93	<0.0001
med	TZ		79.7204	0.4977	6104	160.18	<0.0001
qtr_cont			-2.8430	0.0853	5537	-33.31	<0.0001
age_mc			0.6257	0.0494	6028	12.66	<0.0001
SEX		1	3.4805	0.6633	6020	5.25	<0.0001
SEX		2	0	.	.	.	.
qtr_cont*med	SU		0.5817	0.0903	5310	6.44	<0.0001
qtr_cont*med	TZ		0	.	.	.	.
age_mc*med	SU		-0.0160	0.0512	6035	-0.31	0.7541
age_mc*med	TZ		0	.	.	.	.
med*SEX	SU	1	-1.4721	0.6866	6034	-2.14	0.0321
med*SEX	SU	2	0	.	.	.	.
med*SEX	TZ	1	0	.	.	.	.
med*SEX	TZ	2	0	.	.	.	

Table A6: Inter-disease Multiple Medication Adherence: Fixed Effects for Conditional Growth Models

Effect	med	Gender	Estimate	Std Error	DF	t Value	Pr > |t|
med	LP		77.3629	0.8466	2389	91.39	<0.0001
med	SU		81.1535	0.8028	2438	101.09	<0.0001
med	TZ		81.6540	0.7947	2392	102.75	<0.0001
qtr_cont			-2.6842	0.1411	2124	-19.03	<0.0001
age_mc			0.5144	0.0840	2347	6.12	<0.0001
SEX		1	3.5604	1.0270	2345	3.47	0.0005
SEX		2	0	.	.	.	.
qtr_cont*med	LP		-0.1847	0.1469	1923	-1.26	0.2087
qtr_cont*med	SU		0.5191	0.1478	2056	3.51	0.0005
qtr_cont*med	TZ		0	.	.	.	.
age_mc*med	LP		0.1696	0.0871	2353	1.95	0.0516
age_mc*med	SU		0.09593	0.0896	2354	1.07	0.2842
age_mc*med	TZ		0	.	.	.	.
med*SEX	LP	1	0.5763	1.0653	2353	0.54	0.5886
med*SEX	LP	2	0	.	.	.	.
med*SEX	SU	1	-1.8462	1.0951	2354	-1.69	0.0919
med*SEX	SU	2	0	.	.	.	.
med*SEX	TZ	1	0	.	.	.	.
med*SEX	TZ	2	0	.	.	.	

Table A7: Inter-disease Multiple Medication Adherence: Fixed Effects for Conditional Growth Models

Effect	med	Gender	Estimate	Standard Error	DF	t Value	Pr > |t|
med	AH		82.6801	0.7647	2243	108.13	<0.0001
med	SU		80.2791	0.7904	2300	101.57	<0.0001
med	TZ		80.4139	0.8061	2222	99.75	<0.0001
qtr_cont			-2.7314	0.1385	1985	-19.72	<0.0001
age_mc			0.5930	0.0858	2205	6.91	<0.0001
SEX		1	3.0248	1.0988	2200	2.75	0.0060
SEX		2	0	.	.	.	.
qtr_cont*med	AH		0.7580	0.1383	1878	5.48	<0.0001
qtr_cont*med	SU		0.3826	0.1485	1951	2.58	0.0100
qtr_cont*med	TZ		0	.	.	.	.
age_mc*med	AH		-0.0653	0.0830	2207	-0.79	0.4312
age_mc*med	SU		0.00234	0.0898	2208	0.03	0.9792
age_mc*med	TZ		0	.	.	.	.
med*SEX	AH	1	-2.3466	1.0629	2205	-2.21	0.0274
med*SEX	AH	2	0	.	.	.	.
med*SEX	SU	1	-1.4841	1.1504	2206	-1.29	0.1971
med*SEX	SU	2	0	.	.	.	.
med*SEX	TZ	1	0	.	.	.	.
med*SEX	TZ	2	0	.	.	.	

Table A8: Inter-disease Multiple Medication Adherence: Fixed Effects for Conditional Growth Models

Effect	med	Gender	Estimate	Standard Error	DF	t Value	Pr > |t|
med	AH		76.7130	1.4053	847	54.59	<0.0001
med	LP		85.1435	1.2428	850	68.51	<0.0001
med	SU		82.3388	1.3236	852	62.21	<0.0001
med	TZ		82.3879	1.2834	840	64.20	<0.0001
qtr_cont			-2.3323	0.2326	741	-10.03	<0.0001
age_mc			0.5198	0.1384	823	3.75	0.0002
SEX		1	2.5503	1.7063	822	1.49	0.1354
SEX		2	0	.	.	.	.
qtr_cont*med	AH		-0.3392	0.2315	619	-1.47	0.1434
qtr_cont*med	LP		0.7163	0.2276	686	3.15	0.0017
qtr_cont*med	SU		0.0291	0.2334	705	0.12	0.9009
qtr_cont*med	TZ		0	.	.	.	.
age_mc*med	AH		0.0232	0.1469	824	0.16	0.8745
age_mc*med	LP		-0.0261	0.1347	825	-0.19	0.8463
age_mc*med	SU		0.0501	0.1515	825	0.33	0.7411
age_mc*med	TZ		0	.	.	.	.
med*SEX	AH	1	2.9325	1.8106	824	1.62	0.1057
med*SEX	AH	2	0	.	.	.	.
med*SEX	LP	1	-3.5545	1.6601	825	-2.14	0.0326
med*SEX	LP	2	0	.	.	.	.
med*SEX	SU	1	-1.7493	1.8680	826	-0.94	0.3493
med*SEX	SU	2	0	.	.	.	.
med*SEX	TZ	1	0	.	.	.	.
med*SEX	TZ	2	0	.	.	.	.

Table A9: Inter-disease Multiple Medication Adherence: Fixed Effects for Conditional Growth Models

Effect	med	Gender	Estimate	Standard Error	DF	t Value	Pr > |t|
med	AG		36.4003	3.5094	305	10.37	<0.0001
med	SU		74.9576	2.7807	311	26.96	<0.0001
med	TZ		73.8889	2.9722	306	24.86	<0.0001
qtr_cont			-2.3166	0.4521	258	-5.12	<0.0001
age_mc			0.1489	0.3842	297	0.39	0.6987
SEX		1	4.7621	3.7399	297	1.27	0.2039
SEX		2	0	.	.	.	.
qtr_cont*med	AG		-0.1099	0.5178	243	-0.21	0.8321
qtr_cont*med	SU		0.4843	0.4927	256	0.98	0.3265
qtr_cont*med	TZ		0	.	.	.	.
age_mc*med	AG		0.4364	0.5464	297	0.80	0.4251
age_mc*med	SU		0.1908	0.4262	297	0.45	0.6547
age_mc*med	TZ		0	.	.	.	.
med*SEX	AG	1	-10.5834	5.3200	297	-1.99	0.0476
med*SEX	AG	2	0	.	.	.	.
med*SEX	SU	1	1.5000	4.1498	297	0.36	0.7180
med*SEX	SU	2	0	.	.	.	.
med*SEX	TZ	1	0	.	.	.	.
med*SEX	TZ	2	0	.	.	.	.

Table A10: Additional Analysis on Groups of Subjects or Specific Quarters

Model	Patrons	First five5 Q	Five Q from 2nd onward
Conditional means model: random intercepts	All	0.5466	0.5383
Conditional growth model: ae (SU and TZ)	All	0.6581	0.6347
Conditional means model: random intercepts	Community	0.5520	0.5491
Conditional growth model: ae (SU and TZ)	Community	0.5949	0.5842

Conditional: covariates sex and age included in the model; Q: quarter; ae: association of evolutions; SU: Sulfonylurea; TZD: thiazolidinediones

Table A11: Survival Analysis (Analysis of Maximum Likelihood Estimates)

Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
AGE		1	-0.01009	0.00813	1.5419	0.2143	0.990
SEX	1	1	-0.02412	0.11178	0.0466	0.8292	0.976
cci		1	0.19789	0.09127	4.7008	0.0301	1.219
pdcs		1	0.0008417	0.00174	0.2344	0.6283	1.001
pdct		1	-0.00648	0.00159	16.5827	<.0001	0.994

Difference in PDC test statistic: 6.5447 (p=0.0105); Outcome variable: Diabetes ER; pdcs: PDC for sulfonylurea; pdct: PDC for thiazolidinediones

Table A12: Survival Analysis (Analysis of Maximum Likelihood Estimates)

Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
AGE		1	-0.01016	0.00815	1.5511	0.2130	0.990
SEX	1	1	-0.02674	0.11183	0.0572	0.8110	0.974
cci		1	0.20215	0.09158	4.8722	0.0273	1.224
pdcs_c		1	0.0005078	0.00232	0.0478	0.8269	1.001
pdct_c		1	-0.00710	0.00215	10.9314	0.0009	0.993

Difference in cumulative PDC test statistic: 3.8774 (p=0.0489); Outcome variable: Diabetes ER pdcs_c: cumulative PDC for sulfonylurea; pdct_c: cumulative PDC for thiazolidinediones

Table A13: Survival Analysis Hazard Estimates						
Measurement Period	**Model**	**Approach**	**Parameter estimate**	**Std. Err**	**P**	**Hazard Ratio**
30 days	Uni	All	-0.3257	0.10831	0.0026	0.722
		Atlst1	-0.4188	0.12117	0.0008	0.658
		Avg	-0.0053	0.00149	0.0005	0.995
		Both	-0.3318	0.10845	0.0022	0.718
		Max	-0.0045	0.0015	0.004	0.996
		Min	-0.004	0.00122	0.0011	0.996
	Mul	All	-0.2851	0.10979	0.0094	0.752
		Atlst1	-0.3688	0.12367	0.0029	0.692
		Avg	-0.0046	0.00153	0.0024	0.995
		Both	-0.2911	0.10993	0.0081	0.747
		Max	-0.0038	0.00153	0.0125	0.996
		Min	-0.0035	0.00124	0.0043	0.996
90 days	Uni	All	-0.3969	0.11286	0.0004	0.672
		Atlst1	-0.6151	0.1168	<0.0001	0.541
		Avg	-0.0066	0.00165	0.0001	0.993
		Both	-0.387	0.11342	0.0006	0.679
		Max	-0.0058	0.00166	0.0009	0.994
		Min	-0.005	0.00136	0.0002	0.995
	Mul	All	-0.3588	0.11458	0.0017	0.699
		Atlst1	-0.5796	0.1195	<0.0001	0.56
		Avg	-0.0059	0.00169	0.0005	0.994
		Both	-0.3487	0.11511	0.0025	0.706
		Max	-0.0051	0.00171	0.0027	0.995
		Min	-0.0045	0.00138	0.0011	0.995

Outcome: any diabetes related ER; Uni: univariable; Mul: Multivariable; PDC measured for each period

Atlst1: At least one approach; Avg: Average approach; Max: Maximum approach; Min: Minimum approach

Table A14: Survival Analysis Hazard Estimates						
Measurement Period	**Model**	**Approach**	**Parameter estimate**	**Std. Err**	**P**	**Hazard Ratio**
30 days	Uni	All	-0.4485	0.11012	<.0001	0.639
		Atlst1	-0.5847	0.11832	<.0001	0.557
		Avg	-0.0053	0.00149	0.0005	0.995
		Both	-0.4632	0.11217	<.0001	0.629
		Max	-0.0077	0.00229	0.0015	0.992
		Min	-0.0064	0.00167	0.0002	0.994
	Mul	All	-0.4081	0.11191	0.0003	0.665
		Atlst1	-0.5386	0.12158	<.0001	0.584
		Avg	-0.0046	0.00153	0.0024	0.995
		Both	-0.423	0.11391	0.0002	0.655
		Max	-0.0066	0.00238	0.0056	0.993
		Min	-0.0057	0.00171	0.001	0.994
90 days	Uni	All	-0.3993	0.11268	0.0004	0.671
		Atlst1	-0.4999	0.12328	<.0001	0.607
		Avg	-0.0066	0.00165	0.0001	0.993
		Both	-0.4214	0.11471	0.0002	0.656
		Max	-0.0074	0.00234	0.0026	0.993
		Min	-0.0058	0.00172	0.001	0.994
	Mul	All	-0.3601	0.11456	0.0017	0.698
		Atlst1	-0.4547	0.12659	0.0003	0.635
		Avg	-0.0059	0.00169	0.0005	0.994
		Both	-0.3828	0.11654	0.001	0.682
		Max	-0.0064	0.00243	0.0083	0.994
		Min	-0.005	0.00176	0.0042	0.995

Outcome: any diabetes related ER; Uni: univariable; Mul: Multivariable; PDC measured cumulatively up to a period

Atlst1: At least one approach; Avg: Average approach; Max: Maximum approach; Min: Minimum approach

Table A15: Concordance Analysis on Optimal Cut-off

Measurement	Model	Approach	C-stat/ PL80	Maximization	Concordance
Cumulative 90 day	Multivar	At least one/ max 80	0.5672/12.094	75%	no
		Both/min 80	0.5683/11.048	75%	no
	Univar	At least one/max 80	0.5457/22.031	80%	yes
		Both/min 80	0.5489/9.3371	75%	no
90 day	Multivar	At least one/ max 80	0.582/15.2100	80%	yes
		Both/min 80	0.5679/13.8790	75%	no
	Univar	At least one/ max 80	0.5614/25.7210	80%	yes
		Both/min 80	0.5475/11.8870	75%	no
Cumulative 30 day	Multivar	At least one /max 80	0.5728/18.242	80%	yes
		Both/min 80	0.571/14.18	75%	no
	Univar	At least one/ max 80	0.5531/22.376	80%	yes
		Both/min 80	0.5529/17.619	75%	no
30 day	Multivar	At least one/ max 80	0.5664/8.4171	80%	yes
		Both/min 80	0.5639/7.0427	85%	no
	Univar	At least one/ max 80	0.5385/11.136	85%	no
		Both/min 80	0.541/9.4027	85%	no

Outcome variable: Any diabetes ER; C-stat: Concordance statistics (CT from Kremers); PL80: partial likelihood statistic of PDC dichotomized at 80%; Multivar: multivariable model; Univar: univariable model; Max 80: dichotomization of maximum approach at 80%; Min 80: dichotomization of minimum approach at 80%

* statistic not significant at p=0.0033

Table A16: Comparison Pre-ER and Post-ER Adherence

Variable	N*	Mean	Std Dev	Minimum	Maximum
pdcs_e1	525	76.08	30.56	0	100
pdcs_e2	801	74.27	32.26	0	100
pdcs_e3	801	73.09	34.35	0	100
pdcs_e4	801	71.80	34.25	0	100
pdcs_e5	801	68.66	36.49	0	100
pdcs_e6	546	69.75	36.47	0	100
pdct_e1	525	78.37	30.79	0	100
pdct_e2	801	75.84	32.61	0	100
pdct_e3	801	71.39	35.96	0	100
pdct_e4	801	70.01	36.68	0	100
pdct_e5	801	67.13	38.95	0	100
pdct_e6	546	66.28	39.45	0	100
pdcs_b	801	76.68	26.48	0	100
pdcs_a	801	68.40	33.75	0	99.81
pdct_b	801	77.39	26.98	0	100
pdct_a	801	65.77	35.71	0	99.81

Pdcs_ex: PDC for SU at quarter x; Pdct_ex: PDC for TZD at quarter x; Pre-ER and post-ER quarters are 1 through 3 and 4 through 6, respectively;
Pdcx_b: Average PDC for SU/TZD estimated on all available days before ER
Pdcx_a: Average PDC for SU/TZD estimated on all available days after ER
*Subjects were available for observation for at least 180 days preceding and following an all-cause ER event.

Table A17: Paired t-test Between Pre-ER and Post-ER Adherence

Medication	N*	Mean**	Std Dev	95% CI	t-statistic	p-value
SU	801	-8.28	24.20	-9.96, -6.60	-9.68	<0.0001
TZD	801	-11.6205	24.98	-13.35, -9.89	-13.1	<0.0001

**Difference between average pre-ER and post-ER PDC for SU/TZD estimated on all available days before ER
*Subjects were available for observation for at least 180 days preceding and following an all-cause ER event.

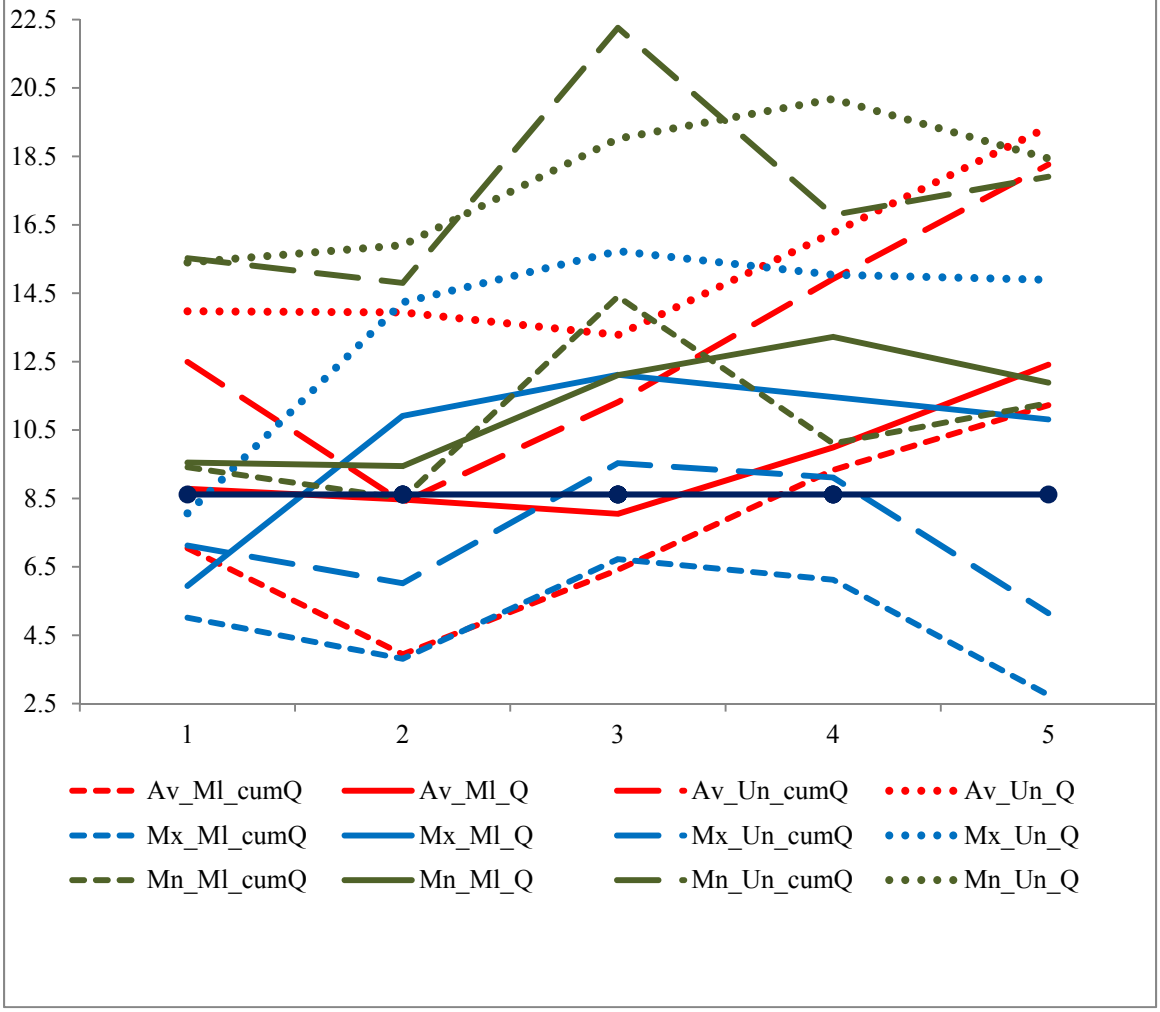
Table A18: Latent Growth Curve Modeling Analysis of Multiple Medication Adherence

Model	N*	Parameter	Correlation	P-value
Uncon. Grt [1]	3772	Int-SU Int -TZD Slp -SU/ Slp -TZD	0.6099 0.5975	<0.0001 <0.0001

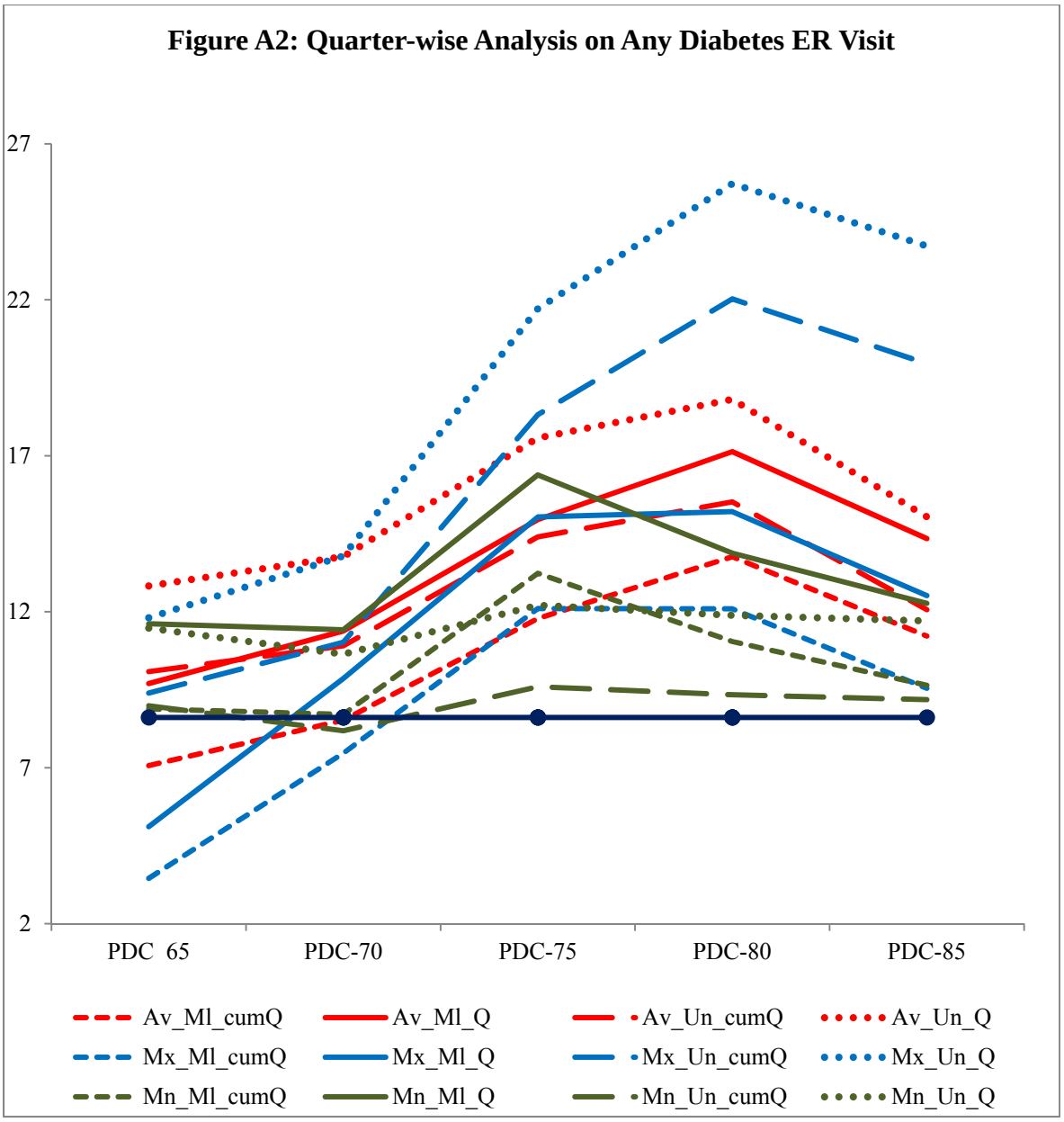
Uncon. Grt.: unconditional growth model with mean centered age and gender as covariates
Int: Intercept; Slp: Slope
SU: Sulfonylureas; TZD: Thiazolidinediones;
*Subjects were available for 7 quarters of observation and all 7 quarters were included in the analysis.

APPENDIX: ADDITIONAL FIGURES

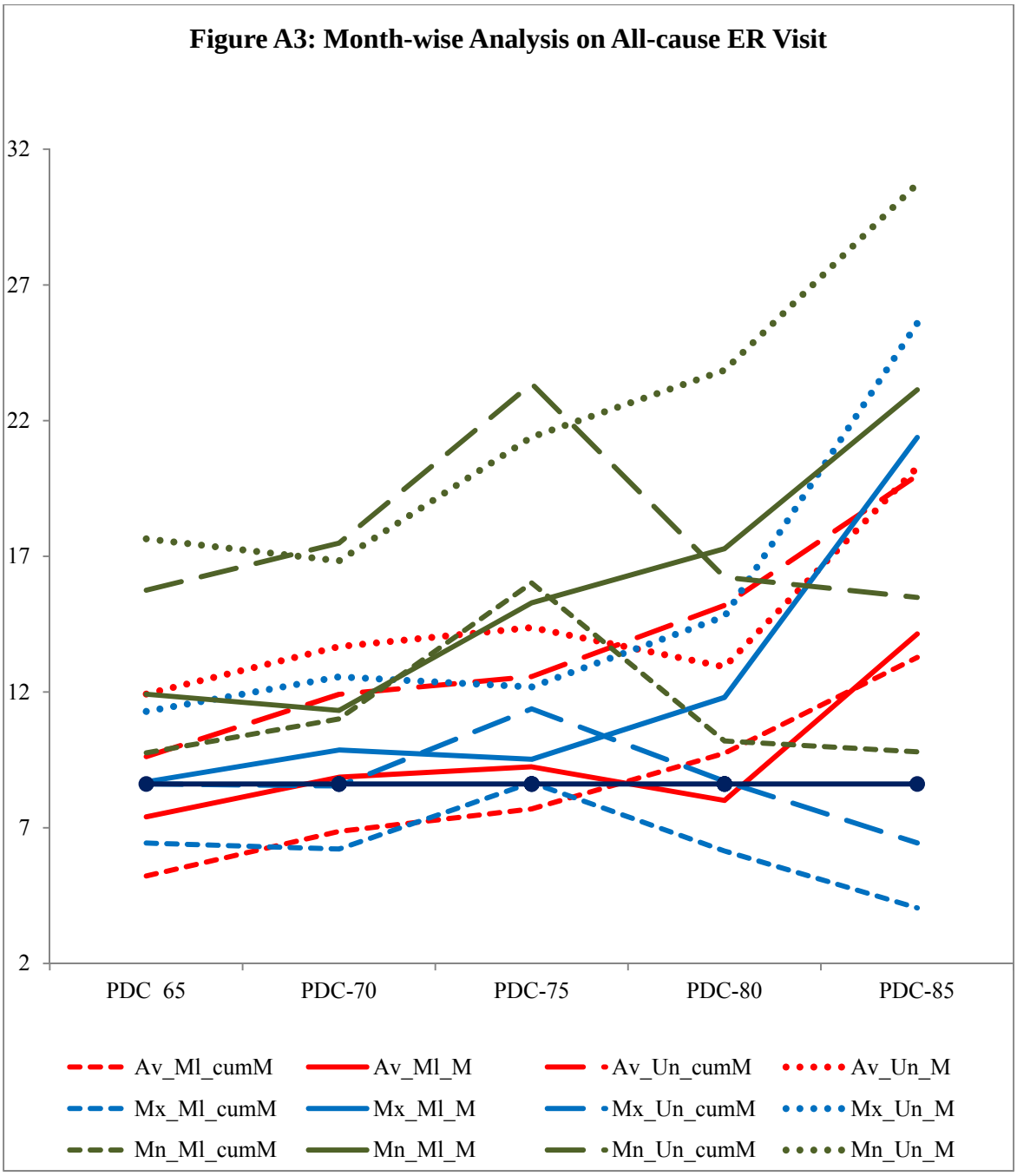
Figure A1: Quarter-wise Analysis on All-cause ER Visit



Y-axis: Partial likelihood estimate; X-axis: PDC dichotomization points at 65%, 70%, 75%, 80%, and 85%

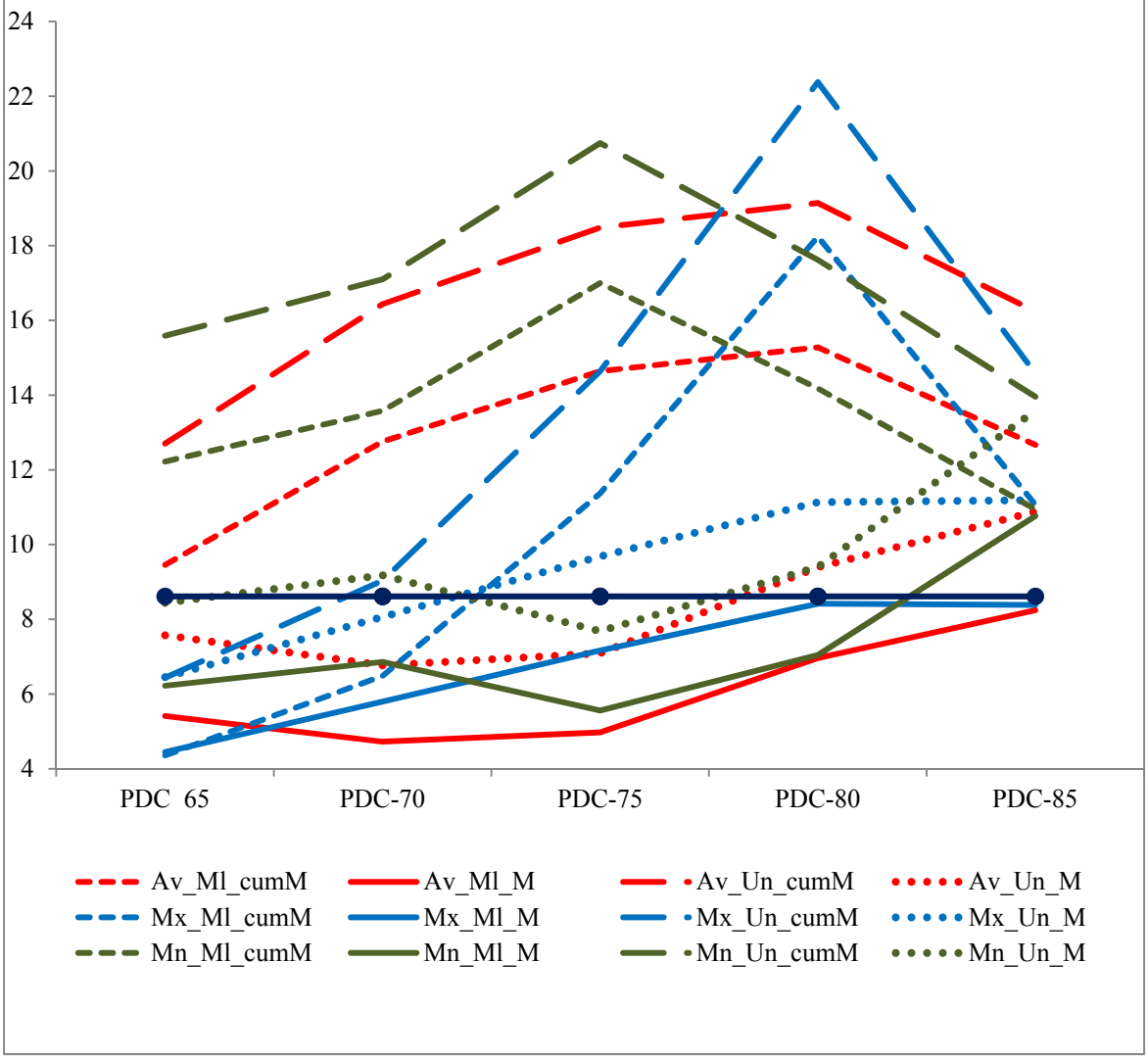


Y-axis: Partial likelihood estimate; X-axis: PDC dichotomization points



Y-axis: Partial likelihood estimate; X-axis: PDC dichotomization points

Figure A4: Month-wise Analysis on Any Diabetes ER Visit



Y-axis: Partial likelihood estimate; X-axis: PDC dichotomization points

VITA

Ram Sankar Basak was born in 1973 in India. Ramsankar is the son of Dhirendra Nath Basak and Kalpana Basak. He completed his Bachelor's of Pharmacy (B.Pharm.) from Jadavpur University in Calcutta, India. After his graduation, Ramsankar worked for a couple of years as a marketing professional for an Indian pharmaceutical company. Due to his passion for learning, he joined the Department of Pharmacy Administration of the University of Mississippi in 2005. Ramsankar completed his Master's degree (MS) with emphasis in pharmaceutical marketing in 2010 and has been working at Inovalon, Inc. located in the DC area. In his current role, he provides support to measure and improve healthcare quality performance metrics. Besides his current role, he has worked in several projects using the primary research technique and secondary data technique and has research interest in diverse areas, including medication adherence, healthcare cost and outcomes, prescribing quality, pharmacist role, patient behavior, and pharmaceutical marketing. Ramsankar is a member of International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and Rho Chi.