Summer 2014

A retrospective data analysis in veterans with inflammatory bowel disease: Using Wagner's Chronic Care Model to explore medication adherence

Lori K. Rizzo

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A RETROSPECTIVE DATA ANALYSIS IN VETERANS WITH INFLAMMATORY

BOWEL DISEASE: USING WAGNER'S CHRONIC CARE MODEL

TO EXPLORE MEDICATION ADHERENCE

A Dissertation

Submitted to the Graduate Faculty of the School of Nursing

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In partial fulfillment of the requirements for

the degree of Doctor of Philosophy

By

Lori K. Rizzo

August 2014

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Approved May 6, 2014

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ABSTRACT

A RETROSPECTIVE DATA ANALYSIS IN VETERANS WITH INFLAMMATORY

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Dissertation supervised by Dr. Alison M. Colbert

Background

Medication adherence in inflammatory bowel disease (IBD) ranges between

7-72%. Increased healthcare utilization has been associated with non-adherence in IBD.

Wagner's Chronic Care Model (CCM) posits that care coordination between primary and

gastroenterology (GI) specialty care could improve adherence and healthcare utilization.

Methods

Guided by the CCM, a retrospective analysis was conducted in veterans with IBD to:

describe medication adherence rates; describe healthcare utilization measured by ER visits and

inpatient admissions; and describe care coordination measured by primary care and GI specialty care use. A secondary study aim was to explore the relationships between those key outcome variables and select demographic/health history characteristics.

A local Veteran's Affairs database was used to extract a cohort of individuals with Crohn's disease and ulcerative colitis for fiscal year (FY) 2011. Medical utilization and IBD medication refills were collected. A dichotomized medication possession ratio (MPR .80) was used in logistic regression to identify factors affecting medication adherence. Logistic regression was also used to examine factors affecting ER visits, inpatient utilization, and care coordination.

Results

The cohort consisted of 165 White male veterans 75 with Crohn's disease and 89 with ulcerative colitis. The overall rate of adherence was 50.9% with a median MPR of .82. Regression models did not render any statistically significant predictors of adherence. ER utilization was significantly associated with adherence (OR=.314, 95%CI=.111-.886, p=.029) and care coordination (OR=45.73,95%CI=9.053-231,p=.001) in multivariate analysis. Inpatient admission was associated with: younger age (OR=.108,95%CI:.019-.609,p=.012), adherence (OR=.113,95%CI=.014-.939,p=.044), IBD diagnosis (OR=.117,95%CI=.017-.784,p=.027), and care coordination (OR=11.89,95%CI=1.228-115,p=.033). Logistic regression identified statistically significance associations with care coordinated between primary and GI specialty care and the following factors: taking both a 5-ASA and immunomodulating medication (OR=5.122,95%CI=1.874-14.00, p=.001), younger age (OR=.905,95%CI=.871-.940,p=.001), and having a comorbidity (OR=2.643,95%=1.171-5.965,p=.027).

Conclusions

No predictors of medication adherence emerged. However, the CCM element of care coordination provided additional insight into the healthcare utilization of veterans with IBD as statistically significant associations between care ER visits and hospitalization were identified. Further inquiry into the influences of medication adherence and healthcare utilization in this population is warranted.

DEDICATION

For Dorothy G. who came before

ACKNOWLEDGEMENT

I wanted to acknowledge my committee for being so generous with their valuable time.

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LIST OF ABBREVIATIONS

ADRRP   Administrative Data Repository Reporting Production

ADL   Activities of Daily Living

CAG   Citrix Access Gateway (CAG).

CBOC   Community Based Outpatient Clinic

CCI   Charlson Comorbidity Index

CCM   Chronic Care Model

CD   Crohn's Disease

CDW   Corporate Data Warehouse

CI   Confidence Interval

CPRS   Computerized Patient Records System

CPT   Current Procedural Terminology

CSA   Continuous, Single-interval measures of medication Availability

CSG   Continuous, Single-interval measures of medications Gaps

CMA   Continuous, Multiple-interval measures of medication Availability

CMG   Continuous, Multiple-interval measures of medication Gaps

CMOS   Continuous Measure of Medication Gaps

CR   Compliance Rate

DBR   Days Between Fills Adherence Rate

DOB   Date of Birth

DSA   Dichotomous, Single-interval measures of medication Availability

DSG   Dichotomous, Single-interval measures of medication Gaps

DMA	Dichotomous, Multiple-interval measures of medication Availability
DMG	Dichotomous, Multiple-interval measures of medication Gaps
DRUGDESC	Drug Description
DSSNDE	Decision Support System National Data Extract
ED	Emergency Department
EMR	Electronic Medical Record
ER	Emergency Room
FY	Fiscal Year
GAO	General Accountability Office
HEDIS	Healthcare Effectiveness Data and Information Set
HSR	Health Services Research
HSR&D	Health Services Research and Development
IBD	Inflammatory Bowel Disease
ICD-9	International Classification of Diseases (ICD-9)
ICN	Patient Integration Control Number
IEN	Internal Entry Number
IPNUM/IPNO	Intermediate Product Number
IRB	Internal Review Board
ISO	Information Security Officer
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
MAS	Medication Assessment Scale
MMAS-8	Morisky Medication Adherence Scale-8
MED-INT	Medication-Interval

MED-TOTAL   Medication-Total

MED-OUT   Medication-Out

MPR   Medication Possession Ratio

MPRm   Medication Possession Ratio Modified

MRA   Medication Refill Adherence

MVA   Missing Values Analysis

NDC   National Drug Code

OPD   Outpatient Department Visit

OR   Odds Ratio

PACT   Patient Aligned Care Teams

PBM   Pharmacy Benefits Management

PCP   Primary Care Provider

PDC   Proportion of Days Covered

PHI   Protected Health Information

PI   Principal Investigator

PPV   Positive Predictive Value

PTSD   Posttraumatic Stress Disorder

RCR   Refill Compliance Rate

RCT   Randomized Controlled Trial

REG-TOTAL   Regime-Total

REG-OUT   Regime-Out

RR   Risk Ratio

SUD   Substance Use Disorder

QUERI	Quality Enhancement Research Initiative
UC	Ulcerative Colitis
VA	Department of Veterans Affairs
VAMC	Veterans Affairs Medical Center
VAS	Visual Analog Scale
VHA	Veterans Health Administration
VIF	Variance Inflation Factor
VISN	Veterans Integrated Service Network
VistA	Veterans Health Information Systems and Technology Architecture
WHO	World Health Organization

Chapter 1

Introduction

Chapter 1 provides an overview for this dissertation study. This chapter includes study background, purpose, aims, as well as operational definition of variables. Additionally, the chapter encompasses study assumptions and limitations. Finally, this chapter concludes with study significance to nursing.

1.1 Background of the Study

Chronic illness affects nearly one-half of those residing in the United States including those who suffer with inflammatory bowel disease (IBD), a set of chronic inflammatory diseases of the GI tract with symptoms that exacerbate and ameliorate (Robert Wood Johnson Foundation, 2013). IBD affects 1.5 million Americans (Kappleman, Moore, Allen, & Cook, 2013) , approximately 45,000 of whom are veterans who utilize Veterans Affairs (VA) for chronic illness care of this disease (Hou, Kramer, Richardson, Mei, & El-Serag, 2013).

Medication Adherence

Long-term medication administration is required in IBD for disease control that is tenuous (Peppercorn, 2012). There are no allowable gaps in treatment, making strict medication adherence critical to successful disease control (Regueiro, 2012a). A systematic review demonstrated that medication adherence in IBD is problematic and in the range of 7-72% corresponding to rates in other chronic disease (C. A. Jackson, Clatworther, Robinson, & Horne, 2010; Krueger, Berger, & Felkey, 2005). However, little is known about medication adherence rates for veterans with IBD who access healthcare through the VA. This gap in scientific

knowledge supported the primary line of inquiry for this study exploring the rates of medication adherence in this cohort.

Over 50 years of medication adherence research exists. However, the topic only came to the forefront in IBD in the last 20 years and remains inconsequential in the minds of clinicians who fail to recognize the need for assessment of medication adherence as part of routine chronic illness care in this population (Trindade, Morisky, Ehrlich, Tinsley, & Ullman, 2011). Furthermore, a review of the literature conducted for this study, demonstrated that those who do conduct an assessment, utilize non-validated tools, calling into question the reliability of the results from this type of inquiry. Therefore, adherence science in IBD continues to stymie.

The majority of adherence research in IBD has taken place in the last five years, using cross-sectional design, conducted in small samples of specialty IBD clinic patients throughout the world. Modifying factors affecting medication adherence in IBD are not distinctive, existing in many chronic diseases and include lack of knowledge regarding illness and treatment, discordance in the physician-patient relationship, low health literacy, pill burden, and depression (C. A. Jackson et al., 2010). Several noteworthy, unique, condition specific factors found to affect adherence included disease duration, remission status, disease type (CD versus UC), new patient status, timing of last colonoscopy, and taking immunosuppressants (C. A. Jackson et al., 2010) . The literature presents conflicting data for non-modifiable risk factors for non-adherence in most diseases, including IBD, such as age, gender, and race, supporting closer examination of these demographics in this study.

Over a decade ago, the international community (National Council on Patient Information and Education, 2007; National Institutes of Health, ; World Health Organization, 2003) recognized medication adherence in chronic disease as a healthcare crisis that today, continues to

consume scarce healthcare resources (Lachaine, Yen, Beauchemin, & Hodgkins, 2013) . Despite international recognition, scientific stalemate persists because uncertainty remains about how best to define and measure medication adherence. After years of intensive review, the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) announced a call to action to standardize both the definition and measurement of medication adherence. These efforts were aimed at improving the quality of adherence research so that results could be compared across studies to move science forward (Cramer et al., 2008). While no "gold standard" to measure adherence exists, IBD experts deemed use of pharmacy refill data as the criterion measure in this cohort, specifically the calculation of the Medication Possession Ratio (MPR) (S. Kane et al., 2012). This recommendation is corroborated by ISPOR (Peterson et al., 2007) and supports the retrospective research design chosen for this study.

Chronic Care Model

Initially, the patient was at the center of non-adherence research. However, as understanding of the concept evolved, the complexity of treatment adherence emerged, demonstrating that healthcare systems providing services were not meeting the treatments needs of those with chronic disease (Wagner, 1998). As a result, adherence research began to change its focus from individual behaviors to examination of healthcare systems as a whole. Treatment deficiencies were the genesis for the Chronic Care Model (CCM) that provides a framework for chronic illness care based on best practices that accounts for intricate systematic influences on the delivery of healthcare (Wagner, Austin, & Von Korff, 1996).

Additionally, as acknowledged by global adherence experts, congruent with the CCM, the impact of healthcare systems outside the U.S. on medication adherence in IBD cannot be understated (World Health Organization, 2003). A study conducted by (Robinson, 2001)

demonstrated the potential influences of the health system on adherence in IBD in a study conducted to examine the rates of non-adherence in European countries. Reported rates of non-adherence varied widely between countries: France 13%, Italy 25%, UK 33%, and Germany 46%. That said, at least 50% of adherence research in IBD has occurred outside the U.S. with virtually no investigations conducted in the U.S. evaluating systematic effects. Therefore, a discrepancy in the literature exists regarding not only the effects of healthcare delivery in the U.S. on adherence in IBD, but also the effects of a closed system such as the VA has on medication adherence in this population. This supports the use of the systems based framework chosen for this study. The results of this investigation aid in rectifying informational inequality existing in IBD adherence research.

Moreover, in 2003, (World Health Organization, 2003) acknowledged that little research on the effects of healthcare teams and system-related factors on adherence exists, which, a decade later, remains true in patients with IBD, supporting further study in this arena (Shah, Tinsley, & Ullman, 2011) . Therefore, the CCM provides the framework for this study exploring the influences of the Veterans Affairs (VA) healthcare system in veterans with IBD. Specifically, the effects of primary and specialty care in this population.

Primary care is at the Model's center since this is the origin of chronic care in this country, including in the VA, because primary care acts as a gatekeeper to access VA specialty care (Kizer, 1996). Moreover, with the advent of evidence based medicine and the development of clinical practice guidelines, primary care is at the forefront of preventing and treating chronic illness (Starfield, Shi, & Macinko, 2005) . However, experts in chronic disease management propose coordination of care between primary and specialty care as a mechanism to attain optimal health (Shi & Singh, 2012).

For this study, gastroenterology was the specialty of focus, consulted through primary care, for the management of IBD. The literature suggests that organizational variables such as number of visits to primary and specialty care, as well as continuity of care, may have far greater impacts on treatment adherence than any other intervention (Albaz, 1997). One of the main functions of primary care is the coordination of care between primary and specialty care service lines (Shi & Singh, 2012) . Coordination of care between these two departments was the CCM element of interest in this study as it relates to medication adherence and healthcare utilization in this population, as the role of care coordination is requisite to improve adherence in chronic disease and was not formally explored in IBD. (MacColl Institute for Healthcare Innovation, 2010; World Health Organization, 2003) .

Care coordination is integral to delivery of chronic illness care in the Veterans Health Administration (VHA), a multifaceted agency governing the largest integrated benefits system in the world, the VA, providing services to honorably discharged members of the U.S. Armed Services (Kizer & Dudley, 2009) . VHA adopted the CCM in the late 1990s as a vehicle for transformation of this closed healthcare system (Perlin, J. B, Kolodner, R. M., & Roswell, R. H., 2004). Care coordination, a priority in VHA, occurs through the "medical home" model that consists of an interdisciplinary team of health professionals housed in primary care with requisite consultation to specialists as warranted (Shi & Singh, 2012) . VA efforts are consistent with the plan for coordination of care set forth by the (MacColl Institute for Healthcare Innovation, 2010) from which the CCM originates.

Intuitively, coordination of primary and specialty care should equate with improved health outcomes. However, the results from a recent Cochrane review (S. M. Smith, Allwright, & O'Dowd, 2009) conducted to assess the effectiveness of care coordination between primary and

specialty care in chronic disease management, were conflicting. Overall, no consistent improvement in outcomes across disease states materialized with the exception of medication adherence that indicated significant benefit with care coordination in this realm, supporting the need for further inquiry into the effects of care coordination on medication adherence for which no data exists in veterans with IBD (Neugaard, Priest, Burch, Cantrell, & Foulis, 2011).

This study builds on existing research by conducting the first medication adherence assessment of veterans to offer a critical evaluation of systematic influences of the VA on coordination of care, medication adherence, and healthcare utilization in patients with IBD. The results of this study may inform clinical practice as well as national health policy on the manner in which chronic illness care occurs in veterans with IBD.

Healthcare Utilization

Evidence suggests that when chronic illness is sub optimally treated, complications may worsen leading to increased consumption of healthcare resources such as ER services, inpatient admissions, as well as office visits (N. H. Miller, 1997), suggesting that higher levels of medication adherence may reduce healthcare costs, assuming the medication was appropriately prescribed (Sokol, McGuigan, Verbrugge, & Epstein, 2005). Repeatedly, research has demonstrated that those with IBD who do not follow prescribed medication regimes are at increased risk for disease relapse, up to five times that compared to those who adhere (Bhatt, Patil, Joshi, Abraham, & Desai, 2009; S. V. Kane & Hanauer, 2000; S. Kane, Huo, & Magnanti, 2003) . A disease flare, perhaps compelled by non-adherence to therapy, could influence the need for health services. Direct healthcare costs estimates are $3.1 billion for CD and $2.1 billion for UC (Kappleman et al., 2011).

World adherence experts (World Health Organization, 2003) provide support for examination of healthcare utilization concurrently with medication adherence rates as this data works synergistically to accurately inform health outcomes and future interventions. Additional support for this study emanates from two recently published papers from IBD experts (Kappelman, Palmer, Boyle, & Rubin, 2010; Shah et al., 2011) that identified gaps in the literature regarding patterns of healthcare utilization in this cohort for which a dearth of information exists due to the decentralized nature of the healthcare system in the U.S. (Kappleman et al., 2011). Therefore, this study began to explore the relationship between medication adherence and healthcare utilization in veterans with IBD as the consequence of these relationships are unknown.

1.2 Purpose of Study

The purpose of this descriptive, retrospective data analysis was to convey medication adherence rates of veterans with IBD and to examine the relationships between care coordination, medication adherence, and healthcare utilization.

1.3 Specific Aims

The primary aim for this study was as follows:

1.   Described medication adherence, healthcare utilization, and care coordination of veterans with inflammatory bowel disease (IBD) who employ Veterans Affairs (VA) healthcare at one Veterans Affairs Medication Center (VAMC).

Secondary study aims were as follows:

1.   Examined the association between medication adherence adjusted for care coordination, age, IBD diagnosis, comorbidity, and IBD medication in veterans with IBD who employ VA healthcare.

2.   Explored the relationship between healthcare utilization adjusted for medication

            adherence, age, IBD diagnosis, IBD medication, coordination of care and

            comorbidities in veterans with IBD who employ VA for healthcare.

1.4 Definition of Terms

Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) is a set of conditions including, ulcerative colitis (UC) and Crohn's disease (CD), that cause chronic inflammation of the GI tract (Peppercorn, 2012). The ICD-9 code of 555.x for CD and 556.x for UC identified subjects with said disease in this study (Thirumurthi, Chowdhruy, Richardson, & Abraham, 2010).

Medication Adherence

Researchers have posited many definitions of medication adherence. This study used the definition of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) that defines medication adherence as the "extent to which a patient acts in accordance with the prescribed interval, dose, and dosing regimen (Cramer et al., 2008, p.46). Adherence is reported as a percentage of total number of doses taken (if prospectively measured) or therapy-days available (if retrospectively measured), in relation to the time period of observation during which compliance is measured" (Burrell, Wong, & Ollendorf, 2005, p.194). Medication adherence was assessed using VA pharmacy refill data to calculate a rate of adherence using the medication possession ratio (MPR) defined as: "the sum of the days' supply of medication divided by the number of days between the first fill and the last refill plus the days' supply of the last refill" (Sikka, Xia, & Aubert, 2005, p. 449). The terms "adherence" and "compliance" are indistinguishable in the literature. For this study, the two terms were synonymous.

Healthcare Utilization

Healthcare utilization was the "use of healthcare resources" (Bernstein et al., 2003, p.1). For this investigation, the following healthcare services represented healthcare utilization: emergency department visits and inpatient admissions

Emergency Department Visit

Emergency department (ED) visit was defined as the "direct personal exchange between a patient and a physician or other healthcare provider working under the physician's supervision, for the purpose of seeking care and receiving personal health services" (Bernstein et al., 2003, p.129). For this study, the total number of ED visits in FY 2011 represented healthcare utilization of ED services as measured by clinic stop code 77 for any diagnosis.

Inpatient Admission

An inpatient admission was "an admission to an inpatient service of a hospital for observation, care, diagnosis, or treatment" (Bernstein et al., 2003, p.130). Inpatient admissions were measured as the total number of inpatient admissions for FY 2011.

Outpatient Department Visit

An outpatient department (OPD) visit was "the direct, personal exchange between an ambulatory patient seeking care and a physician or other healthcare provider to render personal health services within a hospital facility" (Bernstein et al., 2003, p.130). OPD visit measurement consisted of clinic stop codes for primary and specialty (Gastroenterology) care.

Primary Care

Primary care was defined as the provision of "integrated, accessible healthcare services by clinicians who are accountable for addressing a large majority of personal healthcare needs, developing a sustained partnership with patients, and practicing in the context of family and

community" (Vaneslow, Donaldson, & Yordy, 1995, p.192). Identification of healthcare utilization occurred using a clinic stop code, "a required field in the VA OPC Hospital Location file that assigns a number representing a type of care or Service/treating Specialty" (Zivin et al., 2010) . The clinic stop codes of 323, 301, 322, 348, 350, 170, 634, and 172 represented primary care for this study.

Specialty Care

Specialty care was the "delivery of care to individuals based on a certain physiological system or clinical condition or based principally on the age of patients" (S. M. Smith et al., 2009, p.3). Specialty care referred to Gastroenterology as measured by clinic stop code 151.

Care Coordination

Care coordination was the "deliberate organization of patient care activities between two or more participants (including the patient) involved in a patient's care to facilitate the appropriate delivery of healthcare services. Organizing care involves the marshaling of personnel and other resources needed to carry out all required patient care activities, and is often managed by the exchange of information among participants responsible different aspects of care" (McDonald et al., 2007, p.41). The literature characterizes the term "shared care" as tantamount with coordination of care, as was the case for this study (Starfield, 2003). The stop codes for primary care (323, 301, 322, 348, 350, 170, 634, 172) and gastroenterology (specialty care, 151) represented care coordination. Coordination of care was assumed when the patient had clinic stop codes for both primary and specialty care.

Comorbidity

Comorbidity was the "presence of additional diseases in relation to an index disease in one individual" (Valderas, Starfield, Sibbald, Salisbury, & Roland, 2009, p.359) measured by

ICD-9 code as reported by (Deyo, Cherkin, & Ciol, 1992), originating from (Charlson, Pompei, Ales, & MacKenzie, 1987). The index disease in this study was IBD. Therefore, measurement of this construct provided information regarding the influences of diseases additional to IBD on healthcare utilization in the population of interest.

Demographic Variables

Demographic variables included age, gender, and race/ethnicity. VA administrative databases provided this information.

1.5 Assumptions

The assumptions for this study were as follows:

1. Patients who obtained prescriptions for IBD medications consumed the medication starting the first day of the fill, used the drug as prescribed, and consumed all medications obtained. Patients were not stock piling medication, skipping doses, or giving their medications away.

2. When measuring adherence by drug class or by condition, patients were adherent as long as they received medication from a drug class for a specific condition, regardless of dose titration, switching, as well as adding or dropping medications.

3. Medications prescribed for IBD were appropriate for treating the intended condition.

4. The diagnosis of IBD, as documented by ICD-9 code, was accurate.

5. Patients used VA for healthcare services only.

6. Patients received the correct number of tablets equating to the days' supply of fill per dosing instructions.

7. Patients were assumed to have care coordinated if both primary and specialty GI clinic stop codes were present.

1.6 Limitations

The limitations of this study were as follows:

1. Because the study was limited to veterans who utilized the VA for healthcare, the findings may not be generalizable to veterans who do not use the VA for healthcare or to the civilian population.

2. Patients may have filled prescriptions for IBD medications outside the VA pharmacy.

3. Observations made about adherence in this study were not sufficient to characterize the patients' adherence to all medications in his/her regime. Calculated adherence only applied to those medications taken for IBD.

4. Since data extraction occurred from administrative data sets, information captured may be incomplete and data of unknown quality.

5. Patients may have accessed healthcare services outside the VA Healthcare System.

6. Feasibility did not allow a multi-method approach to data collection that included both a self-report and an objective measure, as considered state-of-the-art in measuring adherence behavior (World Health Organization, 2003).

7. Local VA databases did not contain the Sig for medications. Therefore, the researcher was unable to compare the number of tablets dispensed against the dosing instructions to ensure accuracy of prescription refills.

1.7 Significance to Nursing

Non-adherence to medication is an international healthcare crisis resulting in increased morbidity and mortality in many chronic illnesses including IBD (World Health Organization, 2003). Current understanding of medication adherence acknowledges this construct as multifaceted requiring a multidisciplinary team approach to disease management. Yet, who the members of such a team should be, and the definitions of their roles, are not evident. Much of the published literature regarding coordination of care in patients with IBD hales from the position of specialty care synchronization. Little knowledge exists concerning the outcomes of shared care across the primary/specialty care continuum in patients with IBD, particularly rates of medication adherence and healthcare utilization patterns in this cohort.

A recent synthesis of the literature suggested that nurses are the crucial link between primary care and specialty care coordination in the chronic disease management of IBD (Hernandez-Sampelayo et al., 2010). Support of this notion came from a case study conducted in the VA that explored the role of the nurse in coordinated shared medical appointments between primary and specialty care using the CCM as a guiding framework (Watts, Hynes, & Kopp, 2003). Furthermore, the American Academy of Nurse Practitioners and the White House also recognized the unique, integral role nurses play in chronic illness care by endorsing the expanded role of nurse practitioners in chronic disease treatment of our Nation's veterans in a collaborative effort known as Joining Forces (American Academy of Nurse Practitioners, 2012).

This study began to describe the impact of coordination of care on medication adherence and healthcare utilization in patients with IBD. Armed with knowledge regarding the effects of coordination of primary and specialty care on medication taking behavior and resource utilization, nurses are poised to make significant impacts on patient care and to advocate

allocation of scare healthcare resources. Nurses contribute to the chronic illness care in IBD by

generating effective interventions and changing health policy in this population about which,

currently, little information exists.

Chapter 2

REVIEW OF LITERATURE

2.1 Introduction

This chapter presents the theoretical foundation for this study as well as the current state of knowledge of the disease state under consideration, along with a comprehensive discussion surrounding the nomenclature and measurement of adherence as it relates to the population of interest. A summary show casing the gaps in the literature rounds out this chapter.

2.2 Conceptual Framework: The Chronic Care Model

Chronic illness affects more than 133 million individuals in this country with approximately half of these individuals experiencing more than one chronic illness (Bodenheimer, Chen, & Bennett, 2009). Research suggests that system(s) in which individuals obtain care for chronic illness are not conducive to meeting care needs of this vast group and result in deficient management of the most common chronic illnesses (Bodenheimer et al., 2009). In response to these deficiencies, (Wagner et al., 1996) generated a model to improved care for chronic conditions, the Chronic Care Model (CCM).

In broadest terms, the CCM seeks to encompass systems change by examining the interactive relationship between three key areas of influence on chronic illness care: the community, the healthcare system, and the provider organization. Primary care is the principal location of chronic illness care and is therefore, the focus of the Model.
The CCM places a self-motivated patient at the center of chronic care delivery as a method to improve disease management and to prevent complications. However, primary care collaboration between the patient, healthcare provider, and the healthcare system provides the underpinning for

the Model that posits resultant mutual goals, requisite skills for self-management, and improved chronic illness outcomes.

In 1998, the initial CCM contained six key elements that work in tandem to produce high quality outcomes: community; the health system; self-management support; delivery system design; decision support; and clinical information systems as depicted in Figure 2.1. The MacColl Center expanded the CCM into its current format in 2003, to include the previous six domains as well as five new elements. Expanded Model elements include patient safety (in health system), cultural competency (in delivery system design), care coordination (in health system and clinical information systems), community policies (in community resources and policies), and case management (in delivery system design) as illustrated in Figure 2.2.

The Community

The element of Community involves the mobilization of community resources to meet patient needs. By accessing existing assets, healthcare systems expand the depth and breadth of services provided. Ultimately, healthcare institutions, in collaboration with local, state, and national agencies, would act as advocates for patients with chronic disease to affect policy.

Self-Management Support

The self-management component of the CCM consists of patient engagement in: 1) activities that promote health; 2) interactions with healthcare providers and adhering to advised treatment recommendations; 3) ongoing self-assessment with resultant medical decision making; and 4) managing the effects of disease to participate in activities of daily living (Von Korff, Gruman, Schaefer, Curry, & Wagner, 1997). The self-management support plan of care is revised through a collaborative team process (MacColl Center & 1996-2013, 2013) (MacColl Center, 2013).

The Chronic Care Model

Community
Resources and Policies

Health Systems
Organization of Health Care

Self-Management Support

Delivery System Design

Decision Support

Clinical Information Systems

Informed, Activated Patient ↔ Productive Interactions ↔ Prepared, Proactive Practice Team

Improved Outcomes
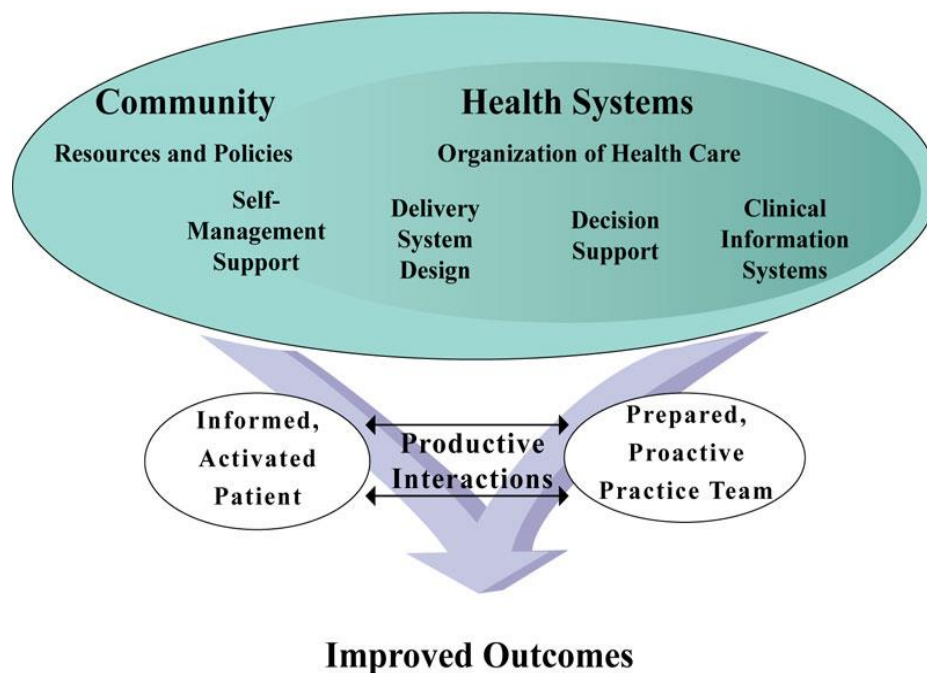
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Figure 2.1. Representation of the Chronic Care Model. Reprinted from "Chronic Disease Management: What Will It Take to Improve Care for Chronic Illness?" by E. H. Wagner, August/September 1998, *Effective Clinical Practice,* 1, p. 4. Copyright 1998 by the American College of Physicians. Reprinted with permission.

The Health System

The Health System in the CCM represents an organization that has identified chronic illness care as a priority and views improvement of this care as a fluid process that will continue to evolve. The organization recognizes that comprehensive institutional change provides the foundation for effective care delivery and has origins at all staff levels with support from senior leadership. Collaboration across the institution is fundamental.

The Care Model

Community — Resources and Policies

Health Systems — Organization of Health Care

Self-Management Support | Delivery System Design | Decision Support | Clinical Information Systems

Patient-Centered | Timely and Efficient | Evidence-Based & Safe | Coordinated

Services

Informed, Empowered Patient and Family ↔ Productive Interactions ↔ Prepared, Proactive Practice Team

Improved Outcomes

Developed by The MaColl Institute

Figure 2.2. Expanded Representation of the CCM. Copyright 1996-2012 .The MacColl Center.

The Improving Chronic Illness Care program is supported by The Robert Wood Johnson

Foundation, with direction and technical assistance provided by Group Health's MacColl Center

for Health Care Innovation. Reprinted with permission.

Delivery System Design

The configuration of healthcare delivery in the CCM necessitates creation of prepared,

proactive practice teams. The system providing treatment becomes proactive by providing

evidenced based care that shifts the focus from acute to chronic illness care. Multidisciplinary

practice teams communicate regularly about the care of a defined group of patients and often

consult professionals outside of a single practice (Starfield et al., 2005).

Decision Support

The decision support component of the CCM necessitates an educational foundation for members of the practice team to allow for the appropriate development of a treatment plan. Clinical reminders and standing orders support implementation of practice standards in medical decision-making. Evidenced based guidelines drive treatment decisions, serve to reduce inconsistencies in clinical practice, and provide standards for optimal chronic care. By sharing practice guidelines, healthcare providers encouraged patients to participate in disease management and treatment adherence. Patients are educated about disease process by employing methods that have demonstrated effectiveness. Decision support also incorporates access to medical specialty expertise.

Clinical Information Systems

Comprehensive clinical information systems are an essential attribute to effective disease management. A critical component of clinical information systems, patient registries generated from an electronic medical record (EMR) allow tracking of individuals with particular chronic disease states. Once the registry is establish, clinical reminders permit practice teams to address condition specific needs. In turn, the EMR can track performance of the team regarding the accomplishment of clinical goals. Additionally, the EMR coordinates care between services across a healthcare system as well as sharing information with patients.

Summary

Successful disease management relies on relations between individuals, healthcare providers, systems, and adherence to recommended protocols. Evidence suggests that clinical outcomes for individuals with chronic disease are suboptimal, due to interactions focused on urgent treatment needs rather than on long-term disease and symptom control, attributed to

widespread deviation from standard medical practice and lack of patient self-management skills. The CCM imparts a template for healthcare organizations to achieve high quality chronic illness care. Core changes to primary care, the location most frequently providing chronic disease management, are required to attain optimal disease management.

The Model has identified characteristics that are common among successful disease treatment programs in the literature. These characteristics are synergistic and include consistently planned follow-up, systematic assessments, acquisition of self-management proficiency, access to disease expertise, and supportive information systems. Implementation of all Model elements results in productive interactions between a prepared, proactive practice team and an informed, activated patient. Preparation of the clinical team incorporates chronic disease expertise as well as the resources to manage conditions effectively. An informed patient is one who possesses the knowledge and self-efficacy to capitalize on exchanges with clinical team members. Productive interactions involve the generation of a patient-centered, collaborative plan of care utilizing effective clinical treatments. Ultimately, use of CCM elements, renders coordinated services that are patient-centered, timely and efficient, as well as evidence based and safe. An application of the Model to this study follows.

2.3 Application of Theory to Study

The literature contains five decades of extensive medication adherence inquiry. When research in the field began, the patient was the center cause for deviation from prescribed treatment regimes. As such, initial theoretical models explained the construct from the perspective of changing individual behaviors. Models such as the Health Belief Model and Transtheoretical Model, as well as the Theory of Reasoned Action, self-efficacy, and the Theory of Planned Behavior pervade the literature in attempts to predict behavior leading to non-

adherence based on individual functioning. However, as the discipline evolved, the complexity of medication adherence became apparent, such that examining individual actions was not sufficient to address the magnitude of this problem, even with the use of intricate conceptual frameworks.
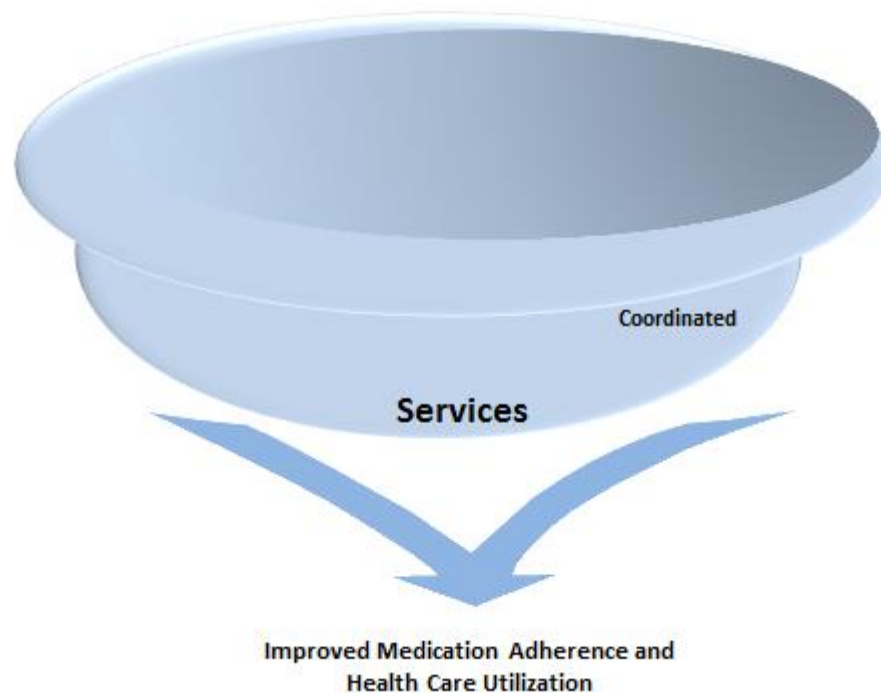
Figure 2.3. Application of Wagner's Chronic Care Model in Veterans with IBD

Therefore, corresponding with the current state of knowledge, a comprehensive system model, the CCM, was the guiding framework for this study. This multidimensional Model addressed how elements of chronic illness care organization within a healthcare system produce improved outcomes. In this study, only one element of chronic illness care was reviewed, the prescribing of medications for veterans with IBD, coordinated between primary care and specialty care. The outcome variable was medication adherence. Congruent with the CCM,

prescribing IBD medication, coordinated between primary and specialty care, may improve medication adherence as well as healthcare utilization as depicted in Figure 2.3.

The CCM provides healthcare systems with salient mechanisms to address the challenges of chronic illness care as evidenced by extensive testing of the Model throughout the world that have yielded promising results (Coleman, Austin, Brach, & Wagner, 2009). Further support of the Model was generated by a meta-analysis performed by (Tsai, Morton, Mangione, & Keeler, 2005) which demonstrated that interventions containing one component of the CCM improved clinical outcomes and processes of care. However, the literature does not present a clear picture of the impact individual Model elements contribute to effective chronic care. Influenced by the disease considered and the characteristics of both the organization under study and the population the organization serves, the effect of single Model elements may fluctuate (Sperl-Hillen et al., 2004) . This supports research examining just one element of the CCM, in this case, coordination of care between primary and specialty care in the VA healthcare system in veterans with IBD. This was the first study to use the CCM in veterans with IBD to explore the relationships between medication adherence, healthcare utilization, and coordination of care in the VA system. The significance of this study was in identifying potential points of intervention in the chronic illness care of this population.

2.4 Inflammatory Bowel Disease

Inflammatory bowel disease is comprised of two major disorders: Crohn's disease (CD) and ulcerative colitis (UC). These disorders have both distinct and overlapping characteristics. However, the pathogenesis of these disorders remains poorly understood. Theories of environmental exposure, genetic influence and autoimmune dysregulation subsist.

Both CD and UC are chronic inflammatory conditions of the GI tract typified by relapsing and remitting symptoms. Representations of CD include transmural inflammation with skip lesions that can occur anywhere from the oral pharynx to the anus which often lead to scarring and obstruction. Whereas, the inflammation found in UC is contiguous, superficial, usually involves the rectum, and is limited only to the mucosal layer of the colon, thereby unable to cause fibrosis of colonic tissue.

Epidemiology

In North America, the incidence rates for ulcerative colitis range from 2.2 to 19.2 cases per 100,000 with a prevalence of 238 per 100,000 (Molodecky et al., 2012).The incidence rates of Crohn's disease range from 3.1 to 20.2 cases per 100,000 with a prevalence of 201 per 100,000. This equates to approximately 1.2 million with IBD in the U.S. (Kappleman et al., 2013).

In North America the prevalence rates of IBD in Hispanics is 4.1% per 100,000 and in Asians 5.6% per 100,000. These rates are much lower when compared to the rates for White individuals of 43.6% per 100,000 and African American individuals at 29.8% per 100,000 (Baumgart & Carding, 2007). Additionally, both CD and UC are more common in Jews than non-Jews (Acheson, 1960).

Current statistics demonstrate that IBD accounts for approximately 45,000 veterans who access VA healthcare services for the chronic illness care of this disease (Hou et al., 2013). This study reported the prevalence of IBD in a national VA sample from 1998-2009 the results of which demonstrated an IBD occurrence primarily in men (>90%) with 50% of this cohort falling between the ages of 55 to 74.

Smoking effects both CD and UC in dichotomous ways. The risk of developing CD is twice as likely in smokers versus nonsmokers (Silverstein, Lashner, Hanauer, Evans, & Kirsner, 1989). While current smokers have a 40% lower risk of developing UC than nonsmokers. Interestingly, former smokers are 1.7 times more likely to develop UC when compared to those who have never smoked (Boyko, Koepsell, Perera, & Inui, 1987). Smoking cessation in UC has been associated with an increase in disease activity as well as hospitalization.

Other risk factors implicated in the occurrence of IBD include diets high in processed, fried, and sugary foods, obesity, GI infections, breast feeding, antibiotic usage, anti-inflammatory medication, oral contraceptives, Isotretinoin, and having an appendectomy (Peppercorn, 2012).

Clinical Manifestation

A comparison of the clinical manifestations of CD and UC are found in Table 1.The clinical manifestations of CD are more variable compared to those with UC and consist primarily of prolonged diarrhea, with or without gross bleeding, fever, weight loss and crampy abdominal pain. While UC typically presents with intermittent rectal bleeding in patients with mild disease confined to the rectum (proctitis). In moderate UC, inflammation extends to the splenic flexure (left-sided colitis) and the patient experiences frequent bloody diarrhea (up to 10x daily), mild anemia, abdominal pain, and fever.

In patients with severe disease, often inflammation extends the entire length of the colon to the cecum (pancolitis), bloody bowel movements number > 10 per day, and the patient may require a blood transfusion. Additionally, rapid weight loss leading to poor nutritional status may result in severe cases. If the inflammation in UC is severe enough, the process may extend

beyond the mucosa to involve the muscle layers of the colon causing impaired colonic motility and possible perforation (Peppercorn, 2012).

A recent review article was published by (Peyrin-Biroulet, Loftus, Colombel, & Sandborn, 2010) who examined the natural history of adult CD from 1935 through 2008. The results showed that while the disease remained stable over time with approximately 10% of the cohort experiencing prolonged periods of remission, half of all patients had intestinal complications within 20 years of diagnosis. The annual incidence of hospitalization was 20%. Additionally, half of the patients required surgery within 10 years of diagnosis with a postoperative risk of recurrence in the 44-55% range 10 years out.

Diagnosis

The diagnosis of CD is established with endoscopic findings and/or imaging studies in patients with a history consistent with the disease. Colonoscopy, with intubation of the terminal ileum, establishes the diagnosis of ileocolonic CD. Inflammation occurs in patches with normal colonic mucosa between lesions. Usually, the rectum is not affected. Colonic biopsies confirm the diagnosis with inflammation found on the small bowel biopsy. Imaging studies are typically done to assess for small bowel activity not evaluated by colonoscopy and include an upper GI with small bowel follow through, Ct, Ct enterography, MRI, and MR enterography.

Initially, flexible sigmoidoscopy establishes the diagnosis of UC (Peppercorn, 2012). Inflammation is in a contiguous pattern with rectal involvement. Biopsy confirms the diagnosis. Colonoscopy is usually not the first line exam in the severely ill patient due to risk for megacolon or perforation. In this country, diagnosis of UC does not depend on imaging studies. However, in Europe, ultrasonography provides information regarding the extent of colitis (Peppercorn, 2012) .

Table 1	
Comparison of Crohn's Disease and Ulcerative Colitis	
Crohn's Disease	Ulcerative Colitis
Inflammation may occur anywhere in the digestive tract and is in patches, the rectum is spared	Inflammation only occurs in the large intestine, is continuous, and typically affects the rectum
Ulcers in digestive track are deep and may extend into all layers of the bowel wall	Mucus lining of large intestine may have ulcers, but they do not extend beyond the inner lining
Bleeding from the rectum during bowel movements is not common	Bleeding from the rectum during bowel movements is common
Symptoms	
Diarrhea Weight Loss Joint Pain Anemia	Bloody Diarrhea Weight Loss Joint Pain Anemia from severe rectal bleeding

Treatment

The goal of treatment is to induce remission, assessed by a variety of methods that include patient subjective report of convalescence in symptoms, blood studies, as well as improvement on colonoscopic exam. However, treatment for IBD is convoluted requiring individualized application of current therapies due to disease heterogeneity. IBD typically has a relapsing, remitting path that requires continuous, particularized, therapy adjustment. Some individuals will have a quiescent disease course, while others have much more aggressive disease. Treatment considerations include the extent of disease, cost of therapy, patient compliance, and risk for toxicity. Because of disease and treatment complexity, there is no

consensus among discipline experts about how best to treat these patients. Many guidelines subsist with no one platform universally adopted. Therefore, the most current evidenced based practice recommendations provided guidance for the following discussion.

Treatment of CD

Generally, two approaches for the treatment of mild to moderate Crohn's disease: step-up therapy and top-down therapy are widely recognized as illustrated in Figure 2.4 (Farrell & Peppercorn, 2012). The most favored approach is step-up therapy that involves using medications that are the least potent, with fewer side effects, first. Medications with more toxic side effects follow, if initial therapy fails. Conversely, top-down therapy starts with potent therapies early on in disease course. Outpatient treatment with oral medication is appropriate for most individuals with mild to moderately active Crohn's disease. However, inpatient management is usually required for those with severely active disease.

Administration of oral medication depends upon the site of disease. Gastroduodenal disease occurs in less than 5% of CD patients, the treatment for which is prednisone. The ileum is the site most commonly involved in CD, the initially treatment for which is a 3-4 week course of an oral 5-aminosalicylate (5-ASA) medication such as mesalamine or sulfasalazine (Farrell & Peppercorn, 2012). Using a 5-ASA as an initial treatment in CD is controversial as studies evaluating its efficacy in this population are mixed.

If patients do not respond to the 5-ASA trial, treatment with either metronidazole alone or in combination with ciprofloxacin is next advised (Sartor, 2012). The mechanism of action of antimicrobials in IBD is not transparent with theories of intestinal bacterial overgrowth or possible microperforation speculated. Four weeks of tapering, oral steroid therapy follows a failed course of antibiotics to treat recalcitrant symptoms.

For intractable cases of CD, treatment consists of immune modulating medication such as azathioprine, 6-mercaptopurine (6MP), or methotrexate that has a response rate of 60-70% in small bowel and colonic disease (Farrell & Peppercorn, 2012). Reaction to these medications typically takes three to six months during such time the patient may need concomitant therapy with oral steroids. These medications have been associated with malignancy, bone marrow suppression, and hepatotoxicity. Therefore, close monitoring of biochemical parameters is required.

Step-up Versus Top-Down Therapy

Step-up Therapy

Anti TNF

Immune Modulator

5-ASA

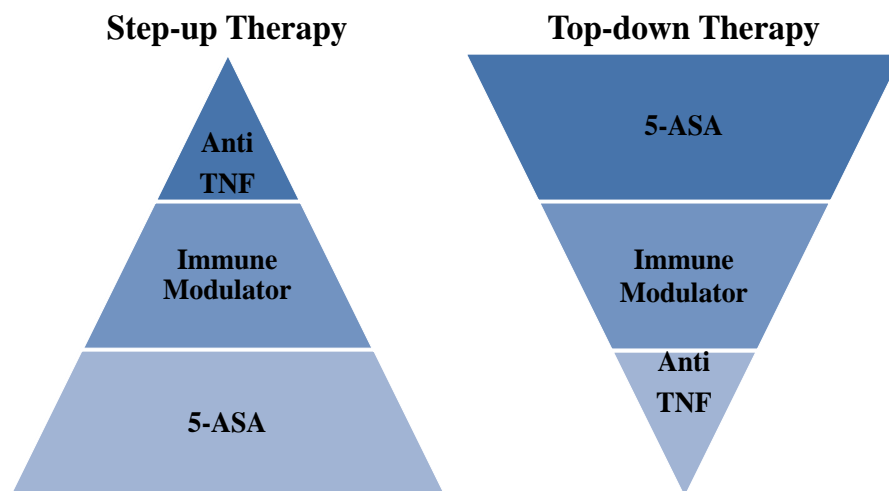**Top-down Therapy**

5-ASA

Immune Modulator

Anti TNF

Figure 2.4 Step-up versus Top-down Therapy for Treatment of Crohn's Disease

In a step-up approach, use of anti-TNF agents, also known as biologics, such as infliximab, adalimumab, and certolizumab represent the top tier of treatment and are not recommended as first line therapy but rather to be used in refractory cases and are often used in conjunction with immune modulating medications (Farrell & Peppercorn, 2012) . Due to immunocompromise with these medications, screening for hepatitis B and C as well as for TB, is advisable prior to initiation of therapy. Many possible serious side effects from anti-TNF medications are possible that include heart failure, malignancy, and demyelinating disease (Stone, 2012). As a recent systematic review demonstrated, it is unclear whether exposure to both immunomodulators and biologics simultaneously exponentially increases cancer risk (Kotlyar et al., 2011).

Approximately 10 to 20 percent of patients experience a prolonged remission after initial diagnosis (Solberg et al., 2007). Additionally, a recent review of the literature (Lichtenstein, Hanauer, Sandborn, & Practice Parameters Committee of American College of Gastroenterology, 2009) provided insight into the state of knowledge regarding treatment outcomes in this population. Important treatment statistics generated from the study analysis included:

- patients in remission for one year have an 80% chance of maintaining remission in subsequent years

- patients with active disease in the past year have a 70% chance of remaining active in the next year

- 13% of patients will have a period from relapse, while 20% have annual relapses, and 67% have a combination of years of relapse and remission with less than 5% of patients having a continuously active disease course.

Treatment of UC.

Similar to CD, treatment for UC focuses on the location of the inflammation. For example, treatment of proctitis, a disease limited to the distal 10 to 15cm of the colon, present in approximately 30% of patients, consists of a topical 5-ASA or steroid suppository (Farrell & Peppercorn, 2012). Treatment for disease extending into the left side of the colon consists of 5-ASA or steroid enema at bedtime, with response seen in four to six weeks (Farrell & Peppercorn, 2012). Treatment for non-responders consists of a second morning enema. Finally, therapy for non-responders to the aforementioned treatments consists of oral 5-ASA preparations that take three to six weeks to exert maximal benefit.

Deployment of tapering oral prednisone occurs for those with severe UC. However, chronic oral steroid use is not beneficial due to multiple deleterious effects such as weight gain, osteoporosis, diabetes, hypertension, cataract development, and mood swings. Additionally, there is no evidence that oral steroids maintain remission. Therefore, immune modulating medication as described, are added for those unable to wean off steroid. If no response occurs with immune modulating medication and/or the patient is unable to tolerate steroid wean, the final drug choices used to treat severe UC, prior to considering colectomy, include IV cyclosporine and Infliximab. However, the role of these medications in treating complicated cases of UC remains contentious.

Complications

CD and UC share a number of extraintestinal manifestations that correlate with the amount of inflammatory activity present. For example, arthritis such as ankylosing spondylitis that affects large joints, occurs in approximately 20% of patients and is the most common extraintestinal complication (Peppercorn, 2012). Eye involvement that exhibits as uveitis or iritis

occurs in 5% of patients (Peppercorn, 2012). Similarly, primary sclerosing cholangitis, also present in 5% of patients, is a consideration when alkaline phosphatase and gamma glutamyl traspeptidase (GGT) are elevated. Erythema nodosum and pyoderma gangrenosum, two common skin conditions, arise in 10% of patients (Peppercorn, 2012).

Several vitamin deficiencies plague patients with IBD, who experience impaired vitamin D and calcium absorption that may result in bone loss related to steroid use. Additionally, pernicious anemia can result from severe ileal inflammation since vitamin B12 is absorbed in the distal 50-60cm of ileum (Peppercorn, 2012).

IBD patients are at risk for renal stones. Calcium oxalate and uric acid kidney stones can result from steatorrhea and diarrhea (Obialo et al., 1991). Uric acid stones also result from dehydration and metabolic acidosis. Although rare, an additional renal complication includes secondary amyloidosis.

Pulmonary complications, although less likely, also exist in this population related to underlying inflammation but may be influenced by the medications used to treat the disease (Black, Mendoza, & Murin, 2007). Lung manifestations include pulmonary embolism, sarcoidosis, and interstitial lung disease.

Individuals with both CD and UC are at increased risk for colorectal cancer when compared to the general population. However, the data in this regard are disparate with much more known about this risk in UC and with no consensus regarding the timing of surveillance colonoscopy declared. Furthermore, a reduction in mortality due to colonoscopic surveillance has not materialized (Peppercorn & Odze, 2012) . Despite this, the general recommendation is to perform annual colonoscopy after eight years of disease duration in those with disease that extends beyond the hepatic flexure and after 12 years for those with left sided colitis (Peppercorn

& Odze, 2012). These surveillance exams do not preclude interim colonoscopic evaluations to assess disease extent as warranted.

Because IBD is an illness that tends to onset during the child bearing years, pregnancy and infertility are concerns that need addressed. Overall, decreased rates of fertility occur for both men and women with IBD (Walsh, Mabee, & Trivedi, 2011). For men, changes in fertility are associated with medication, methotrexate and 6MP, which resolved with cessation of the medication. Similarly, women experience decreased rates of fertility while taking methotrexate as well. Men and women should be counseled about the abortifacient and teratogenic effects of methotrexate and be advised to use two type of birth control while taking this medication (Walsh et al., 2011). While IBD improves during pregnancy, an individualized plan of care coordinated by an experienced gastroenterologist is critical for successful birth outcomes.

Summary

Inflammatory bowel disease is comprised of a set of conditions that cause chronic inflammation in the GI tract for 1.5 million Americans including approximately 45,000 veterans who access VA for healthcare services. The symptoms of IBD and the medications used to treat the disease can be debilitating and are a drain on scarce healthcare resources.

Two recently published papers (Shah et al., 2011) and (Kappleman et al., 2011) raise concerns about the quality of treatment for IBD noting significant variations in clinical practice that contribute to a misappropriation of therapy. Authors of both articles identified gaps in the literature regarding comprehensive evaluation of chronic illness care for this population that includes variations in prescribing practices as well as patterns of healthcare utilization. Not only did the results of these review articles support the need for additional research in medication

adherence and healthcare utilization in this cohort, the authors advise using a framework such as the CCM to do so which provided strong support for this study.

2.5 Medication Adherence

Chronic illness that requires prolonged treatment with medications affects more than 40% of individuals in this country and is the principal variable affecting treatment outcomes (Hoffman, C., & Schwartz, K., 2008). A meta-analysis demonstrated that rates of medication adherence in chronic disease varies and is in the range of 4.6% to 76% (DiMatteo, 2004).

While adherence to long-term therapies for chronic illness has been extensively deliberated for the last 50 years, a consistent profile of factors affecting adherence, or a single strategy that guarantees compliance, has not materialized. Furthermore, how to best define and measure this construct remains elusive. A discussion in this regard follows.

Defining Medication Adherence

Terminology and definitions of medication adherence used in research vary. The most common terms used are adherence, compliance, concordance, and persistence. The connotation of medication-taking language is widely debated (Osterberg & Blaschke, 2005; Steiner & Earnest, 2000). However, there is no consensus in the literature about how best to define this concept. Without homogeneity in construct description, it is problematic to compare research findings. Thus, advancement of knowledge in this field stymies.

In 2008, a paper presented standardization of the terms and definitions used when referring to medication-taking behavior. This publication was based on three years of international appraisal of this topic conducted by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) (Cramer et al., 2008) in which investigations conducted over the last half-century were considered. In an effort to comply with

standardization, the definitions generated from this report will serve to characterize adherence for this study.

The term compliance is purported to be offensive to patients when compared to the term adherence. However, after extensive review of this consideration, the authors concluded that no scientific support for the assumption that the term adherence is a less disparaging term or preferred by patients exists. Therefore, medication adherence was synonymous with compliance and was defined as "the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regime" (Cramer et al., 2008).

Measuring Medication Adherence

Similar to defining medication adherence, no "gold standard" for measuring this conception exists in scientific publication (S. Kane et al., 2012). Methods for measuring medication adherence are direct and indirect. Each measure elucidates a different aspect of this construct, making choice of the appropriate mechanism for research dependent upon study methodology and research questions.

This section presents a discussion of the advantages and disadvantages of the most frequently used methods of direct measures to include: observed therapy, measurement of medicine metabolite, and measurement of serology biologic marker, and indirect measures of: patient self-report, pill counts, pharmacy refill records, and electronic medication monitoring (Osterberg & Blaschke, 2005). Each of these methods, when used in isolation, often yields inaccurate and unreliable data (MacLaughlin et al., 2005). For this reason, use of a subjective and an objective measure to corroborate research findings are advised (Turner & Hecht, 2001). Because of limited resources, deployment of a corroborating source did not occur for this study.

Direct Measures

Directly Observed Therapy

Randomized control trials most often use the method of directly observing a patient receive medication where this type of intensive intervention warrants. However, its applicability in routine clinical settings is limited due to the expensive, labor-intensive nature of this data collection method. Although considered the most accurate means of measuring medication adherence, this method is not full proof as the patient could feign swallowing medication and then remove it from their mouths once the observation period had ceased.

Measurement of Medicine Metabolite

Biologic fluids can identify medication use during a stipulated period. However, presence or absence of a drug metabolite cannot fully substantiate adherence. Serum and urine drug levels do not explain medication consumption. For example, consider "white-coat compliance", a phenomenon where by the patient may exhibit adherence that corresponds with a clinic visit (Feinstein, 1990). Further complicating the use of this measure, are the variations that exist in individual's absorption, metabolism, and excretion that affect drug levels.

Measurement of Serology Biologic Marker

Biologic markers are compounds added to target or placebo medications used in clinical trials and extend similar inadequacies as medicine metabolites. Isotopes, phenobarbital, digoxin, and phenol red are examples of markers that have been used (Farmer, 1999) .

Indirect Measures

Patient Self-Report

Soliciting input from individuals via self-report is crucial to understanding adherence because patients ultimately decide whether to comply with treatment protocols. Self-report

measures are the most common, cost effective, convenient method of assessing medication adherence and include patient diaries, patient interviews, and validated adherence questionnaires (Sakthong, Chabunthom, & Charoenvisuthiwongs, 2009). The basic premise of this measure is simply asking the patient if they have been adherent to a drug regime. A caveat to this is that patients often times overestimate their adherence (Wang et al., 2004). Similarly, clinicians generate inaccurate assessments of patient compliance as well (Osterberg & Blaschke, 2005). Confirmation of findings in studies of medication adherence using a self-report method is advised (Morisky, Green, & Levine, 1986). Despite this recommendation, there are few studies available in the literature that compare self-report to objective criteria such as electronic monitoring (Wang et al., 2004).

Self-report methods have been widely used throughout the last several decades to measure adherence in a variety of chronic illness. However, due to the number of methods used to interview and retrieve information from patients, as well as the lack of psychometric properties of such tools, comparing results across studies can be arduous.

Pill Counts

Second only to self-report, pill counting is the most common method to measure medication adherence that involves counting the number of dosage units (tablets/capsules/drops/puffs) the patient has not taken by the scheduled appointment. A comparison of returned units with the number of units received by the patient in the most recent prescription and the length of time since the medication was dispensed takes place (Farmer, 1999). Calculation of medication adherence occurs by subtracting the number of units returned from the number of units issued which calculates the amount of medication used by the patient

during the observation period that can then multiplied by 100 to determine the percentage of adherence.

Once thought to be a viable mechanism for measuring medication adherence due to ease of use and cost effectiveness, pill counting has fallen out of favor due to overestimation of compliance (Cramer et al., 2008). This method of measuring medication adherence gives no insight of ingestion of medication by the patient. Patients can easily manipulate the results of the data collection. A phenomena known as "pill dumping" may occurs whereby patients ingest large amounts of medication immediately preceding a clinic visit (Rudd et al., 1989). Additionally, patients may not return all residual medications in an attempt to hide their behavior. Even when assessments are accurate, pill counts cannot explain reasons for non-adherence.

Pharmacy Refill Records

Use of prescription refill records to assess medication adherence has become the most common measure of this construct in the last decade (Ho, Bryson, & Rumsfeld, 2009). The advent of the electronic medical record has provided opportunity to access pharmacy data for research purposes. Because this was the chosen data collection method for this study, a detailed discussion occurs further on in this review.

The accuracy of this measure depends in large part if patients are filling prescriptions within a closed pharmacy system (i.e. patients are obtaining medication from a single pharmacy) such as VA (Osterberg & Blaschke, 2005). Measuring medication adherence using electronic claims can be problematic if patients obtain prescriptions from multiple sources. Additionally, pharmacy records do not provide any information about medication consumption. Patients may order refills of medications as scheduled and stockpile them.

Electronic Medication Monitoring

The last four decades have witnessed use of electronic monitors to record the time and date when patients open a prescription container (Osterberg & Blaschke, 2005). The most commonly used device is the Medication Event Monitoring System (MEMS) which costs approximately $100 per monitor, inhibiting its use in routine clinical practice and large studies (Balkrishnan, 2005). When the device communicates to the appropriate computer software, it has the ability to identify non-adherent behaviors such as drug holidays, pill dumping, and white coat compliance (MacLaughlin et al., 2005). However, electronic monitoring cannot document whether the patient actually ingested the medication after opening the container. Despite this fact, electronic monitoring is considered to provide the most reliable adherence data (Osterberg & Blaschke, 2005).

Measuring Medication Adherence Using Administrative Databases

Administrative data are data files assembled for billing of healthcare services (Hess, Raebel, Conner, & Malone, 2006). VA has been keeping such records related to medication refills for over the last twenty years. About the time of electronic medical record development, researchers at VA facilities proposed a method of measuring medication adherence using pharmacy refill records. This method was borne from frustration with the limitations of other methods that were available at that time. The VA, as a closed pharmacy system (i.e. the assumption that patients only receive medications from one pharmacy), provided the ideal laboratory for this type of data collection method.

In 1980, (Inui, Carter, Pecoraro, Pearlman, & Dohan, 1980) used VA pharmacy data to assess for correlations between refill data and mean diastolic blood pressure in a group of patients taking hydrochlorothiazide as well as the resting pulse in patients taking propranolol

(N = 419). The results indicated that hydrochlorothiazide compliance significantly correlated with mean diastolic blood pressure (r = -.63, p<0.05). The results further suggested a correlation between resting pulse and compliance with propranolol (r = -.41, p <0.05).

Subsequently, while the use of administrative data to measure medication adherence was evolving as a viable data collection method, substantive growth was not recognized in this field until the sentinel paper was published in 1988 which introduced a variety of new concepts into the literature that have expanded considerably over the years (Steiner, Koepsell, Fihn, & Inui, 1988). Following, will be a discussion of the history of this method year to date. Table 2 contains simulated data generated to provide a reference for the various mathematical calculations.

MED-INT/MED-TOTAL/MED-OUT/REG-TOTAL/REG-OUT

In 1988, (Steiner et al., 1988) introduced the concepts of: Medication-Interval (MED-OUT); Medication-Total (MED-TOTAL); Medication-Out (MED-OUT); Regimen-Total (REG-TOTAL);and Regime-Out (REG-OUT) in a study that sought to validate a data collection method using VA refill data that incorporated changes in drugs or dosages, variable refill intervals, as well as regimens of multiple medications. The investigation examined compliance to long-term medications used to treat hypertension and seizure disorder.

MED-INT is the ratio of the days' supply obtained at the beginning of a specific time interval to the days lapsed before the next fill. Days' supply, the equation numerator, is calculated, as the number of pills dispensed divided by the number of pills prescribed per day. For example, Patient B taking Sulfasalazine for UC 500mg, two tablets three times daily, who obtains a thirty day supply of medication for the 4th refill during the observation period, the

quantity of pills dispensed would be 180, divided by 6 for number doses in a day, and finally

dividing by 30, the number of days in a refill interval:

$$\frac{\text{(Quantify of pills dispensed 180)} / \text{(pills per dose 2 x doses per day 3)}}{\text{Days in refill interval (30)}}$$

the Medication Interval in this example is 1. The applicability of this equation in clinical

practice has limited use since it only provides adherence information for one refill which cannot

then be extrapolated to draw conclusions about the patient's overall adherence to a drug regime.

For a series of refills, the MED-TOTAL equation provides a method to calculate an overall

measure of compliance. The MED-TOTAL calculation is the total supply of pills

dispensed divided by the total number of days in the refill period. Expanding on the example

above, to examine a six-month refill period for both Patients A and B, the equation would

resemble the following:

$$\frac{\text{Sum of days' supply dispensed (180 days x 6 months)}}{\text{Sum of days in all refill intervals (180 days x 6 months)}}$$

The MED-TOTAL is 1, indicating perfect adherence during the six month observation period.

This example reveals the limitations of this calculation. Both Patients A and B receive a score

that represents perfect adherence. However, Patient A has a gap in treatment because instead of

the patient filling the medication after 90 days had elapsed, the patient fills the medication 100

days after the previous refill, signifying a 10-day gap when the patient was without medication.

The third concept presented by (Steiner et al., 1988) is that of MED-OUT that represents the total

number of days without medications divided by the total days of observation. As discussed

above, in the example of Patient A taking Sulfasalazine, the 2nd refill

Table 2

Simulated Pharmacy Refill Data

Patient A

Drug	Quantity	Days Supplied	Date	Days Elapsed
Sulfasalazine 500mg	540	90	10/01/2010	0
Sulfasalazine 500mg	540	90	04/06/2011	100
Sulfasalazine 500mg	540	90	07/01/2011	185
Sulfasalazine 500mg	540	90	09/30/2011	275

Patient B

Drug	Quantity	Days Supplied	Date	Days Elapsed
Sulfasalazine 500mg	540	90	10/01/2010	0
Sulfasalazine 500mg	540	90	12/29/2010	90
Sulfasalazine 500mg	540	90	04/28/2011	210
Sulfasalazine 500mg	180	30	07/27/2011	300
Sulfasalazine 500mg	180	30	08/26/2011	330
Sulfasalazine 500mg	180	30	09/25/2011	360

Fairman, K. & Motheral, B. (2000). Evaluating medication adherence: Which measure is right

for your program? Journal of Managed Pharmacy. 6(6). 499-504. Reprinted with permission.

demonstrates that the patient went 10days without medication. To calculate MED-OUT for this individual:

$$\frac{\text{(Sum of days without medication)} \quad 10}{\text{(Sum of days in the observation period)} \quad 180}$$

or 0.05. For the individual who never runs out of medication before obtaining a refill, MED-OUT will equal zero.

This calculation is not sensitive to changes in doses that would alter the supply of drug on hand. Such that, if this patient were instructed to increase the medication interval from three times daily to four times daily, this reason for the patient to be out of medication would not be readily apparent by performing this calculation.

The final two concepts put forth by (Steiner et al., 1988), REG-TOTAL and REG-OUT mirror MED-TOTAL and MED-OUT. While the latter equations represents medication adherence as it relates to one drug, the former can be used to examine compliance as it relates to an entire regime since it is recognized that patients may adhere to varying degrees with different medications in the same treatment regime.

To obtain REG-TOTAL and REG-OUT , the MED-TOTAL and MED-OUT are calculated for each drug in the individuals regime respectively, summed and then divided by the total number of observation days for each drug.

The authors validated MED-TOTAL and MED-OUT by demonstrating a correlation between the measures and Dilantin serum levels, correspondingly, ($r = 0.31$, $p = 0.03$, 95% CI 0.04 to 0.54) and ($r = -0.40$, $p = 0.004$, 95% CI -0.14 to -0.61). Expectedly, the MED-OUT correlation was negative because serum Dilantin levels decrease if the patient is without

medication. The investigators attempted to validate REG-TOTAL and REG-OUT by examining all hypertensive medications each individual in the study was taking and comparing these calculations to diastolic blood pressure. There was a correlation found between compliance and diastolic blood pressure for both REG-TOTAL and REG-OUT. However, neither reached a statistically significant level, ($r = -0.14$, $p = 0.23$, 95% -0.35 to 0.09) and ($r = 0.17$, $p = 0.15$, 95% CI -0.06 to 0.39) respectively.

CSA,CSG,CMA,CMG,DSA,DSG,DMA,DMG

Research of medication adherence using pharmacy refill data continued to grow throughout the 1980s and 1990s. (Steiner & Prochazka, 1997) expanded on their 1988 work by performing a systematic review of the literature from 1969 through 1994 to examine the state of knowledge regarding the use of administrative databases to measure compliance. In all, the authors examined 41 studies from the U.S., UK, Australia, and Finland that employed refill compliance measures. Twelve of the 41 studies reviewed occurred in VAMCs that meant that VA pharmacy data informed these studies.

The researchers created a new typology that introduced three new categories into the literature to describe refill measures. The categories included: 1) the distribution of the adherence variable was continuous (C) versus dichotomous (D); 2) the number of refill intervals was either single (S) or multiple (M); and 3) the measure either assessed the time period over which drugs were available to the patient (A) or the time intervals during which gaps in medication possession occurred (G). From this review, the authors generated new classifications by grouping studies by typology.

The first category presented by (Steiner & Prochazka, 1997) is that of continuous, single-interval measures of medication availability (CSA). Similar to MED-INT that provides minimal

information on a patient's overall adherence to a drug regime, CSA is of limited clinical usefulness, as it too, gives little insight into adherence. None of the studies in this review utilized CSA as a measure for compliance.

The second typology offered by the authors is continuous, single-interval measures of medication gaps, CSG. This calculation provides information about gaps in adherence for 1 refill only, typically 30, 60, or 90 days. For example, if a patient fills a medication for 30 days and the observation period is for a total of 90 days, this leaves a gap in the treatment of 60 days. CSG is calculated: $60/90 = 0.67$. When no gaps in treatment occur, CSG will be zero. Analogous to both CSA and MED-INT, CSG will have limited pertinence in medication adherence research due to its confined scope of measurement. The data presented by (Steiner & Prochazka, 1997) did not include any studies that utilized this equation.

The third classification generated is CMA that is a continuous, multiple-interval measure of medication availability. This measure is comparable to MED-TOTAL and provides information on mean adherence over all refill intervals. Dividing the sum of the days' supply obtained over a series of refill intervals by the total days from the beginning to end of the observation period provides the calculation for CMA. For the patient taking Sulfasalazine who refills this medication every 30 days for 6 months, the CMA would be 1 (180/180), which demonstrates perfect adherence. Any number > 1 constitutes an oversupply of medication. Over 50% (23) of the studies in this review used CMA as a measure of adherence. Of these, 11 collected data using VA administrative databases to examine a large variety of medications with 4 of the 11 studies observing adherence for 6months and the remaining studies reviewing data for 12 months or more. The mean CMA for the 11 studies was .87 indicating a high level of compliance.

The fourth concept in this review is the continuous, multiple-interval measure of medication gaps (CMG). This corresponds with MED-OUT and documents the amount of time a patient is without medication. CMG calculation consists of dividing the total number of days in treatment gaps by the duration, in days, of the observation period. The denominator in this equation can be a specific date at the end of the observation period or the date of the last medication fill. If the former is used, all gaps are "embedded" within a series of refills. If the latter is used, a "terminal gap" is present after the last fill. This measure assumes that gaps in treatment correspond to a lack of adherence rather than a temporary or permanent dose change made by the provider.

Eight studies in this review examined medication adherence using CMG, the majority of which were studies conducted in the VA. The mean CMG for these studies was 0.17 indicating small gaps in treatment, i.e. higher levels of adherence. The remaining four equations, DSA, DSG, DMA, DMG, are simply dichotomous measures generated from their continuous counterparts, CSA, CSG, CMA, and CMG.

Dichotomous cutoffs were used to differentiate between complaint versus partially compliant or complaint versus noncompliant individuals. The investigations in this review did not offer clinical or pharmacological justification for the choice of a threshold value. Often the cutoff of .80 represents the ceiling (Esposti et al., 2004). Therefore, those with a calculated adherence of .80 and above are adherent. Whereas those with a score < .80, would be categorized as partially compliant or non-compliant.

Medication Possession Ratio

Included in the review conducted by (Steiner & Prochazka, 1997), however not explicitly addressed, was the construct of Medication Possession Ratio (MPR). (Sclar et al., 1991)

introduced the MPR into the literature and defined it as the number of days' supply obtained by the patient during an observation period. The ultimate outcome is a ratio of 1:1 representing perfect adherence. This equation provides comparable data to MED-TOTAL and CMA in that it provides information about adherence to a drug regime over time.

Considerable research was generated from the preliminary (Sclar et al., 1991) investigation during the next 15 years utilizing the MPR as a method for measuring medication adherence. Consequently, while many adherence measures that used pharmacy refill data exist in the literature during this period, the MPR sustained and gained popularity. The definition of MPR had expanded from what has previously been described into the following: "the sum of the days' supply of medication divided by the number of days between the first fill and the last refill plus the days' supply of the last refill" (Sikka et al., 2005).

MPR was the measure of medication adherence used in a recent study conducted by (Lockwood, Steinke, & Botts, 2009) that examined this concept and readmission rates in the 12 months following discharge, in a sample (N = 82) of Veterans with Posttraumatic Stress Disorder (PTSD), released from an inpatient psychiatric stay for such. Local pharmacy data was used to measure adherence to psychiatric medication regimes, as calculate by the MPR, with adherence defined as a ratio of at least 0.8. The majority of patients (66%), were not adherent to medication during the 12 months following discharge and 20.7% were readmitted for symptomatic PTSD. However, non-adherence was not significantly associated with relapse (p=0.91).

Additionally, the authors reported that the larger the total number of drugs prescribed for a Veteran, the higher the level of adherence (p=0.014). Age, substance abuse, combat service, and service connection were not associated with medication adherence.

Table 3 contains a summary of adherence and persistency measures found in the literature which demonstrated a distinct difference between adherence and persistence. Whereby the MPR calculates adherence through assessing medication availability over multiple refill cycles, persistency denotes the duration of time a patient remains on chronic medication for a specified surveillance interval. Therefore, MPR in isolation may not impart information on the consistency of refilling behavior, i.e. persistency.

Persistency as a function of the MPR

As previously discussed, MPR is a measurement of adherence based on the patient's possession of a medication. A comparable concept, proportion of days covered (PDC), is also found in the literature and is as frequently chosen as the MPR to measure both compliance and persistency (Ho et al., 2009). MED-TOTAL and CMA can also be relegated to this category. The selection of a threshold of .80 to indicate adherence is arbitrary. In the paper written by (Sikka et al., 2005), it was argued that a patient could be considered persistent with an MPR of .80 because it would be reasonable to assume that individuals with this score were continuously refilling medication over a defined time period. (Vink, Klungel, Stolk, & Denig, 2009) conducted a study using automated databases to calculate both MPR and a gap measure of persistence for 3,877 patients. The findings illustrated that both equations yielded similar products.

(Sikka et al., 2005) stressed the importance of using the same measurement endpoints for all subjects to ensure accurate results. Such that, patients with shorter observation periods could generate an MPR that is higher than it actually is when compared to other patients with longer surveillance intervals.

Persistency as a function of medication availability at a fixed point in time

Persistency as a function of medication availability at a fixed point in time measures the availability of medication on hand or the presence of a medication refill on a fixed date after filling the initial prescription. This measure is insensitive as it regards persistent based on one refill and is comparable to MED-INT and CSA where persistent occurs at 2 years if a patient has a single day's supply of medication or a refill available at the end-point of 2 years. This measure is applicable in very short periods of observation since this would improve its accuracy. However, this measure does not reflect changes in refill behavior that occur over multiple refills. The Anniversary Model is another example of a persistence measure calculated based on a fixed point in time (Caetano, Lam, & Morgan, 2006). In the Anniversary Model, a patient is persistent at 1 year if a prescription fill occurs within a specified interval surrounding the anniversary of the first fill (i.e. 30 days). This is a dichotomous measure.

The Minimum-Refills Model is also a measure of persistence based on a fixed point in time, 1 year. Such that, a patient is considered to be persistent at 1 year if a minimum number of refills are dispensed during the year (Caetano et al., 2006). This too is a dichotomous measure.

Persistency as a function of gaps between fills

The most broadly used method for assessing persistency is a tool that examines gaps in treatment. This calculation contains an allowable grace period in which patients can refill medications and is equivalent to MED-OUT and CMG. The Refill-Sequence Model represents another persistency measure that takes into account gaps between refills (Caetano et al., 2006). The Model calculation uses the time between the date of the first fill and the point at which an undesirable gap between refills occurs. Whereby, non-persistence results if the prescription refill

Table 3

Summary of Refill Adherence/Persistency Measures

Definition	Analogous Concepts	Formula Calculations
Single Interval Medication Availability	Medication-Interval MED-INT	(# of pills dispensed) / (Pills dose X doses per day)/Days in refill interval
	Continuous, Single-interval measures of medication Availability CSA	Days' supply obtained per interval / Total days in interval
	Anniversary Model	Dichotomous measure in which a patient is deemed persistent for 1 year if a prescription is filled within a defined anniversary date of the 1st fill (i.e. 30 days)
Medication Possession Over the Entire Surveillance Period	Medication Total MED-TOTAL	Sum of days' supply dispensed / Sum of days in all refills
	Continuous Measure of Medication Acquisition CMA	Cumulative days' supply obtained / Total days from beginning to end of time period
	Medication Possession Ratio MPR	Sum of days' supply / Number of days between first and last fill + Days' supply of last fill
	Medication Possession Ratio Modified MPRm	Total days' supply / Sum of number of days from first fill up to, but not including, the date of last fill + Days' supply obtained at last fill **X** 100
	Medication Refill Adherence MRA	Total days' supply / Number of days of study participation X 100
	Proportion of Days Covered PDC	Number of days patient has medication / Total days in dispensing period
	Compliance Rate CR	Sum of days' supply – Days' supply at last fill / Number of days from first up to, but not including, last fill
	Refill Compliance Rate RCR	Total days' supply X 100 / Number of days from first to last fill
	Minimum-Refills Model	A patient is considered to be persistent at 1 year if a minimum number of refills are dispensed during the year

Table 3 (continued)
Summary of Refill Adherence/Persistency Measures

	Medication-Out MED-OUT	Sum of days without medication/Sum of days in all refills
	Continuous Multiple Interval Measure of Oversupply CMOS	$\dfrac{\text{Total number of days' surplus}}{\text{Days of study participation}}$
Gaps in Treatment	Continuous, Single-Interval Measures of medication Gaps CSG	Days in interval – Days' supply obtained/Total days in interval
	Days Between Fills Adherence Rate DBR	$1 - \dfrac{\text{(Day between fills} - \text{Today days' supply)}}{\text{Number of days between fills}} \times 100$
	Refill-Sequence Model	Is calculated as the interval between the date of the first refill and the point at which an unacceptable gap between refills occurs.
	Continuous Measure of Medication Gaps CMG	Total number of days in treatment gaps/Duration of the observation period

does not occur within a predetermined number of days. This Model generally recognizes switching of medication as an indication of persistence.

The principal challenge encountered when calculating persistency based upon gaps in treatment is to define the permissible gap that specifies length of the grace period between refills. The researcher decides the appropriate length of a grace period by considering a variety of factors that may include the following influences: medication half-life, dosage titration, and number of days in a refill period (i.e. 30, 60, or 90 days). For example, the permissible gap may be one-half the number of days in the previous prescription supply. Such that, a patient who refills a medication for 30 days would be given a 15 day grace period in which to obtain the next fill. Therefore, non-persistence does not occur until day 46.

Innumerable methods for measuring gaps between refills exist in the literature reported dichotomously, persistent versus non-persistent (Vink et al., 2009). The most frequently cited permissible gap in the literature is 30 days. Ultimately, sound clinical validation informs the choice for the permissible gap threshold. However, the rationale for choice of persistency calculation is rarely transparent in published papers. Few studies examine multiple methods of persistency in the same investigation (Vink et al., 2009).

Conversely, a study conducted by (Hudson, Rahme, Richard, & Pilote, 2007) examined refill records of over 20,000 patients who were administered a statin. The authors calculated persistence using three different measures for each patient: (1) MPR, (2) persistency as a function of medication availability based on a fixed point in time, and (3) persistency as a function of gaps between fills. The rates of persistency were variable in the range of 5-94% depending on the calculation used. Kaplan Meier analysis illustrated rates of persistency as a function of a wide variety of gaps between fills, from one to 120 days. As hypothesized, the results demonstrated that longer grace periods increased the level of persistency. Results emphasize the importance of defining a consistent allowable gap for all patients in a study that is scientifically sound. The findings of a study conducted by (Van Wijk, Klungel, Heerdink, & de Boer,) provided further corroboration of the results from the (Hudson et al., 2007) investigation.

Additional Measurement Considerations

About the same time, (Andrade, 2006) also completed a comprehensive review of the literature to examine methods of measuring adherence and persistence using automated databases which included appraisal of 136 articles. The results of this evaluation identified methods previously presented. In addition, this assessment revealed several other considerations when working with pharmacy refill data that includes switching, retentiveness, and turbulence.

Switching

This review included 34 studies that took into consideration a change to a different drug within the same class during the observation period, i.e. switching. The literature contains a myriad of definitions of switching, for example, (Chan, Walker, & Yood, 1993) defined switching as dispensing of a different drug within the same class within 120 days following the initial fill of the drug. Whereas, (Walker, Chan, & Yood, 1992) defined switching as administration of a different drug within the same class within 60 days of the initial fill. The deliberation of switching when examining treatment compliance has been encouraged. However, it should be noted that unless the requisite administrative database utilized for the study makes a specific provision for noting the reason why switching occurred, it would be difficult to discern the reason for a medication switch outside of a reported adverse drug event. Alternatively, a manual chart review may clarify the rationale for the switch. This approach would likely prove too labor intensive in large studies.

Retentiveness

Retentiveness is an additional concept of consideration when switching has indeed occurred. Retentiveness has been defined as "the number of repeat pairs for that drug divided by all the pairs in which the drug was the first one dispensed" (Walker et al., 1992). Retentiveness accounts for the repeat dispensing of the same medication, though not necessarily at the same dose, within the identified timeframe.

Turbulence

Turbulence generates a calculation based on the total number of changes that occur during an observation interval. (Caro, Speckman, Salas, Raggio, & Jackson, 1999) defined turbulence as "the number of changes (i.e. addition of a new drug, dropping of 1 or more drugs,

or a switch to 1 or more other drugs) occurring in 6-month intervals from the time of index prescription" p. 44. Patients noted to have turbulence are less likely to be persistent with prescribed drug regimes. The usefulness of this calculation will depend on the goals of the study.

Standardization of Measurement

A call to action occurred in 2008 for uniformity of medication compliance calculations using administrative data. By this juncture, uncertainty over what constituted compliance versus persistence had emerged from scientific consideration since MPR creates the same discordance as MED-TOTAL and CMA. Whereby Patient A and B can have the same calculated compliance score and yet the rate of continuous refilling (persistence) is not the same for these two patients. Therefore, making it difficult to conclude that Patient A and B are adherent to a drug regime in a similar fashion. Hindrance of scholarship in the field occurred from an inability to compare results across studies.

In an attempt to advance the knowledge of this methodology by generating standardization, the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) published a paper in this regard (Cramer et al., 2008). A discussion of these developments follows.

The work produced by ISPOR was conducted over a three year period and involved a review of the literature that spanned nearly four decades, from 1966-2005. The goal of the workgroup was to provide uniform definition and operationalization of the constructs compliance, adherence, and persistence relating these terms to measurement using administrative databases.

The authors concluded that the terms compliance and adherence can be utilized synonymously and may be defined as follows: "the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regime" (Cramer et al., 2008). A further detailed definition of the concept generated from the ISPOR report will inform the definition of adherence for this study found in Chapter 1.

The ISPOR paper operationalized compliance using the MPR as defined by retrospective assessment of the number of doses dispensed in relation to the dispensing period. Refill of medication equates with compliance. MPR is calculated with the following formula:

$$\frac{\text{Number of days supplied}}{\text{Days of observation}} \times 100$$

The lack of daily dosing detail using this equation is a limitation of this method. Persistence is acknowledged by ISPOR as a construct distinct from compliance that considered the consistency with which a medication is taken during a given surveillance period. In this review, persistence was defined as "the duration of time from initiation to discontinuation of therapy" (Cramer et al., 2008).

Persistence is operationalized by counting the number days of medication availability from initiation of the prescription, or a define point in time during chronic treatment, to the end of the observation period. This calculation must define the permissible gap allowed between refills based on the pharmacodynamics of the medication under consideration (Cramer et al., 2008). Such that, the maximum amount of time a patient could go without taking the medication and not encounter adverse consequences is distinguished. However, currently, no allowable gaps exist for any prescribed medications (Andrade, 2006). The literature contains reports of persistence as both a continuous and a dichotomous variable.

In a separate document, ISPOR presented a systematic approach to study methodology when using pharmacy refill data to assess compliance (Peterson et al., 2007). This paper represents an international consensus on the standardization of study design created to improve the quality of research conducted in the field. The following is a brief overview of these proceedings meant to function as a guideline for research process in this study. The paper should address the suitability of data sources to answer specific research questions as well as the reliability and validity of the source. Procedures for protection of personal health information exist. Conversion of continuous data to categorical data is discouraged and a discussion of the limitations of retrospective data occurs.

There are several inconsistencies in the two papers provided by ISPOR. Both the (Peterson et al., 2007) report as well as the (Cramer et al., 2008) paper advise that a persistence analysis be contained in the methodology as separate from compliance and must include a gap determination. However, there are inconsistencies in the definitions of various adherence constructs found in both works. Therefore, misrepresentation of the terms persistence and compliance continues. Furthermore, the (Peterson et al., 2007) article, also produced by ISPOR, does not specifically endorse the use of a defined allowable gap as a requisite when measuring persistence. Additionally, the authors assert that very few medications have a defined permissible gap in which patients could safely forego taking a prescribed medication and not experience adverse events. Therefore, calculation of tolerable gaps using retrospective pharmacy data remains a challenge. This is the case with all medications prescribed for IBD. For patients with IBD in remission, a scientifically established "drug holiday" that would avoid disease reactivation, has not been ascertained (Regueiro, 2012c). In an effort to achieve remission in IBD patients with active disease, no advisable gap in treatment exists making calculation of

persistence using a permissible gap in this cohort impossible with the state of knowledge that currently exists.

Summary

It is appreciated that medication adherence has a substantial bearing on clinical outcomes and utilization of healthcare resources. As a result, much discourse exists regarding the establishment of the appropriate mechanism for assessing this variable. While many methods for measuring adherence in chronic illness subsist, all have inherent benefits as well as shortcomings. After decades of research, no consensus on how best to measure this construct has been forthcoming. The purpose of the investigation should be the driving force behind the choice of a data collection method in medication adherence research.

Medication Adherence in Patients with IBD

Medication is a key component to controlling disease in IBD. Non-adherence to treatment regimens should be the first issue suspected in patients who are not responding to therapy as poor adherence is the primary reason for suboptimal clinical outcomes (World Health Organization, 2003).

Universally, regardless of disease type or severity, medication adherence is problematic in all situations requiring self-administration of treatment, as is the case in IBD. Despite the availability of effective medication to control the condition, adherence remains a challenge since IBD is an illness at high risk for poor adherence due to onset at a younger age, relapsing and remitting disease course, as well as prescribed difficult to follow therapies (Lopez San Roman, Bermejo, Carrera, Perez-Abad, & Boixeda, 2005a) Rates of non-adherence in IBD mirror those found in other chronic diseases. Adherence to long-term medication treatments in the most common chronic illnesses are in the range of 17% to 80% (Krueger et al., 2005)

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Correspondingly, a recent systematic literature review revealed rates of non-adherence in IBD to be between 7% and 72% (C. A. Jackson et al., 2010).

Earliest published reports to improve adherence in gastrointestinal diseases recognized the complex nature of this construct and encourage healthcare provider assessment of patient participation in treatment (Levy & Feld, 1999). This widely referenced paper, published about the time of CCM promulgation, weighed in well before the majority of adherence research in IBD was completed. Thus, chronic diseases other than IBD provided a benchmark to create discipline recommendations.

Although not explicated stated, (Levy & Feld, 1999) ascribed most of the CCM elements, such as proactive healthcare teams, informed activated patients, self-management support, the health system, and decision support as strategies to expand adherence. Papers of an editorial nature by (Kappleman et al., 2011) and (Shah et al., 2011), provided additional support for examining these CCM components in patients with IBD within the context of the health system and the quality of care delivery in this population.

Therefore, in accordance with the CCM, interpretation of IBD adherence results occurs from the perspective of the health system in which data collection takes place, because at least one-half of all investigations transpire outside the U.S. in countries that have socialized medicine. A study conducted by (Robinson, 2001) demonstrated the potential influences of the health system on adherence in IBD in a study conducted to examine the rates of non-adherence in European countries. Reported rates of non-adherence varied widely between countries: France 13%, Italy 25%, UK 33%, and Germany 46%. Similar variations in adherence rates exist in other countries and disease states (Bovet, Burnier, Madeleine, Baeber, & Paccaud, 2002; Reid, Abramson, Raven, & Walters, 2000). The large disparities in levels of non-adherence in

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countries with government-sponsored healthcare, as noted in above studies, supports the need for further research examining the effects of other government operated healthcare systems, such as the VA, on medication adherence in patients with IBD. Without assessment of systematic influences on adherence and resource utilization, engendered population health outcomes are in danger of failure (World Health Organization, 2003).

Despite this, clinical inertia exists regarding assessment of medication adherence in patients with IBD since research in the discipline did not begin until the early 1980s, while adherence research began decades earlier in many other chronic disease states. Furthermore, authorities in the specialty, generating IBD clinical guidelines, fail to propose formal recommendations to screen for medication adherence, inclusive of comprehensive chronic illness care in this population (Kornbluth & Sachar, 2010).

Yet, a study survey of Gastroenterologists ($n = 395$) in the U.S. who care for patients with IBD demonstrated a large portion of those surveyed (77%) screen for adherence to medication but only 19% used a valid method to do so (Trindade, Ehrlich, Kornbluth, & Ullman, 2011) This may be prejudiced by the fact that only one validated medication adherence survey for use in patients with IBD currently exists, the Morisky Medication Adherence Scale -8 (MMAS-8) (Trindade et al., 2011). Nevertheless, 95% of the physicians in the aforementioned study recognized the importance of determining a patient's level of medication adherence to guide treatment.

Furthermore, the gastroenterology discipline as a whole comprehends the importance of medication adherence in this population as the literature contains five review articles, published in the last five years, regarding rates and factors associated with non-adherence in patients with IBD. Four of the reviews were non-systematic in nature and served to examine the current state

of relevant publications in this regard and to initiate discussion about research methodologies and study findings (Hawthorne, Rubin, & Ghosh, 2008; S. Kane, 2006; Lakatos, 2009; Robinson, 2008) .

One review, the most recent (C. A. Jackson et al., 2010), was the only review that used systematic criteria both in searching for and in evaluating articles, thereby providing a critical assessment of the status of knowledge in this arena. The results of which are addressed below. In all, the paper included 17 studies, 76% of which were cross-sectional, with a total sample of 4,322 subjects over the age of 18, recruited principally from IBD specialty clinics (92%). None of the reviewed studies used a power calculator to estimate sample size and only one study reported procedures for handling missing data. Europe was the country in which 65% of the studies originated with the remaining conducted in North America. Measurement of adherence occurred using an assortment of methods: self-report (interview, questionnaire, VAS, and diaries), serologic and urine samples, as well as administrative pharmacy data and was reported in the range of 7-72%. The highest rates of non-adherence (30-43%) appear with use of self-report tools.

While no variables consistently demonstrated an associated with non-adherence, the following primary factors related to non-adherence were identified: younger age, employment, single status, shorter disease duration, active disease, patients in remission, poly-pharmacy, pill burden, immune modulator medication, lack of confidence in physician, and psychological distress. Intriguingly, non-adherence was not associated with the number of primary care visits, time since last outpatient visit, and time since last colonoscopy.

Further discussion of IBD medication adherence research ensues. The passages that follow provide further detail regarding rates and factors of adherence as well as methods used to measure adherence.

Rates and Predictors of Adherence in IBD

(Linderberg, C. S., Solorzano, R. M., Vilaro, F. M., and Westbrook, L. O., 2001) argued that the initial step in building science is qualitative inquiry. Remarkably, the two qualitative adherence studies conducted in patients with IBD occurred simultaneous to the discipline's quantitative work.

(A. Hall & Porrett, 2006) interviewed six patients from an IBD specialty clinic in the United Kingdom, in a study designed to explore factors affecting medication adherence in patients with IBD. The authors discovered ten categories encapsulating the experiences of patients regarding factors that affected compliance. These included beliefs regarding medication, side effects, length of time and experiences since diagnosis, social support, medication regimen and routine, practicality of the administration of medication, costs of prescription and communication regarding a change in medication, supportive medical staff, access to healthcare services, and information resources. The findings of this study mirror results of quantitative work simultaneously performed by the researchers of the discipline. The authors conceded that factors influencing medication adherence in this cohort are multifactorial, contemporaneous, and fluid.

(Moshkovska, Stone, Baker, & Mayberry, 2008) directed the only other qualitative study to examine medication adherence in IBD. The authors used grounded theory approach to explored patients' experiences and rationale for medication taking behavior in 17 ulcerative colitis patients from specialty clinics in the UK. Analogous with quantitative findings, this study demonstrated the impact of patient information on medication adherence as reflected by two key

determinants: patient beliefs about medication and the quality of the doctor-patient relationship. Lack of perceived benefit and paucity of disease information were barriers to adherence. Factors identified as associated with an increased risk for non-adherence included: complicated dosing regimens, less active disease, younger age, new patient status, forgetfulness, and inadequate information from healthcare providers. All of which have been identified as risk factors for non-adherence by quantitative measure.

Researchers considering findings from quantitative investigations examining IBD medication adherence need to consider the origin of the rates and factors presented, i.e. rates and factors associated with adherence versus non-adherence, as there is no consistency in reporting across studies. Additionally, IBD adherence researchers will report adherence rates as complete or partial, creating further complexity when interpreting results across studies. Because ultimately, accurately identifying barriers to adherence, influences creation of intervention(s) to improve rates targeted to the appropriate audience.

The literature suggests that generation of effective adherence interventions may have a greater impact on the health outcomes of a population than any improvement in medical treatment (Haynes, Ackloo, Sahota, McDonald, & Yao, 2008). Interventions should be tailored to a particular illness as well as healthcare system as no single intervention has proved effective across all patients, conditions, and settings (World Health Organization, 2003). In this case, veterans with IBD receiving care for this disease in the VA healthcare system.

Another consideration of IBD adherence study findings is the fact that very few investigations report use of a power calculation to estimate required sample size. Therefore, there is a risk that some non-significant findings occur due to a lack of power rather than a lack of effect. Generalization of study conclusions due to omission of power analysis occur as well.

Additionally, variables mentioned in the methods segment of publications did not appear in the results section, making it difficult to assess if any significant findings resulted from this data collection.

There were no studies in this review conducted solely to report rates of medication adherence in this population. Intuitively, factors associated with non-adherence provided further insight into the medication taking behavior of this cohort. Reports of adherence rates and factors associated with adherence/non-adherence make up the vast majority of medication adherence investigations in IBD, a summary of which is located in Table 4. As found extensively throughout the literature, organization of adherence factors in IBD for this review is by patient factors, health system factors, and condition factors.

Patient factors

Patient factors regarding adherence include employment status, educational attainment, socio-economic status, treatment cost, race, age, social support, community service utilization, gender, illiteracy, patient beliefs and perceptions, knowledge of condition, marital status, confidence in treatment, patient/provider relationship, disease stigma, comorbidities, and attendance at follow up appointments (S. V. Kane, 2008).

Race

A decade ago, world experts in chronic disease adherence recognized race as an independent predictor of adherence (World Health Organization, 2003) . Conversely, a meta-analysis of the last 50 years of adherence research performed about that same time (DiMatteo, 2004) reported age, gender, level of education, and socioeconomic status as having a significant impact on medication adherence. However, race was not acknowledged in the analysis as a

Table 4

Summary of Non-Adherence Rates and Factors Associated with Adherence and Non-adherence in IBD

Author	Year	Country	Sample Size	Non-Adherence Rate	Factors Associated with Adherence (A) & Non-Adherence (NA)
Baars	2009	Netherlands	1,067	13%	A: shorter disease duration(< 8 years), older age, CD diagnosis
Bermejo	2010	Spain	107	69%	NA: lack of information about disease, > 3x daily dosing
Bernal	2006	Spain	214	43%	A: complicated disease course
Bhatt	2009	India	127	81%	NA: taking >4 meds daily
Bokemeyer	2007	Germany	65	9%	NA: fear of adverse drug reaction, employment
Cerveny(a)	2007	Prague	396	32%	NA: > disease activity
Cerveny	2007	Prague	177	39%	NA: higher levels of education, disease > 10 years, younger age, lack of confidence in treatment
D'Inca	2008	Italy	485	39%	NA: younger age, employment
Ediger	2007	Canada	326	25%M 37%F	NA Men: diagnosis of UC, full time employment; NA Female: younger age
Horne	2009	UK	1,871	29%	NA: doubts about need for medication, younger age, shorter disease duration (<5 years), fewer outpatient visits (<3 a year)
Kane(a)	2000	U.S.	98	<25%	NA: male gender, shorter length of remission
Kane(b)	2001	U.S.	94	60%	NA: less extensive disease, male, single, left sided disease, taking > 4 medications daily

Table 4 (continued)

Summary of Non-Adherence Rates and Factors Associated with Adherence and Non-adherence in IBD

Author	Year	Country	Sample Size	Non-Adherence Rate	Factors Associated with Adherence (A) & Non-adherence (NA) in IBD
Kane(c)	2003	U.S.	99	12%	NA with meds increases disease recurrence
Khan	2013	U.S.	13,062	43%	NA: increased risk of disease flare
Lachaine	2013	Canada	1,681	72%	A: male, older age (>60yo), current use of steroid.
Lopez san Roman	2005	Spain	40	72%	NA: lower quality of life scores, less active disease, high depression scores, high patient MD discordance, longer duration of disease, lack of treatment info, lack of trust in MD
Mantzaris	2006	Greece	28	64%	NA: male gender, single status, taking > 5 meds daily
Mitra	2012	U.S.	1,693	72%	NA: increased healthcare costs
Moshkovska	2009	U.K.	169	32%	NA: younger age, doubts about need for medication, South Asian ethnicity
Nahon	2011	France	1,069	10%	A: older age, treatment with TNF, membership in support group NA: constraints r/t treatment, anxiety, smoking, and moodiness
Nguyen	2009	U.S.	235	35%	A: trust in MD, increasing age, lower QOL, white race
Nigro	2001	Italy	85	18%	A: shorter disease duration, NA: disease severity and psychiatric diagnosis
Robinson	2013	UK.	1,200	39%	NA: greater risk of relapse, switching > risk of relapse
Selinger	2013	UK	356	28.7%	NA: doubts about need for medication
Sewitch	2003	Canada	153	41%	NA: less active disease, shorter disease duration, no scheduling f/u, with MD < 1 year
Shale	2003	U.K.	98	43%	NA: 3x daily dosing, full time employment, depression

variable having considerable influence on this construct. Similar opinion purveys the vast editorial work published on IBD adherence in the last five years and race was not purported to be a mediator of consequence in any of these papers (Bernick & Kane, 2010; S. V. Kane, 2008; Lakatos, 2009; Lichtenstein, 2008; Selinger, Robinson, & Leong, 2011).

Meanwhile, a systematic review was done to examine racial and ethnic disparities in patients who utilize VA health services. (Saha et al., 2008), found inequalities in VA across many clinical areas and service types. Discrepancies were most prevalent for medication adherence, patient-provider communication, and shared decision-making suggesting that intervening may improve outcomes in these subjects. Results of the Saha study provided additional support for further study into the impact of race on non-adherence in veterans with IBD who use the VA to access healthcare.

Literature promulgated by IBD experts suggested focusing efforts on modifiable components of adherence, such as patient/provider relationships, versus emphasizing the impact of a non-modifiable risk factor such as race. Consequently, there was only one study in this review conducted specifically to examine the effect of race on adherence in this cohort. IBD subjects from a specialty clinic (n = 120 Black and 115 White) were included in a cross-sectional, prospective cohort to determine whether medication adherence differed among Black and White IBD patients (Nguyen, Munsell, & Harris, 2009). Overall rate of adherence in this study was 65%. Blacks had significantly higher rates of non-adherence than White counter-parts (50% versus 80%, OR 0.25, 95% CI 0.14-0.48) which persisted after adjustments for confounders had been made (OR 0.29, 95% CI 0.13-0.64).

The only other study in this review that discussed race was conducted by (Moshkovska et al., 2009) in a sample of patients (n = 151) with ulcerative colitis from the UK. The only

demographic variable independently associated with non-adherence was South Asian ethnicity (OR 2.940, 95% CI 1.303-6.638) which made up only 19% of this sample.

Interestingly, an additional goal of the Moshkovska study included assessment of the correlation between adherence and the patient/provider relationship, which was the risk factor concentrated on in the aforementioned editorials as having the utmost impact on improvement of medication taking behavior in this population. Patient trust in the physician displayed the strongest correlation independently associated with adherence ($R = -0.30$) with no observed differences between Blacks and Whites noted ($R = -0.25$ versus -0.30, $p = 0.8$).

Lack of data concerning the influence of race on medication adherence in patients with IBD represents a gap in the literature. The literature suggests that treatment disparities based on race, found in other chronic disease states, may also exist in IBD but this relationship is not readily understood (J. F. Jackson & Kornbluth, 2007). Furthermore, research suggests that racial disparities exist in the VA system (Saha et al., 2008) However, little is known of how race influences chronic illness care in veterans with IBD.

(Sewell, Yee, & Inadomi, 2009) provided support for further investigation of the influences of race on adherence in a study done to assess the trends of hospitalization among minority patients with IBD, which showed statistically significant increases in admissions among all race groups, particularly Asians, as non-adherence has been implicated in increased healthcare utilization. Additionally, a systematic review demonstrated a rise in the incidence rate of IBD among Hispanics (from 2.6 to 7.5 per 100,000 and Asians (from 0.22 to 3.62 per 100,000). This study also showed that minorities have a more complicated disease course. Both of these issues provided support for further inquiry regarding the effects of race on medication adherence, in this growing patient population, for which little is known (Ho et al., 2009).

Age

In other chronic disease states, younger age is widely accepted as a risk factor for non-adherence (DiMatteo, 2004). This too appears to be the case in IBD as demonstrated by many studies in this review (Cerveny et al., 2007; D'Inca, Bertomoro, Mazzocco, Vettorato, & Rumiati, 2009; Ediger et al., 2007; Horne, Parham, & Robinson, 2009; Moshkovska et al., 2009; Sewitch et al., 2003; Shale & Riley, 2003) . Higher rates of non-adherence among younger individuals may be exceptionally problematic in IBD because the onset of disease most often occurs in the late teens and early 20s.

Remarkably, four studies revealed older age as a significant independent predictor of adherence ((Lachaine et al., 2013)) (OR=1.6, CI 1.3-2.0), (Nahon et al., 2011) (p < 0.01), (Nguyen, Tuskey, Dassopoulos, Harris, & Brandt, 2007) (p = 0.01, R = -0.19), and (Baars et al., 2009) (p = 0.01, OR 1.57, 95% CI 1.2-2.02). However, these results are not surprising given that as age increases, so does adherence until the seventh decade when treatment adherence levels off or begins to decrease (Mehta, Moore, & Graham, 1997). This study helped fill a gap in the literature regarding the impact of age on medication adherence in veterans with IBD for which little data exists.

Gender

A meta-analysis conducted to analyze rates and predictors of adherence across disease states in the last 50 years showed a lack of correlation between gender and adherence (DiMatteo, 2004). Additionally, international recommendations to improve adherence to long-term therapies (World Health Organization, 2003), a widely referenced medication adherence paper (Osterberg & Blaschke, 2005), as well as two recent systematic reviews (Gellad, Grenard, & Marcum, 2011) and (Ingersoll & Cohen, 2008) all fail to recognize gender as having significant impact on

medication adherence. However, a comprehensive review done to catalog barriers to medication adherence, demonstrated conflicting results regarding the influences of gender on adherence in a variety of conditions (Krueger et al., 2005).

Similarly, the consequences of gender on adherence in IBD are mixed. Several studies showed no impact of any demographic variable inclusive of gender (Cerveny et al., 2007; Lopez San Roman, Bermejo, Carrera, Perez-Abad, & Boixeda, 2005b) . Men were more likely to be non-adherent in four studies ((D'Inca et al., 2009; S. Kane, Cohen, Aikens, & Hanauer, 2001; Lachaine et al., 2013; Mantzaris et al., 2007)). Whereas, (Waters, Jensen, & Fedorak, 2005) demonstrated women were more likely to be non-adherent in an interventional study.

Noteworthy results were produced by (Ediger et al., 2007) who reported different predictors of low adherence for men and women. For men, predictors of low adherence included a diagnosis of UC (OR 4.42, 95% CI 1.66-11.75), being employed full-time (OR 11.27, 95% CI 2.05-62.08) having high scores on obstacles to medication assessment, and having a low level of personality agreeableness. For women, predictors of low adherence include younger than 30 years of age (OR 3.64, 95% CI 1.41–9.43), high scores on obstacles to medication assessment (OR 3.89, 95% CI 1.90–7.99) , and low level of agreeableness (OR 2.03, 95% CI 1.12–3.66). Research suggests that addressing the impression of non-modifiable demographic variables such as gender, on adherence, are not as important as concentrating on modifiable elements (Albaz, 1997). However, a lack of clear understanding about the impact of gender on medication adherence in patients with IBD warrants further investigation, particularly due to the potential deleterious effects of non-adherence with medical therapy during pregnancy (Katz & Pore, 2001).

Employment, marital status, and education

IBD tends to onset at a younger age when decision regarding employment and education are considered. IBD can have a labile course interfering with fulfillment of pursuits, a course exacerbated by non-adherence to treatment. A review demonstrated that patients with IBD have a higher rate of nonparticipation in the labor force (Marfi & Buchman, 2005). This same review found similar levels of educational attainment among those with IBD when compared to the general population.

Studies conducted by (Ediger et al., 2007) (OR 11.27, 95% CI 2.05-62.08) and (Shale & Riley, 2003) (OR 2.7, 95% CI 1.1-6.9) revealed full-time employment as a risk factor for non-adherence. Whereas, (Bernal et al., 2006) demonstrated that unemployment was a risk factor for non-adherence but was noted to not have reached statistical significance. A weakness of the Bernal study was a lack of reporting of the set level of significance for the analysis.

Only one study in the review found any correlation between non-adherence and level of education. Higher levels of education were associated with increased levels of non-adherence (p = 0.046) in a Czech Republic sample (Cerveny, Bortlik, Vlcek, Kubena, & Lukas, 2007).

Likewise, only one study found any correlation between marital status and non-adherence. Single status was a predictor of non-adherence in the 2006 Mantzaris study. Intriguingly, being married was supportive of adherence (OR, 95% CI 0.39-0.57) (S. Kane et al., 2001) .

These contradictory findings across a variety of demographic factors, speaks to the complex nature of medication adherence in this cohort. In addition, the lack of knowledge related to demographic factors and medication adherence represents a gap in the literature and need for further study.

Health System Factors

Patient/provider relationship, medication access, patient education, patient follow up, interventions to improve adherence, organization and coordination of healthcare services, utilization of healthcare resources, and healthcare costs are all examples of variables categorized as health systems factors in regard to medication adherence (World Health Organization, 2003). Each of these are discussed below.

Patient/provider Relationship

Two studies explored the influence of patient/provider relationships on medication adherence in IBD. Instinctively, lower rates of adherence occur when patient/provider interactions are less than ideal.

Ten gastroenterologists and 153 of their adult IBD patients were the subjects in a prospective, Canadian study performed to identify determinants of non-adherence in IBD and assess the impact of patient-physician discordance on adherence (Sewitch et al., 2003) . Discordance describes physician and patient perceptions of the patient's health status and of the clinic visit, as measured by a survey completed independently immediately after the office encounter. The outcome variable was medication adherence as measured by the validated MAS-4. Results showed total non-adherence to be 41% or 63 of the patients. Patient-physician discordance (OR = 1.59, p = 0.0120), consulting a health professional and new patient status (OR 2.80, p = 0.0239) were predictors of non-adherence. Interestingly, patients treated by the physician for < 1 year had an 84% higher risk of non-adherence than those treated by the same physician > 1 year.

An IBD specialty clinic in Spain was the setting for a 2005 study conducted by (Lopez San Roman, Bermejo, Carrera, Perez-Abad, & Boixeda, 2005a) designed to investigate the

degree of adherence to therapy and to identify factors affecting medication adherence in this cohort (*n = 40)*. The authors also collected data on depression, patient-physician discordance, QOL, and disease activity. Medication adherence measurement took place using the MAS-4.Total non-adherence was 72%. However, to keep this high rate of non-adherence in context, the MAS-4 does not quantify the amount of medication omitted. It merely denotes if the patient had ever missed a dose of medication. The results showed a higher degree of non-adherence was associated with patient-physician discordance scores (p = 0.01) and those who trusted their physicians less (p = 0.03).

Coordination of Care

The literature suggests that organizational variables, such as number of provider visits, both to primary and specialty care, as well as continuity of care, may have a far greater impact on medication adherence than demographic variables (Albaz, 1997). Furthermore, coordination of care between primary and specialty care is requisite to improve adherence (MacColl Institute for Healthcare Innovation, 2010). However, the results from a Cochrane review (S. M. Smith et al., 2009) conducted to assess the effectiveness of care coordination between primary and specialty care, in chronic disease management, were conflicting. Overall, no consistent improvement in outcomes across disease states materialized with the exception of medication adherence that indicated significant benefit with coordination of care in this realm.

(Herrinton et al., 2007) conducted a study to explore the variations in IBD practice patterns and outcomes over a decade (1998-2005) across medical centers in an integrated healthcare plan in the U.S. in 2,892 adults with CD and 5,895 with UC. Health plan administrative data provided information for this study. The healthcare system under investigation had many similar features of the VA such as a closed pharmacy system housed

within multiple medical centers campuses that include inpatient care, outpatient clinics, laboratory, and x-ray services. Most medical centers had GI services but no specialty IBD clinics. No endorsement of IBD practice guidelines existed. Primary care providers had privileges to write for all drugs to treat IBD, save anti-TNF medications. The results showed a striking shift of IBD care from specialty care to primary care with GI consultation provided as deemed necessary.

The notion of coordination of care is widely endorsed by the VA healthcare system (Asch et al., 2004; McQueen, Mittman, & Demakis, 2004). Yet, coordination of care in the VA has not been systematically assessed (Neugaard et al., 2011). The primary care service line in VA acts as a gatekeeper for access to specialty care thereby, coordinating care, such that veterans cannot obtain specialty care without submission of a specialty consult by the primary care provider.

Although a multidisciplinary approach to chronic illness care in IBD is suggested (Hernandez-Sampelayo et al., 2010), IBD management by primary and specialty care has not been critically evaluated (Herrinton et al., 2007) as there were no studies in this review that examined this conception. This may be due in part to the fact that while the discussion of IBD care organization adopts the input of many disciplines, the focus remains on the contributions made from other specialties such as surgery, radiology, pathology, dermatology, rheumatology, and ophthalmology and not primary care (Mikocka-Walus et al., 2012; Ricci, Lanzarotto, & Lanzini, 2008). The dearth of information regarding coordination of care between primary and specialty care in the management of IBD in the VA system supported the need for further inquiry in this realm.

Healthcare Utilization

Direct healthcare costs estimates are $3.1 billion for CD and $2.1 billion for UC. (Kappleman et al., 2008). A disease flare, perhaps compelled by non-adherence to therapy, could influence the need for health services.

World adherence experts (World Health Organization, 2003) provide support for examination of the variables associated with healthcare utilization concurrently with medication adherence rates as this data works synergistically to accurately inform health outcomes and future interventions. Furthermore, the authors encourage exploring these constructs using a systems model such as the CCM as a guide. Therefore, this study began to explore the relationship between medication adherence and healthcare utilization in veterans with IBD who use the VA healthcare system. Healthcare utilization in this study included outpatient visits to primary and Gastroenterology (GI) specialty care, ER usage and inpatient admissions for IBD related illness.

(Kappleman et al., 2011) conducted a study aimed to describe the healthcare utilization associated with IBD in an insured U.S. population 2003-2004 using the administrative databases of 87 health plans in 33 states to identify those with IBD using ICD-9 code 555.x for CD and 556.x UC. The mean number of office visits per 100 patients with CD was 167 primary care and 179 GI-specialty, and for UC, 151 primary care and 128 GI-specialty. Overall, the results demonstrated that healthcare utilization was higher in the IBD population when compared to non-IBD controls. This is consistent with a paper by (Shi & Singh, 2012) which also reported healthcare utilization rates to be much higher in IBD than for other Americans who on average who make three visits a year to see a provider. A lack of healthcare utilization data in veterans with IBD supported analyzing this topic.

Similarly, (Ananthakrishnan, McGinley, Saeian, & Binion, 2010) conducted a study exploring the trends in outpatient and ER visits for IBD in the U.S. 1994-2005. While cohort generation for this study was the same as the (Kappleman et al., 2011) study, other differences in study design make comparison of investigational results difficult. The (Ananthakrishnan et al., 2010) study data source originates from surveys within the National Health Care Survey that is used to inform the conceptual definitions for this study. The results demonstrated a 55% increase (95% CI, 1.4-2.2) in outpatient visits as well as a 165% increase (95% CI, 42,498-112,257) in ER visits in this population during the observation period. The authors advised further investigation into the influences on increased healthcare utilization in patients with IBD. This study began to close this information gap by initiating exploration of the relationship between medication adherence and healthcare utilization in the VA population.

A U.S. based study conducted by ((Mitra, Hodgkins, Yen, Davis, & Cohen, 2012)) examined the association between medication adherence and healthcare utilization in 1,693 subjects using administrative data. Adherent subjects had 31% fewer hospitalizations (p = 0.0025) as well as 34% fewer ER visits (p = 00016) when compared to non-adherent counterparts.

Most recently, researchers in Australia (Sack et al., 2012) conducted a study using the CCM as a template for implementing a formal IBD Service in 100-200 patients with IBD to examine the effects of the Service on healthcare utilization. This is the first study in patients with IBD to use the CCM. While the authors did not declare the specific Model elements tested, application of the Model for this study is counterintuitive as the Model has origins in primary care, not specialty care as the authors present. Use of the Model in this manner is also asynchronous to knowledge building, as the descriptive work in this field is not accomplished.

However, the authors did note that 30% of subjects received IBD care from non-gastroenterologists again, exploration of this relationship did not occur, a critical missing piece to the use of the Model. The intervention consisted of a team approach led by a gastroenterologist, an IBD nurse, surgical team, and radiology. Formal protocols tracked chronic illness care in this cohort. The results demonstrated a lower number of inpatient admissions in the treatment group (1.53) compared to controls (2.54, $p < 0.0001$). The costs of the admission were also lower in the treatment group ($12,857) versus controls ($30, 467, $p = 0.005$). The researchers concluded the intervention a success.

Four studies in this review reported on healthcare utilization variables in relationship to medication adherence. None of the reviewed studies declared healthcare utilization as the primary outcome variable.

The first study, conducted by (Horne et al., 2009) reported on the effects of outpatient IBD visits on medication adherence in 1,871 (63% female, 45% CD, 49% UC, mean age 50) members of the UK National Association for Colitis and Crohn's Disease (NACC) who were randomly chosen from the organization's database. This is the only IBD adherence study to catalog data on the annual number of IBD related visits to the patient's PCP, as well as the number of outpatient and inpatient IBD related visit in the previous year. Roughly, 33% of subjects had three or more IBD related PCP visits in the last year, and an equal percentage of subjects, had no PCP visits in the last year for IBD related illness. While another third, claimed three or more annual IBD specialty visits. Interestingly, the vast majority of subjects (80%) did not have any hospitalizations in the year for IBD related illness. This data is suggestive of quiescent disease in this cohort. Logistic regression showed that younger age, disease duration > 5 years (OR 1.96, 95% CI 1.43-2.69, $p = 0.000$) and fewer outpatient visits were significantly

associated with rates of low adherence. The findings of this study support the need for forthcoming research to examine more fully the effects of healthcare follow-up on mediation adherence in this population.

The second study in this review reporting an association between non-adherence and increased healthcare utilization was done by (Waters et al., 2005) who randomized 69 IBD patients to a nurse-lead education interventions and standard of care. Over the four- week observation period, the subjects had 44 outpatient visits, 16 for symptom control and 33 for follow-up. Patient diaries provided medication adherence information. Subjects also had four ER visits and five inpatient admissions. Although not statistically significant ($t = 1.06$, $p = 0.294$), the educational group had lower rates of healthcare use ($M = 0.63$) than the control group ($M = 0.95$). Those who reported missing medication in their diaries had significantly higher rates of outpatient visits ($p = 0.01$).

(Sewitch et al., 2003) conducted the third study in this review to identify determinants of non-adherence in IBD. The outcome variable was medication adherence as measured by the validated MAS-4 showed total non-adherence to be ($n = 63$) 41%. Scheduling a follow-up appointment ($OR = 0.30$, $p = 0.0059$) and new patient status (OR 2.80, $p = 0.0239$) were significant predictors ($p < 0.05$) of non-adherence. Interestingly, patients treated by the physician for < 1 year had an 84% higher risk of non-adherence than those treated by the same physician > 1 year.

Data for the final study in this review to examine healthcare utilization and medication adherence originated from a community health insurance program database. This sample represents the largest retrospective cohort of patients with IBD year to date ($n = 4,313$) which assessed medication adherence using the MPR to determine the association between adherence

and healthcare costs from the payer's perspective (S. V. Kane, 2008). Overall, just over half (57.2%) of the subjects were adherent to treatment (i.e. MPR > 80%). Adherence was associated significantly ($p < 0.05$) with 62% lower costs for hospital admissions ($p < 0.001$), 13% fewer outpatient visits ($p < 0.05$), 45% fewer ER visits ($p < 0.001$), and 49.8% lower total healthcare costs ($p < 0.001$). The authors also controlled for comorbidity during multivariate analysis. A CCI was generated with ICD-9 codes from administrative data as posited by the (Deyo et al., 1992) algorithm. Study results demonstrated that higher levels of comorbidity were associated with increased healthcare costs ($p < 0.0001$).

Results of these studies demonstrate the impact of non-adherence on healthcare utilization in patients with IBD. However, a lack of information in this regard in VA represents a gap in the literature and endorsed auxiliary exploration into the effects of adherence on healthcare utilization in this cohort.

Interventions to improve adherence in IBD

Ultimately, the results of this study would support future generation of interventions to improve medication adherence in patients with IBD. Therefore, although this is a descriptive study, it was important to establish the state of interventional knowledge promulgated in the field to address adherence issues in this population as this data will apprise the generation of future endeavors.

There was only one interventional study, conducted specifically to examine the effects of an intervention to improve medication adherence in patients with IBD. Stable patients ($n = 81$) from a specialty IBD clinics were randomized to either a 23 week independent ,community, nurse-delivered patient support program ($n = 21$) or standard of care ($n = 60$).

Patients with an MPR > 80% were deemed adherent to treatment as measured at 3 months and 6 months in the Moss study. At three months, the rate of adherence was 39% for the control group and 44% for the experimental group. At six months, rates of adherence increased to 50% in the control group and 67% for those in the patient support group. However, the differences in adherence for the two groups was not statistically significant (p = 0.3). Furthermore, there was no association between the community educated group and adherence at 3 (OR 1.2, 95% CI 0.4-3.8) or 6 months (OR 2, 95% CI 0.6-7). The authors concluded that a nurse-delivered patient-support program did not significantly improve adherence when compared to standard of care.

Condition Factors Affecting Adherence in IBD

Several condition factors were identified as affecting adherence in IBD. Condition related factors were disease recurrence, severity of disease, illness duration, disability, availability of effective treatment, pill burden, duration of treatment, and side effects are condition factors under consideration discussed as follows.

Pill burden

Pill burden refers to the total number of pills an individual takes in a day. Pill burden may also refer to the number of pills and doses required daily for each specific medication regime. Universally, higher pill burden is associated with decreased medication adherence. A systematic review done to examine the impact of regime factors on medication adherence in a variety of chronic illnesses confirmed this notion (Ingersoll & Cohen, 2008).

Pill burden is of particular consequence in IBD as some of the medications used to treat the illness require two or more tablets to be taken up to four times daily with the worst case scenario of a total of 12 tablets to be taken daily for one medication to treat IBD. The impact of a

complex medication regime on adherence, not only because of the number of tablets taken per day, but also dosing frequency, is obvious. This study will provide insight into the impact of pill burden on veterans with IBD by using refill data to measure medication adherence, not only to collate the types of medications taken for this condition, but also to explore the number of tablets and dosing patterns prescribed and the effects of such on adherence.

The literature produced mixed results regarding pill burden. Two studies did not include any information about the influence of pill burden on medication adherence in the results section of the papers (Bokemeyer et al., 2007; Lopez San Roman, Bermejo, Carrera, Perez-Abad, & Boixeda, 2005b). Three studies found no relationship between the type of drug, number of drugs, and the number of pills administered and medication adherence (D'Inca et al., 2009; Ediger et al., 2007; S. Kane, Huo, Aikens, & Hanauer, 2003) .

Two studies showed a relationship between pill burden and medication adherence. (Shale & Riley, 2003) examined adherence in 98 patients from a specialty practice in the UK and found that three-times-daily dosing was the only significant independent predictor of partial non-adherence ($p = < 0.01$, OR 3.7, 95% CI 1.8-8.9). Similarly, (S. Kane, Huo, Aikens et al., 2003) conducted a study to determine adherence rates and predictors of non-adherence in 94 patients from a specialty IBD clinic. The overall rate of adherence was 40%. The results demonstrated that a history of taking more than four concomitant medications was associated with a two and a half times increased chance of non-adherence (OR 2.5, 95% CI 1.4-5.7).

Disease Recurrence

Disease recurrence in patients with IBD, as impacted by medication non-adherence, was the primary variable of interest in several studies published in the last decade   (S. V. Kane & Hanauer, 2000; S. Kane, Huo, Aikens et al., 2003; Khan, Abbas, Bazzano, Koleve, & Krousel-

Wood, 2012; Robinson, Hankins, Wiseman, & Jones, 2013). All investigations measured medication adherence using pharmacy refill data. The largest cohort was found in the (Khan et al., 2012) study that had 13,062 subjects, followed over a 10 year period and demonstrated a 1.17 times increased risk of disease flares in non-adherent subjects.

(S. V. Kane & Hanauer, 2000) documented adherence rates and disease recurrence at 6 and 12 months. At 6 months, 12 patients (12%) had clinical recurrence all of which had medication compliance <75%. The median amount of medication consumed was statistically significant, 26% versus 83% for those still in remission (p = 0.001). At 12 months, an additional 19 patients had recurrence, 68% ($n = 15$) of which were non-adherent. The median amount of medication taken was 80% for those in remission and 45%% with recurrence (p = 0.02).

As well, in the (S. Kane, Huo, Aikens et al., 2003) study, at 6 months, 12 patients had recurrence of disease, all of which were non-compliance with medication. The median percentage of mesalamine refilled was 51% for those who were non-compliant compared to 77% for those still in remission. By 12 months, 19 additional patients had disease recurrence, 68% of which were non-compliant. Patients who were non-adherent had more than a fivefold greater risk of recurrence than patients who adhered (hazard ratio= 5.5, 95% CD 2.3-13, p = <0.001).

Robinson used pharmacy data from the UK to examine the relationship between non-adherence, medication switches, and disease recurrence in 1,2000 subjects. The results of logistic regression revealed that patients who switched mesalamine maintenance preparations had a 3.5 fold greater risk of relapse than those who did not switch (95% CI = 1.16-10.62, p = 0.008). Although not the primary outcome variable, patients with non-adherence were three times more likely to develop disease recurrence (OR 3.389, 95% CI 1.29-8.88, p = 0.012) in a study conducted with 127 patients with IBD (Bhatt et al., 2009).

Methods Used to Measure Adherence in IBD

All of the studies in this review examining medication adherence in IBD occurred in the last decade. Table 5 contains a summary of tools used to measure medication adherence in this population. The majority of investigations (9) used non-validated, study specific instruments to collect adherence data. The method utilized to measure adherence was not transparent in three additional studies. Several studies contained less commonly used adherence measures such as drug serology (1), visual analog scale (VAS) (2), urine drug level (2), and patient diary (1). Five studies contained variations of the same self-report measure, the Medication Adherence Report Scale (MARS): MARS-4 (2) and the MARS-5 (1). The MARS eventually became the Morisky Medication Adherence Scale (MMAS-8). Five studies, all conducted by the same author (Kane) used pharmacy refill data to gather adherence information. Retrospective data analysis was the method of choice in three studies. Further discussion of adherence measurement in IBD will focus on the MMAS-8 as this is only validated self-report tool in IBD and assessment of adherence using pharmacy data as this is the method utilized for this study.

MMAS-8

(Trindale, Ehrlich, Kornbluth, & Ullman, 2011) conducted the first study to validate the MMAS-8 in IBD using gastroenterologists (*n* = 13) and 110 inpatient subjects on a specialized IBD service. The study aim was to determine the level of agreement for adherence between the MMAS-8 and perceptions of the treating physician as well as agreement between the MMAS-8 and pharmacy refill data. Although the cohort consisted of inpatients, the resulting assessment was of outpatient medication adherence.

Table 5

Summary of Tools Used to Measure Medication Adherence in IBD

Author	Year	Measurement Tool
Baars	2009	Unclear, used cut off of > 80% = adherent
Bermejo	2010	Medication Adherence Report Scale (MARS-4)
Bernal	2006	Non-validated study specific self-report survey
Bhatt	2009	Non-validated study specific self-report survey
Bokemeyer	2007	Drug serology/Visual Analog Scale (VAS)
Cerveny[a]	2007	Non-validated modified MARS-4
Cerveny	2007	Non-validated modified MARS-4
Ediger	2007	MARS-5
Horne	2009	MARS-4
Kane	2000	Pharmacy Refill Data
Kane	2001	Pharmacy Refill Data: MED TOTAL
Kane	2003	Pharmacy Refill Data: MED TOTAL
Kane	2012	Morisky Medication Adherence Scale (MMAS-8)/MPR
Khan	2012	Refill data: MPR, CSA, CMG
Lachaine	2013	Prescription and medical claims: MPR
Lopez San-Roman	2005	Non-validated study specific self-report survey
Mantzaris	2006	Unclear, used cut off of > 80% = adherent
Mitra	2012	Insurance Claims
Moshkovska	2009	Non-validated study specific self-report survey/Urine drug level
Nahon	2011	Unclear, used cut off of > 80% = adherent, VAS, patient diary
Ngugen	2009	Modified Hill-Bone Compliance Scale (HBCS)
Nigro	2001	Non-validated study specific self-report survey
Robinson	2001	Non-validated study specific self-report survey
Robinson	2013	Refill data: MPR
Trindade	2011	MMAS-8/pharmacy refill data: CSA/MPR
Shale	2003	One non-validated self-report question/Urine drug level

The foundation for the MMAS-8 stems from the MARS that views non-adherence in the context of forgetting, avoiding, stopping medication, or altering drug dosages. The MARS-4 expanded into the MMAS-8 that includes dichotomous scoring of the following domains: forgetfulness, missing doses, decreasing medication without physician input, forgetting to take medications while traveling, decreasing medication when well, and the inconvenience of taking medications. One Likert scale question regarding remembering to take medications rounds out the questionnaire. A score of 8 on the Scale indicated perfect adherence; scores of 6-7 indicate medium adherence; and scores < 6 indicate low adherence. The results of the MMAS-8 and calculated adherence using the CSA and MPR from refill data were compared. Non-adherence was denoted for subjects with CSA or MPR <0.8.

Results identified 54 patients as low adherers and 56 as either medium or high adherers. Correlation between pharmacy refill data and scores on the MMAS-8 were found as 85% of low adherers had CSA and MPR scores <0.8. Meanwhile, only 11% of medium and high adherers had pharmacy refills scores suggestive of non-adherence. Furthermore, physician perception of adherence correlated with the MMAS-8 for medium and high adherers (95%) but was only 33% for low adherers. Physician overestimation of adherence was statistically significant (p = 0.0001).

(S. Kane et al., 2012) sought to build on Trindade's work by conducting a study aimed at determining if a correlation existed between a self-report measure, the MMAS-8, and pharmacy refill records in 150 (59% female) IBD patients from the Mayo Clinic. Unlike most of the adherence studies in IBD, this investigation used a power estimate to calculate sample size. Refill data collected retrospectively, 3 months before the study began as well as prospectively, 3 months and 6 months after the study started, furnished information on medication adherence

using the MPR, recognized by the authors as the gold standard for measuring adherence in this population. Patients were given an allowable grace period between 80-120% of the expected time for a refill. For example, if a refilled date was 30 days, the grace period was between 24-36 days. Procedures for handling patients falling outside the allowable grace period are unclear. Calculation of MPR occurred separately for each drug the patient took, up to three drugs per patient. Patients with MPR > 80% were considered adherent. A 5-ASA product was taken by 47% of subjects, 54% on a thiopurine, 15% on Infliximab along with oral therapy, 8% on an injectable biologic, and 6% on budesonide. This was the first adherence study in IBD to provide adherence data on most of the agents used to treat the disease.

Median MPR scores were as follows: 5-ASA 50%, thiopurines 60%, Infliximab 75%, injectable biologic 0, budesonide 33%. Scores of < 6 on the MMAS-8 indicated non-adherence, while scores > 6 indicated adherence. The median score on the MMAS-8 was 7 indicating roughly two-thirds of the population fit the definition of adherence. The tool identified a third of patients classified as non-adherent by MPR. However, using a repeated-measures linear regression analysis, the authors demonstrated only one drug class, thiopurines, had an MMAS-8 score significantly associated with refill data (p = 0.02, correlation 0.26). While the correlation between refill data and the MMAS-8 was not noteworthy, use of such a self-report tool in the outpatient gastrointestinal setting, may help clinicians identify those at greatest risk for non-adherence so that generation of individualized patient education and counseling in this regard occurs.

Pharmacy Refill Data

Kane produced three U. S. based articles in the last decade using pharmacy refill information to measure medication adherence in patients with IBD. The first (S. V. Kane &

Hanauer, 2000) examined the effect of non-adherence on disease recurrence in patients with quiescent ulcerative colitis who take mesalamine. A "valid calculation" provided information for medication adherence using pharmacy refill records. Adherence was defined as consumption of <75% of prescribed medication. Patients ($n = 98$) were interviewed at 6 and 12 months. At 6 months, 12 patients (12%) had clinical recurrence all of which had medication compliance <75%. The median amount of medication consumed was significant, 26% versus 83% for those still in remission ($p = 0.001$). At 12 months, an additional 19 patients had recurrence, 68% ($n = 15$) of which were non-adherent. The median amount of medication taken was 80% for those in remission and 45% with recurrence which was statistically significant ($p = 0.02$).

The second study provided information regarding prevalence of medication adherence as well as risk factors for non-adherence in 94 IBD patients with inactive ulcerative colitis (S. Kane et al., 2001). Pharmacy refill data provided adherence information to calculate the MED TOTAL. Consumption of 80% of prescribed medication equated with adherence. The rate of non-adherence was 40%. Those who were male (67% versus 52%, $p < 0.05$, OR 2.06, 95% CI 1.17-4.88), single (68% versus 53%, $p = 0.04$), and had left sided disease versus pancolitis (83% versus 51%, $p < 0.01$) had statistically significant higher rates of non-adherence. Interestingly, two variables, which were statistically significant, were found to be protective against non-adherence included colonoscopy within the last 2 years ($p = 0.03$, OR 0.96, 95% CI 0.93-0.99) and being married ($p = 0.01$ OR 0.46, 95% CI 0.39-0.57).

The final study conducted by this author using administrative data to measure adherence assessed patient satisfaction with once daily dosing of mesalamine versus multiple dosing (S. Kane, Huo, & Magnanti, 2003). Stable UC patients ($n = 22$) were randomized to once daily dosing ($n = 12$) or conventional therapy ($n = 12$). The MED-TOTAL formula supplied

information on adherence at 3 and 6 months. Adherence again equated with consumption of >80% of that prescribed. At 3 months, no patients experienced symptoms of relapse and the rate of adherence was 100% in the daily dosing group and 70% for those taking conventional therapy. At 6 months, one patient from each group experienced symptoms of disease relapse. Both were non-adherent to treatment. The average amount of medication taken in the once daily group was 90% compared to 76% in the conventional group. Patient satisfaction was 83% for the once daily dose group at the end of the pilot compared to 60% for those taking multiple doses daily.

2.6 Veterans Health Administration

Providing benefits for veterans is unique in the world. The United States has done so in some fashion for centuries. The Veterans Health Administration (VHA) is a multifaceted agency, with origins in the 1600s, that governs the largest integrated benefits system in the world, providing services to honorably discharged members of the U.S. Armed Services. VHA's primary mission is to enhance the health and wellbeing of those it cares for, emphasizing functionality of members with service connected injuries (conditions related to military service). Over time, as circumstances dictated, this country has evolved a complex organization within a politically charged environment, to meet the needs of those who served. Ever mindful of the changing demographics of veterans, the many stakeholders associated with veteran benefits, and the economic climate in which allocation of resources occurs, VA repeatedly transforms to emerge from these challenges. Investigators conducting research in such a unique atmosphere will need to be cognizant of how the characteristics of the system affect scientific inquiry.

2.7 Veterans

This study will use a systems model, the CCM, as a foundation for examining relationships within a closed healthcare system, the VA. While having a tangible appreciation of

the VA is crucial, equally important to this investigation, will be a working knowledge of the individuals who use the system under consideration. Veterans are a vulnerable population because of the presence of multiple disabilities, comorbid mental health diagnoses, substance abuse histories, and low incomes in substantive numbers (M. W. Smith & Joseph, 2003).

2011 Survey of Veterans

The characteristics of Veterans are ever changing. In an effort to meet the needs of this divergent population, the federal government has made it a priority to understand the individuals who utilize VA services and what influences their healthcare decision making and health status. To attain this objective, since 1999, an annual VHA Survey of Veteran Enrollees' Health and Reliance upon VA has been conducted by the Office of the Assistant Deputy Under Secretary for health for Policy and Planning (ADUSH/P&P). Statistics from the survey generate a healthcare budget for VA. Additionally, this data informs health policy options that affect medical decision making for Veterans. The annual survey occurs in conjunction with OMB authority that determines the amount of funding apportioned for Veteran benefits. The survey results represent data only for Veterans enrolled in VA healthcare.

The demographics discussed are from Fiscal Year 2011, the period of observation for this study. Therefore, the statistics presented here in should be representative of the population for this investigation. Data generation occurs by the Healthcare Analysis and Information Group and the Enrollment and Forecasting Service within ADAUSH/P&P.

Data collection occurred via telephone survey. The observation period was inclusive of March 4, 2011 through May 27, 2011. Over 45,000 Veteran users of VA healthcare nationwide, chosen randomly, constituted the sample. Weighted results represent the entire population of enrollees of approximately 7.8 million Veterans. The survey included the following variables of

marital status, age, household income, priority level, period of service, combat status, ethnicity and race, employment status, public and private health insurance coverage. Additional variables included Medicare coverage, prescription drug benefit or coverage, number and costs of over-the-counter and prescription medications, key drivers of enrollees' healthcare decision making, perceived health status, smoking status, and perceptions of VA healthcare, and planned future use of VA (Office of the Assistant Deputy Under Secretary for Health for Policy and Planning, 2012). A summary of key variables are below. Unless otherwise noted, all figures are from the Office of the Assistant Deputy Under secretary for Health Policy, 2012 report.

Demographic Variables

The average age of the patients was 62. The majority of enrollees were married (62%), white (80.8%), males (94%) with dependents. Six percent of the population was Hispanic, 11.7% African America, and 4.2% were Native American.

Enrollees served in the military for an average 6.5 years with 43% reporting exposure to combat during their service. The greater part of veterans (41%) served during the Vietnam War Era.

Most enrollees (60%) did not work outside the home. The reported median annual household income was $35,000. This figure is unchanged for the last five years.

Health Status and Future Use of VA

Enrollees under age 45 more often reported positive health status (excellent/very good).Veterans of OEF/OIF had annual incomes greater than $36,000, and were female. This statistic has remained steady in the last decade.

Of those enrolled to access VA services, 75% reported that they use VA for at least some of their healthcare needs. Veterans with annual household incomes of less than $36,000 were more likely to use VA to meet all of their healthcare needs.

Consistently, for the last five years, at least 45% of enrollees plan to access VA for primary care only. Less than 5% plan to use VA for specialty care in the future. The reason for this is unclear. The overwhelming majority of patients who use VA services reported in a positive manner about their experiences. Predictors of future use of VA benefits were quality, cost, and availability and accessibility of services.

Health Insurance Coverage

The survey examined availability and use of health insurance by VA enrollees. Health insurance was defined as "any program that helps pay for medical expenses, whether through privately purchased insurance, social insurance, or non-insurance social welfare programs funded by the government" (p.59). Most enrollees (77%) reported some type of public or private health insurance coverage in addition to VA benefits. This number has been on a steady decline since 2008. Of those with healthcare coverage, 35% are accessing it through an employer. Younger Veterans, the unemployed, and those with lower incomes are more likely to be uninsured. This number has grown steadily since 2008 from 34% to 41% in 2011. Medicare continues to be the most commonly (51%) reported health insurance coverage.

Pharmaceutical Coverage

VA provides both prescription and over the counter drug coverage for all enrollees with some paying a co-pay ($8/30day supply). Yet 40% of those in the cohort were unaware of the pharmacy benefit. Individuals with incomes above $36,000 a year and those who were under age 45 were more likely not to have knowledge of these services.

On average, enrollees take 4.7 different medications in a month with 43% reporting to have taken five prescription medications in a 30-day timeframe. A comparison with non-veteran data showed only 11%, age 60 and older took 5 medications per month. This broad difference exists due to an older, comorbid Veteran population.

Overall, 34% of enrollees do not use VA for prescriptions. The Execute Summary of this survey does not make clear if these individuals do not take any prescription medications at all, or if they are obtaining medications elsewhere. Of those who reported private insurance coverage (77%), only 39% had an associated prescription drug benefit with their health plan. However, it is not transparent if veterans access to private prescription services influences VA use of the same benefit. Knowledge of veteran access to pharmacy services outside VA is a recognized limitation of this study.

In 2006, for the first time, Medicare patients could register for Medicare Part D, a prescription drug benefit. As expected, VA enrollees with higher incomes who could afford the premiums were more likely participate. While 36% of VA enrollees have opted to purchase Medicare Part D, the survey analysis does not make clear the impact of this coverage on VA drug program usage. This is currently under further deliberation. Furthermore, the effects of the Patient Protection and Affordable Care Act (PPACA, 2010) on prescription drug coverage for all U. S. Citizens remains unknown.

VA Reliance.

VA reliance examined outpatient usage and was defined as "the number of visits or trips in a VA setting reported by an enrollee divided by the sum of all visits in both VA and non-VA settings" (p. 79). Nationwide, the average reliance on VA for outpatient care was 47%. Drivers of higher levels of reliance on VA services were: uninsured; reported poor health status; earned

less than $20,000 annually; 50-64 years of age; service during Vietnam Era; unemployed; single; and African American.

2.8 Summary of Gaps in the Literature

Significant support existed in the literature for the primary line of injury for this study. This study addressed several deficiencies in scientific knowledge discovered in this review. While a substantial amount of research subsists regarding medication adherence in IBD, small sample sizes and use of unreliable measurement, chiefly that of non-validated self-report measures, limit the interpretation of study findings. This study provided information on veterans with this disease, about which little data currently exists. Furthermore, this study assessed medication adherence using the prescribed "gold standard" for this cohort, pharmacy refill data. World experts have acknowledged the multifaceted nature of medication adherence, encouraging assessment of systematic influences on this construct in an effort to improve health outcomes. However, adherence research in IBD is in early development, with the majority of studies conducted in the last five years that are descriptive in nature, providing information regarding adherence rates and predictors of the most common demographic variables. The results of this review demonstrated persistence in adherence science in IBD in examination of individual behaviors with very few if any researchers casting a wider net to explore systematic impacts. Therefore, this study was the first of its kind to assess medication adherence in this cohort using a systems Model as a guiding framework to explore coordination of care and its relationship to medication adherence and healthcare utilization in veterans with IBD.

Chapter 3

METHODS

This chapter includes a description of the study research design. This chapter also includes a discussion of the population used for this study as well as how the investigational cohort generation occurs. Additionally, this chapter contains information regarding protection of study subjects. Furthermore, this chapter incorporates information regarding the databases from which study variable retrieval occurs, knowledge of data quality housed within these infrastructures, as well as how study data points are measured. This chapter closes with the details of data handling procedures, planned statistical analysis, and sample considerations.

3.1 Research Design

The design for this study was a descriptive retrospective data analysis. Medical records of veterans with IBD provided the information for analysis. Retrospective analysis has been used to assess medication adherence in patients with IBD using pharmacy refill data retrieved from large healthcare databases (S. V. Kane & Hanauer, 2000; S. Kane et al., 2001; S. Kane, Huo, & Magnanti, 2003; S. Kane et al., 2012; Khan et al., 2012; Lachaine et al., 2013; Mitra et al., 2012; Trindade et al., 2011).(S. V. Kane & Hanauer, 2000; S. Kane et al., 2001; S. Kane, Huo, Aikens et al., 2003; S. Kane et al., 2012; Trindale et al., 2011)However, few frameworks are available to guide methodologic decision making in retrospective studies using administrative data (A. K. Smith et al., 2011; Worster & Haines, 2004) . For this reason, ISPOR generated a consensus document outlining a systematic approach to designing retrospective database studies of medication adherence that informed study methodology as well as final manuscript publication (Peterson et al., 2007).

3.2 Population

The population for this investigation was enrollees in one northeast Department of Veterans Affairs Medical Center (VAMC) who sought care for IBD between October 1, 2010 and September 30, 2011 for IBD, FY 2011.

3.3 Procedures for Protection of Human Subjects

Conducting research entails protection of human subjects participating in such an endeavor, the guidelines for which exist in the Research Act of 1974 (Zucker, 2007). However, it was not until the passage of Public Law 104-191, the Health Insurance Portability and Accountability Act (HIPAA) of 1996, that protection of health information (PHI) came to the forefront. Because PHI access occurred in this study, the implications of HIPAA on study protocols are reported. Table 6 contains a summary of the procedures used to protect human subjects for this investigation.

The intent of HIPPA was to improve portability and continuity of health insurance coverage by allowing chronically ill individuals to change jobs without losing healthcare coverage (Watts et al., 2003). However, the law also contains a provision mandating health systems maintaining healthcare information to implement safeguards ensuring the integrity and confidentiality of PHI that has had consequences for research conducted using administrative data (Nosowsky & Giordano, 2006). Although not specifically directed at research, HIPPA, also known as the Privacy Rule, significantly restricts situations in which PHI are used and disclosed. PHI includes any information collected from an individual, including demographics, related to the person's past, present, or future mental or health condition as well as payment for such, and applies to all healthcare plans and providers transmitting this information in an electronic form

(U.S. Department of Health and Human Services, 2003). This description of PHI applies to all data used in this study.

Typically, in research, data collection occurs after patients have given informed consent. However, there is no direct permission obtained in retrospective studies (VonKoss Krowchuk, More, & Richardson, 1995). The Privacy Rule does allow disclosure of PHI without permission under limited circumstances, such as when using de-identified and limited datasets, contingent upon completion of a Waiver of HIPAA Authorization (Watts et al., 2003). Congruent with 45 CFR 164.512(i)(2), a HIPPAA Waiver is appropriate because this study could not have been conducted without the waiver or without access to the requested PHI (Department of Veteran Affairs, 2012). Furthermore, in accordance with the Privacy Rule, patient authorization is not required for studies using PHI in existence at the time of IRB submission, in this case, FY 2011 (VA Pittsburgh Healthcare System Research and Development, 2010) . Table 7 contains PHI elements omitted from a dataset considered de-identified or limited (Department of Veteran Affairs, 2012).

Because this study is examining the relationship between coordination of care, medication adherence, and healthcare utilization, dates, month and day, of the following variables are required for data analysis: prescription refills, outpatient visits to primary and specialty care, ER visits, as well as inpatient admissions for all services related to IBD as outlined in the measurement section below. While exclusion of all other PHI elements from study datasets occurs, knowledge of the month and day when service rendering occurs, because it is necessary to achieve research aims. As a result, this study protocol included a request to the local VA IRB as well University IRB to obtain a limited dataset through an expedited IRB process. VA Policy 002, VHA Handbook 1605.1, and VHA Handbook 1605.2 outline

Table 6
Summary of Procedures for Protection of Human Subjects

1. Use of a Limited Dataset

2. No effort was made to re-identify de-identified data

3. Dataset access occurred only through a password protected VA machine or CAG through an access restricted SharePoint site

4. All research records were maintained in accordance with the Veterans Health Administration (VHA) Records Control Schedule. Paper records were disposed of using methods deemed appropriate by the VAPHS Privacy Officer, and all electronic data was sanitized using methods rendered appropriate by the VAPHS ISO.

5. Data was only reported in the aggregate

6. The dataset will be retained indefinitely according to policy by the Institution of Record

7. All research records, as defined by VHA Handbook 1200.05, were stored under lock and key in the researcher's VA office with the VA PI having the only access

8. The requested dataset was not reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the requested information would be permitted by the Privacy Rule (VHA Handbook 1200.05, p. 66).

9. Any loss or compromise of any VA sensitive information (including research data), VA equipment or device, or any non-VA equipment or device that is used to transport, access, or store VA information was reported in accordance with the reporting requirements outlined in VA Handbook 6500.

10. In accordance with VHA Handbook 1200.05(63)(a), the study was conducted with a Co-PI

11. Completion of a Waiver of HIPAA Authorization.

12. The PHI requested was the minimum necessary for the stated purposes

13. Data acquisition occurred only for research purposes and future dissemination of findings

steps in requesting a limited dataset (Department of Veterans Affairs, 2006b; Department of Veterans Affairs, 2013).

This study protocol included a VA IRB request to access the limited dataset for use through remote access provided by the VA, known as Citrix Access Gateway (CAG), that permitted password protected access to VA information from a personal computer. This study protocol also included an application submitted to the VA for statistical support through the local VA Research Office. The dataset was returned to the statistician according to current VA policy upon final manuscript publication.

A data safety monitoring plan was implemented to ensure that there were no changes in the benefit/risk ratio during the study and that confidentiality of research data was maintained. Study personnel met weekly to discuss any issues or concerns. Any instances of adverse events, protocol deviations, or other problems identified during the meeting were to be reported within the required timeframes using the standard forms and/or procedures set forth by the IRB. There was no data compromise during this investigation.

Additional data safeguards included reporting of data in aggregate form to ensure patient confidentiality and anonymity, as well as storage of all research records, as defined in VHA Handbook 1200.05, in a locked VA office that only the co-PI had access to. The risks associated with this study were minimal. Data acquisition occurred only for research purposes and dissemination of findings.

3.4 Measurement

The following passages contain information regarding measurement of study variables. The variables included medication adherence, demographic variables, and healthcare utilization.

Table 7

PHI Data Elements Excluded from De-identified and Limited Datasets

Identifiers Excluded in De-identified Datasets	Identifiers Excluded in Limited Datasets
Names	Names
All geographic subdivisions smaller than a state, except for the initial three digits of the zip code of the geographic unit formed by combining all zip codes with the same three initial digits contains more than 20,000 people	Street Address
All elements of dates except year and all ages over 89	
Telephone Numbers	Telephone Numbers
Fax Numbers	Fax Numbers
E-mail Addresses	E-mail Addresses
Social Security Numbers (SSN)	Social Security Numbers (SSN)
Medical Record Numbers	Medical Record Numbers
Health Plan Beneficiary Numbers	Health Plan Beneficiary Numbers
Account Numbers	Account Numbers
Certificate or License Numbers	Certificate or License Numbers
Vehicle Identifiers/License Plate Numbers	Vehicle Identifiers/License Plate Numbers
Device Identifiers and Serial Numbers	Device Identifiers and Serial Numbers
Uniform Resource Locator (URLs)	Uniform Resource Locator (URLs)
Internet Protocol (IP) Addresses	Internet Protocol (IP) Addresses
Biometric Identifiers	Biometric Identifiers
Full-face Photographs/Comparable Images	Full-face Photographs/Comparable Images
Any other unique, identifying characteristic or code, except as permitted for re-identification in the Privacy Rule	

Medication Adherence

Medication adherence was measured using the MPR that was operationalized as: "the sum of the days' supply of medication divided by the number of days between the first fill and the last refill plus the days' supply of the last refill" Figure 3.1 (Sikka et al., 2005). Corroboration between dosing instructions and days' supply of medication did not occur because this information was not available in the databases accessed for this study.

All individuals had a uniform follow-up period to prevent biases upward in calculating MPR for individuals with shorter follow up times, for this study, FY 2011 served as the uniform observation period (Sikka et al., 2005). Adjustment in the denominator of this equation occurred for subjects with inpatient admissions. Therefore, the observation period for patients with an inpatient admission, reflected the omission of hospitalized days from the total days in the observation period (Gellad, 2012).

In the descriptive analysis, MPR was a continuous variable. As found throughout the adherence literature in a variety of chronic diseases where retrospective analysis of pharmacy refill data is employed, (Kreyenbuhl et al., 2010; Krousel-Wood et al., 2009; Siegel, Lopez, & Meier, 2007) further analysis was conducted with the MPR dichotomized so that those with MPR of $\geq.80$ or above were adherent and those with an MPR $< .80$ were non-adherent. The origins of these cut off points are based on the principal that loss of $>20\%$ of a patient population

$$MPR = (30+30+30+30+30)/365 = 41\%$$
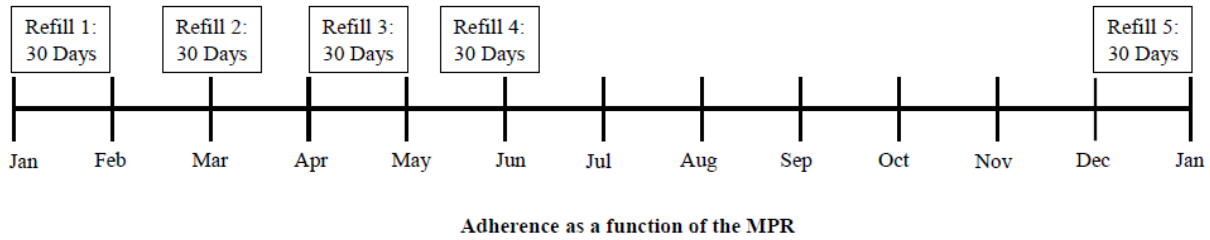
Adherence as a function of the MPR

Figure 3.1 Calculation of MPR. "Reprinted from The American Journal of Managed Care,11(7), Sikka, R., Xia, F., Aubert, R. E., Estimating medication persistency using administrative claims data, 449-457, 2005, with permission from Managed Care & Healthcare Communications"

in a clinical trial makes the results suspect (Guyan, Sackett, & Cook, D. J. for the Evidenced Based Medicine Working Group, 1993).

Essentially, an MPR of .80 equates to taking a medication 80% of the time. This means that 20% of the time, the patient is not taking any medication. Use of this cutoff implicitly assumes that no change in health outcome occurs as result of this "allowable gap" in treatment. As reported in this paper, the 80% cut off is used widely throughout the adherence literature for many chronic disease states, although not supported by any documentation of the clinical validity of this measure (Ho et al., 2009; Peterson et al., 2007) this includes IBD (Regueiro, 2012c). Thereby, adding further to the limitations of measuring medication adherence using pharmacy refill data.

The literature supports the use of adherence cutoffs in IBD as $\geq$.80 as adherent and $<$ .80 as non-adherent (Bhatt et al., 2009; S. V. Kane, 2008; S. Kane et al., 2001; S. Kane, Huo, & Magnanti, 2003; S. Kane, Huo, Aikens et al., 2003; S. Kane et al., 2012; Lachaine et al., 2013;

Mantzaris et al., 2007; Moss et al., 2010; Nahon et al., 2011; Robinson et al., 2013; Trindale et al., 2011) . Additionally, the MPR with these cutoffs appears previously in retrospective adherence studies using a sample of veterans (Khan et al., 2012; Kreyenbuhl et al., 2010). Therefore, these cutoffs were also employed for this investigation. However, to improve the robustness of the evaluation, the analysis was repeated using .90 as a cutoff to assess if the results changed in a statistically significant manner.

MPR calculation occurred for each of the applicable medications in this study for each patient, because it was conceivable that patients could be taking more than one drug for IBD simultaneously. Combination of MPR calculations did not occur across patients due to different denominators for each drug. Therefore, a mean MPR was calculated for each patient taking more than one medication (Hess et al., 2006; Peterson et al., 2007).

It was acknowledged that the MPR will miss those with primary non-adherence i.e. those who are prescribed a medication but never pick it up from pharmacy. Additionally, because the MPR requires at least two medication refills during the observation period, those who filled only one prescription and never fill again were not included. Therefore, the sample for this study was limited to subjects who were relatively more adherent than others in the cohort. While administrative pharmacy data represents a valuable research tool, there are several confounding elements of this measurement to address such as, over- supply of medication, persistence, and switching.

Over-Supply of Medication

Over-supply of medication is a consideration when using refill data to measure adherence. MPR scores typically run 0 to 1.00 with higher values indicating higher levels of medication adherence (Kim, Agostini, & Justice, 2010). The literature demonstrates a variety of

procedures regarding MPR values > 1, indicating oversupply of medication. There were no cases of medication over-supply in this sample.

Persistence

The literature recognizes retrospective measure of persistence as a concept distinguished from adherence and defined as the length of time from initiation to discontinuation of therapy, measured in units of time (Burrell et al., 2005). Such that, individuals who are persistent with therapy, have medication taking behavior that is continuous, filling medications frequently, and regularly, during a specified period (Sikka et al., 2005). Whereas retrospective measure of adherence is the total number of days of medication availability for a defined observation period which does not take into account the consistency with which individuals refill medication (Burrell et al., 2005).

The mostly widely used measure of persistency is measurement based on gaps between refills (Sikka et al., 2005). The literature lacks consensus regarding the appropriate length of the permissible gap (Sikka et al., 2005). Furthermore, there are no allowable gaps in treatment for IBD (Regueiro, 2012b). Therefore, to contribute to adherence science in a meaningful way, persistency was not measured for this study.

Switching

Subjects switching between drugs within the same therapeutic class or between a different therapeutic class were deemed adherent with an MPR of $\geq$ .80 (Andrade, 2006).

Demographic Variables

The analysis included covariate demographic characteristics that have demonstrated, although not consistently, an association with medication adherence in IBD. Demographic variables included age, gender, race, and ethnicity. Age was reported as a continuous variable.

Gender was a categorical variable, male or female. For regression models, females were excluded due to low counts in this group.

Race was also a categorical variable with seven levels. The nationally approved race standardization in VHA originates in Handbook 1601A.01 and Directive 2009-21 and included the following standardized race values American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Pacific Islander, and White, Unknown by Patient, and Declined to Answer (Veterans Health Administration, 2012). VA categories for ethnicity included Hispanic or Latino, not Hispanic, don't know/refused (VA Information Resource Center (VIReC), 2011) . As such, data collection for race and ethnicity reflected these groups. Report of descriptive statistics, including frequencies, took place for all races and ethnicities. However, due to low frequencies in many of the above categories, for further evaluation, race and ethnicity were collapsed as appropriate. Despite categorical collapse, race and ethnicity were excluded as variables in multivariate analysis due to minimal occurrences for many categories. Additionally, IBD diagnosis, CD versus UC, as well as, IBD medication, categorized as 5-ASA, immunomodulator, were both included.

Healthcare Utilization

Healthcare utilization was the "use of healthcare resources" (Bernstein et al., 2003). The services chosen for examination in this study were derived from the National Health Care Survey, a collection of surveys, done to assess how the U. S. healthcare delivery system is being used and by whom. While the main outcome variable for this study was medication adherence, research demonstrates a relationship exists between adherence and consumption of healthcare resources (World Health Organization, 2003). Additionally, while healthcare utilization in IBD has been studied (Ananthakrishnan et al., 2010; Gibson et al., 2008; Longobardi & Bernstein,

2006; Mitra et al., 2012; Nguyen et al., 2007), no information regarding the healthcare utilization of veterans with this disease exists. Therefore, this study began to explore these relationships in the VA for which a gap in science exists.

Data on healthcare utilization originated from FY 2011 VistA datasets. For this investigation, the following healthcare services represented healthcare utilization: ER visits, outpatient department visits that included both primary and specialty GI care clinic visits, as well as inpatient admissions. The frequencies of each visit type for each patient were included in the analysis. For further multivariate evaluation, three logistic regression models were created. In each model, the dependent variable was dichotomous, yes/no. Analysis details of healthcare utilization are contained in subsequent passages.

Comorbidity

Measurement of comorbidity in research occurs to correct for confounding, to establish use as a predictor of a study outcome, and for statistical efficacy (de Groot, V., Beckerman, Lankhorst, & Bouter, 2003). As is established in the literature, healthcare utilization investigations typically include consideration of comorbidities in the population of interest and control for this variable during multivariate analysis (Valderas et al., 2009; Vogeli, Shields, & Lee, 2007) . In turn, this variable was included in this exploratory analysis of healthcare utilization.

There are over 75 million Americans with two or more chronic conditions (Parekh & Barton, 2010). Level of comorbidity is of particular concern in the veteran population because veterans who receive care in the VA are more likely to have multiple chronic health conditions and higher rates of mortality when compared to the general population or veterans who do not use the VA for healthcare (Agha, Lofgren, VanRuiswyk, & Layde, 2000; Lee et al., 2007). Of

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further concern, are the results of studies that suggest patients with multiple medical conditions have poor outcomes and increased healthcare resource utilization (Vogeli et al., 2007). Similar to medication adherence, no consensus exists in the literature regarding how best to define and measure comorbidity (Fortin, 2007). As a result, a review article (Valderas et al., 2009) generated explicit definitions for the nomenclature surrounding comorbidity as well as measurement considerations of this construct, with the aim of consistent usage of these definitions and measures in future research to allow for comparison of results across reports and improve generalizability of study findings. To this end, the recommended definition and measure emanating from this paper informed the measurement of this construct for this study. Hence, the definition of comorbidity for this study was the "presence of additional diseases in relation to an index disease in one individual" (Valderas et al., 2009).

(Valderas et al., 2009) encouraged use of measuring comorbidity with established disease classification systems such as the one chosen for this study, ICD-9. Choice of the (Deyo et al., 1992) comorbidity measure took place based on this recommendation. The Deyo algorithm originates from work completed by (Charlson et al., 1987), who identified 19 medical conditions associated with increased rates of mortality within 12 months and created a tool to measure this risk, the Charlson Comorbidity Index (CCI) which has become the most widely used measure to characterize the risk of death from comorbid disease (Valderas et al., 2009). A comorbidity index reduces the coexistence of illnesses to a single score that allows for comparison with other patients in a study as well as subjects across studies.

The CCI assigns a weighted score to each medical condition that ranges between 1-6. Patients receive a score for each of the medical conditions in the CCI that combined for a total comorbidity score, with higher values, up to 37, indicating more severe levels of comorbidity. To

place the scores in context, in the (Charlson et al., 1987) study, a patient in the first cohort (559 patients) with a score of 0 had a 12% 1year mortality rate, scores of 1-2 with a 26% risk, 3-4 with a 52% risk, and those with a score >5 had an 85% risk of mortality at 1 year. The authors then followed a second cohort (685 patients) for 10 years. The morality risk for the various CCI scores was similar in that those with a score of 0 had a 12% risk of mortality, scores of 1 a 25% risk, 2 a 48% risk, and scores $\geq$ 3 had 59% risk of death. Thereby demonstrating that as CCI scores increased, so did the cumulative affective of comorbid disease ($p < 0.0001$). In the second cohort, age was also a predictor of mortality ($p < 0.001$).

The CCI was included in a critical review of the measures of comorbidity conducted to evaluate the validity and reliability of a total of 13 such methods (de Groot et al., 2003). A correlation coefficient (ICC) exceeding 0.40 supports the concurrent validity of the CCI. The predictive validity or ability of the CCI to predict future events on an outcome measure of interest, has been established by the presences of significant relationship of the Index with various criterion measures such as mortality, disability, hospital readmission rates, and length of stay (Chalson, Szatrowski, Peterson, & Gold, 1994; Librero, Peiro, & Ordinana, 1999; Rochon et al., 1996). Data also exists that the CCI has good test-retest as well as interrater reliability (Extermann, Overcash, Lyman, Parr, & Balducci, 1998; Liu, Domen, & Chino, 1997). Of the 13 comorbidity measures in this review, the authors concluded that only 4 of the 13 are valid, reliable measures of comorbidity, CCI being one of these measures. More recently, (S. F. Hall, 2006) published a paper in a similar vein producing comparable results.

Building on Charlson's work, (Deyo et al., 1992) created a method for calculating the CCI, specifically using administrative data, based on the ICD-9 codes of the 19 medical conditions in the original Index, see Table 8 (permission located in Appendix D) . The Deyo

method has 17 chronic diseases in its algorithm. The only difference between the CCI and the Deyo algorithm is in the category for malignancy. The CCI has three categories for malignancy, classified as any malignancy, leukemia, and lymphoma. However, the Deyo algorithm places all three classifications into one category resulting in the creation of 17 medical condition categories instead of 19. Multivariate analysis in the Deyo (1992) study demonstrated significant association with outcomes post lumbar spine surgery as well as resource utilization in this cohort (p <0.0005).

(Quan, Parsons, & Ghali, 2004) sought to validate the Deyo algorithm by examining the administrative data of 1,200 subjects by comparing algorithm scores using administrative data to scores generated using the same tool calculated from manual chart review. The authors calculated a kappa score to determine the extent of agreement between the two sources above chance. Overwhelmingly, the kappa scores showed moderate (0.41 to 0.60) to substantial agreement (0.61 to 0.80) between the scores calculated using administrative data and the scores calculated from manual chart review. Logistic regression models were used to predict in-hospital mortality using both data sources. While some differences between administrative data and manually retrieved data occurred, overall the ability to predict in-hospital mortality was the same for both groups (OR 1.4; 955 CI 1.3-1.5). Recognizing the limitations of administrative data, the authors concluded that calculation of a comorbidity score using administrative data may adequately characterize the burden of comorbidity.

Use of the Deyo algorithm in the population of interest provided additional support for its use in this study. As reported previously, the investigations conducted by (S. V. Kane, 2008) and (Nguyen et al., 2007) both described in detail previously, are included in this substantiation.

For example, (Anathakrishnan, McGinley, & Binion, 2008) used the Deyo algorithm to estimate mortality in a group of hospitalized IBD patients with Clostridium difficile. The results of study showed that after controlling for comorbidity using the Deyo algorithm during regression analysis, patients with C. difficile had higher odds of death than those admitted for IBD alone (OR = 5.7, 95% CI 2.9-11.3), longer lengths of stay (95% CI 0.8-3.2), and were more likely to undergo bowel surgery (OR = 4.8, 95% CI 2.2-8.1).

(Ananthakrishnan, McGinley, & Binion, 2009) and colleagues again used the Deyo algorithm in a national sample of hospitalized IBD patients examining the frequency of complications, requirements for surgery, and outcomes of hospitalization comparing older patients (>65) to younger patients (<65). Age was recognized as an independent risk factor for IBD related death. After controlling for comorbidity using the Deyo algorithm in regression models, older patients persistently had greater mortality than younger comparisons (OR 3.91, 95% CI 2.50-6.11). Regression models also demonstrated that rates of surgery were not significantly different between the two groups (OR 1.03, 95% CI 0.90-1.18). Additionally, post-operative complication rates were similar in both groups (OR 1.12, 95% CI 0.88-1.43).

Finally, the Deyo algorithm provided information regarding the impact of in-hospital malnutrition on mortality in a national sample of IBD patients (Nguyen et al., 2009). Predicator variables in logistic regression models included age, race, sex, IBD diagnosis, primary health insurance carrier, a comorbidity score calculated using the Deyo algorithm, surgery done during admission, and hospital characteristics. The risk of mortality in IBD patients with malnutrition was three times higher than for those who were not malnourished after controlling for comorbidity, age, sex, health insurance, and hospital factors (95% CI 2.89-23).

Calculation of Comorbidity

Comorbidity for this study was measured using the following procedures. The statistician retrieved the ICD-9 codes associated with the CCI located in Table 8 for each patient in the cohort. The researcher then used the (W. H. Hall, Ramachandran, Narayan, Jani, & Vijayakumar, 2004) age adjusted comorbidity calculator to obtain a comorbidity score that was used in regression analysis for Specific Aim 3.

(W. H. Hall et al., 2004) developed an online CCI calculator using Microsoft Excel Macro that rapidly calculates a comorbidity score that originates from Charlson's original work (1987) and is downloadable onto a desktop through the following link, (http://www.biomedcentral.com/content/supplementary/1471-2407-4-94-S1.xls). The scoring using the Hall calculator as identical to scoring found in the CCI, see Table 8, with a range of 0-37. Like the CCI, the Hall calculator also makes a provision for an age adjusted comorbidity which was applied in this study.

Of the comorbidity calculators that have documented reliability and validity (de Groot et al., 2003), the Index of Coexistent Disease (ICED), Kaplan Index, the Cumulative Illness Rating Scale (CIRS), and the CCI, only the ICED and CCI have easy to use electronic calculators available for clinical use. The ICED has not been used in the population of interest. Whereas the CCI, translated by the Deyo algorithm has been applied in IBD (S. Kane & Shaya, 2008). Therefore, the comorbidity calculator developed by (W. H. Hall et al., 2004) was the chosen calculator for this study. Because the majority of subjects had no comorbidity, this variable was dichotomized yes/no for regression models.

Table 8			
Translation of Charlson Comorbidity Index (CCI) elements into ICD-9 codes			
Diagnostic Category	ICD-9 Codes	Assigned weights for diseases	Condition Description
Myocardial infarction	410-410.9 412	1	Acute myocardial infarction Old myocardial infarction
Congestive heart failure	428-428.9	1	Heart failure
Peripheral vascular disease	443.9 441.441.9 785.4 V43.4 procedure 38.48	1	Peripheral vascular disease, includes intermittent claudication Aortic aneurysm Gangrene Blood vessel replaced by prosthesis Resection and replacement of lower limb arteries
Cerebrovascular disease	430-438	1	Cerebrovascular disease
Dementia	290-290.9	1	Senile and presenile dementia
Chronic pulmonary disease	490-496 500-505 506.4	1	Chronic obstructive pulmonary disease Pneumoconioses Chronic respiratory conditions due to fumes and vapors
Rheumatolgic disease	710.0 710.1 710.4 714.0-714.2 714.81 725	1	Systemic lupus erythematosus Systemic sclerosis Polymyositis adult rheumatoid arthritis Rheumatoid lung Polymyalgia rheumatic
Peptic ulcer disease	531-534.9 531.4-531.7 532.4-532.7 533.4-533.7 534.4-534.7	1	Gastric, duodenal and gastrojejunal ulcers Chronic forms of peptic ulcer disease

Table 8 (continued)			
Diagnostic Category	ICD-9 Codes	Assigned weights for diseases	Condition Description
Mild liver disease	571.2 571.5 571.6 571.4- 571.49	1	Alcoholic cirrhosis Cirrhosis without mention of alcohol Biliary cirrhosis Chronic hepatitis
Diabetes	250-250.3 250.7	1	Diabetes with or without acute metabolic disturbances Diabetes with peripheral circulatory disorders
Diabetes with chronic complications	250.4-250.6	1	Diabetes with renal, ophthalmic, or neurological manifestations
Hemiplegia or paraplegia	344.1 342-342.9	2	Paraplegia Hemiplegia
Renal disease	582-582.9 582-583.7 585 586 588-588.9	2	Chronic glomerulonephritis Nephritis and nephropathy Chronic renal failure Renal failure, unspecified Disorders resulting from impaired renal function
Any malignancy, including leukemia and lymphoma	140-172.9 174-195.8 200-208.9	2	Malignant neoplasms Malignant neoplasms Leukemia and lymphoma
Moderate or severe liver disease	572.2-572.8	3	Hepatic coma, portal hypertension, other sequelae of chronic liver disease
Metastatic solid tumor	196-199.1	6	secondary malignant neoplasm of lymph nodes and other organs
AIDS	042-044.9	6	HIV infection with related specific conditions

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Emergency Department Visit

For this study, the number of all ED visits, with any diagnosis code, represented by clinic stop code 77, during FY 2011, represented healthcare utilization of ED services as represented in the literature in this population (Gibson et al., 2008; Motheral et al., 2003).

Outpatient Department Visit

OPD visit measurement consisted of clinic stop codes for primary (323, 301, 322, 348, 350, 170, 634, and 172) and specialty (Gastroenterology, 151) care. OPD visits did not require a corroborating ICD-9 code for IBD. All OPD visits for the above primary care stop codes and 151 for GI in this cohort, were included for analysis because it is conceivable that IBD patients are seen in either venue for IBD related issues and the diagnosis code for IBD not be rendered (Motheral et al., 2003; Regueiro, 2012a).

Inpatient Admission

Inpatient hospital admissions for any illness, during FY 2011, afforded inpatient admission information (Ananthakrishnan et al., 2010; Kappleman et al., 2011; Motheral et al., 2003; Nguyen et al., 2007; Regueiro, 2012a; Sewell et al., 2009; Sonneberg, Richardson, & Abraham, 2009).

Care Coordination

Care coordination was the "deliberate organization of patient care activities between two or more participants (including the patient) involved in a patient's care to facilitate the appropriate delivery of healthcare services. Organizing care involves the marshaling of personnel and other resources needed to carry out all required patient care activities, and is often managed by the exchange of information among participants responsible different aspects of care" (McDonald et al., 2007).

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The literature characterizes the term "shared care" as tantamount with coordination of care, as was the case for this study (Starfield, 2003). Identification of coordination of care occurred with use of "a clinic stop code, a required field in the VA OPC Hospital Location file that assigns a number representing a type of care or Service/treating Specialty" (Zivin et al., 2010). For this study, stop codes for primary care (323, 301, 322, 348, 350, 170, 634, 172) and gastroenterology (specialty care, 151) represented coordination of care (Regueiro, 2012a). Care coordination was assumed when the patient had clinic stop codes for both primary and specialty care. Care coordination was a critical element of this study, originating from the theoretical model for such, the CCM, that posits improved outcomes when use of healthcare resources are coordinated between primary and specialty care, in this case, gastroenterology.

In VA, primary care serves as the gatekeeper for specialty care access (Kizer, 1996). As a result, patients should be unable to make appointments with a specialist without a consultation placed into the electronic medical record by the PCP for said specialty. However, it is conceivable, due to systematic influences, that patients will access specialty care without intersession by primary care. For example, the institution under investigation serves as a regional GI referral center for four other VAMCs. Therefore, patients seen at the VAMC of interest for GI specialty care will have no records regarding primary care use because this care delivery occurs elsewhere. Additionally, patients may receive a referral for specialty care services through the ER.

3.5 Data Handling Procedures

None of the IBD adherence studies in this review, contained information regarding data handling. To address this issue, a discussion of data handling procedures for this study follows

which included assessment of missing data, normality, linearity, homoscedasticity, multicollinearity, and outliers.

Missing Data

Frequency evaluation yielded eight cases with missing race/ethnicity data that was confirm by the statistician who pulled the data from the local VA database. Eight missing cases corresponds to 5% of the sample, which is an allowable amount of missing data (D. F. Polit, 2010b; Tabachnick & Fidell, 2007). Therefore, no attempt was made to correct this missingness. No other variables had missing data.

Normality, Linearity, Homoscedasticity, and Multicollinearity

Evaluation of univariate normality was assessed using histograms, stem and leaf plots, box plots, as well as skewness and kurtosis. While the outcome variables for this study, medication adherence and healthcare utilization, were not normally distributed, all were dichotomized for logistic regression analysis.

Linearity and Homoscedasticity

Linearity and homoscedasticity *b*etween two variables was evaluated using bivariate scatterplots (Tabachnick & Fidell, 2007). Generation of an oval shaped scatter takes place with normally distributed data. Otherwise, data transformation addressed problems with heterogeneity of variance (univariate) and heterogeneity of variance-covariance (multivariate) (Tabachnick & Fidell, 2007).

Multicollinearity

Bivariate and multivariate correlation took place to assess Multicollinearity. Variance inflation factor (VIF) greater 10 and the tolerance values <.10 were considered representative of

Multicollinearity (Bowerman & O'Connell, 1990) . No variables met this statistical definition of collinearity.

Univariate and Multivariate Outliers

Univariate outliers were assessed via visual screening through histograms and boxplots. If the value remained a true outlier after screening, standardized z scores were generated for each group and those with scores greater than 3.29 (p<.001, two tailed) were considered potential outliers (Tabachnick & Fidell, 2007). Multivariate outliers were detected through Mahalanobis distance at p<.001 (X^2 df = to the number of variables) as this is currently the best method for multivariate outlier detection (Tabachnick & Fidell, 2007).

Expected outliers for healthcare utilization variables were present. However, all healthcare utilization variables were dichotomized yes/no for regression models. Therefore, no additional treatment occurred to these variables.

3.6 Analysis

The Statistical Package for the Social Sciences (SPSS) version 21.0 (Chicago, IL, 2012) was used for data analysis. To control for Type I error, a two-tailed test of significance was used with an alpha set at .05.

Descriptive Statistics

Variable relationship exploration began with descriptive statistics. Frequencies were provided for the categorical variables of comorbidity, IBD diagnosis, care coordination and IBD medication.

Primary Study Aim

Described medication adherence, healthcare utilization, and care coordination of veterans with inflammatory bowel disease (IBD) who employ Veterans Affairs (VA) healthcare at one Veterans Affairs Medication Center (VAMC).

Measures of central tendency characterized medication adherence rates of veterans with IBD as measured by the MPR. An MPR for each drug was calculated as a continuous variable. However, based on the literature, MPR was dichotomized into non-adherent (<.80) and adherent ($\geq$ .80) for further analysis. Frequencies and percentages for adherent and non-adherent patients were computed. The total number of occurrences for the healthcare utilization variables of ER visits and inpatient admissions during the one year observation period were collected. Care coordination measured by total number of occurrences for both primary and GI specialty care during the one year observation period were also collected.

Secondary Study Aim 1

Examined the association between medication adherence adjusted for care coordination, age, IBD diagnosis, comorbidity, and IBD medication in veterans with IBD who employ VA healthcare.

Bivariate Analysis.

Bivariate analysis was assessed using Chi-square test of independence to make inferences about the existence of a relationship between the dependent variable, medication adherence and independent study variables. Phi coefficient and Cramer's V were examined as appropriate. The continuous variable of age was examined through an independent samples t-test. Additionally, in an effort to facilitate future meta-analysis, the odds ratio (OR), 95% confidence intervals (CI) were reported (D. F. Polit, 2010a).

Multivariate Analysis.

Logistic regression yielded information about the probability of an IBD patient being adherent or non-adherent to a medication regime for said disease based on a subscribed set of factors: age, IBD diagnosis, IBD medication, as well as care coordination and comorbidity. Inclusion of all independent variables for regression analysis occurred owing to parsimony in choosing predictors based on study framework, literature, and data availability (Norusis, 2012). The variables of gender, race, as well as ethnicity were not included in the final analysis due to homogeneity of the sample. Main effects were determined by simultaneously entering all of the variables into the model to determine the predictive ability of the overall model. The odds ratio, 95% CI were reported. The Nagelkerke R2 portrayed effect size of the analysis.

Specific Aim 2

Began to explore the relationship between healthcare utilization adjusted for medication adherence, care coordination, age, IBD diagnosis, IBD medication, and comorbidities in veterans with IBD who employ VA for healthcare.

To examine the relationship between variables in preparation for further regression analysis, similar bivariate analysis occurred as described above. Logistic regression yielded information about the probability of an IBD patient having healthcare utilization measured by ER or inpatient admissions based on the following predictors: medication adherence, age, IBD diagnosis, IBD medication, care coordination, as well as comorbidity.

The dependent variable for the two healthcare utilization regression models was dichotomized (yes/no). The variables of gender, race, and ethnicity were not included in final models due to homogeneity of the sample. Main effects of each model were determined by simultaneously entering all of the variables into the model to determine the predictive ability of

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the overall model. As explained previously, all variables from the bivariate analysis were included in this model regardless of the relationship with the dependent variable. The odds ratio and 95% CI were reported. Generation of interaction terms for subsequent models was based on the significance of predictors. The Nagelkerke R2 portrays effect size of the analysis.

3.7 Sample Considerations

Many studies have been conducting examining medication adherence in IBD using logistic regression. However, little information exists regarding formal sample size consequences that could provide a benchmark for this investigation (S. Kane et al., 2012). Therefore, sample size deliberation took place using statistical text references.

Sample size calculations for logistic regression require consideration based on the number of predictors in the models (Bartlett, Kotrlik, & Higgins, 2001) . One simple recommendation exists regarding sample size that advised the use of at least 10-20 subjects for each predictor to reduce the risk of a Type II error (D. F. Polit, 2010c). (D. E. Miller & Kunce, 1973) as well as (Halinski & Feldt, 1970), provided additional support for the use of ten observations per independent variable. One source cited the use of not less than five observations per independent variable to ensure generalizability of study findings (Hair, Anderson, Tatham, & Black, 1995).

 Therefore, based on 10-20 patients per predictor, an appropriate sample size for Specific Aim 2 that included five predictors would be in the range of 50-100. The study sample met this requirement. Using the above metric, a sample size of the same caliber was required for the regression analysis of Specific Aim 3 that also included five predictors.

However, to test that the regression model was significant overall, the researcher also needed to contemplate the size of the effect of the independent variables to predict the outcome.

(Cohen, 1988) established as a benchmark, an effect size of .80 to achieve a high level of power. Cohen further suggests "standard effect sizes" for regression: .02 (small), .13 (medium), and .26 (large). Applying this rubric, using G Power, a sample size of 77 is appropriate, with up to 20 predictors, to achieve a large effect (Field, 2013) . Whereas, a sample of 160 patients, using up to 20 predictors, is required for a medium effect, and the minimum number of subjects of 100 is required with six or fewer predictors for medium effect size (Field, 2013). As noted above, the study sample met these sampling requirements.

3.8 Study Limitations

Overall, compared to primary data collection, secondary data analysis is less time consuming, labor intensive, and cost producing. Furthermore, patient non-response or recall bias does not occur with administrative data because data collection is independent of patient participation (Schneewiss & Avorn, 2005).

However, while secondary data analysis is recognized as a valid investigational methodology for assessing medication adherence (Andrade, 2006), nearly three decades have lapsed since researchers began assessing healthcare practice using retrospective analysis. Yet, the fundamental issues of using administrative data for research remain. Matching study conceptualizations with data element definition is challenging since the collection of database information did not occur for research purposes (Waltz, Strickland, & Lenz, 2010).

Knowledge of the quality of many data elements housed in a variety of administrative databases infrequently exist, inclusive of VA, creating concern about the reliability and validity of this methodology (Waltz et al., 2010). Rarely, can researchers comment on the reliability of original data (Worster & Haines, 2004) . However, by Congressional mandate in 2002, through Section 515 of the Treasury and General Government Appropriations Act, VA is bound to

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maximize the quality of the information it disseminates (U. S. Department of Veterans Affairs, 2003) .

VA researchers have been major contributors to the methodological literature in the area of administrative data use during the last 20 years. Nevertheless, VistA, the chosen database for this study, has more than 1,940 files and 44,960 data fields, generating massive amounts of information available for systematic inquiry, which has limited the science, as few are expert in translating this data into usable information for investigation (Hynes, 2012) . However, investigators who do make use of automated databases, facilitate the translation of data into information, thereby influencing clinical practice and health policy.

VA informatics and analytics professionals at VA Central Office in Washington, D.C. share concerns about the quality of VA data because the ability to capture clinical concepts using standardized data elements found in VA databases remains limited (Francis, 2012) . As a result, VA pays more than $12 million a year to have national manual chart abstractions done instead of electronic data pulls to estimate performance on Healthcare Effectiveness Data and Information Set (HEDIS) measures (Francis, 2012).

Clearly, the impact of poor data quality can have widespread deleterious effects on patient care. To address data quality concerns, the VHA Data Quality Program exists within the Health Information Governance Office of VHA's Office of Informatics and Analytics, whose mission it is to ensure data accuracy for all VHA stakeholders (U. S. Department of Veterans Affairs, 2007). Additionally, each VAMC also has a Clinical Application Coordinator (CAC) who is an authority on the meaning and utility of local VA data (VA Information Resource Center (VIReC), 2012) .

Concerns regarding quality of VA data, lent further support for the goals of this study using local VA data only, to begin examination of coordination of care, medication adherence, and healthcare utilization in a population in which little data currently exists. Some of the largest contributions VA researchers are making currently using administrative data is to provide documentation of the limitations of many widely used variables, as was the case with this study (Atkins, 2012) .

Completeness of data commands attention. Not all variables in VA datasets are of equal quality, as measured by completeness and accuracy of information entered into the system. Missing or erroneous values are possible.

The information about data quality presented below represents information on data quality from a national VA database perspective. To this researcher's knowledge, no data quality information exists on the elements housed in the local VistA modules used for this study.

Systematic evaluation that occurs through the research process strengthens database quality. The passages that follow contain information about processes used for this study to maintain methodologic rigor and include database source for research in VA, cohort generation, clinic stop code quality, pharmacy data, measuring medication adherence and race data quality.

Database Sources for Research in VA

VA represents one of the largest self-contained healthcare systems in the world. For decades, systems data captured and storage has occurred in a variety of administrative databases utilized in health services research. Although VA databases do not exist specifically for research purposes, informational access ensues to measure patient outcomes particularly when chart review would prove too labor intensive and cost prohibitive.

It is important to note, that in accordance with VHA Handbook Policy 1605.1, only VA employees conduct VA research (Department of Veterans Affairs, 2006a). Furthermore, access to any VA data for research purposes, requires prior IRB authorization from the investigator's VA facility, where scrutiny of the application takes place for protocols that address privacy and security concerns.

VA Databases

While many VA databases exist, for this study, only databases that contained variables under examination were accessed which included local VistA and CPRS, as well as local and VISN level pharmacy databases. Data collection for a VA fiscal year (FY) runs October 1-September 30. When retrieving data for a FY, it is advised to wait until January 1st of the following calendar year to ensure that a complete FY dataset can be obtained (Hynes, 2012). Additionally, from a systems perspective, because VA datasets are under constant amendment, it is imperative for growth in database research, to review the most current VA dataset, as interfacing with databases even just a year ago, could provide vastly different information when compared to current database configuration (Mark, Dirani, Slade, & Russo, 2002).

VistA

VistA is an integrated system of software applications that directly supports patient care at VHA healthcare facilities by tying together workstations and personal computers (Hynes, George, & Pfeil, 2002) .VistA provides system management tools that provide uniformity of data across the VA system and yet permit customization of each software package to meet local VA requirements (Brown, Lincoln, Groen, & Kolodner,). The majority of data found in VistA exists due to manual entry of information (VA Information Resource Center (VIReC), 2012) .

Each VistA application generates clinical and administrative data that support the day-to-day operations of VA facilities and contain patients' medical and healthcare utilization histories (Hynes, Perrin, Rappaport, Stevens, & Demakis, 2004). VistA contains the most clinical detail of any VA database and as such, captures many data points that are not currently available in any other national VA data source (VA Information Resource Center (VIReC), 2012). Specifically, information on patient demographics (age, race, ethnicity, and gender), coordination of care, pharmacy refill records, and service utilization (ER visits, inpatient admissions) are examples of some of the variables housed within VistA's powerful applications (Department of Veterans Affairs: Office of Enterprise Development, 2008).

Additionally, located within VistA, are International Classification of Diseases (ICD-9) and Current Procedural Terminology (CPT) codes that are required for use by all VHA sites to map local data, facilitating the origination of patient cohorts for use in health services research (Hynes et al., 2004). VistA contains several mechanisms that allow data analysts to identify unique individuals and subsequently link the identifier to ICD-9 codes during cohort generation. Such was the case for this study.

A saying is proliferated in VA, that "when you have seen one VA, you have seen one VA". Opponents of comparing patient care across hospitals profess that it is not possible to control adequately for the way patient care varies from hospital to hospital, let alone across an entire healthcare system (Temple, 1990). Variations in clinical care among individual VAMCs was of particular concern since a systems framework provides the investigational foundation.

VistA is a good example of the individualized character perpetuated by each VAMC. All VA data housed in VistA originates at the local level of each individual VA site of operation (Justice et al., 2006). Local data is subsequently stored at the VISN (regional) level by

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combining information from multiple facilities into a data warehouse. Finally, consolidated data from local and VISN levels, processed through the National Patient Care Database System (NPCD), is made available for research in a central location in Texas, the Austin Information Technology Center (AITC) (Hynes et al., 2004). Therefore, VistA provides the foundation for all VA databases and is the best source of clinical data (M. W. Smith & Joseph, 2003).

However, while each VAMC has VistA, not all modules are available at each facility creating differences in data fields varying across medical centers (VA Information Resource Center (VIReC), 2012). Additionally, because of the large amounts of information generated by VistA, facilities regularly purge data, further adding to the hazard of heterogeneous data pulls.

Furthermore, local VA procedures may differ in the manner data collection and recordings occur, causing data elements to have slightly different meanings at various VA sites (VA Information Resource Center (VIReC), 2012) . This is true of the outcome variable for this study, medication adherence, as variations exist across facilities in processing pharmacy data (M. W. Smith & Joseph, 2003). Therefore, knowledge of a local VistA system is required to ensure the information obtained is what is requested (Maynard & Chapko, 2004). As a result, this study provided preliminary information regarding systematic VA influences of one VAMC on coordination of care, medication adherence, and healthcare utilization that segway into regional and national investigations examining the relationship of these variables.

CPRS

VistA is comprised of more than 100 applications under constant revision. A keystone VistA application is the Computerized Patient Record System (CPRS), part of the revolution in patient care within VHA in the 1990s and remains the software package most often accessed by clinical personnel throughout the VA healthcare system today (Kizer, 1996). As such, CPRS

generates a large portion of data found in VistA and can provide longitudinal statistics for an individual patient (VA Information Resource Center (VIReC), 2012). Information culminating from CPRS provided foundational elements for the dataset used in this study.

Pharmacy Databases

VA pharmacy data is an important resource for understanding medication adherence because refill data can stratified prescription drug use by patient characteristics, such as age, gender, or race. While inpatient and outpatient pharmacy information exists, this study only captured outpatient pharmacy data as previously outlined.

There are three sources for VA pharmacy data: VistA, the Pharmacy Benefits Management (PBM) package, and DSS NDE Pharmacy SAS datasets. Because this study used local and VISN level VA data only, this discussion will focus on the database used for local as well as VISN level data capture, VistA. An important aspect of VA pharmacies is that they only fill prescriptions promulgated by VA providers with prescriptive privileges. Customarily, the provider enters medication orders into CPRS.

VistA Pharmacy

The VistA pharmacy package is comprised of 13 elements that function synergistically to assemble all pharmacy data at the local level relative to prescriptions filled in the VA (Department of Veterans Affairs: Office of Enterprise Development, 2008). VistA contains both inpatient and outpatient prescription data from 1997 onward and features information on the prescribing origin of the prescription such as primary or specialty care, National Drug Code (NDC), VA product name, VA drug class, prescription fill date, total quantity of medication dispensed, dispensing units (mg, ml, etc.), and days' supply of medication given (M. W. Smith & Joseph, 2003).

To improve the quality of pharmacy data capture, ideally, the days' supply is corroborated with the actual dosing instruction as well as the price per unit of drug. However, dosing instructions are only available in national data warehouses that were not accessed for this study. Due to resource constraints, the price per unit of medication was not retrieved.

Cohort Generation

The literature acknowledges that administrative data is usually of unknown validity. Due to feasibility and cost, validity in secondary data analysis occurs by a diagnosis code (ICD-9 code) and a particular strategy (Harris, Reeder, Ellerbe, & Bowe, 2010). In the case of this study, corroboration between an ICD-9 code and refill of a precise list of medications used to treat IBD, equated as a reliable method for identifying care of interest (Quan et al., 2004). The International Classification of Diseases, ninth revision (ICD-9) codes represent a nosology, an official system of assigning codes to diagnoses and procedures associated with healthcare in the U.S.

ICD-9 codes are frequently used to identify patients for administrative database studies in a variety of chronic illnesses including IBD (Motheral et al., 2003). The inherent limitations of this measure, including the possibility of coding errors that pose a challenge to the credibility of data accuracy, due to institutional variations in data input, are appreciated (Baker, 2007; Waltz et al., 2010). To minimize the threat of institutional variation, this study only retrieved data from one VA facility because local VA data managers possess detailed knowledge of the clinical and administrative processes used to produce various data elements (VA Information Resource Center (VIReC), 2012) .

While VHA uses ICD codes to set resource allocation for its beneficiaries, the validity of using ICD-9 codes as a measure of patient status continues to be widely debated (VA Information Resource Center (VIReC), 2012). Suggestions exist that clinician payment for

services drives the assignment of a diagnosis code (Sarrazin & Rosenthal, 2012). However, in VA, direct reimbursement for care to the provider does not occur, making this a less influential factor. Another argument against using ICD-9 codes in research is the evolution of diagnoses codes overtime (Sarrazin & Rosenthal, 2012). This study controls for this impact by examining only one FY, 2011.

To improve the accuracy of patient selection, a technique validated previously in the study population is used. The study sample consisted of all veterans enrolled in one northeast VAMC between October 1, 2010 and September 30, 2011 with an ICD-9 code of 555.x for CD and 556.x for UC, validated previously in the VA IBD population (Khan et al., 2012; Lachaine et al., 2013; Mitra et al., 2012; Thirumurthi et al., 2010). See Figure 3.2 for study variable extraction. The possibility of selection bias exists in administrative database studies due to lack of randomization. To account for this, all factors utilized in the selection of subjects for this study were clearly delineating as described below.

Inclusion Criteria

Individuals with at least one of the above outpatient ICD-9 codes at any time during FY 2011, with at least one outpatient prescription of the following oral medications used to treat IBD, and who refilled the medication at least twice during the observation period, were included for final analysis: medication (mesalamine 250mg (NDC: 54092-0189-81), mesalamine 375mg (NDC: 65649-0103-02), mesalamine 400mg (NDC: 00149-0752-15) mesalamine 1,200mg (NDC: 54092-0476-12), olsalazine (NDC: 68220-0160-10), balsalazide (NDC:, 00054-0079-28), sulfasalazine (NDC: 43353-0495-80) , azathioprine (NDC: 00054-4084-25), mercaptopurine (6MP) (NDC: 00054-4581-27).

At least two refills of medication were required to calculate the adherence measure for this study, the MPR. Any patient with a 555.x for CD and 556.x for UC, on any occasion in FY 2011, as well as a prescription for any of the above medications confirmed the diagnosis of IBD (Kappleman et al., 2008; Kappleman et al., 2011; Waltz et al., 2010). For patients with ICD-9 codes for both UC and CD, disease assignment occurred according to the majority of codes presented (Kappleman et al., 2011).

Exclusion Criteria

Because of a whole host of treatment specific confounders with oral steroids, biologic medications, rectal preparations, and injectable methotrexate, these drugs were excluded from analysis (Cooper, Hall, Penland, Krueger, & May, 2009; Kappleman et al., 2008). Moreover, exclusions included prescriptions filled prior to October 1, 2010, thereby limiting "carry in" prescriptions filled prior to the measurement period (Cooper et al., 2009).   Patients with ICD-9 codes for IBD but who were note prescribed medications for said disorder were also
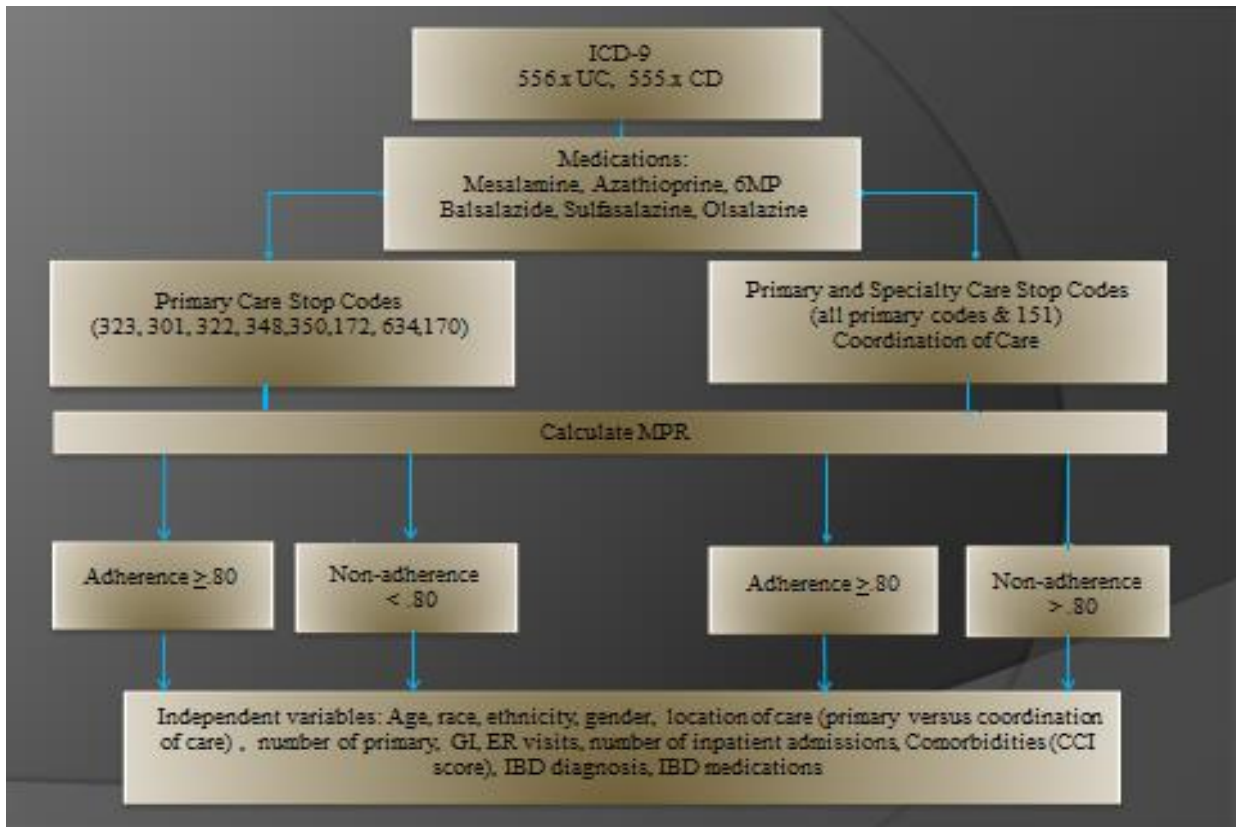
Figure 3.2 Extraction of Study Variables

excluded from analysis, as the aim of this study was to describe the medication adherence rates in this population (Gellad, 2012).

Additional exclusions are the above IBD medications administered while the veteran was an inpatient, since the aim of this study was to describe adherence to long-term therapy in IBD and not adherence to acute medication needs dictated by an inpatient admission. Therefore, adjustment of the denominator in the MPR calculation occurred to reflect the number of days between the first fill and the last refill plus the days' supply of the last refill minus the days of inpatient admission.

Furthermore, patients seen in Gastroenterology not seen by primary care were also excluded from analysis because a critical component of this study was to examine the

relationship between medication adherence and healthcare utilization among subjects cared for in the primary care setting in isolation, versus subjects who received coordination of care. Further discussion of these excluded patient follows. Information on patients receiving GI care alone was included in the final report.

Clinic Stop Code Quality

The study used clinic stop codes, 323, 301, 322, 348, 350, 170, 634, and 172 for Primary Care, 151 for Gastroenterology, and 77 for ER. The literature contained only one study that examined the accuracy of a VA clinic stop code. While the clinic stop code under investigation was not the one used in this study it is the only data that exists that speaks to the validity of using this method to identify points of care. Because the quality of data in VistA is largely uncharted, reviewing a study containing pertinent variables of interest may be the best place to discover information on data quality (VA Information Resource Center (VIReC), 2012) . As a result, the details of this study follow.

(Harris et al., 2010) conducted a study that included over 2,600 subjects, to validate the substantiation with specialty clinic stop codes used to designate treatment for a substance use disorder (SUD) and receipt of SUD care as documented in clinical progress notes. Two raters independently reviewed records and classified them as either documenting or not documenting SUD. The results demonstrated that 14.1% of the progress notes reviewed did not contain a note supporting the diagnosis SUD the day of code entry. Approximately 92% of progress notes contained evidence of SUD treatment when both a clinic stop code and CPT code for such accompanied the medical record. However, the VISN ranges of concordance were variable between 57-100%, which are exacerbation at the local facility level as has been supported in the literature previously (Tarlov & Stroupe, 2010).

The results of this study demonstrate the inability to ascertain data quality in national VA datasets with discordance found between national and local information. National level VA data discrepancies provided further support for the use of local VA data for this investigation.

Additionally, as the above study demonstrated, diligence in the actual process of data mining is required. For example, the use of two independent raters to review data results is suggested to improve the accuracy of data pulls. While resources for this study did not allow for a second data reviewer, concretely defining study variables by creating a coding index served to improve data retrieval accuracy as well as internal validity (Gearing, Mian, Barber, & Ickowics, 2006) and inter-rater reliability (VonKoss Krowchuk et al., 1995) as displayed in Table 9.

While VA databases provide the most comprehensive patient-level clinical data in VHA, the size and complexity of these databases requires in depth understanding to ensure accurate data extraction (VA Information Resource Center (VIReC), 2012). Therefore, VA researchers who wish to use retrospective data for research are strongly encouraged to work closely with a local VA data manager who has expert knowledge of the information contained in each database because extracting data in a structure that can be analyzed using statistical software can be arduous (Maynard & Chapko, 2004). The statistician for this study was the in residence local data expert.

Table 9
Coding Index

Dependent Variables	Definition	Level of Measure
MedAdhere1	Medication Adherence 0 = Non-adherence (MPR < 0.80) 1 = Adherence (MPR $\geq$ 0.80)	Dichotomous
MedAdhere2	Medication Adherence 0 = Non-adherence (MPR < 0.90) 1 = Adherence (MPR $\geq$ 0.90)	Dichotomous
HealthCareU1	Utilization primary + GI 0 = no GI outpatient, primary care only 1 = yes primary care + GI outpatient	Dichotomous
HealthCareU2	Utilization primary + ER 0 = no ER visits, has primary care only 1 = yes primary care + ER visits	Dichotomous
HealthCareU3	Utilization primary + inpatient admission 0 = no inpatient, primary care only 1 = yes primary care + inpatient	Dichotomous
Independent Variables	Definition	Level of Measure

Demographic

Age	Age	Continuous
Gender	Gender 0 = Male 1= Female	Dichotomous
RaceEth	0 = White 1 = Non-White: Black, American Indian or Alaska Native, Asian, Native Hawaiian or Pacific Islander, Hispanic or Latino, not Hispanic	Dichotomous

Table 9 (continued)
Coding Index

Independent Variables	Definition	Level of Measure
Medication		
MPR	Medication Possession Ratio (MPR) Pharmacy refill records to calculate the MPR: the sum of days' supply of medication divided by the number of days between the first fill and the last refill plus the days' supply of the last fill	Continuous
Fill Date	Date of fill, date	Date
Days' Supply	Day Supply of medication (30, 90)	Continuous
Tablets Dispensed	Number of tablets dispensed	Continuous
IBD		
IBD Diagnosis	Diagnosis: 555x. CD, 556.x UC 0 = UC 1 = CD	Categorical
IBDMED	IBD Medication 0 = 5-ASA 1 = Immunomodulator 2 = Both	Categorical
IBD Medication: 5-ASA		
Balsalazide	Balsalazide 0 = no 1 = yes	Dichotomous
Mesalamine	Mesalamine 0 = no 1 = yes	Dichotomous

Table 9 (continued)
Coding Index

Independent Variables	Definition	Level of Measure
IBD Medication: 5-ASA		
Olsalazine	Olsalazine 0 = no 1 = yes	Dichotomous
Sulfasalazine	Sulfasalazine 0 = no 1 = yes	Dichotomous
IBD Medication: Immunomodulator		
Azathioprine	Azathioprine 0 = no 1 = yes	Dichotomous
Mercaptopurine (6MP)	Mercaptopurine 0 = no 1 = yes	Dichotomous
Comorbidity		
Comorbidity	Comorbidity Deyo (1992) with Hall (2004) Calculator	Continuous
ComorbidityII	Comorbidity 0 = no 1 = yes	Dichotomous

Table 9 (continued)
Coding Index

Independent Variable	Definition
	Diagnostic Category (All comorbidities are dichotomous coded yes/no for each diagnostic category by ICD-9)
MI	Myocardial Infarction: 410-410.9, 412
CHF	Congestive Heart Failure: 428-428.9
PVD	Peripheral Vascular Disease:443.9, 441, 441.9, 785.4, V43.4, 38.48
Cerebro	Cerebrovascular Disease: 430-438
Dementia	Dementia: 290-290.9
Lung	Chronic Pulmonary Disease: 490-496, 500-505, 506.4
Rheum	Rheumatologic Disease: 710.0, 710.1, 710.4, 714.0-714.2, 714, 81, 725
Peptic	Peptic Ulcer Disease: 531-534.9, 531.4-531.7, 532.4-532.7, 533.4-533.7, 534.4-534.7
LiverMild	Mild Liver Disease: 571.2, 571.5, 571.6, 571.4, 571.49
Diabetes	Diabetes: 250-250.3, 250.7
DiabetesCom	Diabetes with Chronic Complications: 250.4-250.6
Paralysis	Hemiplegia/Paraplegia: 344.1, 342-342.9
Renal	Renal Disease: 582-582.9, 582-583.7, 585, 586, 588-588.9
Malignancy	Any Malignancy: 140-172.9, 174-195.8, 200-208.9
LiverMoSev	Moderate/Severe Liver Disease: 572.2-572.8
MalignancyMets	Metastatic Solid Tumor: 196-199.1
AIDS	HIV Infection: 042-044.9

Table 9 (continued)
Coding Index

Independent Variable	Definition	Level of Measure
Healthcare Utilization		
CoordinationCare	Coordination of care, FY 2011 0 = Primary Care only 1 = Primary Care + GI Specialty Care	Dichotomous
PrimeCare	Total primary care visits, FY 2011 stop codes 323, 301, 322, 348, 350, 170, 634, and 172	Continuous
GIOutpt	Total GI specialty visits, FY 2011 stop code 151	Continuous
ERVisit	Total ER visits, FY 2011: stop code 77	Continuous
InPt	Total inpatient admissions, FY 2011	Continuous
LOS	Length of Stay	Continuous

Pharmacy Data

Data quality is a limitation when using pharmacy refill information in research. While a large body of literature has been generated using VA pharmacy data, a gap in the literature exists regarding the exactness of this material (M. W. Smith & Joseph, 2003) . VistA is the primary source for clinical data in VA for which no record is available against which to validate information because all data entry occurs directly into the system through CPRS (M. W. Smith & Joseph, 2003).Pharmacy administrative database have a high specificity, if medications are obtained from a closed pharmacy system such as in VA and patients are not obtaining medications from other sources as is assumed for this study (Hynes, 2012). Moreover, pharmacy

datasets support analysis of population based prescribing habits, drug utilization trends, unwarranted variations in clinical practice, and estimate drug usage at local, regional, or national levels (Cunningham, Sales, & Valentino, 2001).

Accuracy of medication identification using VA pharmacy databases was the focus of a national VA study of 268,774 individuals (Schutte, Hu, Schmitt, & Phibbs, 2011). Subjects with at least one outpatient or inpatient diagnosis for bipolar disorder between FY02 and FY09 based upon ICD-9 codes for this mental illness. Eligible patients were then paired with descript list of medications (26) used to treat this condition. Similar to how cohort generation will take place in this study.

Subsequently, a systematic review of patient's medication compared the presence of one or more of the identifiers noted below in a national VA database using such combinations as: IEN only, NDC only, IEN + NDC, and IEN + NDC + IPNUM/IPNO. There are four variables in VA national databases that provide medication name and strength: Internal Entry Number (IEN), National Drug Code (NDC), Intermediate Product Number (IPNUM/IPNO), Drug Description (DRUGDESC) (Schutte et al., 2011), the first three of which were used in this study. Omission of the DRUGDESC identifier occurred since an unknown quantity of misspellings and abbreviated drug names exist in this file (Schutte et al., 2011) .

Overall, the results established with 99.3% accuracy that the assigned IEN, NDC, and IPUNUM/IPNO identifying codes were in full agreement about whether a prescription for bipolar medication existed. Results for all identifiers were statistically significant (p. <0.05) with higher levels of significance found with multiple identifies (p.<0.001). The authors recommended the use of multiple-drug identifiers for completeness. To enhance the accuracy of pharmacy data in this study, the use multiple medication identifiers was deployed when possible.

Medication adherence is a multifaceted construct, such that any measurement used in isolation for measurement is a recognized study limitation. Pharmacy data is not a proxy for adherence it represents just one part of this complex construct.

For example, in this study, the use of pharmacy refill data did not take into account the additional activities that may influence medication adherence in this regard, such as a visit to the clinician to obtain said prescription, filling the prescription, taking the medication as prescribed, as well as refilling the medication. Therefore, this study examined just one of the many aspects of medication adherence.

Lack of a consensual definition of medication adherence in the literature is another limitation of this study. Significant enhancement to external validity or reproducibility occurs with the standardization of data (Jansen et al., 2005). A critical component of secondary data analysis will be to establish operationalized definitions of chosen measurements to aid in reclamation of data from databases. To add to the current adherence literature in a meaningful way, the definition of medication adherence advised by ISPOR (Cramer et al., 2008) in a consensus document served as the definition of adherence for this study. Additionally, during methodologic decision-making, every attempt to utilize standard measures as outlined by the international retrospective adherence experts of ISPOR occurred (Peterson et al., 2007) .

The outcome variable for this study was medication adherence, assessed using VA pharmacy refill data, measured for one year, FY 2011, for several reasons. One, the theoretical foundation for this investigation, the CCM, is a systems model. The system under consideration, the VA, is constantly changing how it organizes care delivery, assigns clinical priorities, and allocates funding appropriated by Congress. Therefore, examination of recent FY data to

describe current systematic influences on all variables, specifically the relationship between coordination of care, medication adherence, and healthcare utilization was consistent with the CCM. Additionally, to ensure completeness of information, use of FY datasets that are closed is advised (Hynes, 2012) . At the time of this publication, FY 2011 is the most recent complete dataset available. Two, VA databases are under constant revision. Therefore, how data compilation takes place, using current databases, may not be how data aggregation occurred even a year ago (Hynes, 2012). Additionally, database attributes can vary widely depending on the research question(s) and analysis performed (Motheral et al., 2003).

Moreover, this study examined only 1 year of medication adherence because medication adherence changes over time and this study was meant to describe the medication adherence patterns of a group about which little is known. While the greatest decline in adherence for many chronic medications occurs over the first year of therapy (Deizii, 2000), it was not the intent of this study to explore adherence rates of new users versus those with longer disease durations.

The following were assumptions when using pharmacy refill data to measure medication adherence: medications prescribed were appropriate, pharmacy records were accurate, medication acquisition from another person or venue did not occur, lack of a refill equated with medication not consumed during that period, and no healthcare provider treatment interruptions occurred during the refill period (Williams, Amico, Bova, & Womack, 2012). An additional assumption was that patients refilling medication were unlikely to pick up medications with no intentions of taking them (S. Kane et al., 2001).

Local VA databases did not contain any information regarding private insurance coverage outside of VA. Therefore, it was conceivable that a patient may fill a prescription for IBD medications outside the VA. This was a study limitation.

Race Data Quality

All race data originates at the local VA level in VistA and is then compiled into national VA datasets. Heterogeneity in defining race exists in VA national level race data. For example, the VHA Office of Informatics and Analytics compared data extraction for race from two national VA databases, Corporate Data Warehouse (CDW) and the Administrative Data Repository Reporting Production (ADRRP) that demonstrated a lack of consistency in defining race across the VA system. Review of four million unique patient records housed in CDW, revealed 31 non-standard race values with different race values for the same individual across facilities. A patient may have up to seven race assignments in CDW. Whereas ADRRP, provides only standardized race values contained in a single demographic record for each patient. However, race data was missing for 171,000 individual demographic records. These inconsistencies provided further support for the use of local VA data only to improve the accuracy of data capture. An additional race limitation of this study was homogeneity in this cohort that limits generalizability of study findings beyond VHA.

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Chapter 4

Manuscript: Results and Discussion

The results for study aims are below which included the primary study aim: described medication adherence rates, healthcare utilization, and care coordination of veterans with inflammatory bowel disease (IBD) who employ Veterans Affairs (VA) healthcare at one Veterans Affairs Medication Center (VAMC). Secondary study aims included: examination of the association between medication adherence adjusted for care coordination, age, IBD diagnosis, comorbidity, and IBD medication in veterans with IBD who employ VA healthcare; and exploration of the relationship between healthcare utilization adjusted for medication adherence, age, IBD diagnosis, IBD medication, care coordination and comorbidities in veterans with IBD who employ VA for healthcare. The manuscript was prepared for submission to a journal with a GI focus entitled, Inflammatory Bowel Diseases. The title for this manuscript is "A retrospective data analysis: Using Wagner's Chronic Care Model to explore predictors of medication adherence in veterans with inflammatory bowel disease". ISPOR retrospective database publishing recommendations informed final manuscript construction.[1]

Abstract

Background

Medication adherence in inflammatory bowel disease (IBD) ranges between 7-72%. Increased healthcare utilization has been associated with non-adherence in IBD. Wagner's Chronic Care Model (CCM) posits that care coordination between primary and gastroenterology (GI) specialty care could improve adherence and healthcare utilization.

Methods

Guided by the CCM, a retrospective analysis was conducted in veterans with IBD to: describe medication adherence rates; describe healthcare utilization measured by ER visits and inpatient admissions; and describe care coordination measured by primary care and GI specialty care use. A secondary study aim was to explore the relationships between those key outcome variables and select demographic/health history characteristics.

A local Veteran's Affairs database was used to extract a cohort of individuals with Crohn's disease and ulcerative colitis for fiscal year (FY) 2011. Medical utilization and IBD medication refills were collected. A dichotomized medication possession ratio (MPR .80) was used in logistic regression to identify factors affecting medication adherence. Logistic regression was also used to examine factors affecting ER visits, inpatient utilization, and care coordination.

Results

The cohort consisted of 165 White male veterans 75 with Crohn's disease and 89 with ulcerative colitis. The overall rate of adherence was 50.9% with a median MPR of .82. Regression models did not render any statistically significant predictors of adherence. ER utilization was significantly associated with adherence (OR=.314, 95%CI=.111-.886, p=.029) and care coordination (OR=45.73,95%CI=9.053-231,p=.001) in multivariate analysis. Inpatient

admission was associated with: younger age (OR=.108,95%CI:.019-.609,p=.012), adherence (OR=.113,95%CI=.014-.939,p=.044), IBD diagnosis (OR=.117,95%CI=.017-.784,p=.027), and care coordination (OR=11.89,95%CI=1.228-115,p=.033). Logistic regression identified statistically significance associations with care coordinated between primary and GI specialty care and the following factors: taking both a 5-ASA and immunomodulating medication (OR=5.122,95%CI=1.874-14.00, p=.001), younger age (OR=.905,95%CI=.871-.940,p=.001), and having a comorbidity (OR=2.643,95%=1.171-5.965,p=.027).

Conclusions

No predictors of medication adherence emerged. However, the CCM element of care coordination provided additional insight into the healthcare utilization of veterans with IBD as statistically significant associations between ER visits and hospitalization were identified. Further inquiry into the influences of medication adherence and healthcare utilization in this population is warranted.

key words: *adherence to medication, Wagner's chronic care model, coordination of care, veterans, inflammatory bowel disease*

Introduction

Ulcerative colitis (UC) and Crohn's disease (CD) comprise inflammatory bowel disease (IBD), a set of chronic inflammatory diseases of the GI tract. The financial burden of IBD in the United States (U.S.) is considerable, in the range of 3-8 billion dollars annually.[1] Nearly 1.5 million Americans suffer with IBD.[2] However, little is known about the 45,000 veterans with this disease who access the world's largest integrated healthcare system, the Veterans Health Administration (VHA).

Life-long medication administration is required in IBD to control this often tenuous condition. However, medication adherence for those who are diagnosed is problematic, in the range of 7-72%.[3] Modifying factors affecting medication adherence in IBD are not distinctive, existing in many chronic diseases and include age, lack of knowledge regarding illness and treatment, discordance in the physician-patient relationship, low health literacy, pill burden, employment, and depression.[4] Several noteworthy, unique, condition specific factors found to affect adherence include remission status, disease type (CD versus UC), new patient status, timing of last colonoscopy, and taking immunosuppressants.[4] No consistent variables that could be used to direct interventions have emerged as predictors of adherence in this population.

Furthermore, there have been no studies conducted to date that have explored predictors of medication adherence in veterans with IBD. While two studies have been published examining medication adherence in this cohort, the studies focused on disease recurrence. The authors found the adherence rate of veterans to be between 37-48%, with non-adherent patients at increased risk for a disease flare.[49,50]

Evidence indicates that when chronic illness is sub optimally treated, complications may worsen leading to increased consumption of healthcare resources such as ER services, inpatient admissions, as well as office visits,[4] suggesting that higher levels of medication adherence may reduce healthcare costs.[5] Repeatedly, research has demonstrated that those with IBD who do not follow prescribed medication regimes have higher rates of healthcare utilization.[6-8] World adherence experts provide support for examination of healthcare utilization concurrently with medication adherence as this data works synergistically to accurately inform health outcomes and future interventions. [9]

Often IBD care is multidisciplinary requiring input from other specialty services and departments such as the emergency room (ER), inpatient medicine, surgery, radiology, pathology, dermatology, rheumatology, and ophthalmology.[10] Contributions from primary care, the gatekeeper to specialty healthcare in the United States, are rarely considered.[16] Inquiry into the effects of a closed system such as VHA, using Wagner's Chronic Care Model (CCM) may provide insight into the associations of both primary and specialty care with medication adherence and healthcare utilization of veterans with IBD. [11] VHA adopted the CCM in the late 1990s as a vehicle for transformation. [12] The CCM element of care coordination became integral to delivery of chronic illness care of veterans orchestrated by primary care with consultation to specialists as warranted. Intuitively, coordination of primary and specialty care should equate with improved health outcomes. However, results from a Cochrane review revealed conflicting results.[13] Medication adherence was the only clinical outcome that demonstrated improvement with care coordination. The effects of the VHA system on medication and healthcare utilization in this population are unknown supporting the primary line of inquiry to describe medication adherence and healthcare utilization in veterans.

Study Purpose

Guided by the CCM, a retrospective analysis was conducted in veterans with IBD to: describe medication adherence rates; describe healthcare utilization measured by ER visits and inpatient admissions; and describe care coordination measured by primary care and/or GI specialty care use. A secondary study aim was to explore the relationships between those key outcome variables and select demographic/health history characteristics.

Ethical Considerations

Approval was obtained from the appropriate institutional review boards.

Methods

Design & Data Source

A descriptive, retrospective data analysis was conducted by extracting information from a local VA data warehouse, Veterans Health Information Systems and Technology Architecture (VistA), containing information about patients treated in the VA Healthcare System which is updated nightly. VistA is an integrated system of software applications that directly supports patient care at VA healthcare facilities by tying together workstations and personal computers, providing a system of management tools that create uniformity of data across the VA system. [15] Each VistA application generates clinical and administrative data that support the day-to-day operations of VA facilities and contain patients' medical and healthcare utilization histories. [16] VistA contains the most clinical detail of any VA database and as such, captures many data points that are not currently available in any other national VA data source [10] and was used to collect the following study measures: International Classification of Diseases, Ninth Revision (ICD-9) codes, outpatient pharmacy, patient demographics, and healthcare utilization. VistA

and Veterans Integrated Service Network (VISN) data were collected for outpatient medication refills only to ensure completeness of pharmacy data capture.

Study Population

The population for this investigation consisted of enrollees in one northeast VA who sought care for IBD between October 1, 2010 and September 30, 2011 for IBD, fiscal year FY 2011. Cohort inclusion and exclusion criteria are located in Table 1.

Study Measures

Medication adherence was measured using the medication possession ratio (MPR).[17] The MPR was the sum of the days' supply of medication divided by the number of days between the first fill and last fill including the days' supply of the last fill.[16] MPR was calculated for each medication for each patient and a mean MPR was calculated for each patient taking more than one medication. [18] As is widely used in the literature, the MPR was a continuous variable for descriptive analysis, dichotomized for logistic regression models so that those with an MPR $\geq$ .80 were adherent and those with an MPR < .80 were non-adherent. [19-30] MPR was an examined both as a dependent variable in a logistic regression model and was then an independent variable in the regression models for ER utilization and inpatient admission. The MPR would not include those with primary non-adherence such as those who were prescribed a medication but had not picked it up from the pharmacy. Additionally, because the MPR requires at least two medication refills during the observation period, those filling only one prescription were not included in the final analysis.

Healthcare utilization variables included ER visits and inpatient admissions, represented by respective clinic stop codes. For descriptive purposes, the total number of occurrences over

the one year observation period for each visit type for each patient was collected. However, for logistic regression, all healthcare utilization variables were dichotomized, yes/no.

Care coordination was measured using clinic stop codes for primary care and gastroenterology (GI) specialty care. For descriptive purposes, the total number of occurrences over the one year observation period for each visit type for each patient was also collected. Veterans with IBD were assumed to have care coordination if both primary and specialty GI clinic stop codes were present.

Demographic variables included age, gender, race, ethnicity, IBD diagnosis (CD versus UC) and IBD medication (5-aminosalycilate (5-ASA), immunomodulator, or both) were used to describe the population under study.

The Deyo adaptation [31] of the Charlson Comorbidity Index (CCI) [32] was used to calculate comorbidity. Deyo identified 17 categories of medical conditions using ICD-9 codes and assigned a weighted score for each condition that was summed (Table 1). Higher values indicated more severe levels of comorbidity.

Statistical Analysis

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 21.0. [33] A two-tailed test of significance was used with alpha set at .05.

Variable analysis began with descriptive statistics for all study variables including distribution of continuous variables. Chi-squared tests for categorical variables and *t*-test (normally distributed) or Mann-Whitney U tests (non-normally distributed) for continuous variables were conducted to examine bivariate associations between the primary outcomes of medication adherence and healthcare utilization and remaining study variables. Similar

procedures were used to explore care coordination as an outcome. All variables were entered into logistic regression models regardless of bivariate analysis results.[34]

Simultaneous logistic regression was used to examine the effect of age, IBD diagnosis, IBD medication, comorbidity, and care coordination on adherence, dichotomized (yes (MPR $\geq$.80)/no MPR <.80). Medication adherence was then entered as an independent predictor in ER and inpatient regression models.

Similar logistic regression model construction was used to explore the impact of age, IBD diagnosis, IBD medication, comorbidity, medication adherence, and care coordination on ER utilization and inpatient admission (both dichotomized yes/no). Because IBD diagnosis was not a significant bivariate predictor, the interaction terms: IBD diagnosis * coordination of care; IBD diagnosis*age; and IBD diagnosis*medication adherence were created and entered separately into the inpatient regression model. Odds ratio, 95% CI, and P-values were reported for all three regression models.

Results

A cohort of 247 (Figure 1) patients extracted from a local VA database with at least one ICD-9 code for 555.x (CD) and 556.x (UC) were identified between October 1, 2010 and September 30, 2011. Females (n=11) and non-Whites (n=14) were excluded because of minute representation. Patients receiving GI specialty care alone (n=36) were also excluded because a critical study component was to examine relationships between patients cared for in the primary care setting in isolation, versus patients who received care coordination through primary and GI specialty care. The final study sample consisted of 165 patients who met all inclusion and exclusion criteria (Table 2).

Study Population

The final study sample was homogenous, consisting of White males. The mean age was 69.2 years (SD± 13.4) with 81% of the sample falling between 60 and 89 years. In the study cohort, 75 had CD (46%) and 89 had UC (53.9%). A 5-ASA product was prescribed for 76% of patients while 24% of the sample refilled an immunomodulating medication. Comorbidity was not present in 44.8% of the sample. The median comorbidity score was 3, SD ± 2.9. The top three comorbidities were COPD (23%), malignancy (15.2%), and cerebrovascular disease (9.1%).

Medication Adherence Descriptive Results

The adherence rate for the entire sample was 50.9%. The median MPR was .82. As Table 3 demonstrates, the range of adherence for all IBD medications was as high as 78% for mesalamine 375mg and as low as 60% for those taking both a 5-ASA and an immunomodulator. Table 4 presents a summary comparison of study variables by adherence in bivariate analysis which did not reveal any statistically significant factors associated with adherence.

Healthcare Utilization Descriptive Results

ER Utilization

The mean number of ER visits was .37. The median was 0 .00; 83.1% of patients did not utilize ER services. Seventeen of the 28 patients who used the ER had 1 ER visit. Bivariate analysis revealed a statistically significant relationship between ER utilization and patients with care coordinated between primary and GI specialty care indicating that patients with care coordination were more likely to engage ER services (OR=29, 95%CI=6.67-129.6, p<.001). Bivariate analysis also identified medication adherence as a predictor of ER utilization

suggesting that adherent patients were less likely to use the ER (OR=.321, 95%CI=.132-.779, p=.009).

Inpatient Admission

Only 10 patients (6%) had an inpatient admission, the mean length of which was .71 days, SD ± 3.9. The median number of inpatient admissions was zero as most patients were not hospitalized. Bivariate analysis revealed a statistically significant relationship between inpatient utilization and care coordination suggesting that patients with care coordination are more likely to have an inpatient admission (OR=14.64, 95%CI=1.809-118.547, p=.001). Medication adherence was also a statistically significant bivariate predictor of inpatient admission demonstrating that adherent subjects were less likely to experience an inpatient admission (OR=.223, 95%CI=.046-1.082, p=.044). Bivariate analysis likewise revealed a statistically significant difference in age between patients with an inpatient admission and patients without an inpatient admission (*t* (163)=2.654, 95%CI=2.982-19.943, p =.009). Those with an inpatient admission were younger (M = 57.3) versus those who without (M = 70.6).

Care Coordination Descriptive Results

The final primary study aim was to describe care coordination of veterans with IBD measured by primary care and GI specialty care visits. Care presumed to be coordinated between primary and GI specialty care was found in 41% of the sample. A statistically significant percentage of patients who had care coordination were prescribed both a 5-ASA and an immunomodulating medication (30%) compared to those managed by primary care alone (13.2%) X^2(14.182, p=.001).

Independent samples *t-t*est demonstrated a statistically significant difference in age between those cared for in primary care alone and those who received care coordination

(*t* (163)=4.829, 95%CI=.166-.396, p<.001). Those who received care coordination were younger, (M=62.9, SD $\pm$14.1) than those seen in primary care alone (M=74.4, SD$\pm$10.3). More patients with CD (24.2%) than UC (17.1%) had chronic illness care coordinated between primary and GI specialty care which was statistically significant (OR=2.421, 95%CI=1.283-4.567, p =.006).

The mean number of primary care visits for patients with care coordinated between primary and GI specialty care was 2.21 (SD $\pm$ 1.073) compared to 1.40 (SD$\pm$ .623) visits for those seen in primary care alone, which was statistically significant (t(163)= 6.066,95%CI=.542-1.066, p=.001). Comparatively, 46% of patients with care coordination had 3 (SD$\pm$ 2.76) or more visits to GI which was also statistically significant (t(163) = 10.724, 95%CI =.2.472-3.587, p=.001). Interestingly, 58.8% of those with a diagnosis of IBD were never seen in a GI specialty clinic.

Multivariate Results

Medication Adherence

A secondary aim of this study was to explore predictors of medication adherence and healthcare utilization. Multivariate analysis showed no statistically significant relationships between medication adherence and the variables of age, IBD diagnosis, IBD medication, comorbidity, and care coordination (Table 5).

ER Utilization

The logistic regression model with ER utilization dichotomized (yes = ER and no = no ER) containing all predictors was statistically significant, *X (*7, n=165) = 50.218, p<.001. The model revealed a statistically significant association between ER utilization and care coordinated between primary care and GI specialty care (p=.001) and medication adherence (p=.029) (Table 5).

Inpatient Admission

The full model with all predictors was able to distinguish between patients who did and did not have an inpatient admission (X (7, N=165) = 23.681, p<.001). Table 5 shows that four of the six independent variables had a statistically significant relationship with inpatient healthcare utilization. Care coordination was the strongest multivariate predictor of inpatient admission (p=.033). Addition of interaction terms did not produce any statistically significant results.

Discussion

This is the first study known that critically appraised chronic illness care in veterans with IBD through the CCM lens of care coordination between primary care and GI specialty care relative to medication adherence and healthcare utilization. Study strengths included: use of a theoretical framework recognized by IBD experts as a mechanism to improve outcomes in patients with IBD; [35-37] generation of a cohort using an administrative definition validated in this population; [38] use of the gold standard for measuring medication adherence in IBD, the MPR; [19] and use of the consensus definition and measure for adherence propagated by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR). [18,39]

The overall level of adherence in this study (50.9%) is congruent with previous investigations that included other closed government sponsored healthcare systems and continues to demonstrate adherence levels well below the accepted value of 80%. [3,47] This study used local and VISN level VA pharmacy data only. Although slightly higher in this study, the level of adherence was comparable with recent adherence studies that revealed overall levels of adherence in this population to be between 37-48%. [41,42] as evidenced in large national samples of veterans that used the same administrative definition for IBD and similar MPR calculations.

However, this is the first study to examine adherence in the IBD population that was not able to identify predictors. Regression model construction was parsimonious, guided by the literature. One possible reason for the lack of significance in our adherence model could be characteristics unique to our sample. Only two studies have been published that examined medication adherence rates in veterans with IBD, neither had the goal of identifying predictors of adherence in this population. [48-50] The samples of both studies consisted primarily of White males with UC, prescribed oral mesalamine. Our study included patients with both CD and UC who were prescribed a variety of oral 5-ASA products and/or an immunomodulator. Additionally, a recent systematic review conducted to examine factors associated with non-adherence in IBD demonstrated that patients in IBD adherence studies are younger than the patients in our study and are an equal mix of males and females.[3]

An additional consideration for these results is the power of the study. It is plausible that these analyses could have been underpowered, even though steps were taken to address this issue a priori. The only published data that exists related to medication adherence in veterans with IBD utilized considerably large samples (n=13,062)[50] and (n=4,452)[49]. However, these same data had been shown to demonstrate significance using other statistical tests. This provides evidence that the current sample size provided adequate power. For example, medication adherence dichotomized as the MPR (.80) was a significant predictor of ER and inpatient utilization which speaks to adequate power of the study. Nonetheless, our adherence regression model was only able to explain 2% (Cox and Snell) to 3% (Nagelkerke) of the variance of those who were adherent versus those who were non-adherent. Future adherence studies in veterans with IBD should include larger sample sizes and explore additional variables for clinical relevance to medication adherence.

There is a lack of scientific agreement regarding measurement and definition of medication adherence using administrative data in the literature. Measuring adherence using pharmacy refill data has been deliberated for decades. [40] Notwithstanding, even consensus documents promulgated by ISPOR contain discrepancies in advised definition and measure of adherence [18,39]. Most recently, Raebel [41] and colleagues, which included Steiner whose sentinel paper in 1988 [42] started the evolution of electronic database measurement, developed a conceptual model for standardization of adherence measurement using an algorithmic approach. The model introduces new concepts into the adherence lexicon. Terms such as adequate secondary adherence, inadequate secondary adherence, later-stage persistence, later-stage non-persistence are presented. A new measure of adherence based on medication gaps, new prescription medication gap (NPMG), is also offered. In an attempt to provide a comprehensive approach to adherence measurement, new layers of complexity appear. One issue that was beyond the scope of the paper was the acceptance of an MPR of .80 as representative of adherence. Although the MPR is the most frequently used administrative measure, it too has its limitations. [43] An MPR of .80 equates to taking a medication 80% of the time. This means that 20% of the time, the patient is not taking any medication. Use of this cutoff implicitly assumes that no change in health outcome occurs as result of this "allowable gap" in treatment. The 80% cut off is used widely throughout adherence literature for many chronic disease states, although not supported by any documentation of the clinical validity of this measure. [44,45] The origins of these cut off points are based on the principal that loss of >20% of a patient population in a clinical trial makes the results suspect. [46] In the interim, the .80 value is the acceptable cut off for measuring adherence in patients with IBD using administrative data.

As an independent predictor, medication adherence emerged in our study as having a strong association with both ER visits and inpatient admissions, suggesting that patients more adherent to their medications were less likely to engage these services. Our findings were consistent with a recent study (n=1,693) that also used the MPR to measure adherence and controlled for comorbidity using the Deyo adaptation method, which demonstrated 34% fewer ER visits (p=.0016) and 31% fewer hospitalizations (p=.0025) in adherent IBD patients.[8] Our findings also corroborate previous work that demonstrated 45% lower ER (p<.001) and 62% lower inpatient (p<.001) resource utilization in adherent IBD patients. [7]

The percentages of patients who utilized the ER (16.9%) and had an inpatient admission (6%) in our cohort were small. One explanation for these healthcare utilization figures may be the limited one year observation period used in this study because many researchers have investigated utilization in the IBD population over multiple years. [7,8,51-57,,58] However, healthcare utilization data in this study was part of an exploratory analysis as the influences on healthcare utilization in veterans with IBD has not been researched. [8,59] Therefore, further inquiry into the healthcare utilization patterns of veterans with IBD is warranted.

Care was coordinated in 41% of the sample. Our data demonstrated that the CCM element of care coordination was found to have several statistically significant bivariate associations between study variables. Patients with care coordinated between primary care and GI specialty care were less healthy than patients who were not, as represented by the statistically significant bivariate characteristics found among patients with care coordination that included: younger age; more likely to have CD compared to UC; had been prescribed a 5-ASA + immunomodulating medication; had comorbidities; and had an increased propensity for both ER and inpatient utilization. One explanation for the characteristics of patients cared for in the GI

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specialty setting may be that primary care providers do not feel comfortable providing care for patients with IBD more affected by their illness which prompts consultation to the specialist. [62] While it is accepted that a majority of patients with IBD are followed on a long-term basis in an outpatient GI specialty clinic,[63] 58.8% of patients in our study were never seen in the GI clinic which may be due to a more quiescent course of illness in patients with IBD seen in primary care. This corroborates the comorbid characteristics of our patients with coordinated care suggesting PCP willingness to treat less complicated patients with IBD by referring them to the GI specialist as necessary. An alternative explanation for the increased propensity of patients with care coordination to consume ER and inpatient services could be that these services were accessed for patient comorbid conditions. However, without specific ICD-9 codes for each type of healthcare utilization, this is unfeasible to discern.

Limitations

A main study limitation is the definition of care coordination. No consensus in the literature exists regarding how best to define and measure this variable. Often, research reports do not include information regarding the definition of this variable.[61] Therefore, to contribute to science in a meaningful way, the definition of care coordination in our study was derived from the CCM which adopted the definition from the Agency for Healthcare Research and Quality (AHRQ) Technical Review and was as follows: "the deliberate organization of patient care activities between two or more participants (including the patient) involved in a patient's care to facilitate the appropriate delivery of healthcare services. Organizing care involves the marshaling of personnel and other resources needed to carry out all required patient care activities, and is often managed by the exchange of information among patients responsible different aspects of care" (p.41). [61] Care coordination in our study was assumed when the patient had clinic stop

codes for both primary and specialty care. Further exploration of the influences of care coordination on medication adherence and healthcare utilization in veterans with IBD is warranted.

An additional limitation of our study is lack of consideration of veteran access to healthcare outside the VA system. An assumption of our study was that veterans did not access health services outside the VA for IBD chronic illness care. However, a survey of veterans conducted during the observation for this study, FY 2011, reported that 45% of enrollees have access to prescription drug coverage outside the VA, the details of which were unavailable for this study, and may influence many key study variables. [65] More than 65% of our study sample was age 65 and over qualifying them for Medicare. The use of Medicare services in veterans was the focus of a 2012 study conducted by Trivedi that reviewed over 1 million records and confirmed that 50% of veterans used both Medicare and VA for a variety of healthcare services. All of this said, access to healthcare outside the VA represents a serious confounder that will need to be addressed in future veteran research.

Finally, there are several study limitations precluding generalizability of study findings. Our cohort consisted of White males over the age of 65. However, a recent national survey of veterans suggested these characteristics are representative of the veteran population.[65] Our study relied on administrative data that were not verified by comparison with health records due to resource constraints. Furthermore, these data may reflect the specific practice patterns of the local VA facility and may not be representative of IBD care delivery across VA. Data used in this study were not originally generated for research purposes and are subject to coding errors both during data entry phase by hospital staff and during the data extraction process. We created a coding index containing detailed definitions of each study variable that was used to retrieve

data elements to ensure accuracy of data capture. Another study limitation is the fact that a medication refill does not equate with consumption of medication. A prescription may have been filled but the patient may not have ingested the medication.

Conclusions

The overall adherence rate in this study, which was consistent with the literature, demonstrates the need for interventions to improve medication use among patients with IBD. No predictors of medication adherence emerged, yet medication adherence was an independent predictor of both ER and inpatient utilization which indicated that adherent patients were less likely to access these services. The CCM element of care coordinated care was significantly associated with all healthcare utilization variables suggesting those with care coordinated between primary care and GI specialty care were overall more likely to access health services compared to patients cared for in primary care in isolation. The solution to non-adherence and consumption of healthcare resources in patients with IBD will likely be as complex and individualized as the treatments they receive. To advance knowledge in this area, this study suggests that Wagner's Chronic Care Model can provide a solid foundation for further inquiry.

Table 1			
Translation of Charlson Comorbidity Index (CCI) elements into ICD-9 codes			
Diagnostic Category	ICD-9 Codes	Assigned weights for diseases	Condition Description
Myocardial infarction	410-410.9 412	1	Acute myocardial infarction Old myocardial infarction
Congestive heart failure	428-428.9	1	Heart failure
Peripheral vascular disease	443.9 441.441.9 785.4 V43.4 procedure 38.48	1	Peripheral vascular disease, includes intermittent claudication Aortic aneurysm Gangrene Blood vessel replaced by prosthesis Resection and replacement of lower limb arteries
Cerebrovascular disease	430-438	1	Cerebrovascular disease
Dementia	290-290.9	1	Senile and presenile dementia
Chronic pulmonary disease	490-496 500-505 506.4	1	Chronic obstructive pulmonary disease Pneumoconioses Chronic respiratory conditions due to fumes and vapors
Rheumatolgic disease	710.0 710.1 710.4 714.0-714.2 714.81 725	1	Systemic lupus erythematosus Systemic sclerosis Polymyositis adult rheumatoid arthritis Rheumatoid lung Polymyalgia rheumatic
Peptic ulcer disease	531-534.9 531.4-531.7 532.4-532.7 533.4-533.7 534.4-534.7	1	Gastric, duodenal and gastrojejunal ulcers Chronic forms of peptic ulcer disease

Table 1 (continued)			
Diagnostic Category	ICD-9 Codes	Assigned weights for diseases	Condition Description
Mild liver disease	571.2 571.5 571.6 571.4- 571.49	1	Alcoholic cirrhosis Cirrhosis without mention of alcohol Biliary cirrhosis Chronic hepatitis
Diabetes	250-250.3 250.7	1	Diabetes with or without acute metabolic disturbances Diabetes with peripheral circulatory disorders
Diabetes with chronic complications	250.4-250.6	1	Diabetes with renal, ophthalmic, or neurological manifestations
Hemiplegia or paraplegia	344.1 342-342.9	2	Paraplegia Hemiplegia
Renal disease	582-582.9 582-583.7 585 586 588-588.9	2	Chronic glomerulonephritis Nephritis and nephropathy Chronic renal failure Renal failure, unspecified Disorders resulting from impaired renal function
Any malignancy, including leukemia and lymphoma	140-172.9 174-195.8 200-208.9	2	Malignant neoplasms Malignant neoplasms Leukemia and lymphoma
Moderate or severe liver disease	572.2-572.8	3	Hepatic coma, portal hypertension, other sequelae of chronic liver disease
Metastatic solid tumor	196-199.1	6	secondary malignant neoplasm of lymph nodes and other organs
AIDS	042-044.9	6	HIV infection with related specific conditions

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Table 2
Inclusion Criteria
At least one outpatient ICD-9 code
CD (555.x)
UC (556.x)
At least two refills of any oral IBD medication
Mesalamine 250mg
Mesalamine 375mg
Mesalamine 400mg
Mesalamine 1,200mg
Olsalazine
Balsalazide
Sulfasalazine
Azathioprine
Mercaptopurine
Exclusion Criteria
✓ **Oral steroids, biologic medications, rectal preparations, injectable methotrexate**
✓ **Inpatient IBD medications**
✓ **Patients treated in GI specialty care in isolation with no follow up to primary care**
✓ **Patients with only one refill of outpatient IBD medication(s)**

CD=Crohn's disease; UC=ulcerative colitis; IBD: inflammatory bowel disease; GI=gastrointestinal;
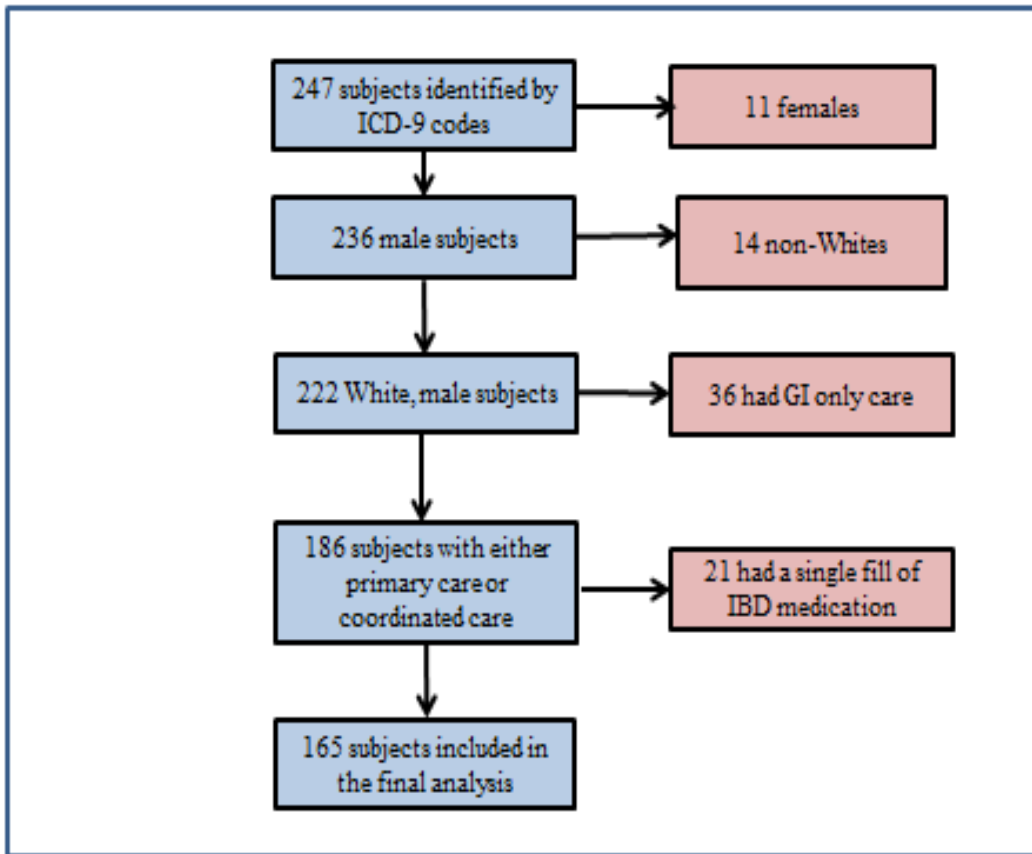
Figure 1   Cohort Generation

Table 3. Mean MPR by drug

Drug Class: 5-ASA	Frequency (*n*=165)	Mean MPR
Balsalazide	2(1.2)	.74
Olsalazine	1(.6)	.99
Mesalamine 250mg	11(6.7)	.71
Mesalamine 375mg	74(44.8)	.78
Mesalamine 400mg	48(29.1)	.73
Mesalamine 1,200mg	7(4.2)	.66
Sulfasalazine	24(14.5)	.74
Drug Class: Immunomodulator		
Azathioprine	21(12.7)	.65
Mercaptopurine	18(10.9)	.77
Aza + 5-ASA	16(9.7)	.60
Mercaptopurine + 5-ASA	16(9.7)	.83

MPR=medication possession ratio;5-ASA=5-aminosalicylate; Aza=azathioprine

Table 4. Bivariate analysis of study variables in adherent and non-adherent patients (*n=165)*

Variable	Adherent >.80		Non-Adherent<.80		*P*	Odds Ratio	
	n	%	*n*	%		OR	95%CI
Coordination of Care	30	18	38	23	.144	.629	.337-1.17
IBD Diagnosis							
CD	38	23	38	23	.829	.935	.507-1.725
UC	46	28	43	26	.829	.935	.507-1.725
IBD Medication							
5-ASA	65	39	61	37	.739	----	-----
Immunomodulator	3	2	5	3	.739	----	-----
Both	16	10	15	9	.739	----	-----
Comorbidity	44	27	47	28	.466	.796	.430-1.472
Age	84	51	81	49	.158	----	-.164-.077

CD=Crohn's disease; UC=ulcerative colitis: 5-ASA=5-aminosalicylate; IBD=inflammatory bowel disease

Table 5. Logistic Regression Summary

Variable	Adherence			ER Visits			Inpatient Admit		
	OR	P	95%CI	OR	P	95%CI	OR	P	95%CI
Age	1.014	.322	.986-1.042	1.009	.641	.971-1.049	.108	**.012***	.971-1.004
MPR ≥.80	-----	-----	-----	.314	**.029***	.111-.886	.113	**.044***	.014-.939
IBDDx	.837	1.070	.564-2.029	.478	.166	.168-1.360	.117	**.027***	.017-.784
IBDMed	.666	1.202	.520-2.778	.537	.305	.164-1.762	1.111	.907	.190-6.490
Comorbid	.343	.727	.377-1.404	1.494	.457	519-4.298	3.222	.166	.616-16.839
CareCoor	.372	.713	.339-1.499	45.73	**.001***	9.053-231.035	14.862	**.022***	1.463-150.245

*statistically significant .05
ER=emergency room; MPR=medication possession ratio; IBD=inflammatory bowel disease; IBDMed=inflammatory bowel disease medication; IBDDx=IBD diagnosis; Cormorbid=comorbidity; CareCoor=care coordinationOR=odds ratio; 95%CI=95% confidence interval

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Dear Ms. Rizzo;

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Figure 1, Effective Clinical Practice, 1998, Vol1, Chronic Disease Management: What Will It Take to Improve Care for Chronic Illness? Wagner EH

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Thank you for your interest in Annals of Internal Medicine. If you have any further questions or would like to discuss the matter further, please contact me at 856-489-8555 or fax 856-489-4449.

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From: Lori Rizzo [anamcara6611@yahoo.com]
Sent: Monday, March 26, 2012 11:23 AM
To: Fred Curtiss
Cc: fredcurtiss@earthlink.net
Subject: Permission to Use Table from Journal of Managed Care Pharmacy

Dr Curtiss:

I am a PhD student who would like to include the following table in my Dissertation:
Fairman, K. & Motheral, B. (2000). Evaluating medication adherence: Which measure is right
for your program? Journal of Managed Care Pharmacy, 6(6), 499-504. The table appears on page
501 and is entitled: Table 1: Drug Profile of Hypothetical Patients.

This material will not be distributed. The table will only be used in my dissertation.

Thank you for consideration of my request. I await your reply.

Best,

Lori K. Rizzo, RN,MSN,FNP-BC
Nurse Practitioner
Division of Gastroenterology and Hepatology
Pittsburgh VA Healthcare System

From: Fred Curtiss [mailto:fcurtiss@amcp.org]
Sent: Monday, March 26, 2012 11:29 AM
To: kathleen@kathleenfairman.com; Fred Curtiss PhD
Subject: FW: Permission to Use Table from Journal of Managed Care Pharmacy

Lori:

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fred

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APPENDIX E

07/12/2013

IRB Approval-Initial Review

From: Linda Fried
To :   Lori Rizzo

Study# Pro00000762

R   Retrospective data analysis in veterans with inflammatory bowel disease: Using the Chronic Care Model to explore medication adherence

The following items were reviewed and approved through Expedited Review:

IRB Study Application
Support Letter – Medical Specialty
Email from Research Office – Statistical Support
Appendix A: Comorbidity Index ICD-9 Codes
Waiver of HIPAA Authorization – Full Study
Waiver of Informed Consent – Full Study
Coding Index
Cohort Generation
Student/Trainee Research: Co-PI Certification signed by Dr. Khalid

Expedited Approval was granted on 07/12/2013. Approval is granted from 07/12/2013 to 07/11/2014.

The VAPHS IRB has determined that this project meets the definition of Human Subjects Research.

This request for initial review was reviewed and approved by the IRB Chairman under the following expedited review category:

Category 5: Research involving materials (data, documents, records or specimens) that have been collected (for any purpose, including research), or will be collected solely for non-research purposes (such as medical treatment or diagnosis).

Research presents no more than <u>MINIMAL RISK</u> to subjects (considering physical, psychological, social and economic risk)

AND

Identification of the subjects and/or their responses <u>WOULD NOT</u> reasonably place them at risk of criminal or civil liability or be damaging to the subject's financial standing, employability, insurability, reputation, or be stigmatizing, <u>OR</u> reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are minimal.

Risk Assessment: Minimal; IRB Level of Scrutiny: Low (The risk assessment was made considering Social; Physical; Psychological; and Economic Risk).

AE Reporting: All unexpected/unanticipated, serious adverse events, whether related or unrelated to the research must be reported to the IRB within 5 business days of the investigator becoming aware of the event.

Data Security Level: Level 1 – VA Sensitive Information is collected/used and subjects are unaware of the use/disclosure

The protocol is approved for a sample size of: 2000.

Sincerely,

Linda Fried
Electronically Signed

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APPENDIX F

Dr. James Phillips
Interim Chair, IRB-Human Subjects
Office of Research
Phone (412) 396-4290 Fax (412) 396-5176
e-mail: phillips@duq.edu

September 27, 2013

Re: A retrospective data analysis in veterans with inflammatory bowel disease: Using the Chronic Care Model to explore medication adherence (PROTOCOL #13-128)

Alison Colbert, PhD
School of Nursing
Duquesne University
Pittsburgh PA 15282

Dear Dr. Colbert,

Thank you for submitting the research proposal of you and your student co-investigator to the Institutional Review Board at Duquesne University.

Based on the review of IRB representative Dr. Denise Lucas, and my own review, I have determined that your research proposal is consistent with the requirements of the appropriate sections of the 45-Code of Federal Regulations-46, known as the federal Common Rule. The intended research poses no greater than minimal risk to human subjects. Consequently, the research is approved under 45CFR46.101 and 46.111 on an **expedited** basis under 45CFR46.110.

The approval pertains to the submitted protocol. If you wish to make changes to the research, you must first submit an amendment and receive approval from this office. In addition, if any unanticipated problems arise in reference to human subjects, you should notify the IRB chair before proceeding. In all correspondence, please refer to the protocol number shown after the title above.

Once the study is complete, please provide our office with a short summary (one page) of your results for our records.

Thank you for contributing to Duquesne's research endeavors.

Sincerely yours,

James Phillips, Ph.D.

C: Dr. Denise Lucas
IRB Records

APPENDIX G

From: Rizzo, Lori K
Sent: Friday, November 15, 2013 9:38 AM
To: 'nbeagin@ajmc.com'
Cc: 'bhaug@ajmc.com'
Subject: Permission

All:

I have unsuccessfully been trying to obtain permission to use a Figure from your publication, The American Journal of Managed Care.

I am a PhD student. I would like to use Figure 3 on page 453 from the article below in my dissertation: Sikka, R., Xia, F., Aubert, R. E. (2005). Estimating medication persistency using administrative claims data. The American Journal of Managed Care. 11(7), 449-457.

I look forward to your reply.

Best,

Lori

From: Nicole Beagin [mailto:nBeagin@ajmc.com]
Sent: Friday, November 15, 2013 9:58 AM
To: Rizzo, Lori K
Subject: Re: Permission

Hello,

Please forgive the delay in reply. The editorial staff is currently out of office at our conference.

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Sent from my iPhone

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