Pharmaceutical Outcomes Research to Better Understand Medication Non-Adherence in Patients with Systemic Lupus Erythematosus

by

Pavandeep Mehat

B.A., Boston University, 2014

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF SCIENCE in THE FACULTY OF GRADUATE AND POSTDOCTORAL STUDIES (Pharmaceutical Sciences)

THE UNIVERSITY OF BRITISH COLUMBIA (Vancouver)

July 2016

© Pavandeep Mehat, 2016
Abstract

Introduction: This thesis comprises a systematic review and a pharmacoepidemiological study aimed at improving the understanding about medication non-adherence to antimalarials (AM) in Systematic Lupus Erythematosus (SLE). AM is the conventional and effective long-term treatment option that has resulted in substantial decreases in deaths associated with SLE disease activity. However, there seems to be no such decline in the deaths associated with the sequelae of SLE (such as circulatory disease). Since deriving therapeutic effects from AM depends not only on physicians prescribing the appropriate treatment, but also on patients’ adherence with selected treatment, there is the need for a better understanding of medication non-adherence to AM in SLE.

Objective: 1) To systematically review and synthesize the literature on medication adherence in SLE to identify key gaps in the literature; and 2) to evaluate the burden and determinants of medication non-adherence to AM in SLE.

Methods: To address Objective 1, I have conducted a systematic review. I conducted a mapped search of Medline, Embase, and Web of Science to identify original, observational studies that indicated the data source and measurement tool to assess medication adherence in a SLE patient sample. To address Objective 2, I have conducted a longitudinal pharmacoepidemiological study of a population-based SLE cohort. I used a Cox’s proportional hazard ratio model to examine factors that were significantly associated with discontinuation of AM.
**Results:** 1) 11 studies were included in the systematic review, and the majority of these studies reported that less than 50% of SLE patients are sufficiently adherent to their medications; 2) After five years, only 33% of patients remained on AM therapy; and 3) Higher SES and the following time-varying covariates updated monthly: glucocorticoids use, traditional NSAIDs use, rate of rheumatologist visits, and rate of dermatologists were statistically significantly protective against discontinuation of AM therapy.

**Conclusion:** Altogether as a collective work, this thesis provides evidence that demonstrates medication non-adherence is a substantial problem in SLE. In addition, it highlights the importance of developing adherence interventions to help support patients taking their medications as prescribed.
Preface

This dissertation (including the initial design, conception, analyses, and written work) is an original, unpublished intellectual product of the author, Pavan Mehat. The studies conducted as part of this work were reviewed and approved by the UBC Behavioural Research Ethics Board (BREB) under ethics certificate number H07-03088.

I am also grateful for the support of the data stewards, Population Data BC who have allowed me to access the data in order to undertake the study. Please note that all inferences, opinions, and conclusions drawn in this dissertation are those of the author, and do not reflect the opinions or policies of the data stewards.
Table of Contents

Abstract ........................................................................................................................................... ii
Preface ............................................................................................................................................... iv
Table of Contents ........................................................................................................................... v
List of Tables .................................................................................................................................... ix
List of Figures ................................................................................................................................... x
List of Abbreviations ....................................................................................................................... xi
Acknowledgements ....................................................................................................................... xii

Chapter 1: Introduction ......................................................................................................................... 1
  1.1 Thesis Overview .......................................................................................................................... 1
      1.1.1 Research Statement ........................................................................................................... 1
      1.1.2 Overview of Thesis Themes and Chapters .......................................................................... 2
  1.2 Systematic Lupus Erythematosus .............................................................................................. 3
      1.2.1 Epidemiology of Systemic Lupus Erythematosus ............................................................... 3
      1.2.2 The Management of SLE .................................................................................................. 4
  1.3 Antimalarials (Hydroxychloroquine and Chloroquine) ............................................................ 5
  1.4 Medication Adherence ................................................................................................................. 8
  1.5 Overview of Thesis Studies ......................................................................................................... 12
      1.5.1 Specific Objectives of Thesis Studies ............................................................................... 13
      1.5.2 Systematic Review of Medication Adherence Non-Adherence in SLE ....................... 13
      1.5.3 Pharmacoepidemiologic Study of Medication Non-Adherence in SLE ....................... 13
          1.5.3.1 Data Sources for Thesis Pharmacoepidemiologic Studies ................................... 14

Chapter 2: Medication Non-Adherence in SLE: A Systematic Review .............................................. 17
Chapter 3: The Burden and Determinants of Medication Non-Adherence in SLE

3.1 Introduction .................................................................................................................. 35

3.1.1 Medication Adherence in SLE ................................................................................ 36

3.2 Methods ......................................................................................................................... 37

3.2.1 Data Sources and Study Population ........................................................................ 37

3.2.2 Assessment of Discontinuation ................................................................................ 39

3.2.3 Assessment of Poor Execution ................................................................................ 41

3.2.4 Assessment of Covariates ....................................................................................... 42
C.2 Histogram of the Difference Between SLE Diagnosis Date and the First AM Prescription
List of Tables

Table 2-1 Characteristics of Studies Included in the Systematic Review of Medication Adherence in SLE ............................................................................................................................................. 23
Table 2-2 Summary of the Results of the Included Studies.................................................................................. 26
Table 2-3 Determinants of Medication Adherence from the Included Studies .............................................. 30
Table 3-1 Characteristics of SLE Cohort of Incident Drug Users (n = 881) .................................................... 48
Table 3-2 Life Table Survival Analysis.............................................................................................................. 50
Table 3-3 Univariate Survival Analysis............................................................................................................. 52
Table 3-4 Adjusted Hazard Ratios and 95% CI for Determinants of AM Discontinuation .................. 53
Table 3-5 Mean PDC of Antimalarial Adherence ............................................................................................ 55
Table 3-6 Proportion of Patients Adherent to Antimalarial Treatment ...................................................... 56
Table 3-7 Univariate Chi Square Tests........................................................................................................... 57
List of Figures

Figure 2-1 Overview of Medication Non-Adherence ................................................................. 18
Figure 2-2 Systematic Review Study Flow ............................................................................. 22
Figure 3-1 Overview of Medication Non-Adherence ............................................................ 36
Figure 3-2 Schematic of Discontinuation .............................................................................. 41
Figure 3-3 Schematic of Delayed Entry ............................................................................... 45
Figure 3-4 Schematic of Cohort Creation .............................................................................. 47
Figure 3-5 Kaplan Meier Curve of Discontinuation of AM Therapy .................................... 50
Figure 3-6 Schematic of Poor Execution ............................................................................... 54
Figure 3-7 Distribution of the Proportion of Days Covered ..................................................... 55
List of Abbreviations

SLE – Systemic Lupus Erythematosus
AM – Antimalarial
RCT – Randomized Controlled Trial
HCQ – Hydroxychloroquine
CQ – Chloroquine
SARD – Systemic Autoimmune Rheumatic Disease
CVD – Cardiovascular Disease
AMI – Acute Myocardial Infarction
CVA – Cerebral Vascular Accident
DMARD – Disease Modifying Anti-Rheumatic Drug
NSAID – Non-Steroidal Anti-Inflammatory Drug
Cox-2 – Cyclooxygenase 2
COPD – Chronic Obstructive Pulmonary Disease
HRT – Hormone Replacement Therapy
OC – Oral Contraceptives
UK – United Kingdom
UBC – University of British Columbia
EMR – Electronic Medical Record
GPRD – General Practice Research Database
Acknowledgements

Firstly, I need to acknowledge Dr. Mary De Vera, the best supervisor a graduate student could ask for. You were the perfect infusion of caring and inspiration. You helped push me through my own insecurities and doubts, but also were brutally honest when I did not perform to the fullest of my potential. I have learned and grown so much not only as a scientist but as a person as well during my last two years at UBC.

I have to thank all of my committee members for pushing me past my comfort zone, and challenging me to grapple with the complex problems involved in conducting health service research. I would like to thank Dr. Mike Law for fostering my passion for exemplary study design. Also, I appreciate the constant reminder you display to not take yourself too seriously, always make time to laugh, and to remain humble. Dr. Avina-Zubieta, thank you so much for the frank advice that has always been helpful, and for allowing me to use your data to conduct my thesis. Dr. Anne Townsend, thank you so much for challenging my epistemological perspectives, and helping me discover “different realities”. Lastly, Dr. John Esdaile, I would like to thank you for agreeing to be part of my committee, and for sharing your wisdom that was instrumental in helping make my decision about my future career path.

I would like to thank my wonderful colleagues at Collaborations for Outcomes Research and Evaluation and at Arthritis Research Canada that were always willing to drop what they were doing to help me. Special shout out goes to Sharan Rai and Nicole Tsao, who gave me a crash course on what it takes to be a successful graduate student that was instrumental in allowing me to successfully transition from undergraduate to graduate school. Also, I am indebted to Natalie
McCormick, who helped me when I felt utterly overwhelmed while learning the ins and outs of SAS and the SRE. Further, I would like to thank Mohammed Atiq for the great work he did on helping me complete the systematic review. The environment and support from the Faculty of Pharmaceutical Sciences has been an integral part in allowing me to successfully complete my program and pursue my training at the Faculty of Medicine at UBC. Lastly, I would like to thank my friends and family for dealing with my ups and down during the journey of graduate school.
Chapter 1: Introduction

1.1 Thesis Overview

1.1.1 Research Statement

The goal of this thesis is to gain a better understanding of the burden and determinants of medication non-adherence to antimalarials (AMs) in Systematic Lupus Erythematosus (SLE). AM therapy has been shown to be very effective in a withdrawal randomized controlled trial (RCT) in which the risk of a clinical flare-up, defined as the development of specific clinical manifestations of SLE or an increase in their severity, was 2.5 (95% CI: 1.08-5.88) times higher for patients on placebo than those on AM therapy (1). This breakthrough in SLE treatment has resulted in marked decreases over the last few decades in deaths associated with SLE activity (such as renal disease) (2). However, there seems to be no such decline in deaths associated with the sequelae of SLE (such as circulatory disease) (2). However, in a multivariable analysis, adequate dosing of AMs in disease progression resulted in significantly less (OR = 0.34 95% CI 0.132–0.867) organ damage (including cardiovascular system) (3). As with many chronic diseases requiring long-term pharmacotherapy, recent evidence suggest poor adherence to prescription medications in SLE is associated with high-cost service utilization, specifically visits to the emergency departments (OR =1.45) (4). “Since drugs do not work in patients who do not take them,” (5) an important factor that could potentially be driving poor long-term outcomes in SLE patients due to the downstream effects of the disease could be medication non-adherence to AMs.
1.1.2 Overview of Thesis Themes and Chapters

This thesis unifies two separate investigations about medication non-adherence to AMs in SLE: investigation 1 is “Medication Non-Adherence in SLE: a Systematic Review,” which aims to fill a key gap in the literature and systematically addresses the question: what is the current state of the literature examining medication non-adherence in SLE?

Investigation 2, “The Burden and Determinants of Medication-Non Adherence in SLE,” aims to fully characterize the problem of medication non-adherence in SLE and to identify determinants of non-adherence among patients. Thus investigation 2 addresses the question: What proportion of patients failed to take their medications as prescribed by their physician and what are the determinants of medication non-adherence?

Addressing these research questions under the thesis guiding investigations has resulted in the combination of a systematic review and an original pharmacoepidemiological study. Following this introductory chapter, which covers relevant background material and rationale, are the content chapters of the thesis. Chapter 2 systematically reviews the current literature on medication adherence in SLE and identified key gaps in the literature. Chapter 3 is a population-based pharmacoepidemiological study that describes the burden of medication non-adherence in SLE and identifies determinants of medication non-adherence. To date, there are no large-scale studies and none have been based on generalizable data at the population level. Chapter 4, the concluding chapter, synthesizes findings from each thesis study and discusses strengths, limitations and potential implications of the collective work.
1.2 Systematic Lupus Erythematosus

SLE, the health problem of interest of this thesis, is a chronic systemic autoimmune rheumatic disease (SARD). SLE specifically attacks collagen and results in multifarious clinical manifestations including joint pain, photosensitivity, malar rash and clinical nephritis. This section reviews the epidemiology of SLE and the management of SLE.

1.2.1 Epidemiology of Systemic Lupus Erythematosus

SLE occurs predominantly in women (approximately 9:1 female to male) during their childbearing years and has a higher prevalence in minority populations (6). For example, the one-year period prevalence SLE rate in the United Kingdom (UK) was 207/100,000 for Afro-Carribbeans and 48.8/100,000 for Asians while only 20.3 for Whites (7). Prevalence estimates for SLE have ranged from 40 to 150 per 100,000 persons in Canadian and American general populations (8) (9). In Quebec, Bernatsky et al. estimated the prevalence of SLE to range from 33 to 51 per 100,000 persons and the incidence to be 3 per 100,000 persons (10). Furthermore, population based data suggests that SLE incidence has tripled over the last four decades (11). Canadian studies have estimated that the mean annual direct cost of SLE, which is based on healthcare utilization, is as high as $10,608 per patient (2010 Canadian dollars) (12). Furthermore, the mean annual indirect costs of SLE, which is based on the value assigned to labour and non-labour market activity, is as high as $22,604 per patient (1997 Canadian dollars) (13). Altogether, SLE is a multi-system condition that is associated with a rapidly increasing disease burden.
SLE can be a severe and life threatening disease. Mortality associated with SLE may be due to lupus activity (when vital organs are involved), complications of treatment (particularly infections), or long-term sequelae (such as cardiovascular disease) (2). The mortality risk associated with SLE has been evaluated across different populations and settings. Studies have consistently shown that SLE is associated with increased mortality, with death rates in SLE being 2.4 to 3.0 fold higher than in the general population (2)(14). The role of cardiovascular diseases (CVD) as the main cause of excess of mortality in SLE has been consistently suggested in previous studies (2)(14). Other causes of premature mortality in SLE include infections, cancer, and renal disease (2). The highest SMR estimates were seen in patient groups characterized by younger age, female sex, SLE Duration < 1 year and black/African American race (2).

1.2.2 The Management of SLE

There is no cure for SLE. Therefore the goals of treatment are to not only decrease autoimmunity and to slow down disease progression, but to also prevent damage to other organ systems from the downstream effects of SLE (6). The conventional option to achieve these goals in SLE with minimal organ involvement is the long-term use of AMs (15) (16)(1). For patients with SLE with multiple organ systems involved other immunosuppressive medications will be added (15)(16). Given recommendations for long-term therapy with AMs for SLE patients with and without organ involvement, for the purposes of this thesis I will be primarily focusing on analyzing medication adherence on AMs, namely hydroxychloroquine (HCQ), and chloroquine (CQ).
1.3 Antimalarials (Hydroxychloroquine and Chloroquine)

Hydroxychloroquine and chloroquine are both 4-amino-quinolines quinine derivatives. Beyond their well-established antimalarial properties, they have been demonstrated to have additional effects on inflammation in SLE. In this section, a closer look at these drugs includes a brief chronicle of their history and development, and examination of their anti-inflammatory properties.

The history of HCQ/CQ dates back to 1638 when the wife of the Viceroy of Peru, Countess Cinchona, acquired malaria while living in the New World (17). She opted out of the standard treatment protocol at the time for malaria and instead was cared for by an Incan Herbalist. The herbalist used the bark of a tree (later named after her – Cinchona Tree) to treat her condition. The treatment cured her condition so quickly that it caused the bark of this tree to be an integral component in folk medicines for centuries (17). Despite this remedy being widely used to treat malaria, it took almost two centuries for the active component, quinine, to be isolated (17). By the 1940’s, chloroquine, a derivative of quinine was used widely by soldiers fighting in World War II. Even though chloroquine was very effective, it was discovered that this compound had significant toxicities, most notably retinal and cardiac toxicity. In 1945, modifying chloroquine by hydroxylating it resulted in HCQ, which was found to be less toxic and is the current first line treatment against SLE (17).

Due to the phenomenal success in treating malaria with HCQ and CQ, henceforth AMs, physicians began using these medications for other conditions, such as in the early 1950’s when they tried using AMs as a treatment for SLE (17). Compared to other available treatments at the
time, patients given AMs experienced relief of articular and cutaneous symptoms, whereas other available treatments provided no such relief (17).

Despite the anecdotal and clinical cases backing up the use of AMs in SLE, it was not until 1991 that the Canadian HCQ Study Group conducted a double blind, randomized, placebo controlled withdrawal study examining the effect of withdrawing HCQ in SLE patients in remission on the development of subsequent SLE flares (1). They found that the rate of clinical flares was 2.5 (95% CI: 1.08 to 5.58) times higher in the placebo group, and that the risk of severe exacerbations resulting in withdrawal from the RCT was 6.1 (95% CI: 0.72 to 52.44) times higher in the placebo group (1). In 1994, Williams et al. conducted a prospective double blind, placebo controlled, randomized clinical trial examining the safety and efficacy of HCQ to treat the articular complaints of SLE in 71 SLE patients (18). They found that patients on HCQ reported a lower self assessed severity of joint pain (p = 0.02) compared to the placebo group (18). A subsequent placebo controlled RCT by Meiano et al. examined the efficacy of CQ in the treatment of SLE with no life threatening manifestations over a 12-month period (19). They found that prednisone levels dropped significantly in the CQ group compared with the placebo group, and the risk of flares was 4.6 times (no CI reported) greater in the placebo group (19). Altogether, these RCTs were an integral first step in firmly establishing the efficacy of the long-term use of AMs in SLE.

However, further observational studies examining the effect of the use of AMs were essential in examining the effectiveness and safety of AMs in real world settings. A retrospective controlled study on 35 patients examined the predictors of sustained remission of lupus nephritis, which is
one of the most life-threatening manifestations of SLE where the renal system is compromised (20). They found that more patients sustained remission from lupus nephritis on HCQ versus no treatment (94% vs. 53%, p =0.01) (20). Cortés-Hernández et al. prospectively studied fetal and maternal health outcomes in SLE to find that CQ discontinuation significantly increased flares (p = 0.02) (21). Further, Costedoat-Chalumea et al. conducted a blinded prospective cohort study examining the relationship between HCQ blood concentrations and disease exacerbations (22). Multivariable logistic regression showed that blood HCQ concentration was the only significant predictor of exacerbation (odds ratio 0.4 [95% CI 0.18-0.85], p = 0.01) (22). Lastly Kasitanon et al. study examined the effect of HCQ on lupus nephritis remission in SLE patients first treated with mycophenolate mofetil (MMF) (23). They found a higher rate of lupus nephritis remission (64% vs. 22%, p = 0.036) for patients taking HCQ in conjunction with MMF versus patients just taking MMF. These observational studies demonstrated the effectiveness of AM therapy in real world settings and provided evidence why AMs are recommended as the conventional long-term option to treat both mild and more severe forms of SLE.

With respect to their safety profile, AM drugs are very well tolerated. The majority of the side effects experienced (e.g. gastrointestinal intolerances or cutaneous manifestations) by patients disappear with dose reduction and rarely require withdrawal of the treatment (24). The main concern of patients that prompts discontinuation of AM therapy is retinal toxicity. The incidence of retinal toxicity is very low and several studies of patients with rheumatic disease report little or no retinal toxicity among cohorts consisting of 1000’s of patients (25)(26)(27). The incidence of retinal toxicity is lower for patients taking HCQ (25). In 4 studies examining the incidence of retinal toxicity for 647 SLE patients on CQ 16 (2.5%) of patients were diagnosed with definite
retinal toxicity (25). On the other hand, only 2 (0.1%) of 2043 SLE patients on HCQ (OR = 25.88; 95% CI: 6.05 to 232.28; P < 0.001) from 6 studies were diagnosed with definite retinal toxicity (25). Overall, AM therapy is an effective and safe treatment option for SLE.

1.4 Medication Adherence

The World Health Organization has declared non-adherence to medications an **epidemic** – only 50% of adults are adherent to treatment (28). Adherence to a medication regimen is generally defined as the extent to which patients take medications as prescribed by their health care providers (5). Even though understanding the construct of medication adherence is quite intuitive, operationalizing and measuring medication adherence is deceptively complex.

The University of British Columbia (UBC) Medication Adherence Research Group at the Faculty of Pharmaceutical Sciences has established a framework for understanding medication non-adherence that I will apply in my thesis. I used this framework to understand the two equally important but distinct aspects of medication non-adherence: 1) **poor execution** of the dosing regimen, such that scheduled doses are delayed or omitted, which may lead to transient interruptions in drug action (29)(30), and 2) **discontinuation** of the medication, which may lead to intermittent or permanent loss of drug effects (29)(30). Another construct, **persistence**, is reciprocal to discontinuation and refers to conforming to a recommendation of continuing treatment for the prescribed length of time.

For the purposes of my thesis, I am going to focus on the constructs of poor execution and discontinuation.
There are a myriad of methods to measure the two different constructs of adherence that can be broadly classified as either direct or indirect methods (5). Direct measures include observation of drug taking, and laboratory detection of the drug, a metabolite of the drug, or another biologic marker in body fluids (31). These direct methods are the only way to definitively ascertain if the patient consumed their medication or not, but they are expensive and impractical for the majority of studies, especially when studying large populations. In addition, since there is substantial interaction between the researcher and patient, the medication taking behaviour observed is most likely not going to reflect a patient’s normal medication-taking behaviour (31).

Indirect methods to measure adherence and persistence include patient self-report, pill counts, electronic monitoring and measures of drug availability, as estimated using pharmacy records (5). These methods are considered indirect because they rely on surrogates of medication adherence (e.g. possession of medications) and cannot ascertain if the patient actually consumed their medication as indicated by their physician (31). Due to logistical and financial considerations, indirect measures of medication adherence are much more common.

Patients can be queried to self-report their medication use in a variety of ways through diaries, interviews, or the use of patient questionnaires (31). There is a wide breadth of self-report patient questionnaires used to assess medication adherence. Some of these questionnaires just assess medication-taking behaviour such as the Morisky Medication Adherence Scale (MMAS-8) (32). While others assess medication taking behaviour as well as barriers to adherence such as the Brief Medication Questionnaire (33). Questionnaires such as the MMAS-8 are generic and have been well validated for use in a wide variety of chronic diseases (32). While questionnaires such
as the 19-item Compliance-Questionnaire Rheumatology (CQR) have been validated for use specifically in rheumatology patients such as those suffering from SLE (34). Self-report methods are easy to implement and inexpensive, but are subject to information bias due to social desirability bias and recall bias (31).

Another commonly used indirect measure of medication adherence is pill counts. Patients are instructed to bring their medications when meeting with their clinician or researcher. The number of pills are counted, and compared with the date and supply of prescription drug dispensation. Although this is a simple and objective measure of adherence, it is subject to significant distortion by the patient. For example, they may neglect to bring in medication not stored in the original container, or throw out medications to intentionally mask non-adherent behaviour (31).

To assess poor execution of dosing regime, electronic monitoring of medication taking have become increasingly common because it is a reliable method that can collect information on dosing frequency, intervals and timing. The most prevalent electronic monitoring is a Medication Event Monitoring System (MEMS). MEMS is a microchip in the lid of the pharmacy container that records the date and time when a container is opened (31). MEMS provides very detailed and precise information about medication taking behaviour. Further, this data can be easily quantified to assess patterns of medication taking (5). Unfortunately this measurement tool is subject to significant distortion by the patient. For example, the patient could move their medications to another container, or could open the lid but not consume the medication (5). In addition, this system is quite expensive, cumbersome and subject to reactivity bias, where patients change their behaviour because they are aware they are being monitored (31).
The last indirect method of measuring adherence and persistence is through using administrative pharmacy records to measure medication possession as a proxy for medication adherence. In closed pharmacy systems, for example in health maintenance organizations or in jurisdictions with public drug coverage, where all dispensed prescriptions are entered into a single computerized claims database, the rate at which patients fill their prescriptions over time can be used to estimate adherence and persistence with medication (35). By knowing the amount of drug dispensed to a patient and the interval between fills, any short gaps in drug availability or extended periods of discontinuation can be identified, and measures of adherence and persistence can be calculated (5).

Administrative pharmacy records provide systematic and extensive data to efficiently conduct pharmacoepidemiological studies at the population level in a ‘real world setting’ (36). In addition, since the data can be completely anonymized for research purposes and do not typically require patient consent, there is no bias associated with patients knowing their drug-taking behaviour is being observed (35). Lastly, there are a myriad of checks to ensure completeness and accuracy of data, and a number of Canadian databases, including PharmaNet, that have been previously used for pharmacoepidemiological research (37)(38)(39)(40).

It is important to note the limitations of using administrative pharmacy records to assess medication adherence. It is quite effective at assessing medication adherence for chronic diseases, but will produce significant distortions when assessing medication adherence for short-term therapy regimens (5). Also administrative pharmacy records are unable to detect patients
who never fill a prescription (primary non-adherent) (41), unless prescribing information from an electronic medical record (EMR) is also available (42). Lastly, it is important to realize that this method is measuring a patient’s possession of medication and not necessarily their consumption. However, it has been shown that measurements from administrative pharmacy records are correlated with other direct and indirect measures of medication adherence (43) (44). In addition, medication non-adherence, as determined from pharmacy records, has been shown to be associated with a broad range of outcomes (45).

Despite the variety of techniques available to assess medication adherence there is no gold standard (5). Therefore, it is essential to be cognizant of the strengths and limitations of each method so that the appropriate methods are chosen based on the study objectives and the study population characteristics. Administrative pharmacy records, for example, are best used to measure adherence in population based cohorts over a long time period while other measurement methods (e.g., self report, MEMS and pill counts) are better for short-term use on a smaller scale, such as in clinical trials.

1.5 Overview of Thesis Studies

In this concluding section, specific objectives addressed in each of the ensuing thesis chapters are highlighted. These chapters represent one systematic review and one pharmacoepidemiologic study that separately and collectively contribute to addressing the overall thesis goal of gaining a better understanding of medication non-adherence to AMs in SLE. Following the objectives, pertinent background to pharmacoepidemiology and systematic reviews are briefly highlighted.
1.5.1 Specific Objectives of Thesis Studies

Objective 1. To systematically review and synthesize the literature on medication adherence in SLE to identify key gaps in the literature.

Chapter 2 is a systematic review of studies examining medication non-adherence in SLE.

Objective 2. To evaluate the burden and determinants of medication non-adherence to AM (HCQ/CQ) in SLE

Chapter 3 is a population based longitudinal study describing the burden and determinants of medication non-adherence to AMs in SLE.

1.5.2 Systematic Review of Medication Adherence Non-Adherence in SLE

Chapter 2’s systematic review of studies evaluating medication non-adherence in SLE falls under Theme 1 by systematically synthesizing and analyzing the literature on medication non-adherence in SLE. There have been systematic reviews examining medication adherence in inflammatory arthritis, including SLE (46). However, presently to my best knowledge there are no systematic reviews examining medication adherence in SLE alone and those previous systematic reviews are dated and need to be updated. Addressing this need called for the rigorous identification of published studies, standardized appraisal and selection processes, and synthesis of all research evidence, which are all provided by a systematic review (47).

1.5.3 Pharmacoepidemiologic Study of Medication Non-Adherence in SLE

Chapter 3 of this thesis is a pharmacoepidemiologic study evaluating the burden and determinants of medication non-adherence to AM in SLE. Regarded by some as a relatively new science, pharmacoepidemiology is the study of the use of and effects of drugs in large
populations that bridges the two disciplines of pharmacology and epidemiology (48). Methods and concepts of pharmacoepidemiology encompass a wide spectrum of studies including hypothesis-testing studies of drug expected benefits (48) and assessment of patterns of drug use and associated outcomes (48) as applicable to objective 2 of the Thesis.

### 1.5.3.1 Data Sources for Thesis Pharmacoepidemiologic Studies

In the past few decades, so-called “automated databases”, that is, computerized databases containing medical care data have grown to be a hallmark of pharmacoepidemiologic studies in North America. These data are largely administrative in origin and generated from claims for health services (physician visits, drug prescriptions) by the population covered. Examples in the US include federal programs like Medicaid and managed care organizations like the Kaiser Permanente Medical Care Program. In Europe, medical record databases, such as the UK General Practice Research Database (GPRD), developed for use by researchers are important data sources for pharmacoepidemiologic research. In Canada, provinces administer a universal and publicly funded health system. Provincial administrative health data that have become resources for pharmacoepidemiologic research as a result of this universal health care system include established databases of Saskatchewan (Health Services Databases in Saskatchewan), Quebec (Régie de l’assurance maladie du Québec [RAMQ]), and British Columbia (Population Data BC).

The data source for the pharmacoepidemiologic study in this thesis are administrative health data files from British Columbia (BC) where a provincially administered, and largely publicly funded health insurance covers acute and extended care hospitalizations, in-home care, prescription
drugs, diagnostic tests, and fees to physicians (49). Specific data files include the Medical Services Plan (MSP), which covers information on all provincially funded health services and includes data on date of service, practitioner, and diagnosis most closely associated with the record, using International Classification of Disease Version 9 (ICD-9) (50). The Hospital Separations file on inpatient hospitalizations includes information on admission date, up to 10 diagnoses fields representing the reason for admission or complications during hospitalization, procedure/intervention codes (following Canadian classification of diagnostic, therapeutic, and surgical procedures), and separation date (51). Prescription data was drawn from BC PharmaNet, which is a prescription monitoring and repayment information database (52). By law, every prescription dispensed in BC is recorded in PharmaNet, regardless of recipient or payer (53). PharmaNet claims extracts include date prescription was dispensed, drug identification number (Canadian drug identity code [CDIC]), drug name, dose, and days supplied in the prescription (52). Finally, information on death including date of death and underlying cause of death (ICD-10 codes) was obtained from vital statistics in the Canadian Mortality Databases (54).

Specific data were drawn from a previously established population-based SLE cohort (n=5831) in British Columbia (BC) with data coverage from January 1st 1990 to December 31st 2010 (40). Administrative billing data for the reimbursement of physician visits from the BC Ministry of Health were used to identify individuals ≥18 years old with SLE who were diagnosed with SLE between January 1997 and December 2009. Individuals with SLE were identified with a previously validated algorithm(40) : a) 1-ICD-9 code by a rheumatologist in the outpatient database, b) 1-ICD-9 or 1-ICD-10 code in the hospital database, or c) 2-ICD-9 codes at least 2 months apart and no more than 2 years apart by a non-rheumatologist in the outpatient database.
Individuals were excluded if they had at least 2 visits with the diagnoses of another systemic autoimmune rheumatic disease (Sjögren's syndrome, Systemic Sclerosis, Wagner’s Disease, Polymyositis, Dermatomyositis), if an SLE diagnosis by a non-rheumatologist was not confirmed on a subsequent rheumatologist visit, or if they had no subsequent SLE-coded physician visits.
Chapter 2: Medication Non-Adherence in SLE: A Systematic Review

2.1 Introduction

Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune rheumatic disease (SARD) that specifically attacks collagen and results in multifarious clinical manifestations including joint pain, photosensitivity, malar rash, and clinical nephritis (55)(56). It occurs predominantly in women (approximately 9:1 female to male) during their childbearing years (6). As there is no cure for SLE, the goals of treatment include decreasing autoimmunity to slow down disease progression, and to prevent damage to other organ systems from the downstream effects of SLE (6). The conventional option to achieve these goals among patients with SLE with minimal organ involvement is the long-term use of antimalarials (AM), namely hydroxychloroquine (HCQ) and chloroquine (CQ) (1)(15)(16). It is recommended that SLE patients with multiple organ systems involved should additionally be taking other immunosuppressive medications (azathioprine, cyclophosphamide, methotrexate, chlorambucil, and cyclosporine) (15)(16). Advances in SLE treatments over the last few decades have resulted in marked decreases in deaths associated with SLE activity(2), but there seems to be no such decline in deaths associated with the sequelae of SLE (2).

Poor adherence to long-term AM or immunosuppressive treatment may be an important factor that could potentially be driving poor long-term outcomes in SLE patients due to the downstream effects of the disease. Medication non-adherence is a complex construct that encompasses the distinct problems of: 1) poor execution of the dosing regimen such that scheduled doses are delayed or omitted, which may lead to transient interruptions in drug action, and 2)
discontinuation of the medication, which may lead to the intermittent or permanent loss of drug effects (Figure 2-1). An additional construct, persistence, is reciprocal to discontinuation and refers to conforming to a recommendation of continuing treatment for the prescribed length of time (57).

While a potential contributor to therapeutic challenges in SLE, medication non-adherence has not been well described among SLE patients. To date, one systematic review in 2009 has summarized medication adherence across a variety of rheumatic diseases, including four studies published from 1999 to 2006 which reported adherence rates among SLE patients (58). To update this data as well as synthesize empirical evidence on the burden and determinants of medication non-adherence in SLE, I systematically reviewed the literature examining medication adherence among SLE patients in real-world settings.

**Figure 2-1 Overview of Medication Non-Adherence**
2.2 Methods

2.2.1 Literature Search Strategy

I conducted a mapped search of the following databases: Medline (1946 – Dec 2015), Embase (1974 - Dec 2015), and Web of Science (1900 – Dec 2015) (Appendix A). I used Medical Subject Headings (MeSH) for concepts underlying my search: SLE (MeSH: ‘Lupus Erythematosus, Systemic’) and medication adherence (MeSH: ‘health behaviour’, ‘patient compliance’, ‘medication adherence’). I applied keyword searches for terms that did not map to MeSH terms. To supplement the database searches, I conducted a manual search of the bibliographies of selected articles.

2.2.2 Study Selection

Titles and abstracts were reviewed by two independent reviewers for the inclusion of published studies that evaluated and/or reported medication adherence among patients with SLE in clinical or real-world settings. Specific inclusion criteria were: 1) observational study design, 2) defined patient sample that included SLE, 3) indicated the data source and measurement tool to quantify medication adherence, and 4) publication in English, French, or Spanish. I excluded randomized controlled trials (RCTs) as I was primarily interested in treatment of patients in clinical or real-world settings because medication adherence has been shown to be higher among patients participating in clinical drug trials (59).
2.2.3 Data Extraction and Quality Assessment

I extracted the following information from the included studies: year of publication, country, study setting, sample size, and data source used (e.g., patient self-report, electronic monitoring devices, clinical records, and pharmacy refill data). Of particular importance was information on the burden of medication adherence, including type of non-adherence problem evaluated (e.g., poor execution, or discontinuation/persistence), adherence measurement tool (e.g., Medication Event Monitoring System, self-report, pharmacy records), adherence measure (e.g., proportion days covered [PDC], medication possession ratio [MPR]), cut-off values to define subjects who were adherent and non-adherent, and adherence estimates (e.g., mean score, adherence rate, % of adherent patients).

Using the World Health Organization’s five dimensions of medication adherence as a framework, I also extracted information on determinants or factors shown to be independently associated with adherence in multivariable analyses, grouping them according to: 1) patient factors, 2) condition factors, 3) therapy factors, 4) social/economic factors, and 5) health care system factors (28). Information on determinants of adherence based on univariate or bivariate analyses were not included.

I used the ‘STrengthening the Reporting of OBservational studies in Epidemiology’ (STROBE) checklists for cohort, cross-sectional and case-control studies combined to assess how well the observational research was reported (60). For purposes of my systematic review, I adapted the checklist to include 22 items (maximum score 22 points), which I applied to appraise the quality of included studies.
2.3 Results

2.3.1 Literature Search
I identified 4,111 studies with my search strategy and after screening for titles and abstracts, and reviewed the full text of 36 articles (Figure 2-2). Based on this review, I included 11 articles and categorized them according to measurement of adherence as studies based on self-report (n = 5), electronic monitoring devices (n = 1), clinical records (n = 3), and pharmacy refill data (n = 2). Table 2-1 summarizes details of the included studies including country, setting and population, sample size, number of years of follow-up, indicator of whether data on determinants of adherence were reported, and the quality score.
Articles identified from mapped search (n = 4111)
  • 1195 Medline
  • 1873 Embase
  • 1043 Web of Science

Articles excluded as duplicates (n=1139)

Articles included for title review (n = 2972)

Articles included for abstract review (n = 93)

Articles excluded after abstract review (n=57)
  • Adherence was not the main outcome

Articles included for manuscript review (n = 36)

Articles excluded (n=25)
  • Adherence was not the main outcome

Final articles included in systematic review (n=11)

Figure 2-2 Systematic Review Study Flow
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Cohort</th>
<th>Setting</th>
<th>Sample Size *</th>
<th>Follow-up</th>
<th>Date on Determinants of Adherence</th>
<th>Quality Score (out of 22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies based on Self-Report Data</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mosley-Williams 2002</td>
<td>US</td>
<td>Prevalent</td>
<td>Tertiary Care</td>
<td>122</td>
<td>n/a</td>
<td>No</td>
<td>17</td>
</tr>
<tr>
<td>Garcia-Gonzalez 2008</td>
<td>US</td>
<td>Prevalent</td>
<td>Secondary Care</td>
<td>32</td>
<td>n/a</td>
<td>No</td>
<td>19</td>
</tr>
<tr>
<td>Daleboudt 2011</td>
<td>New Zealand</td>
<td>Prevalent</td>
<td>Secondary Care</td>
<td>106</td>
<td>n/a</td>
<td>Yes</td>
<td>16</td>
</tr>
<tr>
<td>Santos 2011</td>
<td>Brazil</td>
<td>Prevalent</td>
<td>Secondary Care</td>
<td>246</td>
<td>n/a</td>
<td>Yes</td>
<td>16</td>
</tr>
<tr>
<td>Abdul-Sattar 2015</td>
<td>Egypt</td>
<td>Prevalent</td>
<td>Secondary Care</td>
<td>80</td>
<td>n/a</td>
<td>Yes</td>
<td>16</td>
</tr>
<tr>
<td>Studies based on Electronic Monitoring Devices</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marengo 2012</td>
<td>US</td>
<td>Prevalent</td>
<td>Secondary Care</td>
<td>78</td>
<td>2 yrs</td>
<td>Yes</td>
<td>18</td>
</tr>
<tr>
<td>Studies based on Clinical Records</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morand 1992</td>
<td>Australia</td>
<td>Prevalent</td>
<td>Secondary Care</td>
<td>37</td>
<td>8 yrs</td>
<td>No</td>
<td>14</td>
</tr>
<tr>
<td>Wang 1999</td>
<td>Canada</td>
<td>Prevalent</td>
<td>Secondary Care</td>
<td>156</td>
<td>20 yrs</td>
<td>No</td>
<td>15</td>
</tr>
<tr>
<td>Sjoe 2014</td>
<td>Netherlands</td>
<td>Prevalent</td>
<td>Tertiary/Secondary Care</td>
<td>139</td>
<td>n/a</td>
<td>No</td>
<td>18</td>
</tr>
<tr>
<td>Studies based on Pharmacy Refill Information</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Koneru 2007</td>
<td>US</td>
<td>Prevalent</td>
<td>Secondary Care</td>
<td>55</td>
<td>n/a</td>
<td>No</td>
<td>17</td>
</tr>
<tr>
<td>Koneru 2008</td>
<td>US</td>
<td>Prevalent</td>
<td>Secondary Care</td>
<td>63</td>
<td>n/a</td>
<td>Yes</td>
<td>16</td>
</tr>
</tbody>
</table>

* Sample Size (number of SLE patients) for evaluation/reporting of medication adherence; ** Based on multivariate analyses §Clinical Data vs. electronic pharmacy data
Abbreviations: n/a - not applicable
2.3.2 Quality Assessment

Quality scores ranged from 14 to 19, with a mode of 16 (in 4 studies), indicating the number of items out of 22 that pertains to reporting observational research according to STROBE. An important consideration in this systematic review was whether studies appropriately described and calculated adherence measures as well as reported appropriate statistics (e.g., mean/median adherence scores, proportion of adherent patients). While all of these studies provided descriptions of adherence measurement tools and adherence measures, many failed to report appropriate statistics to describe their adherence rate (7 out of 11) and proportion of adherent patients (6 out of 11). The latter is particularly problematic as the lack of appropriate statistics precludes interpretation of the results. In addition, the majority of these studies failed to report methods to account for bias (10 out of 11), as to how they arrived at their sample size (6 out of 11), and their funding sources (5 out of 11).

2.3.3 Burden of Non-Adherence

2.3.3.1 Studies Based on Self-Report Data

Five studies assessed adherence to SLE medications based on self-reports from patients in various settings. Mosley-Williams et al. queried 122 patients (68 African American women and 54 White women) from 2 rheumatology clinics at urban tertiary care medical centers regarding the frequency of failing to take their SLE medications on a five-point scale (1 = never, 2 = rarely, 3 = sometimes, 4 = often, 5 = all the time) during the last year (61). The difference between the
average medication adherence self-report scores of African American women was 2.3 (SD = 1.2) and for White women it was 2.5 (SD = 1.3) (61).
Table 2-2 Summary of the Results of the Included Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Medication(s)</th>
<th>Types of Non-Adherence Problem</th>
<th>Primary tool to assess adherence</th>
<th>Adherence Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mean Adherence or Adherence Rate</td>
<td>% of Patients that are Adherent</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Studies based on Self-Report Data</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mosley-Williams 2002</td>
<td>NS</td>
<td>a. poor execution</td>
<td>5 point scale of the frequency failed to take medications</td>
<td>--</td>
</tr>
<tr>
<td>Garcia-Gonzalez 2008</td>
<td>NS</td>
<td>a. poor execution</td>
<td>Compliance Questionnaire Rheumatology</td>
<td>68.0</td>
</tr>
<tr>
<td>Daleboudt 2011</td>
<td>NS</td>
<td>a. poor execution</td>
<td>Medication Adherence Self Report Inventory</td>
<td>86.7%</td>
</tr>
<tr>
<td>Santos 2011</td>
<td>NS</td>
<td>a. poor execution</td>
<td>Morisky Medication Adherence Scale (MMAS) (Dichotomous Variable)</td>
<td>--</td>
</tr>
<tr>
<td>Abdul-Sattar 2015</td>
<td>NS</td>
<td>a. poor execution</td>
<td>Compliance Questionnaire Rheumatology ≥80%</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Studies based on Electronic Monitoring Devices</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marengo 2012</td>
<td>HCQ</td>
<td>a. poor execution</td>
<td>Medication Events Monitoring System ≥80%</td>
<td>61.2%</td>
</tr>
<tr>
<td></td>
<td>MTX</td>
<td></td>
<td></td>
<td>73.6%</td>
</tr>
<tr>
<td></td>
<td>MMF</td>
<td></td>
<td></td>
<td>49.8%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Studies based on Clinical Records</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morand 1992</td>
<td>HCQ</td>
<td>b. discontinuation</td>
<td>Electronic Prescription Records</td>
<td>--</td>
</tr>
<tr>
<td>Wang 1999</td>
<td>AM</td>
<td>b. discontinuation</td>
<td>Clinical Records</td>
<td>--</td>
</tr>
<tr>
<td>Sjoe 2014</td>
<td>AM</td>
<td>b. discontinuation</td>
<td>Clinical Records</td>
<td>--</td>
</tr>
</tbody>
</table>

| **Studies based on Pharmacy Refill Information** |               |                                |                          |                          |
| Koneru 2007         | HCQ           | a. poor execution              | Pharmacy Refill Data ≥80%                                             | --                 |
| Koneru 2008         | HCQ           | a. poor execution              | Pharmacy Refill Data ≥80%                                             | 73%                |
|                     | Other IS      | a. poor execution              | Pharmacy Refill Data ≥80%                                             | 75%                |

* Where relevant, cut-off point used to dichotomize subjects as adherent/non-adherent provided;
Abbreviations: NS – not specified; MTX – methotrexate; MMF - mycophenolate mofetil; HCQ – hydroxychloroquine; AM - antimalarials; IS – immunosuppressives
This difference was not statistically significant. Garcia Gonzales et al. evaluated self-reported adherence and the determinants of non-adherence among 32 SLE patients from outpatient rheumatology clinics in Houston, Texas (62). As part of this evaluation, patients were asked to complete the Compliance Questionnaire Rheumatology (CQR), a self-reported measure of medication adherence with 19 items specifically developed for patients with rheumatic diseases, which was validated through electronic monitoring (62). The score for this measure ranges from 0 (complete non-adherence) to 100 (perfect adherence) (62). Overall, the mean CQR score for patients was 68.0 (SD = 8.3) (62). Also, self-reported adherence was assessed by asking patients: 1) how often they forget their medications, 2) how often they discontinued their medications on their own because of the side effects, and 3) how often they discontinued their medications because they were not helping. Possible answers were 1 = never, 2 = rarely, 3 = sometimes and 4 = often. The average responses to those three questions were 2.0 (SD = 0.8), 1.5 (SD = 0.7), and 1.2 (SD = 0.5) respectively (62).

Further, Daleboudt et al. assessed the level of self-reported adherence and administered questionnaires to identify determinants of non-adherence in 106 SLE patients from the outpatient rheumatology clinic of the Auckland City Hospital on at least one immunosuppressive agent (63). Part A of the Medication Adherence Self-Report Inventory (MSARI) was used to assess medication adherence. The mean self-reported adherence was 86.7% (SD = 18.0%) for all patients (63). Santos et al. examined the prevalence of adherence to medications in 206 SLE patients from the lupus outpatient clinic at the Pedro Ernesto University Hospital. Adherence was measured using the Morisky Medication Adherence Scale (MMAS) (64). Patients were classified
as either adherent or non-adherent based on response to MMAS survey items. They found that only 31.7% of patients were adherent to their treatment regimen for their SLE (65). Lastly, Abdul-Sattar et al. cross sectionally examined medication adherence and its determinants in SLE patients from outpatient rheumatology clinics from the university hospitals in Egypt. The CQR was used to assess adherence and were classified as non-adherent if taking <80% of their medications correctly. They found that only 52.5% of patients were adherent to their SLE medication regimen (66).

2.3.3.2 Studies Based on Electronic Monitoring Devices

One included study by de Marengo et al. used the MEMS to assess medication adherence over two years of follow-up among 78 SLE patients from outpatient rheumatology clinics (67). Adherence was determined as the percentage of days (weeks for methotrexate) that the patients took the medications as prescribed; mean adherence was 62% for all drugs combined (HCQ, mycophenolate mofetil, methotrexate, prednisone) with 25% of patients classified as adherent (average adherence ≥ 80%) (67).

2.3.3.3 Studies Based on Clinical Records

Three studies utilized clinical records to assess discontinuation of SLE medications. Morand et al. utilized an Australian clinical drug use database that has the dates of initiation and commencement of HCQ of 37 SLE patients over an eight-year period. At the end of follow-up (8 years) 35% (13) of patients had discontinued AM therapy (68). Wang et al. used a Canadian clinical lupus database to assess the timing and reasons for discontinuation of AM in 156 SLE patients. They found that the median duration, which a SLE patient persisted with AM therapy,
was 6.1 years per patients (69). Lastly, Sjoe et al. conducted a longitudinal cohort study, which used the Amsterdam Lupus Cohort, to assess discontinuation of AM in 139 SLE patients. Here, 73.2% of SLE patients were using AMs at the end of the follow-up of the cohort (70).

2.3.3.4 Studies Based on Pharmacy Refill Data

Koneru et al. conducted two studies (71)(72) examining medication adherence in SLE using pharmacy refill information. In this instance, these were not refill records in automated databases (48), instead they inquired for information about where participants obtained their medications. These pharmacies were contacted and the four most recent medication prescriptions (amounts, and dates) were collected and the Medication Possession Ratio (MPR) was calculated and patients were categorized as adherent (MPR ≥ 80%) or non-adherent (MPR < 80%) (73). In this group’s early work, they assessed a convenience sample of 55 patients recruited from university-affiliated rheumatology clinics to determine the reliability and concurrent validity of the MSARI with the “gold standard” criterion, pharmacy refill information. They found that 39% of patients were non-adherent to prednisone and 51% to hydroxychloroquine (71). Finally, although Koneru’s more recent study on medication adherence in SLE was a qualitative study, I included it in my systematic review as they used pharmacy refill information to identify non-adherent patients, which were then invited to face-to-face interviews to discuss barriers to adherence and interventions to support adherence (72). They assessed adherence and conducted interviews of 63 SLE patients and found: 39% of patients were non-adherent to prednisone, 51% to hydroxychloroquine, and 43% to other immunosuppressant medications (72).
### 2.3.4 Determinants of Adherence/Non-Adherence

**Table 2-3 Determinants of Medication Adherence from the Included Studies**

<table>
<thead>
<tr>
<th>Factors</th>
<th>Associated with Higher Adherence</th>
<th>Associated with Lower Adherence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient Factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family Support (yes)</td>
<td>+Santos</td>
<td></td>
</tr>
<tr>
<td>Behaviour towards adverse reaction</td>
<td>+Santos</td>
<td></td>
</tr>
<tr>
<td><strong>Condition Factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mucocutaneous manifestations (yes)</td>
<td>+Santos</td>
<td></td>
</tr>
<tr>
<td>Hematological alterations (no)</td>
<td>+Santos</td>
<td>+Santos</td>
</tr>
<tr>
<td>Depression (yes)</td>
<td>+Marengo, +Abdul-Sattar</td>
<td></td>
</tr>
<tr>
<td><strong>Therapy Factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polypharmacy</td>
<td>+Marengo, +Abdul-Sattar</td>
<td></td>
</tr>
<tr>
<td><strong>Social / Economic Factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low SES</td>
<td>+Santos</td>
<td>+Abdul-Sattar</td>
</tr>
<tr>
<td>Education (more)</td>
<td>+Santos</td>
<td>+Abdul-Sattar</td>
</tr>
<tr>
<td>Education (less)</td>
<td></td>
<td>+Abdul-Sattar</td>
</tr>
<tr>
<td>Rural Residency</td>
<td></td>
<td>+Abdul-Sattar</td>
</tr>
<tr>
<td><strong>Health Care System Factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Legibility of physician prescription</td>
<td>+Santos</td>
<td></td>
</tr>
</tbody>
</table>

Data on the determinants of medication adherence among SLE patients, based on multivariable analyses, were reported in 3 studies (65)(67)(74). Table 2-3 summarizes these determinants according to the WHO’s five dimensions of medication adherence. Among social/economic factors, lower education level as a predictor of non-adherence was reported in two studies (65)(66). Among condition factors, having depression was associated with lower adherence in 2 studies (65)(66). With respect to treatment factors, polypharmacy was associated with non-adherence (66)(67).
2.4 Discussion

The objective of this systematic review was to synthesize the data on the burden and determinants of medication adherence among SLE patients. With the percentage of adherent patients ranging from 25% - 57%, and mean adherence rate of 69.61%, an important finding of this systematic review is the sub-optimal treatment adherence in SLE. Overall less than half of the SLE patients are adherent with AM treatment according to the included studies. These studies assessed adherence in small regionally specific clinical samples, with the number of patients ranging from 32 to 246. The key determinants that were reported in multiple studies were education (65)(66), depression (66)(67) and polypharmacy (66)(67). Altogether, this systematic review confirms that the burden of non-adherence is substantial and significant in SLE. This also highlights the need for more research on adherence using more heterogeneous samples from different care settings as well as interventions to support adherence among SLE patients.

In synthesizing the evidence of medication non-adherence in SLE I identified important limitations in the literature to date. First, no study has examined both poor execution and discontinuation, the distinct but equally important aspects of medication adherence. In addition, some of these studies did not specify the medications being studied, which is problematic because some medications such as prednisone are used primarily on a temporary basis to treat flares and are not intended for long-term use unlike AMs or immunosuppressive agents (15)(16). Further, all of the included studies were based on small and regionally specific clinical samples (ranging from 32 to 246), which may not be generalizable to the population of all SLE patients. Lastly, every studied used a prevalent SLE cohort, therefore they are prone to survivorship bias.
because SLE a patient would need to survive until they receive treatment. The percentage of adherent patients varied widely, which is most likely due to such a wide range of methods used to measure adherence. The most common method to ascertain adherence of the included studies was self reported measures. This measure tends to overestimate adherence because of social desirability bias, whereby patients tend to over-report good behaviours when they are being directly queried, which is a recognized problem in measurement of adherence (5).

As expected, studies based on self-report data estimated higher levels of adherence when compared with electronic monitoring devices, which is most likely due to social desirability bias. Surprisingly, studies based on pharmacy refill information estimated higher levels of adherence as well when compared with electronic monitoring devices. This may have occurred for two reasons: pharmacy refill information is only measuring a patient’s possession of medication and not their actual medication taking behaviour or due to the fact that small regionally specific samples were chosen, and this difference observed may be simply due to chance. Only three studies (65)(66)(67) examined determinants of medication non-adherence in SLE. This is worrisome because it is necessary to first understand the modifiable factors that are significant associated with medication non-adherence before appropriate interventions can be designed. None of the included studies utilized administrative electronic prescription records to assess adherence, which counters the recent trends of the increased use and wide acceptance of retrospective, computerized databases for medication adherence research (35)(75).

Since there was a wide range of tools and methods to assess medication adherence, there was not a well-validated and appropriate tool to assess the quality of the measurement and report of
medication adherence. Therefore, the STROBE statement was used to assess how well the observational research was reported. Although studies met standards for describing rationale, and methods, I found that many studies did not report their findings completely in a clear and transparent fashion. In light of limitations we identified future research quantifying the burden and determinants of medication non-adherence in SLE.

This synthesis of the literature of medication adherence in SLE has highlighted some notable gaps and future steps for clinicians and researchers to improve medication adherence and outcomes in SLE patients. The burden of medication non-adherence in SLE seems to be substantial and contributing towards poor long-term outcomes due to the sequelae of SLE (76)(77). However, there is a large gap in the literature for medication adherence to be assessed in larger more heterogeneous SLE cohorts, using well validated methods, and reported in a clear and transparent method to fully characterize this problem and inform policy makers.

Additionally, this review has highlighted some recommendations for health care providers to best help support adherence and improve outcomes. Medication non-adherence is a substantial problem in SLE. One should not assume automatically that their patient is adherent. In addition, providing access to education material about treatments, trying to reduce pill burden, and being observant of depressive symptoms and providing support as needed could be potential interventions to facilitate optimal medication adherence to SLE treatments that would improve outcomes.
Strengths and limitations of this systematic review deserve discussion. Study strengths include a structured approach to synthesizing evidence on medication adherence in SLE in terms of its burden and determinants. Furthermore, because of my interest in methods of measuring adherence, my review also centered around the various methods used to measure adherence (e.g., self-report, clinical records, electronic monitoring devices) and aspects of adherence in terms of poor execution of the therapy or discontinuation of therapy. My work also builds on a recent review article by Costedoat-Chalumeau (78) through systematic searching of the literature and comprehensive capture of studies. Nonetheless, limitations of my systematic review bear discussion. First, identification and selection of studies for inclusion may be limited by publication bias. Second, while I assessed studies based on how well they reported their observational research, I did not assess the quality of medication adherence measurement due to lack of an appropriate tool that would be applicable to different methods used in the included studies.

Overall, by demonstrating that less than half of the SLE patients are adherent with AM treatment across the included studies, this systematic review confirms that medication adherence is sub-optimal and a significant problem in SLE. This systematic review also highlights the need for more research on non-adherence in a more heterogeneous SLE patient population as well as interventions to support adherence among SLE patients. Altogether, findings have important implications for SLE patients, healthcare providers who prescribe SLE medications, and other healthcare professionals involved in pharmacological care by emphasizing the importance of monitoring, discussing, and supporting adherence with therapy.
Chapter 3: The Burden and Determinants of Medication Non-Adherence in SLE

3.1 Introduction

Systemic Lupus Erythematosus (SLE) is a chronic Systemic Autoimmune Rheumatic Disease (SARD) that specifically attacks collagen and results in multifarious clinical manifestations including joint pain, photosensitivity, malar rash, and clinical nephritis (55)(56). It occurs predominantly in women (approximately 9:1 female to male) during their childbearing years, and has a strong minority representation (6). The one-year period prevalence SLE rate in the UK was 207/100,000 for Afro-Carribbeans and 48.8/100,000 for Asians while only 20.3 for Whites (7). As there is no cure for SLE, chronic prescription medications are used to slow down disease progression, and to prevent damage to other organ systems from the downstream effects of SLE (6). The conventional treatment option for patients with SLE with minimal organ involvement is the long-term use of antimalarials (AMs), namely hydroxychloroquine (HCQ) and chloroquine (CQ) (1)(15)(16). It is recommended that SLE patients with multiple organ systems involved should additionally be taking other immunosuppressive medications (azathioprine, cyclophosphamide, methotrexate, chlorambucil, and cyclosporine) (15)(16). Advancements in SLE treatments over the last few decades have resulted in marked decreases in deaths associated with SLE activity, (2) but there seems to be no such decline in deaths associated with the sequelae of SLE (2).
3.1.1 Medication Adherence in SLE

Poor adherence to long-term AM or immunosuppressive treatment may be an important factor that could potentially be driving poor long-term outcomes in SLE patients due to the downstream effects of the disease. Medication non-adherence is a complex construct that encompasses the distinct problems of: 1) poor execution of the dosing regimen such that scheduled doses are delayed or omitted, which may lead to transient interruptions in drug action, and 2) discontinuation of the medication, which may lead to the intermittent or permanent loss of drug effects (Figure 3-1) (79). An additional construct, persistence, is the reciprocal to discontinuation and refers to conforming to a recommendation of continuing treatment for the prescribed length of time (57). While a potential contributor to therapeutic challenges in SLE, medication non-adherence has not been well described among SLE patients. As determined in the systematic review of medication non-adherence in Chapter 2 of this thesis, eleven studies have examined medication adherence as the primary outcome in a SLE study population. Of these studies, only three explored determinants of medication non-adherence. Further, these studies all used small regionally specific clinical samples and none examined the two distinct but equal important aspects of medication adherence: discontinuation and poor execution. To fill this gap in the literature, I conducted a population based pharmacoepidemiological study. My objective was to
evaluate medication non-adherence in a heterogeneous SLE cohort and identify determinants, that is, patient conditions, and health care system factors that are significantly associated with medication non-adherence.

3.2 Methods

3.2.1 Data Sources and Study Population

Population Data BC (Pop Data) is an extensive data resource that contains all BC Linked Health data for applied health services and population health research covering the entire population of BC (estimated 4.7 million residents, January 2016). The Pop Data spans a long time period (1990-2012), with most variables being available from 1996 onwards, allowing both the opportunity to conduct retrospective studies of a large generalizable data set and also prospective studies of individuals over time as the data expands longitudinally. Each eligible resident is assigned a Personal Health Number (PHN), which is captured in all records of health care resource utilization, which enables linkage between datasets. For the purposes of this study, I will use data from five different data files: BC Medical Services Plan, BC Discharge Abstract Database, Consolidation file, BC Vital Statistics, BC PharmaNet (external to BC Linked Health Databases).

- **Medical Services Plan (MSP):** This captures all outpatient medical services including physician visits, service date, type, laboratory tests and procedures, diagnosis most related with each record, and total paid amount (50).

- **Discharge Abstract Database (DAD):** This captures hospital separation records and includes admission date, length of stay, and up to 25 discharge diagnostic codes.
representing the reason for admission (primary position) or complications during hospitalization (secondary position) using ICD-9 and/or ICD-10 codes, procedure/intervention codes, and separation dates (51).

- **Consolidation File (MSP registration file):** This captures the birth date, sex, and registration status of the person with a health authority as well as the postal code and neighbourhood income quartile of each person in each fiscal year (80).

- **BC PharmaNet:** This is a population-based prescription drug database that captures dispensing episodes on a prescription-by-prescription basis for the vast majority of the population (excluding first nations and federally insured populations) and paid for by the provincial government or privately. The file contains the patients’ age, sex, the drug dispensed, instructions for use, and the date and total quantity dispensed (52).

I used data from a previously established population-based SLE cohort (N = 5,831; Jan 1990 – Dec 2010) (40). In brief, administrative data for the reimbursement of physician visits from the BC Ministry of Health were used to identify adults (≥18 years) with SLE who received care for their SLE between January 1990 and December 2010. The case definition for SLE was the same as previously published for this cohort (40); inclusion criteria were at least 2 physician visits >2 months apart with an SLE diagnostic code (International Classification of Diseases, Ninth Revision [ICD-9], 710.0) and exclusion criteria were at least 2 visits subsequent to the second SLE visit with diagnoses of other systemic autoimmune rheumatic disease (SARD), or an SLE diagnosis by a non-rheumatologist that was not confirmed on subsequent rheumatologist visit. This algorithm has a very high specificity of 99.9% and a sensitivity that was ~ 80%, which varies based on patient characteristics (81). From this population-based cohort of SLE patients, I
identified SLE patients with incident AM use. Incident SLE patients were defined as those who had no prior SLE visit during the 5 years prior to the date of SLE diagnosis (5-year sliding run-in period). As this period was based on each patient’s SLE diagnosis date, it was variable (sliding). Incident AM users were incident SLE patients who had at least one AM prescription after the date of their SLE diagnosis, whereby the date of the first AM prescription was assigned as the “index AM date.” I also applied a 1-year wash-out period to ensure no prior AM prescription in the year prior to the date of SLE diagnosis. The purpose of excluding prevalent AM users was to ensure that the start of AM treatment regimen was known so appropriate adherence measures could be calculated.

3.2.2 Assessment of Discontinuation

The primary outcome of this study is the discontinuation of the AM regimen. In a long-term follow-up of the randomized withdrawal study conducted by the Canadian HCQ study group to evaluate the long-term effectiveness of HCQ, it was found that the relative risk of a major flare for those on HCQ versus placebo was 0.42 (95% CI: 0.17 – 1.12) (82). These patients were taking HCQ in a real world setting with no support to promote optimal adherence. Therefore, it is likely that many of these patients were poorly executing their regimen despite persisting with the treatment because of the suboptimal level of adherence in SLE that was demonstrated in Chapter 2’s systematic review. “Since drugs do not work for patients who do not take them” (5), it is paramount to analyze whether SLE patients persist with their treatments, even if they are poorly executing their AM regimen. Using data on prescription dispensing date and the number of days supplied, I established the AM therapy course for each subject to determine the time until the event of interest (discontinuation of AM therapy). I defined the discontinuation
of AMs to occur when a permissible gap was exceeded after the completion of a prescription (date of prescription plus the days supplied) (Figure 3-2). Since BC Pharmacare, the public drug insurance plan in BC, and private drug insurance plans do not pay for more than 90-100 days of supply of a drug at a time, prescriptions for chronic medications typically need to be filled every 30 or 90 days, which is sometimes denoted as a prescription “cycle” (83). Therefore, a common permissible gap in treatment is set to 90 days as it represents that the patient has missed a full prescription “cycle” (83). Since the response of AMs is quite slow, taking approximately 6 weeks for an effect to be seen (6) while a full prescription “cycle” is 90 days, I set the permissible gap used to identify when a patient has discontinued AMs as 90 days. Switches from HCQ to CQ were not considered as a discontinuation of therapy. Using this definition of persistence, I determined which patients were persisters (who did not exceed the permissible gap between prescriptions) and non-persisters (who did exceed the permissible gap).
3.2.3 Assessment of Poor Execution

Measuring adherence (poor execution) was a secondary outcome for this study. To prevent major flares, it seems it is more important that the patient remains on AM therapy even if they are not executing optimally (82). Nevertheless, evaluating how well SLE patients execute their AM regimen is important to fully characterize medication non-adherence in SLE. Medication adherence (poor execution) was measured using the proportion days covered (PDC), a common measure of daily medication availability (5). PDC is defined as the total number of days with possession of medication in a period of time, which can be calculated by using the following formula:

\[
PDC = \frac{\text{Total Days Drug Available}}{\text{Last Rx Date} + \text{Last Rx Days Supply} - \text{First Rx Date}}
\]

Figure 3-2 Schematic of Discontinuation
PDC was assessed using data on prescription dispensing dates and number of days supplied only over the time period in which the patient is persistent to treatment (first prescription until first gap in therapy > 90 days). I calculated PDC over the entire follow-up period (overall PDC) and over the 1st year of follow-up (1-year PDC) for persistent and non-persistent AM users. Adherence (poor execution) was analyzed separately for persisters and non-persisters to evaluate if they were statistically significant differences between the distributions of covariates in adherent versus non-adherent patients within each group (persisters or non-persisters). Since there is not a clinically relevant cut-off, I followed the convention in the literature to dichotomize PDC. I used the conventional cut-off between adherent and non-adherent patients, which is that adherent patients consume ≥ 80% of recommended treatment dosages.

3.2.4 Assessment of Covariates

I examined the association of factors known to influence AM discontinuation or adherence (‘poor execution’) that were available in our data in univariable and multivariable regression models. Variables that may be associated with AM discontinuation were selected based on prior studies of determinants of medication non-adherence in SLE from the systematic review of medication non-adherence in SLE as described in Chapter 2 of my thesis. Demographic variables included: 1) age; 2) gender; 3) socio-economic status (SES) (neighbourhood level SES based on residence); and 4) type of residence (rural versus urban) as determined by using Census Metropolitan Area/Census Agglomeration (CMA/CA) from geographical census data. Fixed-in-time binary variables measured over a period of 1 year preceding the start of follow-up evaluated chronic co-morbid medical conditions and were based on physician visits (ICD-9 codes) or medication use. These included diabetes (use of insulin or oral hypoglycemic agents),
depression (296.x, 309.x, 300.4, 311.x), cardiovascular disease (including angina [411.x, 413.x], use of nitrates or cardiac medications [anti-hypertension medications, congestive heart failure medications, anticoagulants and anti-arrhythmia medications]), chronic obstructive pulmonary disease (490.x – 496.x), as well as the use of other medications as markers of polypharmacy or those that may confound AM discontinuation, namely hormone replacement therapy and oral contraceptives. For each subject, I calculated a modified Charlson Comorbidity Score over the 1-year period preceding the beginning of follow-up using a version adapted for administrative data (84)(85). Finally, I also considered any prior cardiovascular event [acute myocardia infarction (AMI) and cerebrovascular accident (CVA) (434.x, 436.x)] at any time between 1990 and the beginning of the follow-up.

The following variables, evaluated over study follow-up, were considered as proxy indicators of SLE severity: use of DMARDs (cyclophosphamide, methotrexate, leflunomide, azathioprine, cyclosporine, sulfasalazine, mycophenolate mofetil, chlorambucil), rate of rheumatologist, nephrologist, dermatologist and psychiatrist visits, and the rate of hospitalizations. I quantified the variables representing the rate of visits to specialty physicians as time-dependent covariates representing the cumulative rate of visits for each patient since SLE onset, updated monthly. I also determined use of other SLE medications that could influence AM discontinuation or poor execution, including glucocorticosteroids, traditional non-steroidal anti-inflammatory drugs (NSAIDs), and (Cox-2) inhibitors, as monthly updated, time-dependent covariates.
3.2.5 Statistical Analysis

3.2.5.1 Descriptive Statistics

Characteristics of the cohort of incident SLE patients with incident AM use were summarized using descriptive statistics, including means and standard deviations for continuous variables and counts and proportions for categorical variables.

3.2.5.2 Assessment of Discontinuation

For the descriptive analysis of persistence to AMs, I estimated the median time to discontinuation with Kaplan-Meier survival curves and the proportion of patients that discontinued with AM therapy. I used information on date of deaths from the Vital Statistics database and registration information from the MSP database to account for right censoring of the data. I considered an individual to be censored if they were deceased or no longer registered for MSP before a permissible gap was exceeded. I also calculated the proportion of patients persistent at 1-year intervals for the duration of follow-up by using life tables derived from the survival curves.

To identify determinants of AM discontinuation, a Cox’s proportional hazards model with delayed entry and time-varying covariates was used (86)(87). For all patients in the cohort the index date (time = 0) was set to date of SLE diagnosis. Therefore, person-time of follow-up was computed from the index date to discontinuation of AM therapy (as described in Sec 3.2.2), last health care service use, death, or end of study period (December 31, 2010), whichever occurred first. However, as AM therapy was not always initiated at the same time as
the date of SLE diagnosis, there is a gap between the date of SLE diagnosis and initiation of AM therapy during the follow-up period in which the patient was not at risk for AM discontinuation for many cases. A traditional Cox’s proportional hazards model assumes that every individual is at risk for an event at time 0 and continues to be until an event occurs or they are censored (86). Since that assumption would be invalid in this instance, I applied delayed entry into the risk set, in which the date when the index AM prescription was dispensed was used to indicate when an individual entered the risk set (Figure 3-3).

From my starting list of variables (Table 3-3), I examined the bivariate association of all variables with discontinuation. All variables that were statistically significantly (p < 0.05) associated in the bivariate analysis with discontinuation of AM were then included in the multivariable Cox’s model. The final multivariable Cox’s models proportional hazards model included variables representing age at index date, sex, and the most parsimonious set of covariates that minimized the AIC score.

**Figure 3-3 Schematic of Delayed Entry**
3.2.5.3 Assessment of Poor Execution

Adherence (poor execution) was measured by calculating PDC over the entire follow-up period (Overall PDC) and over the 1st year of follow-up (1-year PDC) for persisters and non-persisters. Patients from these two groups were then classified as either adherent or non-adherent using the conventional cut-off of PDC ≥ 0.80. For each of these two groups of SLE patients (persisters and non-persisters), unadjusted chi-squared tests (or t-tests for continuous variables) were conducted between adherent and non-adherent patients examining whether the observed difference of a covariate between adherent and non-adherent patients for a particular group arose by chance.

3.3 Results

3.3.1 Descriptive Statistics

Of the 3555 incident SLE patients, only 2267 received at least one AM prescription. Only 881 of these SLE patients were incident AM users as determined by a 1-year wash-out period (Error! Reference source not found.). I have shown in Appendix B the breakdown of the cases that were excluded because they were not incident AM users. The median time between SLE diagnosis date and the “index AM date” is 2.5 months. Further, I have shown in Appendix C the distribution, and median time between SLE diagnosis date and the first AM prescription. The cohort included 881 individuals with SLE who were incident AM users. Characteristics of the cohort are summarized in Table 3-1.
Figure 3-4 Schematic of Cohort Creation

Abbreviations:  
SLE – systemic lupus erythematosus; AM – Antimalarials  
* 5 year sliding run-in period to define incident SLE patients  
** 1 year washout period to define incident AM use
Women comprised 91% of the cohort and at index date, mean age was 44.8 ± 15.2 years. 37.12% of patients were categorized as belonging to the highest SES status and 39.84% in the lowest SES status. Only 12.83% of patients resided in rural areas.

Table 3-1 Characteristics of SLE Cohort of Incident Drug Users (n = 881)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>44.83 ± 15.21</td>
</tr>
<tr>
<td>Female</td>
<td>822 (90.83)</td>
</tr>
<tr>
<td>Socioeconomic status</td>
<td></td>
</tr>
<tr>
<td>High SES (\Sigma)</td>
<td>327 (37.12)</td>
</tr>
<tr>
<td>Middle SES (\Sigma)</td>
<td>203 (23.04)</td>
</tr>
<tr>
<td>Low SES (\Sigma)</td>
<td>351 (39.84)</td>
</tr>
<tr>
<td>Rural residence</td>
<td>113 (12.83)</td>
</tr>
<tr>
<td><strong>Comorbidities</strong></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular event (AMI/CVA) (\S\W)</td>
<td>55 (6.24)</td>
</tr>
<tr>
<td>Serious infection (\S\W)</td>
<td>126 (14.30)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease (COPD) (\F)</td>
<td>140 (15.89)</td>
</tr>
<tr>
<td>Depression (\F)</td>
<td>175 (19.86)</td>
</tr>
<tr>
<td>Diabetes (\S\F)</td>
<td>37 (4.20)</td>
</tr>
<tr>
<td>Cardiovascular disease (CVD) (\F)</td>
<td>242 (27.47)</td>
</tr>
<tr>
<td>Charlson comorbidity index</td>
<td>0.75± 1.05</td>
</tr>
<tr>
<td><strong>Use of Medications</strong></td>
<td></td>
</tr>
<tr>
<td>COX-2 Inhibitors (\F)</td>
<td>76 (8.63)</td>
</tr>
<tr>
<td>COX-2 Inhibitors (\S)</td>
<td>127 (14.42)</td>
</tr>
<tr>
<td>Other DMARDs (\S)</td>
<td>68 (7.72)</td>
</tr>
<tr>
<td><strong>Use of Medications</strong></td>
<td></td>
</tr>
<tr>
<td>Other DMARDs (\S\S)</td>
<td>229 (25.99)</td>
</tr>
<tr>
<td>Glucocorticoids (\S)</td>
<td>266 (30.19)</td>
</tr>
<tr>
<td>Glucocorticoids (\S)</td>
<td>503 (57.09)</td>
</tr>
<tr>
<td>Hormone Replacement Therapy (HRT) (\S)</td>
<td>77 (8.04)</td>
</tr>
<tr>
<td>Oral Contraceptives (OC) (\S)</td>
<td>90 (10.22)</td>
</tr>
<tr>
<td>Traditional NSAIDs (\S)</td>
<td>385 (43.70)</td>
</tr>
<tr>
<td><strong>Health Care Utilization</strong></td>
<td></td>
</tr>
<tr>
<td>Number of outpatient visits (mean) (\S)</td>
<td>23.62 ± 17.11</td>
</tr>
<tr>
<td>Visited Rheumatologist (\S)</td>
<td>753 (85.47)</td>
</tr>
<tr>
<td>Visited Dermatologist (\S)</td>
<td>268 (30.41)</td>
</tr>
<tr>
<td>Visited Nephrologist (\S)</td>
<td>59 (6.70)</td>
</tr>
<tr>
<td>Visited Psychiatrist (\S)</td>
<td>104 (11.80)</td>
</tr>
<tr>
<td>Hospitalized (\S)</td>
<td>247 (28.07)</td>
</tr>
</tbody>
</table>

Values are N (percentages) unless otherwise indicated.
\(\Sigma\) Socioeconomic Status (SES) was measured in quintiles. Low SES comprised the 1st
and 2nd quintile. Middle SES comprised of the 3rd quintile. High SES comprised of the 4th and 5th quintile
§ Evaluated prior to index date (SLE diagnosis) since 1990 (earliest available data);
ψ Based on Hospital Data
⊗ Based on Hospital and MSP Data
† Evaluated over 1 year preceding index date (SLE diagnosis);
* Determined by drug definition
η Taken anytime after index date (SLE diagnosis) and up until end of follow-up
ζ Cardiovascular Disease includes: angina, hyperlipidemia*, hypertension* or taking:
anti-arrhythmic agents, anti-congestive heart failure of anticoagulants.
ξ Other Disease Modifying Anti-Rheumatic Drugs (DMARDs) included:
cyclophosphamide, methotrexate, sulfasalazine, leflunomide, azathioprine, cyclosporine,
mycophenolate mofetil, chlorambucil, biologics

3.3.2 Assessment of Discontinuation

The average person’s years of follow up was 5.88 ± 3.54. The median time until AM discontinuation was 2.42 years (2.08, 2.75), with 612 out of 881 patients discontinuing AM therapy over the follow-up period. The survival rate at for each year during the follow-up period is shown Table 3-2. After 1 year, only 77% of patients remained on AM therapy or in other words 23% had discontinued AMs. After 5 years, only 33% of patients remained on AM therapy, or in other words 57% had discontinued AMs.
Figure 3-5 Kaplan Meier Curve of Discontinuation of AM Therapy

Table 3-2 Life Table Survival Analysis

<table>
<thead>
<tr>
<th>Year</th>
<th>Survival Rate</th>
<th>Standard Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.771</td>
<td>0.0142</td>
</tr>
<tr>
<td>2</td>
<td>0.558</td>
<td>0.0170</td>
</tr>
<tr>
<td>3</td>
<td>0.448</td>
<td>0.0174</td>
</tr>
<tr>
<td>4</td>
<td>0.384</td>
<td>0.0174</td>
</tr>
<tr>
<td>5</td>
<td>0.328</td>
<td>0.0174</td>
</tr>
<tr>
<td>6</td>
<td>0.278</td>
<td>0.0173</td>
</tr>
<tr>
<td>7</td>
<td>0.235</td>
<td>0.0173</td>
</tr>
<tr>
<td>8</td>
<td>0.211</td>
<td>0.0172</td>
</tr>
<tr>
<td>9</td>
<td>0.196</td>
<td>0.0172</td>
</tr>
<tr>
<td>10</td>
<td>0.166</td>
<td>0.0173</td>
</tr>
</tbody>
</table>
In the bivariate analyses of determinants of AM discontinuation, the following time-fixed variables were significantly associated with the discontinuation of AMs: SES (Low vs. High) (HR, 1.230; 95% CI 1.025 – 1.476); and serious infections (HR, 1.314; 95% CI 1.050 – 1.644). Furthermore, in the bivariate analyses the following time-varying variables updated monthly were significantly protective against discontinuation of AM: glucocorticoids (HR, 0.657; 95% CI 0.540 – 0.798); other DMARDs (HR, 0.701; 95% CI 0.546 – 0.900); traditional NSAIDs (HR, 0.670; 95% CI 0.499 – 0.901); rate of SLE visits (HR, 0.599; 95% CI 0.427 – 0.731); rate of rheumatologist visits (HR, 0.389; 95% CI 0.274 – 0.553); and rate of dermatologist visits (HR, 0.467; 95% CI 0.226 – 0.996) (Table 3-3).

Entering these variables into a multivariable Cox’s model yielded the final model shown in Table 3-4, which minimized AIC score with the most parsimonious list of variables. In this model, SES (Low vs. High) (HR, 1.223; 95% CI 1.018 – 1.468) was the only statistically significant time-fixed determinant of discontinuation of AMs. Compared to the high SES group, being in a low SES group was associated with 22.3% increased risk of discontinuation of AM therapy regimen. Additionally, in this model the following time-varying variables updated monthly were statistically significantly associated with the discontinuation of AMs: glucocorticoids (HR, 0.731; 95% CI 0.599 – 0.891); traditional NSAIDs (HR, 0.655; 95% CI 0.488 – 0.880); rate of rheumatologist visits (HR, 0.415; 95% CI 0.228 – 0.598); and rate of dermatologist visits (HR, 0.453; 95% CI 0.220 – 0.936). These time-varying variables updated monthly were markers of disease severity suggesting that patients with milder forms of SLE had a higher risk of discontinuation of AM therapy. Additionally, visits to a rheumatologist or dermatologist may represent a reminder to patients to persist with their treatment. Since our
permissible gap is 90 days and these variables are updated monthly, a visit to a specialist could potentially interrupt a gap and remind the patient to recommence with treatment.

Table 3-3 Univariate Survival Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time-Fixed Variables</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.999 (0.994, 1.004)</td>
<td>0.677</td>
</tr>
<tr>
<td>Sex (M vs. F)</td>
<td>0.824 (0.614, 1.107)</td>
<td>0.199</td>
</tr>
<tr>
<td>Residence (Rural vs. Urban)</td>
<td>1.081 (0.856, 1.364)</td>
<td>0.513</td>
</tr>
<tr>
<td>SES (Low vs. High)</td>
<td>1.230 (1.025, 1.476)</td>
<td>0.026</td>
</tr>
<tr>
<td>SES (Medium vs. High)</td>
<td>1.157 (0.938, 1.428)</td>
<td>0.172</td>
</tr>
<tr>
<td><strong>Comorbidities</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular events</td>
<td>1.115 (0.835, 1.598)</td>
<td>0.384</td>
</tr>
<tr>
<td>Serious infections</td>
<td>1.314 (1.050, 1.644)</td>
<td>0.017</td>
</tr>
<tr>
<td>COPD</td>
<td>1.113 (0.912, 1.408)</td>
<td>0.26</td>
</tr>
<tr>
<td>Depression</td>
<td>0.939 (0.764, 1.153)</td>
<td>0.546</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.006 (0.679, 1.490)</td>
<td>0.977</td>
</tr>
<tr>
<td>Charlson comorbidity index</td>
<td>1.060 (0.996, 1.143)</td>
<td>0.0655</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>0.874 (0.729, 1.047)</td>
<td>0.143</td>
</tr>
<tr>
<td><strong>Medication use the year before SLE Diagnosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hormone replacement therapy</td>
<td>1.162 (0.890, 1.517)</td>
<td>0.27</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>0.802 (0.610, 1.054)</td>
<td>0.114</td>
</tr>
<tr>
<td><strong>Time Varying Variables Updated Monthly</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>0.657 (0.540, 0.798)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other DMARDs</td>
<td>0.701 (0.546, 0.900)</td>
<td>0.005</td>
</tr>
<tr>
<td>Traditional NSAIDs</td>
<td>0.670 (0.499, 0.901)</td>
<td>0.008</td>
</tr>
<tr>
<td>Cox-2 inhibitors</td>
<td>0.907 (0.581, 1.417)</td>
<td>0.699</td>
</tr>
<tr>
<td>Other non-SLE medications</td>
<td>0.992 (0.759, 1.295)</td>
<td>0.931</td>
</tr>
<tr>
<td><strong>Healthcare Utilization</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rate of SLE visits</td>
<td>0.599 (0.427, 0.731)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Rate of rheumatologist visits</td>
<td>0.389 (0.274, 0.553)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Rate of dermatologist visits</td>
<td>0.467 (0.226, 0.996)</td>
<td>0.04</td>
</tr>
<tr>
<td>Rate of nephrologist visits</td>
<td>0.607 (0.258, 1.430)</td>
<td>0.254</td>
</tr>
<tr>
<td>Rate of psychiatrist visits</td>
<td>1.111 (0.953, 1.296)</td>
<td>0.178</td>
</tr>
<tr>
<td>Rate of hospitalizations</td>
<td>0.561 (0.250, 1.258)</td>
<td>0.161</td>
</tr>
</tbody>
</table>
Table 3-4 Adjusted Hazard Ratios and 95% CI for Determinants of AM Discontinuation

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.998 (0.992, 1.004)</td>
<td>0.478</td>
</tr>
<tr>
<td>Sex (M vs. F)</td>
<td>0.979 (0.724, 1.322)</td>
<td>0.888</td>
</tr>
<tr>
<td>SES (Low vs. High)</td>
<td>1.223 (1.018, 1.468)</td>
<td>0.032</td>
</tr>
<tr>
<td>SES (Medium vs. High)</td>
<td>1.132 (0.917, 1.397)</td>
<td>0.250</td>
</tr>
<tr>
<td><strong>Time Varying Variables Updated Monthly</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>0.731 (0.599, 0.891)</td>
<td>0.002</td>
</tr>
<tr>
<td>Traditional NSAIDs</td>
<td>0.655 (0.488, 0.880)</td>
<td>0.005</td>
</tr>
<tr>
<td><strong>Healthcare Utilization</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rate of rheumatologist visits</td>
<td>0.415 (0.228, 0.598)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Rate of dermatologist visits</td>
<td>0.453 (0.220, 0.936)</td>
<td>0.032</td>
</tr>
</tbody>
</table>

3.3.3 Assessment of Poor Execution

Of the 881 patients included in this study, 633 patients (234 persisters and 399 non-persisters), who had > 1 AM prescriptions were included in this secondary analysis. (Figure 3-6) With respect to analyses of adherence (poor execution), the overall PDC for persistent patients was 0.886 ± 0.095 and for non-persistent patients, it was 0.637 ± 0.157, t-test p-value < 0.001. There was a similar statistically significant difference between persistent and non-persistent patients for the 1-year PDC. (Table 3-5)
SLE patients with incident AM use
(Jan 1 1996 – Dec 31 2009)
N = 881

Having > 1 AM prescription

Excluded
N = 248

Included for assessment of poor execution
N = 633

Persisters
N = 234

Non-persisters
N = 399

Adherent
N = 191

Non-adherent
N = 43

Differences examined between these two groups

Adherent
N = 58

Non-adherent
N = 341

Differences examined between these two groups

Figure 3-6 Schematic of Poor Execution
Table 3-5 Mean PDC of Antimalarial Adherence

<table>
<thead>
<tr>
<th>Measures</th>
<th>Persistent (n=234)</th>
<th>Non-Persistent (n =399)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall PDC</td>
<td>0.886 ± 0.095</td>
<td>0.637 ± 0.157</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>1-year PDC</td>
<td>0.859 ± 0.165</td>
<td>0.628 ± 0.264</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Abbreviations PDC = proportion of days covered  
*Calculated using student’s t-test

Table 3-6 shows that only 14.54% of non-persistent patients were adherent to their therapy regimen compared with 81.62% of persistent patients adhering to their therapy regimen. Over the first year of follow-up, only 31.58% of non-persistent patients were adherent compared with 76.39% of persistent patients. The observed difference of the proportion adherent patients for persistent vs. non-persistent patients over the entire follow up and the first year of follow-up was statistically significant.

![Figure 3-7 Distribution of the Proportion of Days Covered](image-url)
Table 3-6 Proportion of Patients Adherent to Antimalarial Treatment

<table>
<thead>
<tr>
<th>Overall Cut-off for Adherence</th>
<th>Persistent (n = 234)</th>
<th>Non-Persistent (n = 399)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDC ≥ 80%</td>
<td>191 (81.62)</td>
<td>58 (14.54)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PDC ≥ 85%</td>
<td>171 (73.08)</td>
<td>30 (7.52)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PDC ≥ 90%</td>
<td>135 (57.69)</td>
<td>7 (1.75)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PDC ≥ 95%</td>
<td>60 (25.64)</td>
<td>4 (1.00)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>1 year</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PDC ≥ 80%</td>
<td>178 (76.39)</td>
<td>126 (31.58)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PDC ≥ 85%</td>
<td>157 (67.38)</td>
<td>106 (26.57)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PDC ≥ 90%</td>
<td>129 (55.36)</td>
<td>80 (20.05)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PDC ≥ 95%</td>
<td>87 (37.34)</td>
<td>43 (10.78)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Abbreviations PDC = proportion of days covered
*Calculated using chi-squared test

Lastly in the unadjusted bivariate chi-squared tests the only statistically significant differences between adherent and non-adherent patients from the subset of persistent patients were glucocorticoid use and having at least one rheumatologist visit. The only statistically significant difference between adherent and non-adherent patients from the subset of non-persistent patients was the use of glucocorticoids. (Table 3-7)
Table 3-7 Bivariate Chi Square Tests

<table>
<thead>
<tr>
<th>Variable</th>
<th>Persistent (n = 243)</th>
<th>Non-Persistent (n = 399)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-Adherent (n = 43)</td>
<td>Adherent (n = 191)</td>
</tr>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>45.74 ± 14.70</td>
<td>45.80 ± 14.91</td>
</tr>
<tr>
<td>Female</td>
<td>41 (95.35)</td>
<td>174 (91.10)</td>
</tr>
<tr>
<td>Rural residence</td>
<td>4 (9.30)</td>
<td>20 (10.47)</td>
</tr>
<tr>
<td>High SES</td>
<td>18 (41.86)</td>
<td>73 (38.22)</td>
</tr>
<tr>
<td>Middle SES</td>
<td>12 (27.91)</td>
<td>44 (23.04)</td>
</tr>
<tr>
<td>Low SES</td>
<td>13 (30.23)</td>
<td>74 (38.74)</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular events</td>
<td>3 (6.98)</td>
<td>11 (5.76)</td>
</tr>
<tr>
<td>Serious infections</td>
<td>9 (20.93)</td>
<td>28 (14.66)</td>
</tr>
<tr>
<td>COPD</td>
<td>5 (11.63)</td>
<td>24 (12.57)</td>
</tr>
<tr>
<td>Depression</td>
<td>7 (16.28)</td>
<td>37 (19.37)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0</td>
<td>11 (5.76)</td>
</tr>
<tr>
<td>Charlson Comorbidity Index</td>
<td>0.907 ± 1.065</td>
<td>0.733 ± 1.009</td>
</tr>
<tr>
<td>CVD</td>
<td>11 (25.58)</td>
<td>57 (29.84)</td>
</tr>
<tr>
<td>Medication Use the year before SLE diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HRT</td>
<td>4 (9.30)</td>
<td>19 (9.95)</td>
</tr>
<tr>
<td>OC</td>
<td>2 (4.65)</td>
<td>17 (8.90)</td>
</tr>
<tr>
<td>Medication Use ever after SLE Diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cox-2</td>
<td>6 (13.95)</td>
<td>30 (15.71)</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>19 (44.19)</td>
<td>130 (68.06)</td>
</tr>
<tr>
<td>Other DMARDs</td>
<td>9 (20.93)</td>
<td>49 (25.65)</td>
</tr>
<tr>
<td>Traditional</td>
<td>18 (41.86)</td>
<td>87 (45.55)</td>
</tr>
<tr>
<td>NSAIDs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthcare Utilization ever after SLE Diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rheumatologist</td>
<td>34 (79.07)</td>
<td>174 (91.10)</td>
</tr>
<tr>
<td>Visit</td>
<td>17 (39.53)</td>
<td>101 (52.88)</td>
</tr>
</tbody>
</table>
3.4 Discussion

My objective was to evaluate non-adherence with antimalarial therapy, in terms of discontinuation and poor execution of the regimen, among SLE patients in a real-world setting. In this population-based study of a Canadian cohort of individuals with SLE prescribed with AMs, I found adherence to be suboptimal. Specifically, my primary analyses indicate a high rate of discontinuation of AM, with 23% patients discontinuing therapy after 1 year and 67% after 5 years. Factors significantly associated with the discontinuation of AM included SES, glucocorticoid use, traditional NSAID use, rate of rheumatologist visits, and rate of dermatologist visits. In my analysis of poor execution, I found that among SLE patients who persist with AM therapy, 18.28% are non-adherent or poorly execute the treatment regimen. Among SLE patients who are non-persistent with AM, an even higher proportion, 85.46%, are non-adherent. Overall, these results emphasize the need to raise awareness, among physicians and patients with SLE, about the importance of adherence with AM therapy.

To date, this is the first population-based study of adherence to AMs in patients with SLE. An important feature of is the evaluation of both discontinuation and poor execution, the two distinct but equally important aspects of medication non-adherence. Indeed findings of disappointing persistence to AMs, with median time to discontinuation of 2.42 years suggest a potential gap in the care of SLE. In comparing my findings with those from prior studies evaluating discontinuation of AMs, I found that the rates of discontinuation observed in this
populations based SLE cohort were much higher. Monrad et al. utilized an Australian clinical drug use database that has the dates of initiation and commencement of HCQ of 37 SLE patients over an eight-year period. At the end of follow-up (8 years) 35% (13) of patients had discontinued AM therapy. Wang et al. used a Canadian clinical lupus database to assess the timing and reasons for discontinuation of AM in 156 SLE patients. They found that the median duration, which a SLE patient persisted with AM therapy, was 6.1 years per patient (69). Lastly, Sjoe et al. conducted a longitudinal cohort study, which used the Amsterdam Lupus Cohort, to assess discontinuation of AMs in 139 SLE patients who were followed up for an average of 10 years. Here, 73.2% of SLE patients were using AMs at the end of the follow-up of the cohort (70). The difference between previous reported findings in the literature and mine may be due to the fact that they exclusively examined SLE patients receiving care in specialized SLE clinics, while I examined SLE patients in both general and specialized care settings.

Equally important to understanding persistence and patterns of discontinuation of AMs are factors that are significantly associated with discontinuation as these may represent potential targets for adherence interventions. In the Cox’s proportional hazards model, time varying covariates, acting as markers for severity of SLE (e.g. rate of rheumatologist and dermatologist visits, glucocorticoids, and traditional NSAIDs), were associated with a decrease in the hazard of discontinuation of AM therapy. This may seem counterintuitive, but it is reasonable that patients with more severe manifestations of SLE would have greater motivation to adhere to their therapy regimen versus a patient with a milder form of SLE. Specifically, with regard to the time-varying covariates related to healthcare utilization, it seems that greater follow up
with rheumatologist and dermatologist during the course of the disease supports better overall medication taking behaviour by acting as a reminder. Since these variables were updated monthly, a visit to a rheumatologist or dermatologist could interrupt a gap in treatment and remind the patient to recommence AM treatment. Additionally, the intake of glucocorticoids and traditional NSAIDs was associated with a decreased risk of discontinuing AM therapy. This is most likely again due to the increased motivation patients with more severe SLE manifestations have to adhere to their prescription medications. It seems as if the increasing severity of SLE disease manifestations is a more important factor for SLE patients than having to cope with polypharmacy. Lower SES levels were associated with an increased risk of AM discontinuation, which is concurrent with previous studies (88).

Unsurprisingly, there was a statistically significant difference of adherence between persisters and non-persisters. Since I defined discontinuation, as when a permissible gap of 90 days is exceeded, it is unlikely that patients who discontinued were executing perfectly and then suddenly had a gap greater than 90 days after a prescription. There were most likely many smaller gaps that were occurring before the patient had exceeded the permissible gap. As a result, being able to flag poor execution early on in the treatment course is essential because unlike SES it is a potentially modifiable factor. Therefore, interventions that are developed to improve execution of the dosing regimen should also have a positive effect on improving persistence.

In further sub-group analyses comparing adherent and non-adherent patients among persisters and non-persisters, I found that among persisters there was a higher proportion glucocorticoid
use among adherent patients (68.06%) as compared to non-adherent patients (44.19%), (p-value, 0.03). Similarly among non-persisters there was a higher proportion glucocorticoid use among adherent patients (71.69%) as compared to non-adherent patients (54.55%), (p-value, 0.022) Glucocorticoid use could be acting as a marker of severity of diseases, which would mean that patients with more severe forms of SLE are more motivated to execute their medication regimen in spite of polypharmacy. Additionally, since glucocorticoids are extremely effective at treating the symptoms of SLE, patients may be willing to execute all medications because of the greater improvement of their symptoms. Further work is needed to substantiate this link and uncover the mechanism. Glucocorticoids are traditionally used to treat flares on a short-term basis because of the myriad of long-term side effects including: osteoporosis, weight gain, and cardiovascular disease ((89)). Therefore, it would not be recommended that long-term glucocorticoids use should be used to improve medication adherence in SLE.

Study strengths and limitations deserve comment. This was the first comprehensive evaluation of medication adherence in SLE that has examined both poor execution and discontinuation, the equally important but distinct aspects of medication adherence. The universal nature of the Canadian health care system has provided a population-based cohort of individuals with SLE, free of sampling bias, thus increasing external validity of our findings. However, observational studies using administrative data are vulnerable to diagnostic uncertainty. Specifically, because I used administrative diagnostic codes to define SLE, some misclassification of diagnosis likely occurred. However, I used the strictest published case definition for SLE and improved specificity with additional exclusions, as described in the Methods. While the use of
administrative pharmacy records and registries have been well established in pharmacoepidemiologic studies (39)(90)(91) and our data has the advantage of including all medications dispensed (public or private payee) to the entire SLE population in BC. The data is limited to prescriptions dispensed and I did not have information on whether pills were actually taken or reasons for AM discontinuation. For example, patients may be instructed by or come to an agreement with their physician to discontinue their medication due to intolerability. Therefore, the act of discontinuation is representing that they are actually conforming to their physician’s recommendations. Finally, although I adjusted for all known risk factors for discontinuation available in our data, I could be missing other important factors significantly associated with medication non-adherence for which I could not estimate using administrative data. In conclusion, our population-based data indicate that 67% of patients discontinued their AM prescription after five years. Given the established effectiveness of AMs in treating SLE, these findings emphasize the need to raise awareness, among health professionals and people with SLE, of the importance of adherence with AM therapy.
Chapter 4: Conclusion

The body of work comprising this thesis is unified by the common goal of gaining a better understanding of medication non-adherence to AMs in SLE. In this concluding chapter, key results from each study are highlighted and discussed within the thesis as well as relevant content. Strengths and limitations of the collective work are further discussed along with some recommendations for future research on this important topic.

4.1 Key Findings

To address the goal of a better understanding medication non-adherence to AMs in SLE it was essential to synthesize the current evidence before conducting an original pharmacoepidemiological study. Chapter 2’s systematic review of medication non-adherence in SLE demonstrated the burden of this problem. Overall according to the current evidence, less than half of SLE patients are adherent to their prescription medications for their condition. Furthermore, only 3 studies examined determinants of medication non-adherence in SLE, which is a major gap in the literature because this knowledge is an essential part in developing effective adherence interventions. The synthesis of the current evidence also highlighted key limitations that need to be addressed in future studies. These included: 1) small regionally specific clinical samples were studied; 2) two distinct but equally important aspects of medication adherence were not examined in the same study; and 3) medications studied were not always specified.

Chapter 3 is an original population-based longitudinal pharmacoepidemiological study that used the results from Chapter 2’s systematic review to inform the study design and implementation. Chapter 3 examined the burden and determinants of medication non-adherence to AMs in a
large heterogeneous SLE patient population. Findings indicate a high rate of discontinuation of AM, with 23% patients discontinuing therapy after 1 year and 67% after 5 years. In the final multivariable Cox model, the following time-varying variables updated monthly were statistically significantly associated with the discontinuation of AMs: use of glucocorticoids (HR, 0.731; 95% CI 0.599 – 0.891); traditional NSAIDs (HR, 0.655; 95% CI 0.488 – 0.880); the rate of rheumatologist visits (HR, 0.415; 95% CI 0.228 – 0.598); and the rate of dermatologist visits (HR, 0.453; 95% CI 0.220 – 0.936). These time-varying variables updated monthly were markers of disease severity suggesting that patients with milder forms of SLE are at an increased risk of discontinuation of AM therapy. Also, visits to a rheumatologist or dermatologist could represent a reminder to patients to persist with their treatment. Since our permissible gap was 90 days and these variables are updated monthly, potentially a visit to a specialist could interrupt a gap and remind the patient to recommence with treatment. Therefore, it seems as if patients may require both a reminder to remain on their medications as well as education and guidance from a health care professional to support medication taking.

4.2 Integration and Implications of the Research

This thesis integrates a systematic review (Chapter 2) with an original population-based pharmacoepidemiological study to thoroughly describe medication non-adherence to AM in SLE. The results from Chapter 2’s systematic review were used to drive the design and implementation of Chapter 3’s pharmacoepidemiological study.

Overall this thesis has identified that the burden of medication non-adherence to AM in SLE to be substantial and factors significantly associated with medication non-adherence, which are
important to know when designing an adherence intervention. There are several implications from this collective work. First, the large number of SLE patients that have never taken AMs during the longitudinal follow-up period was surprisingly high given that AMs are the recommended first-line and long-term treatment for SLE (15)(16). Therefore, this highlights an important gap in treatment, in which the actual treatments patients receive is not consistent with the treatment guidelines. Second, medication non-adherence in SLE is a substantial problem and if addressed appropriately, it could result in improvements in patient outcomes. Lastly, it seems that patients could use more frequent visits and/or support from their healthcare professional to support them taking their medication as prescribed.

4.3 Strength and Limitations of the Research

As each manuscript chapter provided its own discussion of study-specific strengths and limitations, this examination of strengths and limitations will focus on the collective thesis work, with particular emphasis on the pharmacoepidemiologic study. Where applicable, issues that were consistent across studies will be highlighted.

As identified in Chapter 2’s systematic review, many methods were used to measure medication adherence in SLE in prior studies, with the most common method being self-report. There were a myriad of methods to measure adherence, and none of the studies examined the two distinct but equally important aspects of medication adherence. Therefore, I was unable to compare the quality of adherence measurement, which would have been helpful when comparing the results
of the studies. Nevertheless, I used the findings about the limitations in the current literature to aid in the design of Chapter 3.

Methodological strengths in Chapter 3 include the application of time-dependent covariates that were updated monthly to act as proxies for SLE disease severity. Since SLE is the “disease with a 1000 faces,” it was essential to include variables that were shown in previous studies (92)(93) to differentiate between milder forms of SLE and the more severe forms of SLE with multiple organ involvement. However, if these variables were not time-dependent, I would lose important information pertaining to the changing nature of the disease. Further, I systematically measured the two distinct but equally important components of medication adherence: discontinuation and poor execution. It is necessary to investigate both the components of medication adherence to fully characterize it. Additionally, since I examined medication adherence in an incident SLE cohort and did not require patients to survive until a certain date to enter my cohort, I avoided survivorship bias. Lastly, to the best of my knowledge, this is the first examination of medication adherence in a population-based cohort. To fully characterize medication adherence in SLE, it is essential to examine adherence in SLE patients from different care settings.

Data sources play a particularly important role in pharmacoepidemiologic research; thus further comment on data used for the thesis analytic studies are warranted. As described in Chapter 1 and methods sections for Chapter 3, I used population-based administrative health data for a cohort of SLE patients in BC. With capture of health care utilization data for 881 individuals with SLE, this data source represents one of the larger SLE cohorts for epidemiologic and health
services research. In particular, complete information on all dispensed prescription medications for the cohort makes it an excellent resource for pharmacoepidemiologic research. Available information in each database (i.e., MSP, Hospital Separations, PharmaNet) lends to the richness of the data - for example date of prescription and number of drug days’ dispensed in pharmacy records - and provides potential for application of novel methods to mine important and relevant information, as done in this thesis.

It is important to acknowledge limitations of administrative health data. A fundamental limitation is the fact that data is collected for billing purposes or reimbursement for health services incurred and not primarily meant for research. Given this problem, one important limitation as discussed in Chapter 3, is that studies may be vulnerable to diagnostic uncertainty of SLE. I used the strictest published case definition with SLE, which is following the trend of prior publications on this cohort. A validation study of this definition estimated the specificity of the case definition as being 99.9% and the sensitivity being around 80% (81). Furthermore, additional exclusions attempted to improve specificity for SLE, as described in the methods sections of respective chapters. Aside from diagnostic uncertainty, another important limitation of administrative health data is the vulnerability to potential unmeasured and/or unobserved confounders. By failing to capture information on risk factors such as cigarette smoking and alcohol exposure, family histories, diet, and physical activity, their confounding effects may persist and should be acknowledged.
Overall, in considering their potential and acknowledging their limitations, administrative health data sources such as BC health data will continue to be a resource for pharmacoepidemiologic research.

4.4 Future Research and Recommendations

This thesis has provided a thorough description of medication non-adherence to AM in SLE, but there are still further questions to be answered and research to be conducted. Firstly, it needs to be understood why so many SLE patients never take AM therapy, despite it being the recommended conventional long-term treatment for SLE (15)(16). A qualitative study examining rheumatologists and SLE patients’ beliefs and attitudes about AMs would be an important first step in better understanding this gap in treatment.

Secondly, further research is needed linking adherence and outcomes to determine a clinically relevant level of adherence that patients should aim for, instead of an arbitrary level determined by research scientist. In HIV research, they have completed this by providing patients a clear-cut and compelling level of adherence that is needed to achieve clinical improvements with their medications (94). Additionally, before studies testing adherence interventions are conducted, it is essential to understand SLE patients’ perspectives and incorporate them into the development of adherence interventions. Further exploring the reasons for discontinuation is essential, and the link between discontinuation and health care expenditures is very important. Lastly, it would be helpful to examine the temporal trends of persistence, discontinuation, and rate of AM prescriptions to see if we are improving at administering treatment and supporting adherence.
Overall by holistically understanding medication non-adherence in SLE, it should be possible to achieve optimum levels of adherence that improves patient outcomes.

4.5 Conclusion

In this pharmacoepidemiologic evaluation of medication non-adherence to AMs in SLE, several concluding points are emphasized. First, in a population-based pharmacoepidemiological study, persistence to AM therapy dropped off precipitously after the first year. Second, variables acting as proxies for disease severity were significantly associated with improved persistence to AM therapy. Altogether as a collective work, this thesis demonstrated that the burden of medication non-adherence in SLE is substantial, the factors that are significantly associated with medication non-adherence and additionally highlights the importance of developing adherence interventions to support SLE patients taking their medications as prescribed.
References


32. Tan X, Patel I, Chang J. Review of the four item Morisky Medication Adherence Scale (MMAS-4) and eight item Morisky Medication Adherence Scale (MMAS-8). INNOVATIONS in pharmacy [Internet]. 2014 Jan 1;5(3). Available from: http://pubs.lib.umn.edu/innovations/vol5/iss3/5


Appendix A  Systematic Review Formal Search Strategy

A.1  Medline Search Strategy

1. exp Lupus Erythematosus, Systemic/
2. SLE.mp.
3. Lupus.mp.
5. 1 or 2 or 3 or 4
6. exp Medication Adherence/
7. exp Patient Compliance/
8. exp Healthy Behaviour
9. adherence.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
10. adhere*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
11. compliance.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
12. persistence.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

13. discontinuation.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

14. 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13

15. 5 and 14

A.2 Embase Search Strategy

1. systemic lupus erythematosus/

2. Lupus.mp.

3. SLE.mp.


5. 1 or 2 or 3 or 4

6. health behaviour/

7. medication compliance/

8. adherence.mp.

9. adhere*.mp.


11. discontinuation.mp.

12. 6 or 7 or 8 or 9 or 10 or 11
13. 5 and 12
Appendix B  Breakdown of Prevalent AM Users

Of the 1386 excluded patients :

1)  285 had no AM prescription after SLE diagnosis

2)  1069 deleted because of 1 year washout period

3)  8 were deleted because of no prescription before 2010

4)  24 were deleted because they were children and could not be sure if measuring their adherence or their parent’s adherence.
Appendix C  Distribution of the Difference Between First AM Prescription and SLE Diagnosis Date

C.1  Median Time Between SLE Diagnosis Date and the First AM Prescription

The median time between SLE diagnosis date and the first AM prescription was – 5.63 months.
C.2  Histogram of the Difference Between SLE Diagnosis Date and the First AM Prescription

![Histogram of the Difference Between SLE Diagnosis Date and the First AM Prescription Date](image)

Figure C-1 Distribution of the Difference Between SLE Diagnosis Date and the First AM Prescription