Risk Factors For Drug-Related Problems Causing Emergency Department Visits In Older Adults

by

Shanna Trenaman

Submitted in partial fulfilment of the requirements
for the degree of Master of Applied Health Services Research

at

Dalhousie University
Halifax, Nova Scotia
August 2014

DEDICATION PAGE

For Maxwell who made this process take a bit more time, but brings so much joy.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABSTRACT

Prior research has shown that polypharmacy and the use of inappropriate medication increases the risk of drug-related emergency department visits. This has been investigated in the context of medications alone without considering social, economic and patient specific factors. The present study investigated which factors increase the risk of drug-related emergency department visits in older adults. Potential factors included frailty, medication appropriateness, cognitive status, education level achieved and social vulnerability. Backward stepwise binary logistic regression was used to examine multiple potential risk factors for drug-related emergency department visits in older adults. The analysis showed that narcotic drug use, any anticholinergic drug use, lack of social supports and increased use of inappropriate medications as identified by an increased medication appropriateness index increased the risk of drug-related hospital visits. This suggests that avoidance of inappropriate medications and adequate social support are important in avoiding drug-related emergency department visits in older adults.

LIST OF ABBREVIATIONS USED

CGA	Comprehensive Geriatric Assessment
MAI	Medication Appropriateness Index
MMSE	Mini Mental State Examination
NSAID	Non-Steroidal Anti-Inflammatory Drug
START	Screening Tool to Alert doctors to Right Treatment
STOPP	Screening Tool of Older Person's Prescriptions

ACKNOWLEDGEMENTS

Thanks for the support of my committee without whom this project would never have been completed. Thank you to Dr. Susan Bowles, Dr. Melissa Andrew, and Dr. D. David Persaud. Thanks to Christopher who supported me the whole way through.

Thank you to the Drug Safety and Effectiveness training program through CIHR for financial support.

CHAPTER 1 INTRODUCTION

1.1 POLYPHARMACY

Use of multiple medications is common in those over 65 years of age. Ninety-seven percent of Canadian seniors living in health care institutions and 76% of community dwelling seniors take at least one medication on a daily basis (Ramage-Morin, et al., 2009). More recent data shows that 65.9% of seniors were taking drugs from five or more drug classes and 27.2% of seniors were taking drugs from 10 or more drug classes (Canadian Institute for Health Information, 2014). Canadian data supports that polypharmacy is a major concern in older persons (Ramage-Morin, et al., 2009). Polypharmacy refers to the consumption of many medications and the definition varies from two or more medications to six or more medications (Frazier, 2005, Millar, 1998). In 2012 Gnjidic et al. published a study that supports five or more medications to be consistent with the current definition of polypharmacy and a predictor of medication-related events (Gnjidic, et al., 2012). Medication is considered any prescription and or non-prescription medication and includes vitamins, minerals and natural and alternative medicines. Medications is an umbrella term for any dosage form and includes capsules, tablets, puffers, liquids, patches, lozenges, tinctures, and sprays. A Canadian study found polypharmacy, defined as an individual taking more than five medications concurrently, in 53% of institutionalized seniors and in 13% of community dwelling seniors (Ramage-Morin, et al., 2009).

Polypharmacy is of concern as increasing the number of medications an individual consumes imparts certain risks to the individual. As the number of medications consumed by a person increases, so does the risk of an adverse drug event. It has also been shown that polypharmacy leads to an increased risk of hospitalization likely attributable to the increased incidence of adverse drug events (Olivier, et al., 2009, Chan, et al., 2001, Tipping, et al., 2006). Increasing the number of medications also increases the risk of a potentially inappropriate medication being used. A study by Lund et al. showed that nearly 99% of patients aged 65 or older seen in primary care clinics had at least one medication with an inappropriate rating on the medication appropriateness index (2010). Inappropriate medication use compounds the problems inherent with polypharmacy as exposure to inappropriate medication increases the risk of adverse drug events and hospitalization even more.

1.2 Medication Inappropriateness

Medication appropriateness has been described by both explicit and implicit measures. Explicit measures are expert consensus listings of the medications that are not appropriate for a population. When dealing with seniors the Beer's list is the most commonly used explicit measure of medication appropriateness. The Beer's list was first developed in 1991 (Beers, et al., 1991) and has been recently updated (American Geriatrics Society 2012 Beers Criteria Update Expert Panel, 2012). Implicit measures of medication appropriateness consider the unique characteristics of the individual and do not rely on generalized lists. The most commonly used implicit measures of medication appropriateness are the Medication Appropriateness Index or the Screening Tool of Older Person's Prescriptions (STOPP) and Screening Tool to Alert doctors to Right Treatment (START) criteria and the Medication Appropriateness Index (Hanlon, et al., 1992). The STOPP and START screening tools were created with input from a consensus panel of 18 experts. The STOPP tool utilizes 65 criteria to evaluate drug therapy appropriateness while the START tool contains 22 criteria to evaluate lack of treatment (Gallagher, et al., 2008).

TABLE 1: Medication Appropriateness Index

Answer the question for each drug and give the applicable score	Indicated	Marginally Indicated	Not Indicated	Weight
1. Is there an indication for the drug?	1	2	3	3
2. Is the medication effective for the condition?	1	2	3	3
3. Is the dosage correct?	1	2	3	2
4. Are the directions correct?	1	2	3	2
5. Are there clinically significant drug-drug interactions?	1	2	3	2
6. Are there clinically significant drug-disease/condition interactions?	1	2	3	1
7. Are the directions practical?	1	2	3	1
8. Is there necessary duplication with other drug(s)?	1	2	3	1
9. Is the duration of therapy acceptable?	1	2	3	1
10. Is this drug the least expensive alternative compared to others of equal utility?	1	2	3	1

(Hanlon, et al., 1992)

The Medication Appropriateness Index is a validated research tool that quantifies the degree to which medications are appropriate for any given patient. It relies on the 10 criteria outlined in Table 1 that measure and quantify the appropriateness of the medications a person receives. Table 1 demonstrates the scoring system the Medication Appropriateness Index employs. Each question can be weighted to give the most commonly reported modified Medication Appropriateness Index per drug of 0 (no prescribing problems) to 18 (the most possible prescribing problems). The Medication Appropriateness Index has been validated for older persons for both inter-rater and intra-rater validity. Their overall inter-rater agreement for medication appropriateness was found to have a kappa value of 0.83. The intra-rater agreement was found to have an overall kappa of 0.92 (Hanlon, et al., 1992). These kappa values are considered high for both inter-rater and intra-rater agreement suggesting there is no significant variation in Medication Appropriateness Index between raters. The inter-rater agreement for each of the individual Medication Appropriateness Index items was high for both appropriate and inappropriate ratings and ranged from 80% to 100% (overall kappa = 0.64) (Fitzgerald, et al., 1997).

Polypharmacy and medication inappropriateness have considerable potential impact on the Canadian healthcare system. Polypharmacy leads to an increased risk of hospitalization attributable to the increased incidence of adverse drug reactions (Olivier, et al., 2009, Chan, et al., 2001). Inappropriate medication use is predictive of adverse drug events, with each one point increase in the Medication Appropriateness Index corresponding to the odds of an adverse drug event increasing by 13% (Lund, et al., 2010). Polypharmacy and inappropriate drug use are enormous problems for the healthcare system, especially when one considers that between 21 and 99% of ambulatory seniors are prescribed a potentially inappropriate medication (Lund, et al., 2010, Zhan, et al., 2001).

1.3 Drug-Related Healthcare System Visits

There is considerable variation in the definition of a drug-related hospital admission. Many previous studies focus on adverse drug reactions. Adverse drug reactions usually include side effects that the subject perceives as attributable to a drug (Chan, et al., 2001, Leendertse, et al., 2008, Steinman, et al., 2011). Some studies use only patient self-report of adverse drug reactions (Steinman, et al., 2011) while others also consider those events evaluated by health care professionals (Chan, et al., 2001, Leendertse, et al., 2008). Given that medications can cause effects that the subject may not attribute to their drugs, assessment of potential adverse drug effects by a health care professional, in addition to patient report, using information from patient assessment and health care records would seem the most inclusive. Using a health care professional to make the assessment requires most of the studies in this area to consider those events that led to contact with the healthcare system thus adverse drug reactions that subjects fail to contact the healthcare system for resolution are not well represented in these studies. Relying on subject report means missing some events that are not perceived to be drug-related and using only subjects in contact with the healthcare system means missing less serious events. Thus both methods of drug-related event identification have limitations.

The numbers of emergency department visits secondary to problems with medication have been investigated. Canadian data suggests that medications are implicated in 24.1% of hospital emergency department visits (Samoy, et al., 2006). These findings are supported by data from other publicly funded health care systems. Australian studies suggest that the proportion of emergency hospital admissions that are drug-related vary between 15 and 31% in older adults. Chan et al. showed 30.4% of hospital admissions are as a result of drug-related problems. Overall, data from these studies suggest that between one fifth and one third of hospital admissions in the older patients are drug-related.

1.4 Drug-Related Problems

The literature contains multiple definitions of drug-related problems. The most commonly considered drug-related problem is the adverse drug reaction. Two examples of adverse drug reaction definitions include Leendertse et al. who considered adverse effects of medication use or medication errors as an adverse drug reaction (2008) and Lund et al. who included any side effects, unwanted reactions or other problems from medications as an adverse drug event (2010). Limiting drug-related events to adverse drug reactions is a somewhat narrow definition. Medications can have far reaching effects, especially in older adults so a broader definition is desired. Previous work by Samoy et al. (2006) considered drug-related events as drug-related problems as defined by Hepler and Strand (1990). This is a more comprehensive definition of a drug-related event as drug-related problems are defined as any patient and time-specific event or situation involving the medication regimen that interferes with the achievement of an optimum outcome (Hepler and Strand, 1990). There have been eight types of drug-related problems described (Hepler and Strand, 1990; Strand et al., 1990). These drug-related problems include untreated indication, improper drug selection, sub-therapeutic dosage, failure to receive drugs (intentional or unintentional), over-dosage, adverse drug reactions, drug interactions, and drug use without indication. Drug-related problems can lead to therapeutic failure (Hepler and Strand, 1990) by producing an adverse or toxic effect or failing to produce the desired effect in the expected time frame. A broad definition of drug-related problems defined as any drug-related adverse patient event was adopted in a study by Grymonpre et al. (1988). This Canadian study looked at any undesired effect associated with drug therapy to characterize drug-related hospitalizations. While adverse drug events accounted for the majority of events (48%), non-adherence was also a substantial contributor to the events discovered.

1.5 NARANJO SCORE

To quantitate the likelihood of the adverse drug events identified a Naranjo score has been employed in this study. A Naranjo score defines the possibility of a drug-related adverse event by the categories of definite, probable, possible and doubtful. There are ten criteria that are applied to a potential drug-related event and scored as shown below in Table 2.

TABLE 2: Naranjo Scoring System

	Yes	No	Do not know	Score
I. Are there previous conclusive reports on this reaction?	1	0	0	
2. Did the adverse event appear after the suspected drug was administered?	2	-1	0	
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	1	0	0	
4. Did the adverse reaction reappear when the drug was readministered?	2	-1	0	
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	2	0	
6. Did the reaction reappear when a placebo was given?	-1	1	0	
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	1	0	0	
8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	1	0	0	
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	1	0	0	
10. Was the adverse event confirmed by any objective evidence?	1	0	0	

(Naranjo, et al., 1981)

The score is then used to classify the event. A score greater than or equal to nine denotes a definite drug-related event, a score of five to eight signifies a probable drug-related event, a score from one to four suggests a possible drug-related event and a score of zero indicates that a drug-related event is doubtful. The Naranjo score has been validated for inter-rater reliability (83% to 92%) and intra-rater reliability (80% to 97%) (Naranjo, et al., 1981). This methodology has become the standard for identifying adverse drug reactions. The current study has included drug-related events other than adverse drug reactions and this analysis relies on the skill of the assessor in verifying the presence or absence of a drug-related emergency department visit. For comparison purposes the population will be assessed by the Naranjo nomogram separating the population into two groups as definite and probable drug-related events versus the possible and doubtful drug-related events. This will provide a more conservative analysis than including all events as deemed drug-related by the reviewer.

1.6 Frailty

Frailty is a concept that pervades geriatric medicine. There are a number of approaches to measuring frailty, however the definitions have the common theme and all accept that the frail are more vulnerable to health insults than are the fit (Hogan et. al., 2003). The present study considers two measures of frailty. The first to consider is the frailty index used by Mitnitski et al. that calculates an index based on deficits present in a total number of potential deficits. Work by Mitnitski et. al. has demonstrated that increasing frailty is correlated with increased mortality with an average 4% increase in mortality for each unit increase in deficits (Mitnitski, et al., 2005). Many of these deficits likely impact the incidence of drug-related events. Deficits such as poor vision, cognitive impairment, low levels of education and poor mobility are some of the factors that constitute frailty and may impede an individual's ability to acquire medication, correctly take their medication or make them more susceptible to adverse drug reactions all of which may increase risk of a drug-related hospital visit. To our knowledge there has been no previous work to investigate the effect of frailty on the incidence of drug-related emergency department visits, however it can be hypothesized that increased frailty increases the risk of drug-related events. Due to shortfalls in the database used for the present study this particular study utilized a clinical frailty scale to quantify frailty as shown in figure 1.

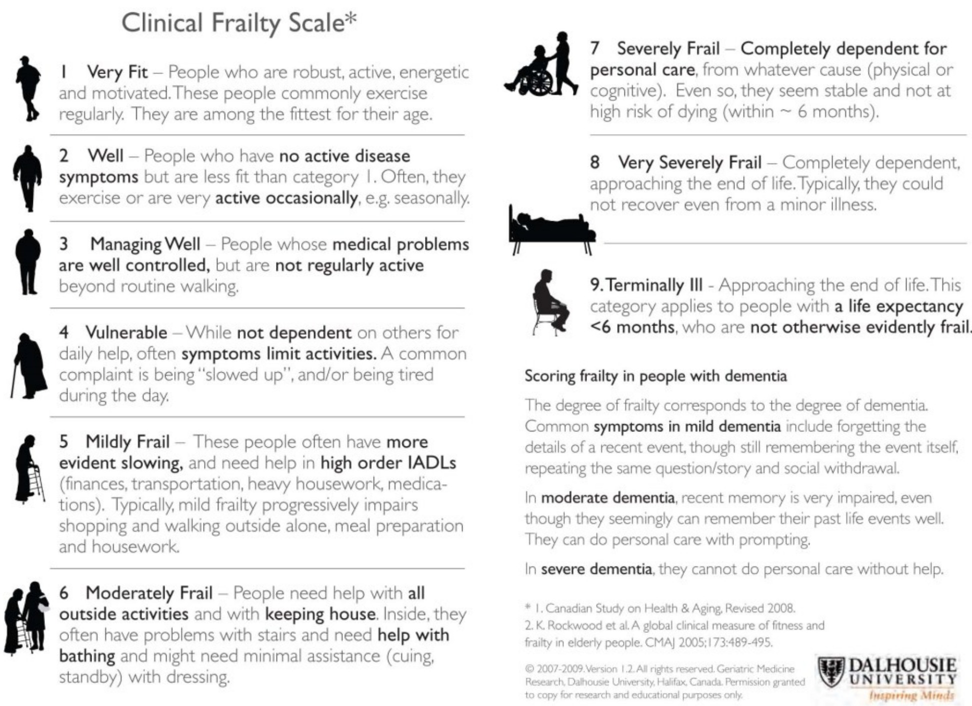

Figure 1: Clinical Frailty Scale (Rockwood, et. al., 2005)

The clinical frailty scale has been compared to the frailty index and is highly correlated with the frailty index. Each one category increment of the scale increases the risk of death within 70 months and also increases risk of need for institutionalization. The clinical frailty scale in some respects is easier to implement than a frailty index as it does not require large quantities of data, instead it can be inferred from the clinical assessment of cormobidity and function (Rockwood, et. al., 2005).

1.7 SOCIAL VULNERABILITY

In recent years there has been interest in social vulnerability as a risk factor for increased mortality and cognitive impairment in older adults (Andrew, et al., 2008, Andrew, et al., 2010, Andrew, et al., 2012). Similar to frailty findings suggest that after adjusting for age, sex, and frailty, social vulnerability increases as the number of social problems a person experiences accumulate; each additional social problem is associated with an increased mortality (Andrew et al., 2008). Social vulnerability has been operationalized by 40 items that include living situation, marital status, social engagement, social support, feelings of mastery and empowerment and socio-economic status as some examples. While these 40 items are not readily available for many retrospective analyses prior reports have shown that other social factors such as poverty predicts dependence and admission to an institution and death among the elderly (Branch, et al., 1989), and high levels of education (Harris, et al., 1989) and high family income are reported to have favourable effects on the health of aging people (Guralnik, et al., 1989, Shahtahmasebi, et al., 1992, Wong, et al., 2010). Social vulnerability may contribute to drug-related emergency department visits so further investigation of the relationship between social factors and drug-related events is needed.

1.8 Objective

Drug-related problems are the cause of emergency department visits and hospital admissions for adults. In the senior population medications are a common cause of these healthcare system visits. Previous studies of drug-related healthcare system visits have focused on a narrow definition of risk factors such as demographic characteristics or medical history. Very few studies have considered a comprehensive overview of the many potential contributing risk factors as outlined. The goal of the present study is to further examine medication appropriateness in relation to medical, social and economic factors as predictors of or risk factors for drug-related emergency department visits.

CHAPTER 2 LITERATURE REVIEW

2.1 Incidence of Drug-Related Problems That Lead to Healthcare System Visit

Numerous factors have been previously identified in the literature as contributors to drug-related problems that cause emergency department visits, and hospital admissions. There has also been some work done in examining the burden that falls to primary care providers in managing adverse drug reactions in family medicine clinics, although this is less well characterized. Gandhi et al. (2003) examined adverse drug events in adult primary care practices in Boston. This group found 25% of those outpatients contacted had an adverse drug event in the preceding 90 days (Gandhi, et al., 2003). The only risk factor for an adverse drug event was the number of medications that a patient took ($p<0.001$). Statistical analysis suggested that the mean number of events per patient increased by 10 percent for each additional medication. Likely due to the greater ease of conducting studies in the hospital setting there is a larger body of evidence to review when considering adverse drug events that led to emergency department visits or hospital admissions. Lund, et al., (2010) found that 44.8% of emergency department visits in adults were potentially the result of an adverse drug event. A study by Chan et al. focused on older adults aged 75 years or older and the incidence of hospital admission due to a drug-related problem. Results showed that up to 30.4% of admissions could be attributed to a drug-related problem (Chan, et al., 2001). Grymonpre et al. (1988) identified 718 adults over 50 years of age that were admitted in a four month period and were taking drugs on admission. Of these 718 patients 23% were deemed to have a drug-related cause for admission to a medical ward.

2.2 Factors Contributing to Drug-Related Healthcare System Visits

Factors that have been shown to increase the incidence of adverse drug event include: (1) number of medications (Vliet, et al., 2006, Olivier, et al., 2009, Chan, et al., 2001, Leendertse, et al., 2008, Sikdar, et al., 2010, Merle, et al., 2005, Tipping, et al., 2006); (2) drug interactions (antidepressants, antipsychotics, antiarrhythmics, beta-adrenoceptor antagonists, morphine derivatives, and rifampin) (Merle, et al. 2005); (3) specific medications such as digoxin, non-steroidal anti-inflammatory drugs, antiplatelet or anticoagulent drugs, diuretics, calcium channel antagonists, chemotherapeutic agents (Merle, et al., 2005, Tipping, et al., 2006); and antibacterial drugs (Olivier, et al., 2009); (4) older age (Vliet, et al., 2006, Leendertse, et al., 2008, Sikdar, et al., 2010); (5) increased number of comorbidities (Vliet, et al., 2006, Olivier, et al., 2009, Leendertse, et al., 2008, Sikdar, et al., 2010); (6) impaired cognition (Vliet, et al., 2006, Olivier, et al., 2009, Leendertse, et al., 2008), (7) impaired renal function (Vliet, et al., 2006, Leendertse, et al., 2008), (8) dependence for activities of daily living (Vliet, et al., 2006, Leendertse, et al., 2008), (9) incontinence (von Reneln-Kruse, et al., 2000), (10) falls (Merle, et al., 2005), (11) self-medication management (Vliet, et al., 2006, Olivier, et al., 2009), (12) lack of social support (Vliet, et al., 2006), (13) frailty (Merle, et al., 2005), (14) malnutrition (von Reneln-Kruse, et al., 2000), and (15), medication non-adherence (Vliet, et al., 2006, Leendertse, et al., 2008, Merle, et al., 2005).

2.3 MEDICATION NON-ADHERENCE

Non-adherence to a medication regime in older adults was shown to be increased by male gender, poor recall of medications, greater number of regular physician visits, living alone, more than two medications, higher monthly costs for medications, lower income (Col, et al., 1990), large caregiver burden, impaired hearing and older age (Caradenas-Valladolid, et al., 2010). A review of the literature evaluating the improper intake of medication by older adults described many of the risk factors for this situation such as polypharmacy, greater number of doses required in a day, higher number of non-prescription medications, greater number of comorbidities, cognitive impairment (dementia or depression), past history of poor compliance, increased number of physicians, male gender, lower income, ethnicity, patient medication beliefs, knowledge, anxiety, financial limitations, and lack of social supports (family or caregivers) (van Vliet, et al., 2006). Medication non-adherence is a substantial problem and likely is second only to adverse drug reactions as the cause for drug-related healthcare system visits. Grymonpre et al. (1988) found that 27% of adults over 50 years of age and consuming at least one medication had non-adherence as the reason for their hospital admission. Clearly there are many connections between factors that predict adherence and those that predict adverse drug events that lead to healthcare system contact.

2.4 MEDICATION APPROPRIATENESS

Medication appropriateness is another contributor to medication related healthcare system contact. Medication appropriateness has been measured with explicit methods such as Beer's list as well as with implicit measures such as the Medication Appropriateness Index or the Screening Tool of Older Person's Prescriptions (STOPP) and Screening Tool to Alert doctors to Right Treatment (START) criteria. In the study by Lund et al., (2010) inappropriate prescribing, defined as one or more medication in a patient's regimen meeting the 2003 Beer's criteria, predicted a subsequent adverse drug reaction. Lund showed that 98.7% of veterans aged 65 or older were receiving at least one medication with at least one inappropriate rating according to the medication appropriateness index. More recently an investigation in Australia found that 97.7% of the 251 305 subjects who were 65 years of age or older and living in Western Australia were likely taking a potentially inappropriate medication according to Beers list. Exposure to a potentially inappropriate medication was associated with a significantly increased risk of unplanned hospitalization. The risk of hospitalization increased as the subject was exposed to more potentially inappropriate medications (Price, et. al., 2014). Dalleur et. al. undertook a prospective cross-sectional study of frail older adults admitted to a 975 bed teaching hospital in Belgium. Patients assessed by a geriatric liaison team were included if they were 75 years of age or older, admitted for an acute illness and had a positive frailty profile determined by possessing two or more of the following: need for help in activities of daily living, an increase in this need in relation to the current illness, memory problems, altered vision, hospitalization in the past six months, and daily use of more than 3 medications. The study included 302 subjects and each was evaluated for the presence of inappropriate prescribing by the 65 STOPP criteria and 22 START criteria. This analysis considers patient specific factors such as contraindications to therapy as evaluable based on the electronic patient record. Results of this study showed that according to the 65 STOPP criteria 210 events of potentially inappropriate medication were detected. The drugs most implicated as potentially inappropriate were benzodiazepines, aspirin and opiates. This corresponded to a prevalence of 47.7% of those assessed receiving a potentially inappropriate medication. The START criteria focus on potential prescribing omission and drug therapy that is likely indicated and not being received.   The study population of 302 individuals there was a prevalence of 62.9% for potential prescribing omissions. Considering both STOPP and START criteria there were 82 hospital admissions in the 302 assessed subjects. This study clarifies that potentially inappropriate medications are being used in nearly half of the frail elderly that present to a teaching hospital in Belgium. And more than 60% of the population failed to receive potentially helpful medications. These problems contributed to 27.1% of the subjects being admitted to hospital. Clearly medication appropriateness impacts hospital admission rates in frail older adults (Dalleur, et. al., 2012).

The medication appropriateness index is a tool to quantify the appropriateness of medication use. Previous work does suggest that the medication appropriateness index does correlate with risk of adverse drug events, but there is little work to suggest how the medication appropriateness index in comparison relates to risk of hospitalization or if inappropriate medication use as denoted by the medication appropriateness index is a risk factor for drug-related hospital visits.

CHAPTER 3 METHODS

3.1 Hypothesis

H_1: A high medication appropriateness index is a risk factor for drug-related emergency department visits in adults 65 years of age or older assessed by a geriatric internal medicine service.

H_2: Social vulnerability as measured by lack of social support is a risk factor for drug-related emergency department visits in adults 65 years of age or older assessed by a geriatric internal medicine service.

H_3: Lower cognitive status is a risk factor for drug-related emergency department visits in adults 65 years of age or older assessed by a geriatric internal medicine service.

H_4: Low educational level is a risk factor for drug-related emergency department visits in adults 65 years of age or older assessed by a geriatric internal medicine service.

H_5: Frailty is a risk factor for drug-related emergency department visits in adults 65 years of age or older assessed by a geriatric internal medicine service.

3.2 Specific Objectives

The current study's goal was to determine if medication inappropriateness as defined by a higher medication appropriateness index is a risk factor for drug-related emergency department visits in older adults. As well the study investigated whether social vulnerability denoted by the level of social support the subject received or education level in years would affect the risk of a drug-related healthcare system visit. The study investigated whether cognitive status as defined by either Mini Mental State examination score or clinical history of cognitive impairment would affect the risk of a drug-related healthcare system visit. And the study also aimed to identify if frailty was a risk factor for drug-related healthcare system visit.

As described prior research has shown that many factors are contributors to drug-related emergency department visits. The present study included gender; age; the number of medications; use of digoxin; use of non-steroidal anti-inflammatory drugs; use of antiplatelet or anticoagulent drugs; use of diuretics; use of calcium channel antagonists; receiving chemotherapeutic agents; receiving antibacterial agents; any psychoactive medication; sedatives; antipsychotics; antidepressants; lithium; anti-epileptics; narcotics; anticholinergics; the number of comorbidities; presence of kidney dysfunction; history of falls; self-medication management; and medication appropriateness index score as variables that may show a relationship to the risk of a drug-related emergency department visit based on prior work and my hypotheses. Therefore, these variables will be included as a method of controlling for identifying new findings, potential confounders and to replicate previous work.

3.3 Data Sources

The present study is an examination of drug-related emergency department visits and the contributing factors in older adults assessed by the geriatric internal medicine service at a tertiary care teaching hospital. The geriatric medicine service is a consulting service and is only referred to when emergency room physicians require specialist expertise. Information from patient assessments of a selection of the physician group that assess patients in the emergency department for the geriatric internal medicine servce are collected and housed in an Excel database. The database does not include all physicians that perform this assessment, but those physicians that chose to contribute. The database dates back to the summer of 2006 and contains entries until the fall of 2013. Over 900 entries are contained in the database. The information collected is that from the Comprehensive Geriatric Assessment (CGA) that is a part of the assessment of a patient over the age of 65 in the emergency department. While the CGA technique has not changed since the database was developed, the data collection form has evolved. Thus there is missing data, predominantly in earlier entries (approximately the first 300) as subsequent iterations of the data collection form became more complete. Thus there was be missing data that was needed to be either located in the historical electronic health record or to be accounted for statistically. Patient records were available and were consulted to collect what missing data was possible. All subjects in the database of 65 years of age or older were evaluated.

3.4 SAMPLE SIZE

The sample size was to be a convenience sample of the 950 entries in CGA database noted above. Due to an unforeseen technical problem with the database only data for 360 subjects was available for the current study. Of these potential subjects 159 could not be included in the study. 17 were too young (<65 years of age), 36 did not have a corresponding medical record to use to locate missing data, 99 potential subjects had ID numbers that did not correspond to any patient, 6 were subsequent visits for previously included individuals and one subject had no medication information included despite it being clear that they did use medications regularly. This left complete data for 201 subjects that was available for analysis.

3.5 Study Design

A cross-sectional cohort study was utilized to assess the contribution of gender, age, number of medications, use of digoxin, non-steroidal anti-inflammatory drugs, antiplatelet or anticoagulent drugs, diuretics, calcium channel antagonists, chemotherapeutic agents, antibacterial agents, any psychoactive medication, sedatives, antipsychotics, antidepressants, lithium, anti-epileptics, narcotics, anticholinergics, number of comorbidities, impaired hearing, impaired vision, impaired cognition, baseline education, dependence for activities of daily living, presence of kidney dysfunction, incontinence, history of falls, social support, living alone, self-medication management, medication appropriateness index, and frailty (Table 3) to the incidence of drug-related emergency department visits.

TABLE 3: Risk Factor Variables Included in Regression Analysis and their Measurement

Risk Factor Variable	Measurement
Gender	Dichotomous: 1=male, 0=female
Age	Continuous: age
Number of medications	Continuous: number of medications
Digoxin	Dichotomous: 1=yes, 0=no
Non-steroidal anti-inflammatory drugs	Dichotomous: 1=yes, 0=no
Antiplatelet or anticoagulent drugs	Dichotomous: 1=yes, 0=no
Diuretics	Dichotomous: 1=yes, 0=no
Calcium channel antagonists	Dichotomous: 1=yes, 0=no
Chemotherapeutic agents	Dichotomous: 1=yes, 0=no
Antibacterial agents	Dichotomous: 1=yes, 0=no
Any psychoactive medication	Dichotomous: 1=yes, 0=no
Antipsychotics	Dichotomous: 1=yes, 0=no
Sedatives	Dichotomous: 1=yes, 0=no
Antidepressants	Dichotomous: 1=yes, 0=no
Anti-epileptics	Dichotomous: 1=yes, 0=no
Lithium	Dichotomous: 1=yes, 0=no
Narcotics	Dichotomous: 1=yes, 0=no
Anticholinergics	Dichotomous: 1=yes, 0=no
Number of comorbidities	Continuous: number of comorbidities
Impaired hearing	Dichotomous: 1=hard of hearing, 0=no hearing concerns
Impaired vision	Dichotomous: 1=impaired vision, 0=no

	vision concerns
Impaired cognition by MMSE score	Continuous: MMSE score
Impaired cognition by previous diagnosis	Ordinal: Normal, Dementia, Mild cognitive impairment
Baseline education	Continuous: Years in school
Dependence for activities of daily living	Dichotomous: 1=yes, 0=no
Presence of kidney dysfunction by history	Dichotomous: 1=yes, 0=no
Incontinence of bowel and/or bladder	Dichotomous: 1=yes, 0=no
History of falls reported by family	Dichotomous: 1=yes, 0=no
Social support	Ordinal: Formal, Informal/Family, None
Living alone	Dichotomous: 1=yes, 0=no
Self-medication management	Dichotomous: 1=yes, 0=no
Medication appropriateness index score (Hanlon, et al., 1992)	Continuous: Medication Appropriateness Index score
Frailty (Rockwood, et. al., 2005)	Continuous: Frailty Scale

For the medication appropriateness index the list of medications was taken from the best possible medication history recorded in the emergency department by a trained individual. The best possible medication history reflected what the patient was actually taking at home and not just the medications as prescribed. If the best possible medication history was not available the medication data recorded in the database was used. Prescription drugs, as well as non-prescription drugs and any natural health products were included in the list assessed.

For the first analysis the database was divided into two groups. These groups contained those subjects who were deemed to have a drug-related emergency department visit and those who have not had a drug-related cause for their healthcare system contact based on data reviewer assessment. These two groups were then compared using a binary logistic regression. Subsequent analysis used the Naranjo scoring system (Table 2) (Naranjo, et al., 1981) to allocate the subjects to groups and complete the statistical analysis. Using the Naranjo score an ordered logistic regression was completed based on the groupings of doubtful, possible, probable and definite drug-related events. The final analysis using the Naranjo score combined the groups to give two groups doubtful and possible compared to probable and definite drug-related events in a binary logistic regression. This final logistic regression was far more conservative as the number of drug-related events was smaller.

3.6 Outcome Measures

The primary outcome measure was a drug-related healthcare system visit. A drug-related visit was considered if the subject was found to have a drug-related problem defined as any of the following: (1) any untreated indication as defined as any noxious, unintended or undesired effect resulting from failure to treat a known indication; (2) have had improper drug selection defined as any noxious, unintended or undesired effect due to use of a drug not optimal for treatment of a confirmed indication; (3) received a sub-therapeutic dosage as defined as any noxious, unintended or undesired effect caused by failure to receive sufficient drug dosage or sufficient duration of therapy for a given indication or patient failed to receive drugs (intentional or unintentional); (4) suffered an over-dosage (intentional or unintentional) defined as any noxious, unintended or undesired effect caused by excessive drug dose or excessive duration of therapy for a given indication or patient; (5) had an adverse drug reaction defined as any noxious, unintended or undesired effect of a drug that occurs at doses used in humans for prophylaxis, diagnosis or treatment; (6) includes all reactions when drugs are used at appropriate doses and may include abnormal laboratory values; (7) a drug interaction defined as any noxious, unintended or undesired effect caused by the concomitant administration of 2 or more drugs; and (8), drug use without indication defined as any noxious, unintended or undesired effect caused by use of a drug for which there is no clear indication as the reason for the emergency department visit based on the work by Hepler et al. (1990) and as used by Samoy et al. (2008). Only those drug-related events that were related to the presenting patient complaint were deemed a drug-related hospital admission. Each subject's data in the database was reviewed and any missing data was searched for in the historical electronic database. Once the subject's corresponding dataset was as complete as possible the reviewer decided if the visit was for a drug-related problem as defined by Hepler and Strand (1990).

To further investigate the effect of medication appropriateness, social vulnerability approximated by social supports, cognition, education and frailty as risk factors for drug-related emergency department visits, a logistic regression was completed based on a Naranjo score (Naranjo, et al., 1981). Logistic regression was performed using a binary dependent variable in which "definite and probable" drug-related visits were distinguished from "possible or doubtful" drug-related visits. This provided a more conservative analysis as only those events that can be defined as any noxious, unintended, and undesired effect of a drug after doses used in humans for prophylaxis, diagnosis, or therapy were placed in the drug-related visit groups that included definite and probable drug-related visit and all other subjects' data (possible and doubtful drug-related events) comprised the comparator group. An ordinal logistic regression using the groups definite, probable, possible or doubtful as defined by the Naranjo score was also completed.

The database provided data for most of the risk factors that were evaluated. Demographic variables sex and age were evaluated. Sex was noted as biological female or male. Age was noted in years. The number of medications taken was recorded as a whole number and included all medications prescription and non-prescription, and included, pills, tablets, puffers, patches, creams, ointments, sprays, and liquids. The number of comorbidities was counted from the database. Comorbidity was considered any chronic or sub-acute medical condition from which the patient suffers. Constipation was not considered a comorbidity unless it was related to or directly the cause for admission. A history of falls, poor vision, and poor hearing, incontinence (bowel or bladder or both), whether independent or requiring any level of assistance for taking medications, education level as years in school to a maximum of 13, living status as alone, or other which included with a spouse, with other family, or in a facility, and dependence for any activities of daily living by self or family report was considered. Impaired hearing and impaired vision were collected in the database as present or not. Dependence for activities of daily living was considered to exist if any one activity of daily living required assistance regardless of a cognitive or physical need for dependence. Incontinence of either bowel or bladder constituted the presence of incontinence. Support from family, friends or hired personnel was counted as a social support, and anyone living in a nursing home had social support. Family was considered an informal social support despite family members' potential education in a healthcare field. Any hired caregivers or nursing home supports were considered formal support. Living alone was considered as present if an individual lived alone, regardless of the amount of support or family who visit. Self-medication management was anyone who was independent for medication administration. The presence of cognitive impairment as a known medical diagnosis and cognitive impairment as measured by the Mini Mental Status Examination (MMSE) score were considered. The MMSE measures general cognitive function. This is a widely-used and well-validated screening instrument that tests orientation, concentration, memory, visuospatial ability, and language (Folstein, et al., 1975). The published cut-off of $<24/30$ has been used to indicate cognitive impairment but this does not measure executive function which may be an important domain for organizing medication taking. As well, cognitive impairment by physician diagnosis was also included in analysis. Frailty was denoted by the clinical frailty score in Figure 1. A complete listing of the risk factors for exploration is listed in Table 3.

Risk factors for evaluation that were not housed in the database included presence of kidney dysfunction, and medication appropriateness. Kidney dysfunction was noted as present if the medical history included a diagnosis of chronic kidney disease or related kidney impairment. Medication appropriateness as described (Hanlon, et al., 1992, Fitzgerald, et al., 1997) was assessed and calculated for each patient in the database. This required examination of each patient's database entry and the historical health care record of the event under consideration to assess the unique medical history and medication list and allow calculation of a medication appropriateness index.

3.7 Data Analysis

All statistical calculations were completed on IBM® SPSS® Statistics Version 22.0.0.0 with Excel Microsoft Office 2010 to prepare tables and calculate some simple descriptive statistics.

Initially the data reviewer broke the dataset into two groups based on the presence or absence of a drug-related cause for the emergency department visit based on the Hepler and Strand definition of a drug-related problem and the data reviewer's clinical assessment. The two groups were then compared using binary logistic regression to determine if the following factors (gender, age, number of medications, use of digoxin, non-steroidal anti-inflammatory drugs, antiplatelet or anticoagulent drugs, diuretics, calcium channel antagonists, chemotherapeutic agents, antibacterial agents, any psychoactive medication, sedatives, antipsychotics, antidepressants, lithium, anti-epileptics, narcotics, anticholinergics, number of comorbidities, impaired hearing, impaired vision, impaired cognition, baseline education, dependence for activities of daily living, presence of kidney dysfunction, incontinence, history of falls, social support, living alone, self-medication management, medication appropriateness index, and frailty) were associated with increased risk of a drug-related emergency department visit. The two (drug-related and nondrug-related) groups were compared using backwards stepwise binary logistic regression to identify the factors associated with drug-related emergency department visits in older adults.

A second analysis utilized logistic and ordinal logistic regression with the groups divided as by the Naranjo score. The ordered logistic regression allowed consideration of each Naranjo grouping (doubtful, possible, probable and definite) and the second logistic regression used the Naranjo score and divided the groups based on doubtful and possible drug-related events as no event and probable and definite as a drug-related event. These analyses were used to identify risk factors for drug-related emergency department visits.

The first task was to describe the data. Complete data was available from 201 subjects' data for the final analysis. 360 subjects' data was presented in the original dataset that was released for analysis however 159 subjects were unable to be included in the dataset for analysis. In 17 instances the subjects were too young (<65 years of age), 36 had no medical records for the visit to allow necessary data to be collected, 99 study

ID numbers did not match any actual individual, 6 were duplicate entries, and 1 did not have any medication information available which made any medication related analysis impossible and thus these 159 potential subjects were not included. The 6 duplicate entries that were not included were subjects that had more than one entry in the database. Originally the hope had been to include subsequent visits for the same individual but due to difficulty with the quality of data in the database any subsequent visit was not included in the analysis. This occurred for six of the entries in the database and these six potential subjects were not included in the analysis.

Data was described with subjects broken in their two respective groupings of drug-related or non drug-related emergency department visits. Univariate analysis was then conducted to look for associations between each variable and whether or not the emergency department visit was drug-related or not. From this analysis risk factors with a significance of 0.2 or less were then included in a binary logistic regression. Backward stepwise logistic regression was used to get the model of best fit.

Based on the Naranjo score an ordinal regression test was conducted to identify if certain risk factors were more likely to be associated with more increased drug-related emergency department visits. And a second binary logistic regression was conducted in a backward stepwise fashion comparing a grouping of doubtful and possible drug-related events with probable and definite drug-related events.

CHAPTER 4 Results

4.1 Descriptive Statistics

There were 201 subjects' data included in the final analysis. Table 4 shows the descriptive statistics for the continuous variables included in the analysis. It should be pointed out that the database did have some missing data that could not be collected from the medical record and therefore the variables that were left with missing data can be readily seen in Table 1 as the number of subjects with a value available is less than the expected 201.

TABLE 4: Descriptive statistics of included continuous variables that were potential risk factors for drug-related emergency department visits

Continuous Variable	Total number of subjects (N)	Mean (± standard deviation)	Minimum	Maximum
Age	201	81.1 ± 8.1	65	102
Number of Medications	201	9.0 ± 5.6	0	33
Number of Comorbidities	201	8.8 ± 3.3	2	18
MMSE Score	170	20.9 ± 8.7	0	30
Education in Years	174	10.2 ± 2.7	0	13
Medication Appropriateness Index	201	12.5 ± 13.0	0	76
Clinical Frailty Scale	198	5.6 ± 1.6	2	9

The average age was 81.1 years. Subjects were taking on average 9 medications regularly. Subjects also carried a disease burden of approximately 9 comorbidities. The average MMSE score was almost 21. The average subject had completed some highschool as the average duration of education in years was 10 years. It should be pointed out that the maximum number of years of education was considered 13 and this was given to any subject that had completed any amount of post-secondary education. This allowed for consistency given the difficulty for some highly educated individuals in identifying the exact number of years they were in school. The calculated MAI average score was 12.5. Of interest the standard deviation would allow for negative MAIs but this is not possible as the lowest score someone can receive is 0 and the variation likely can be accounted for by the fact that the maximum MAI is quite high at 76. The average clinical frailty scale was 5.6. At a clinical frailty scale of between 5 and 6 we would see individuals that require help with some to all instrumental activities of daily living and may also require help with bathing or dressing.

TABLE 5: Descriptive statistics of included dichotomous and categorical variables that were potential risk factors for drug-related emergency department visits

Categorical Variable	Total number of subjects (N)	Number of subjects (%)
Male Sex	201	94 (46.8%)
Digoxin	201	5 (2.5%)
NSAID	201	11 (5.5%)
Antiplatelet or Anticoagulent	201	109 (54.2%)
Diuretic	201	87 (43.3%)
Calcium Channel Blocker	201	55 (27.4%)
Chemotherapy	201	5 (2.5%)
Antibiotic	201	35 (17.4%)
Any Psychoactive Agent	201	107 (53.2%)
Antipsychotic	201	11 (5.5%)
Sedative	201	54 (26.9%)
Antidepressant	201	62 (30.8%)
Antiepileptic	201	13 (6.5%)
Lithium	201	1 (0.5%)
Narcotic	201	39 (19.4%)
Any Anticholinergic Medication	201	155 (77.1%)
Normal Hearing	192	133 (66.2%)
Normal Vision	181	116 (57.7%)
Baseline Cognition	182	
Normal Cognition		101 (50.2%)

Mild Cognitive Impairment		26 (12.9%)
Dementia		55 (27.4%)
Dependent for any ADL(s)	199	29 (14.4%)
Known Kidney Dysfunction	201	51 (25.4%)
Incontinence of either bowel or bladder	193	46 (22.9%)
Prior Fall(s)	183	73 (36.3%)
Social Support	187	
No Support		55 (27.4%)
Informal Support		74 (36.8%)
Formal Support		58 (28.9%)
Living Alone	197	60 (29.9%)
Self Medication Management	198	82 (40.8%)

47% of the included subjects were male. All of the medications and medication classes that were previously shown in the literature to increase risk of drug-related emergency department visits were used in the population studied. However some of these medications were rarely used in the population under study. One subject was receiving lithium, 5 received digoxin, and 5 received chemotherapy. The most commonly used agents were antiplatelets/anticoagulents, psychoactive medications as a class, and anticholinergic medications. Cognition was recorded as within normal limits for 101 subjects; mild cognitive impairment for 26 subjects, and dementia for 55 subjects; with the remaining subjects having no cognitive status at baseline recorded. Only 60 of the included subjects lived alone. The remaining 137 subjects either lived with family or in an environment with 24 hour care from family or facility staff. Eighty-two subjects were independent for medication management; fifty-five had no social supports at all; 74 relied solely on informal supports such as family and friends, and 58 had formal support from either a nursing home facility or homecare worker.

TABLE 6: Descriptive statistics organized by data reviewer deemed groupings for drug-related emergency department visit versus nondrug-related emergency department visit for comparison

Variable	Drug-Related	Not Drug-Related	p values
Total (N)	40	161	
Male Sex (%)	15 (37.5%)	79 (49.1%)	0.22[a]
Digoxin	0 (0%)	5 (3.1%)	0.59[a]
NSAID	4 (10.0%)	7 (4.3%)	0.23[a]
Antiplatelet/Anticoagulent	26 (65.0%)	83 (51.6%)	0.16[a]
Diuretic	19 (47.5%)	68 (42.2%)	0.59[a]
Calcium channel blocker	10 (25.0%)	45 (28.0%)	0.84[a]
Chemotherapy	2 (5.0%)	3 (1.9%)	0.26[a]
Antibiotic	8 (20.0%)	27 (16.8%)	0.64[a]
Any Psychoactive Medication	25 (62.5%)	82 (50.9%)	0.22[a]
Antipsychotic	4 (10.0%)	7 (4.3%)	0.23[a]
Sedative	11 (27.5%)	43 (26.7%)	1.00[a]
Antidepressant	14 (35.0%)	48 (30.0%)	0.57[a]
Antiepileptic	4 (10.0%)	9 (5.6%)	0.30[a]
Lithium	1 (2.5%)	0 (0)%	0.20[a]
Narcotic	11 (27.5%)	28 (17.4%)	0.18[a]
Anticholinergic Medication	36 (90.0%)	119 (73.9%)	**0.035**[a]
Normal Hearing	30 (72.5%)	104 (64.6%)	0.26[a]
Normal Vision	21 (52.5%)	95 (59.0%)	0.48[a]
Dependent for any ADL(s)	3 (7.5%)	26 (16.1%)	0.21[a]
Known Kidney Dysfunction	9 (22.5%)	42 (26.1%)	0.69[a]
Incontinence of bowel or bladder	9 (22.5%)	37 (23.0%)	1.00[a]
Prior Falls	14 (35.0%)	59 (36.6%)	1.00[a]
Living Alone	13 (32.5%)	47 (29.2%)	0.70[a]
Self Medication Management	16 (40.0%)	66 (41.0%)	1.00[a]
Social Supports			
None	15 (37.5%)	40 (24.8%)	0.12[a]
Informal	17 (42.5%)	57 (35.4%)	0.46[a]
Formal	7 (17.5%)	51 (31.7%)	0.082[a]
Baseline Cognition			
Normal	19 (47.5%)	82 (50.9%)	0.73[a]
Mild Cognitive Impairment	7 (17.5%)	19 (11.8%)	0.43[a]
Dementia	12 (30.0%)	43 (26.7%)	0.69[a]
Age (years) ± standard deviation	81.5 ± 7.8	81.0 ± 8.2	0.72[b]
Number of medications ± standard deviation	9.2 ± 5.1	9.0 ± 5.7	0.83[b]

Number of Comorbidities ± standard deviation	8.7 ± 2.2	8.8 ± 3.4	0.82[b]
MMSE Score ± standard deviation	21.5 ± 7.7	20.8 ± 8.9	0.62[b]
Education in years ± standard deviation	10.7 ± 1.9	10.1 ± 2.9	0.12[b]
Clinical Frailty Index ± standard deviation	5.5 ± 1.3	5.6 ± 1.6	0.68[b]
MAI ± standard deviation	13.6 ± 14.4	12.3 ± 12.7	0.60[b]

[a] Level of significance according to Fisher`s exact test, 95% confidence interval

[b] Level of significance according to t-test, 95% confidence interval.

There were 40 drug-related emergency department visits based on the data reviewer's (ST) assessment of the clinical data provided in the database and the Hepler and Strand drug-related problem criteria. This represents an incidence of 20.0%. The groups also were organized by Naranjo score where a score of 0 represented a doubtful drug related event, a score of 1 to 4 represented a possible drug-related event, a score of 5-8 represented a probable drug-related event and a score of 9 or more represented a definite drug-related event. Table 7 shows the descriptive statistics based on the Naranjo score groupings.

TABLE 7: Descriptive statistics organized by Naranjo Score groupings for drug-related emergency department visit versus nondrug-related emergency department visit for comparison

Variable	Doubtful	Possible	Probable	Definite
Total (N)	166	28	6	1
Male Sex (%)	80 (48.2%)	11 (39.3%)	2 (33.3%)	1 (100.0%)
Digoxin	5 (3.0%)	0 (0%)	0 (0%)	0 (0%)
NSAID	7 (4.2%)	4 (14.3%)	0 (0%)	0 (0%)
Antiplatelet/Anticoagulent	85 (51.2%)	4 (14.3%)	2 (33.3%)	1 (100.0%)
Diuretic	69 (41.6%)	16 (57.1%)	1 (16.7%)	1 (100.0%)
Calcium channel blocker	47 (28.3%)	7 (25.0%)	0 (0%)	1 (100.0%)
Chemotherapy	3 (1.8%)	1 (3.6%)	1 (16.7%)	0 (0%)
Antibiotic	29 (17.5%)	5 (17.9%)	1 (16.7%)	0 (0%)
Any Psychoactive Medication	82 (49.4%)	20 (71.4%)	4 (66.7%)	1 (100.0%)
Antipsychotic	7 (4.2%)	2 (7.1%)	2 (33.3%)	0 (0%)
Sedative	43 (25.9%)	8 (28.6)	3 (50.0%)	0 (0%)
Antidepressant	48 (28.9%)	12 (42.9%)	2 (33.3%)	0 (0%)
Antiepileptic	10 (6.0%)	3 (10.7%)	0 (0%)	0 (0%)

Lithium	0 (0%)	0 (0%)	0 (0%)	1 (100.0%)
Narcotic	28 (16.9%)	9 (32.1%)	2 (33.3%)	0 (0%)
Anticholinergic Medication	123 (74.1%)	26 (92.9%)	5 (83.3%)	1 (100.0%)
Normal Hearing	115 (69.3%)	22 (78.6%)	4 (66.7%)	1 (100.0%)
Normal Vision	112 (67.5%)	19 (67.9%)	4 (66.7%)	1 (100.0%)
Dependent for any ADL(s)	26 (15.7%)	3 (10.7%)	0 (0%)	0 (0%)
Known Kidney Dysfunction	42 (25.3%)	7 (25.0%)	1 (16.7%)	1 (100.0%)
Incontinence of bowel or bladder	37 (22.3%)	6 (21.4%)	2 (33.3%)	1 (100.0%)
Prior Falls	61 (36.7%)	9 (32.1%)	3 (50.0%)	0 (0%)
Living Alone	50 (30.1%)	10 (35.7%)	0 (0%)	0 (0%)
Self Medication Management	70 (42.2%)	10 (35.7%)	1 (16.7%)	1 (100.0%)
Social Supports				
None	44 (26.5%)	10 (35.7%)	0 (0%)	0 (0%)
Informal	57 (34.3%)	12 (42.9%)	4 (66.7%)	1 (100%)
Formal	51 (30.7%)	5 (17.9%)	2 (33.3%)	0 (0%)
Baseline Cognition				
Normal	83 (50.0%)	14 (50.0%)	2 (33.3%)	1 (100.0%)
Mild Cognitive Impairment	21 (12.7%)	4 (14.3%)	1 (16.7%)	0 (0%)
Dementia	43 (25.9%)	9 (32.1%)	2 (33.3%)	0 (0%)
Age (years) ± standard deviation	81 ± 8.1	82 ± 8.2	79.7 ± 8.5	80
Number of medications ± standard deviation	8.8 ± 5.7	10.0 ± 4.8	11 ± 4.2	5
Number of Comorbidities ± standard deviation	8.8 ± 3.4	9.1 ± 2.2	7.8 ± 2.3	7
MMSE Score ± standard deviation	20.8 ± 9.0	22.1 ± 7.4	20.3 ± 5.6	14
Education in years ± standard deviation	10.1 ±2.9	10.6 ± 1.9	11.4 ± 1.9	11
Clinical Frailty Scale ± standard deviation	5.6 ± 1.6	5.4 ± 1.4	6.5 ± 1.3	5
MAI ± standard deviation	12.0 ±12.6	11.6 ± 9.8	28.5 ± 23.8	27

4.2 Binary Logistic Regression

General linear univariate regression of all risk factors shown in Tables 1 and 2 showed only 11 risk factors that met a significance level of less than 0.2. Those that reached a significance of 0.2 or less are shown in bold in Table 8.

TABLE 8: Results of Initial General Linear Univariate Regression for drug-related emergency department visit versus nondrug-related emergency department visits baseb on Hepler and Strand criteria of a drug-related event

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
Intercept	Hypothesis	0.071526748	1	0.071526748	0.295334313	0.61
	Error	1.106841646	4.570154916	.242[a]		
AGE	Hypothesis	0.022023535	1	0.022023535	0.157658226	0.69
	Error	10.05779772	72	.140[b]		
MEDICATIONS	Hypothesis	0.026491155	1	0.026491155	0.189640242	0.66
	Error	10.05779772	72	.140[b]		
COMORBIDITIES	**Hypothesis**	**0.237555804**	**1**	**0.237555804**	**1.700572864**	**0.20**
	Error	10.05779772	72	.140[b]		
MMSE	Hypothesis	0.000109692	1	0.000109692	0.000785243	0.98
	Error	10.05779772	72	.140[b]		
EDUCATION	Hypothesis	0.102577967	1	0.102577967	0.734317179	0.39
	Error	10.05779772	72	.140[b]		
MAI	Hypothesis	0.114088822	1	0.114088822	0.816719067	0.37
	Error	10.05779772	72	.140[b]		
CLINICAL FRAILTY	Hypothesis	0.026223505	1	0.026223505	0.187724232	0.67
	Error	10.05779772	72	.140[b]		
SEX	**Hypothesis**	**0.295046178**	**1**	**0.295046178**	**2.112124884**	**0.15**
	Error	10.05779772	72	.140[b]		
DIGOXIN	Hypothesis	0.163130136	1	0.163130136	1.167787438	0.28
	Error	10.05779772	72	.140[b]		
NSAID	**Hypothesis**	**0.853867298**	**1**	**0.853867298**	**6.1125156**	**0.016**
	Error	10.05779772	72	.140[b]		
ANTIPLATELET	Hypothesis	0.003565522	1	0.003565522	0.025524238	0.87
	Error	10.05779772	72	.140[b]		
DIURETIC	Hypothesis	0.039478724	1	0.039478724	0.282613369	0.60
	Error	10.05779772	72	.140[b]		
CCB	Hypothesis	0.050917789	1	0.050917789	0.364501347	0.55
	Error	10.05779772	72	.140[b]		
CHEMO	Hypothesis	0.043019021	1	0.043019021	0.307957032	0.58
	Error	10.05779772	72	.140[b]		
ANTIBIOTIC	Hypothesis	0.006256475	1	0.006256475	0.044787761	0.83
	Error	10.05779772	72	.140[b]		

PSYCHOACTIVE	Hypothesis	0.014676949	1	0.014676949	0.105066774	0.75
	Error	10.05779772	72	.140[b]		
ANTIPSYCHOTIC	Hypothesis	0.062417835	1	0.062417835	0.446825863	0.51
	Error	10.05779772	72	.140[b]		
SEDATIVE	Hypothesis	0.160353526	1	0.160353526	1.147910725	0.29
	Error	10.05779772	72	.140[b]		
ANTIDEPRESANT	Hypothesis	0.001751087	1	0.001751087	0.012535374	0.91
	Error	10.05779772	72	.140[b]		
ANTIEPILEPTIC	**Hypothesis**	**0.300479568**	**1**	**0.300479568**	**2.151020486**	**0.15**
	Error	10.05779772	72	.140[b]		
LITHIUM	**Hypothesis**	**0.550002364**	**1**	**0.550002364**	**3.937260556**	**0.051**
	Error	10.05779772	72	.140[b]		
NARCOTIC	**Hypothesis**	**0.487929817**	**1**	**0.487929817**	**3.492906484**	**0.066**
	Error	10.05779772	72	.140[b]		
ANTI-CHOLINERGIC	**Hypothesis**	**0.350973855**	**1**	**0.350973855**	**2.512490139**	**0.12**
	Error	10.05779772	72	.140[b]		
HEARING	Hypothesis	0.169232827	1	0.169232827	1.211474306	0.27
	Error	10.05779772	72	.140[b]		
VISION	Hypothesis	0.023474702	1	0.023474702	0.168046587	0.68
	Error	10.05779772	72	.140[b]		
COGNITION	**Hypothesis**	**0.479238303**	**2**	**0.239619152**	**1.715343598**	**0.19**
	Error	10.05779772	72	.140[b]		
ADLs	Hypothesis	0.151871651	1	0.151871651	1.087192168	0.30
	Error	10.05779772	72	.140[b]		
KIDNEY DISEASE	**Hypothesis**	**0.415117429**	**1**	**0.415117429**	**2.971669919**	**0.090**
	Error	10.05779772	72	.140[b]		
INCONTINENCE	Hypothesis	0.015470263	1	0.015470263	0.110745808	0.74
	Error	10.05779772	72	.140[b]		
FALLS	Hypothesis	0.06873566	1	0.06873566	0.4920528	0.49
	Error	10.05779772	72	.140[b]		
SUPPORTS	**Hypothesis**	**1.06878543**	**2**	**0.534392715**	**3.825516934**	**0.026**
	Error	10.05779772	72	.140[b]		
HOME	**Hypothesis**	**0.424839524**	**1**	**0.424839524**	**3.041266749**	**0.085**
	Error	10.05779772	72	.140[b]		
MEDICATION MANAGEMENT	Hypothesis	0.000252386	1	0.000252386	0.001806735	0.97
	Error	10.05779772	72	.140[b]		

a. .007 MS (SEX) + .038 MS (DIGOXIN) + .038 MS (NSAID) + .006 MS (ANTIPLATELET) + .008 MS (DIURETIC) + .009 MS (CCB) + .122 MS (CHEMO) + .010 MS (ANTIBIOTIC) + .021 MS (PSYCHOACTIVE) + .040 MS (ANTIPSYCHOTIC) + .014 MS (SEDATIVE) + .014 MS (ANTIDEPRESANT) + .030 MS (ANTIEPILEPTIC) + .195 MS (LITHIUM) + .014 MS (NARCOTIC) + .010 MS (ANTICHOLINERGIC) + .009 MS (HEARING) + .007 MS (VISION) + .008 MS

(COGNITION) + .022 MS (ADLs) + .009 MS (CKD) + .011 MS (INCONTINENCE) + .008 MS (FALLS) + .006 MS (SUPPORTS) + .006 MS (HOME) + .007 MS (MANAGEMENT) + .332 MS (Error)

b. MS (Error)

These were the variables included in the original binary logistic regression; comorbidities, sex, NSAID use, antiepileptic drug use, lithium use, narcotic use, presence of any anticholinergic drug, baseline cognition, chronic kidney disease at baseline, social supports and living situation. Age was forced into the model due to a priori relevance.

Backward stepwise binary logistic regression led to removing the factors until the final model included age, sex, NSAID use, narcotic use, any anticholinergic drug use and presence of social supports. Age, sex and NSAID use did not reach statistical significance while narcotic use, any anticholinergic drug use and the presence of social supports did reach statistical significance (Table 9).

TABLE 9: Binary Logistic Regression of Final Model for drug-related emergency department visit versus nondrug-related emergency department visit based on Hepler and Strand definition of a drug-related event

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	AGE	.018	.026	.514	1	.473	1.019
	SEX(1)	.733	.421	3.030	1	.082	2.081
	NSAID(1)	-1.110	.737	2.268	1	.132	.330
	NARCOTIC(1)	-1.024	.486	4.435	1	.035	.359
	ANTICHOLINERGIC(1)	-1.218	.600	4.125	1	.042	.296
	SUPPORTS			8.622	2	.013	
	SUPPORTS(1)	1.575	.576	7.480	1	.006	4.832
	SUPPORTS(2)	1.421	.542	6.870	1	.009	4.140
	Constant	-2.245	2.170	1.071	1	.301	.106

a. Variable(s) entered on step 1: AGE, SEX, NSAID, NARCOTIC, ANTICHOLINERGIC, SUPPORTS.

Narcotic drug use, any anticholinergic drug use and lack of social supports made a drug-related hospital visit more likely. Therefore, hypothesis 2 which stated social vulnerability as described by lack of social support as a risk factor for drug-related emergency department visits in adults 65 years of age or older as assessed by a geriatric internal medicine service was supported.

4.3 Ordinal Regression

An ordinal regression was completed for the outcome of drug-related event as described by the Naranjo score. The Naranjo score varies from 0-9 with equal to or greater than 9 being a definite drug-related event, 5-8 a probable drug-related event, 1-4 a possible drug related event and 0 being a doubtful drug-related event. The groups were broken into definite, probable, possible and doubtful based on the score as described and these four ordered groups made the groups of the ordinal regression. Variables identified as having a significance of less than 0.2 in a general linear regression were included in the ordinal regression. No variable reached statistical significance. This was likely due to the size of the groupings (Table 10).

TABLE 10: Ordinal Regression for drug-related emergency department visit versus nondrug-related emergency department visit based on Naranjo score grouping

		Estimate	Std. Error	Wald	df	Sig.	95% Confidence Interval Lower Bound	95% Confidence Interval Upper Bound
Threshold	[Naranjo = 0]	-31.707	2.702	137.708	1	.000	-37.002	-26.411
	[Naranjo = 1]	-29.703	2.735	117.916	1	.000	-35.064	-24.342
	[Naranjo = 2]	-14.715	676.162	.000	1	.983	-1339.967	1310.538
Location	AGE	.017	.029	.345	1	.557	-.040	.074
	COMORBIDITIES	.024	.075	.103	1	.748	-.122	.170
	[SEX=0]	.848	.476	3.180	1	.075	-.084	1.780
	[SEX=1]	0[a]			0			
	[NSAID=0]	-1.057	.853	1.533	1	.216	-2.729	.616
	[NSAID=1]	0[a]			0			
	[ANTIEPILEPTIC=0]	.462	.920	.252	1	.616	-1.342	2.266
	[ANTIEPILEPTIC=1]	0[a]			0			
	[LITHIUM=0]	-34.729	0.000		1		-34.729	-34.729
	[LITHIUM=1]	0[a]			0			
	[NARCOTIC=0]	-.934	.518	3.250	1	.071	-1.949	.081
	[NARCOTIC=1]	0[a]			0			
	[ANTICHOLINERGIC=0]	-1.354	.707	3.665	1	.056	-2.740	.032
	[ANTICHOLINERGIC=1]	0[a]			0			
	[COGNITION=0]	-.685	.506	1.833	1	.176	-1.677	.307
	[COGNITION=1]	-.088	.675	.017	1	.897	-1.411	1.236
	[COGNITION=2]	0[a]			0			
	[CKD=0]	.506	.566	.799	1	.371	-.604	1.616
	[CKD=1]	0[a]			0			
	[SUPPORTS=0]	1.105	.630	3.077	1	.079	-.130	2.340
	[SUPPORTS=1]	1.394	.574	5.889	1	.015	.268	2.519

	[SUPPORTS=2]	0[a]			0			
	[HOME=0]	.142	.480	.087	1	.768	-.799	1.083
	[HOME=1]	0[a]			0			

4.4 BINARY LOGISTIC REGRESSION BY NARANJO SCORE

Given the difficulty obtaining meaningful results from ordinal regression due to the small group size the binary logistic regression was repeated but the drug-related hospital visit was determined by Naranjo score, where doubtful and possible drug-related events were considered not drug-related and probable and definite drug related events were considered to be drug-related hospital visits.

A generalized linear regression found 9 variables that had a significance less than 0.2 and these 9 were included in the initial binary logistic regression. These variables included social support, kidney disease, any anticholinergic drug, lithium, antidepressant, antipsychotic, diuretic and MAI. Age and sex were forced into the model. Completing backward stepwise logistic regression there was only one significant risk factor that remained and it was that higher MAIs increased the risk of a drug-related hospital admission (Table 11). Sex and age when forced into the equation did not seem to be related and MAI as the last variable was significantly related to the drug-related hospital visit categorized by Naranjo score. Therefore, hypothesis 1 which states that a high medication appropriateness index is a risk factor for drug-related emergency department visits in adults 65 years of age or older assessed by a geriatric internal medicine service was supported.

TABLE 11: Binary Logistic Regression dependent on Naranjo Score as divided into definite and probable drug-related event compared to possible and doubtful drug-related event

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	SEX(1)	-.088	.833	.011	1	.916	.916
	AGE	-.002	.054	.002	1	.967	.998
	MAI	.057	.021	7.406	1	.007	1.058
	Constant	-4.148	4.391	.893	1	.345	.016

a. Variable(s) entered on step 1: SEX, AGE, MAI.

CHAPTER 5 DISCUSSION

5.1 Discussion

This study showed that narcotic drug use, any anticholinergic drug use, lack of social supports and increased MAI increase the risk of drug-related hospital visits. These results support hypotheses 1 and 2. This is the first time that medication appropriateness as quantified by the MAI has been shown to increase the risk of a drug-related event leading to a hospital visit. This solidifies the importance of appropriate medication use and avoidance of polypharmacy as burdens to the healthcare system and the emergency department. It clarifies that polypharmacy is not just a benign bother to older adults who are required to manage complex medication regimens but that it increases the risk of emergency department visit solely due to a drug-related cause.

The findings in this study of narcotic use increasing the risk of a drug-related emergency department visits are generally supportive of previous work by Merle, et al. (2005) who have previously shown that morphine derivatives increase the incidence of clinically meaningful drug-interactions that lead to hospital visits (Merle, et al. 2005). This is not surprising given the pharmacologic effects of narcotics to cause drowsiness and their ability to precipiate delirium in frail older adults. In Nova Scotia there is a province wide prescription monitoring program for narcotic prescriptions. This focuses on the number of tablets and days supplied but does not force a review for appropriateness. And despite efforts at encouraging family physicians to manage narcotics carefully there is no incentive for family physicians caring for seniors to minimize narcotic use as a goal of care. Age related changes in drug distribution, metabolism and elimination may mean that narcotic drugs should be more rigorously evaluated for chronic therapy in seniors and rather than accepting a chronic dose. More focus could be placed on regular evaluation of narcotic drugs with goals of discontinuation for pain management when possible may help minimize narcotic drug use and decrease drug-related hospital visits secondary to narcotic use. Perhaps given the signal that narcotic use in seniors increases drug-related emergency department visits this should become a greater focus of care.

Lack of social supports has been suggested as a risk factor for a drug-related hospital visit (Vliet, et al., 2006). This finding was confirmed in the present study. Fewer social supports increased the risk of drug-related emergency department visits. It is imperative that adequate social supports are available for older adults. This provides benefits to the senior and decreases pressure on the healthcare sytem by reducing drug-related emergency department visists. At the present time there are limited resources available for seniors and there are differences in services available depending geographic region as well as financial abilities. Seniors without local family or friends who offer informal support must qualify for care based on low income or be able to pay privately for service. It is also problematic that many seniors are reluctant to look for formal support until it is a necessity based rather than as a preventative measure. The lack of social support as a risk factor for drug-related events leading to emergency department visit is expected given the significant role social vulnerability plays in the health and welfare of frail older adults. It is interesting to note that education which was another potential factor that is representative of social vulnerability had no relationship to the outcome of interest in this investigation. Therefore hypothesis 4 was not supported. Impaired cognition was hypothesized to increase drug-related emergency-department visits however this did not reach statistical significance and thus hypothesis 3 was not supported. Perhaps the presence of social supports for the cognitively impaired is a stronger marker for drug-related emergency department visits and offers some protection against drug-related emergency department visits. Interestingly frailty based on the clinical frailty scale (Figure 1) did not show a significant relationship as a risk factor for a drug-related events leading to emergency department visits. Thus hypothesis 5 was not supported. The outcome may have been different and increased frailty may have increased the risk of drug-related emergency department visits if a frailty index had been employed instead of a clinical frailty scale. A recent paper by Pugh et. al. (2014) demonstrated that frailty-related diagnoses in veterans aged 65 years or older as determined by presence of coagulopathy, involuntary weight loss, fluid and electrolyte imbalance, anemia and falls or fracture was a predictor of readmission to hospital within 30 days of the original admission. This study did not find any relationship between use of high risk medications for elderly subjects and readmission. This suggests that populations at risk for readmission are more frail and the original admission is not as strongly related to the frailty of the subject (Pugh et. al., 2014).

This study represents the first time that anticholinergic drugs as a group have been implicated as a risk factor for drug-related hospital visit. Anticholinergic drugs are those that antagonize the acetyl-choline receptor and cause a host of unpleasant side effects. These commonly include dry mouth, urinary retention, constipation and confusion in frail older adults. Given this, it is not unexpected that anticholinergic drugs lead to drug-related emergency department visits. Minimizing anticholinergic drug use in seniors should always be the goal. This is especially true as anticholinergic burden will increase for each anticholinergic medication in a patient's medication regimen. Rather than patient's accepting these side effects, or medicating with more drugs to combat the anticholinergic side effects we should be less tolerant of these medications and their side effects and look at non-pharmacologic methods to manage conditions whenever possible.

The Naranjo regression analysis did not repeat the results of the original binary logistic regression. More specific selection of the population based on the nature of the drug-related events altered the population characteristics. Using more specific criteria for selecting drug-related events with a Naranjo scale seemed to select a population that was using the most inappropriate medication. The regression that was based on the more liberal definition of a drug-related event by the criterion of Hepler and Strand (1990) did not depend on the medication appropriateness as much but did show a significant relationship with increased risk of a drug-related emergency department visit with use of narcotic drugs and anticholinergic drugs as classes of drugs. In addition, increased social supports were also found to decrease the risk of a drug-related emergency department visit.

5.2 Limitations

This study is limited by its retrospective nature. The database also had missing data; in 159 instances there was not enough data available to include the potential subjects in the statistical analysis. For the 201 subjects included in the analysis there still were many instances where a portion of the data was unavailable. All attempts were made to verify data or locate missing values but in some occurrences no data could be identified as it was not recorded as deemed unnecessary by clinicians making the assessment in the emergency department.

The missing data combined with the size of the database limits the study. The small size reduces the power of the statistical analyses. This posed a greater problem for the ordinal logistic regression as some of the groups were exceedingly small. The definite drug-related event group had less than five subjects. This also made for a smaller group for the logistic regression that focused on Naranjo scores of doubtful and possible in comparison to probable and definite as the probable and definite drug-related events group had only 7 subjects. The database originally contained data for 900 subjects but due to some unfortunate technical difficulties where the database was scrambled when being transferred from its storage location to the researcher responsible for its release for study purposes the final dataset for statistical analysis contained data from only 201 subjects. This is an unfortunate limitation of the study.

Medication non-adherence is a known contributor to drug-related emergency department visits (Vliet, et al., 2006, Leendertse, et al., 2008, Merle, et al., 2005). This data is not collected in comprehensive geriatric assessment and thus was not captured unless it was purposefully commented on by the clinician. Given the likelihood that medication non-adherence increases as the number of medications increases it seems that medication non-adherence may have played a role in some hospital admissions but could not be captured. This leads to a number of potential drug-related emergency department visits that were not captured and thus results in an underestimation of the outcome.

Furthermore, how drugs are prescribed may not be how they are taken. Thus the medication appropriateness index and the medications that are recorded and analyzed may not accurately represent what the patient was taking at home.

The study is also limited in its generalizablitiy as the data comes entirely from one academic health sciences centre, and by one specialty's (Geriatric Medicine) consulting service. Nevertheless, this academic health sciences centre provides tertiary care as well as emergency services to a metropolitan area, thus a variety of patient subjects should have been obtained due to a variety of socioeconomic groups who would present to the emergency department.

The data collected was recorded by a variety of clinicians who may have used the data collection form slightly differently or presented data differently. The data was entered into the database by the same research assistant which should help improve data consistency but there was still a limitation in this regard as information was not consistently presented in the same way on the CGA form. This made data recording a challenge and potentially caused some important information to be missed in collection or overlooked in recording.

The largest issue with regard to the variety of individuals contributing data to the database related to how the medications were recorded on the form. Many clinicians recorded drug names and doses but some did not. The incomplete lists gave only drug names and in some instances only gave names of drugs the clinician wished to alter or comment on in their assessment. Luckily the tertiary care centre used a medication reconciliation process whereby a complete listing of medication used by the subject just prior to emergency department visit was captured by a trained health-care professional.

These lists were used for this study to verify the list recorded in the database as it was in a much more complete form. For those transported to the emergency department by ambulance the paramedics often kept record of the subject's medications, but this did not usually include doses either. This did allow corroboration of the medications with the list in the database though. Unfortunately this was not available for all subjects and so when not available the list in the database was used without being verified.

In identifying the emergency department visits as drug-related or not only emergency department records were consulted. So if someone was admitted to hospital and subsequent information came to light that the visit was likely drug-related this would not be captured. This could mean an underestimation of the number of drug-related emergency department visits in the present study.

A frailty index was desired to capture the frailty as a risk factor for a drug-related hospital admission. However this was unable to be calculated and released for the purposes of this study. Thus frailty was measured with a clinical frailty scale based on the functional status of the individual. This was usually completed by the clinician assessing the patient and recorded on the comprehensive geriatric assessment but if it was not selected and recorded in the database it could easily be inferred based on the data in the database.

The present investigation did not include cholinesterase inhibitors as a potential drug risk factor for a drug-related emergency department visit. As a drug used only for dementia, it may have been better than relying on medical history as a marker of cognitive status. Using the presence of a cholinesterase inhibitor may have shown some relationship between cognition and drug-related emergency department visit as shown previously (Vliet, et al., 2006, Olivier, et al., 2009, Leendertse, et al., 2008).

Chronic kidney disease is a common issue in older adults. Chronic kidney disease is also a known risk factor for drug-related events (Vliet, et al., 2006, Leendertse, et al., 2008). This particular comorbidity can exist without a person being aware. Kidney disease was only included if the subject had a known history of chronic kidney disease. A serum creatinine measure, a laboratory measure of kidney function, may have been helpful to quantify the level of kidney dysfunction due to the nature of this medical condition and may have allowed this study to identify chronic kidney disease as a risk factor for drug-related emergency department visit.

One potential limitation is changes over time in practice. The medication lists were evaluated on current best practice, and these current best practices were used to analyze and develop the medication appropriateness indexes. Given that medical practice is constantly evolving this is likely a limitation of all retrospective studies.

The maximum number of years of education was considered 13 and this was given to any subject that had completed any amount of post- secondary education due to the significant variation in the recording of advanced education by clinicians. This may have made it more difficult to see a relationship between education in years and the risk of a drug-related emergency department visit.

Prior cataract surgery was not considered a marker for visual impairment. Only clinician report of visual impairment was included as actual visual impairment.

Initial plans were to include subjects that had more than one entry in the database. When conducting data entry and analysis it because clear that subsequent visit for the same subject was too complex to include in the analysis based on the recorded information in the provided database. Thus only initial entries were included for each subject.

There were a number of considerations that were made when analyzing the data. Trazodone was counted as an antidepressant even though it may and likely was used as a sleep aid or for behavioural and psychological symptoms of dementia. Tramadol was included as a narcotic even though it does not require the same prescribing standards as morphine and its derivatives. Use of pregabalin was counted as an anti-epileptic medication despite its frequent use as an adjunctive pain medication. Tobramycin eyedrops were included as an antibiotic given that they would be used to treat or prevent infection. Levodopa-carbidopa was included as a psychoactive medication. Celecoxib use was included as a nonsteroidal anti-inflammatory drug. Celecoxib use was present in four individuals in the dataset. However use of a topical NSAID by two study subjects was not included as a nonsteroidal anti-inflammatory drug. Prior research has shown that calcium channel blockers are implicated in drug-related emergency department visits (Merle, et al., 2005, Tipping, et al., 2006). For the purposes of this study both dihydropyridine and non-dihydropyridine calcium channel blockers were included. Given the potent nature of tiotropium and ipratropium these two medications were counted as an anticholinergic medication even though they are used topically as inhaled dosage forms. Benzodiazepine drugs were counted as sedatives and not anti-epileptic drugs even though they may have been prescribed as antiepileptics. Combination puffers and combination tablets were counted as only one medication when counting the number of medications used by each subject. This is because the number of tablets or items consumed is believed to be more related to total burden than the number of active ingredients (O'Connor et. al., 2013). In trying to calculate the medication appropriateness index it frequently occurred that one individual was receiving two sleeping pills. In cases of duplicate therapy where two medications were used for sleep neither was considered effective for the condition of insomnia. If a subject was receiving both formal and informal supports they were counted as having the highest level of support which was deemed formal as this may have been a better measure of the level of support required. If family was the only source of support this was counted as informal support.

5.3 Potential Bias

The assessment of this study was completed by one reviewer so there is the potential for the reviewer to place subjects into the drug-related group more or less often than appropriate. This bias is also possible for the calculation of the medication appropriateness index and the Naranjo score.

The patients housed in the database reflected only patients that are seen by the geriatric internal medicine sevice. This subset of patients may be more complicated, more likely to have polypharmacy and may be inherently more likely to have drug-related problems thus results from this study will only be applicable to a comparable population and will need to be interpreted with that in consideration.

In an attempt to select a consistent list of anticholinergic drugs the anticholinergic burden list was used. This included a subject as having an anticholinergic drug if they were taking any anticholinergic drug listed on the anticholinergic burden list. Once the analysis was initiated there was some consideration that an anticholinergic drug score may have been better to quantify the total anticholinergic drug burden. An anticholinergic drug score would quantify the amount of anticholinergic activity and differentiate low and high burdens. This may have allowed differentiation of the potential effects of anticholinergic drugs on the risk of drug-related emergency department visits.

CHAPTER 6 CONCLUSIONS

This study showed that narcotic drug use, any anticholinergic drug use, lack of social supports and increased MAI increased the risk of drug-related emergency department visits. The results of the present investigation highlight the importance for social supports for frail older adults at risk of drug-related emergency department visits. A paradigm shift is essential to improve acceptability of formal support and as well a policy shift to make formal support services more easily and readily available for those in need.

We also must consider a high medication appropriateness index score as a risk factor for drug-related hospital events. It is crucial that rationalization of drug therapy occurs at a regular interval for frail older adults. This needs to be performed by someone with knowledge and expertise with geriatric medicine. Family Physicians managing their patients are not supported for the in-depth assessment required for comprehensive geriatric assessment but this process may improve medication appropriateness and thus should prevent drug-related emergency department visits.

While drug-related emergency department events are likely not completely preventable we can work to minimize these events. Areas for improvement would be rationalization of drug therapy frequently for seniors with minimization of narcotics and anticholinergic drugs, and improved formal social support with increased acceptability of the social supports provided.

BIBLIOGRAPHY

American Geriatrics Society 2012 Beers Criteria Update Expert Panel. (2012). American Geriatrics Society Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. Journal of the American Geriatrics Society. doi: 10.1111/j.1532-5415.2012.03923.x. [Epub ahead of print].

Andrew, M.K., Mitnitski, A.B., & Rockwood, K. (2008). Social vulnerability, frailty and mortality in elderly people. PLoS ONE, 3(5): e2232. doi:10.1371/journal.pone.0002232.

Andrew, M.K., & Rockwood, K. (2010). Social vulnerability predicts cognitive decline in a prospective cohort of older Canadians. Alzheimer's & Dementia, 6(4), 319-325.

Andrew, M.K., Mitnitski, A., Kirkland, S.A., & Rockwood, K. (2012). The impact of social vulnerability on the survival of the fittest older adults. Age and Aging, 41(2),161-165.

Beers, M.H., Ouslander, J.G., Rollingher, I., Reuben, D.B., Brooks, J., & Beck, J.C. (1991). Explicit criteria for determining inappropriate medication use in nursing home residents. Archives of Internal Medicine, 151(9), 1825–1832.

Branch, L.G., & Ku, L. (1989). Transition probabilities for the elderly over a decade: uses in long-term care financing. Journal of Aging and Health, 1(3), 370-408.

Canadian Institute for Health Information. *Drug Use Among Seniors on Public Drug Programs in Canada, 2012*. Ottawa, ON: CIHI; 2014.

Cardenas-Valladolid, J., Martin-Madrazo C., Salinero-Fort, M.A., Carrillo de-Santa Pau, E., Abanades-Hrranz, J.C., & de Burgos-Lunar, C. (2010). Prevalence of adherence to treatment in homebound elderly people in primary health care: A descriptive, cross-sectional, multicentre study. Drugs Aging, 27(8), 641-651.

Chan, M., Nicklason, F., & Vial, J.H. (2001). Adverse drug events as a cause of hospital admission in the elderly. Internal Medicine Journal, 31(4), 199-205.

Col, N., Fanale, J.E., & Kronholm, P. (1990). The role of medication noncompliance and adverse drug reactions in hospitalizations of the elderly. Archives of Internal Medicine, 150(4), 841-845.

Dalleur, O., Spinewine, A., Henrard, S., Losseau, C., Speybroeck, N., & Boland, B. (2012). Inappropriate prescribing and related hospital admissions in frail older persons according to the STOPP and START criteria. Drugs Aging, 29(10),829-837.

Fitzgerald, L.S., Hanlon, J.T., Shelton, P.S., Landsman, P.B., Schmader, K.E., Pulliam, C.C., & Williams, M.E. (1997). Reliability of a modified medication appropriateness index in ambulatory older persons. The Annals of Pharmacotherapy, 31(5), 543-548.

Folstein, M.F., Folstein, S.E., & McHugh, P.R. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. Journal of Psychiatric Research, 12(3), 189-198.

Frazier, SC. Health outcomes and Polypharmacy in elderly individuals: an integrated literature review. (2005). Journal of Gerontological Nursing , 31(9), 4-11.

Gallagher, P., Ryan, C., Byrne, S., Kennedy, J., & O'Mahony, D. (2008). STOPP (screening tool of older person's prescriptions) and START (creening tool to alert doctors to right treatment). Consensus validation. 46(2), 72-83.

Gandhi, T.K., Weingart, S.N., Borus, J., Seger, A.C., Peterson, J., Burdick, E., Seger, D.L., … Bates, D.W. (2003). Adverse drug events in ambulatory care. The New England Journal of Medicine, 348(16), 1556-1564.

Gnjidic, D., Hilmer, S. N., Blyth, F. M., Naganathan, V., Waite, L., Seibel, M. J., McLachlan, A. J., … Le Couteur, D. G. (2012). Polypharmacy cutoff and outcomes: five or more medicines were used to identify community-dwelling older men at risk of different adverse outcomes. Journal of Clinical Epidemiology, 65(9), 989-995.

Grymonpre, R.E., Mittenko, P.A., Sitar, D.S., Aoki, F.Y., & Montgomery, P.R. (1988). Drug-associated hospital admissions in older medical patients. The Journal of the American Geriatrics Society. 36(12),1092-1098.

Guralnik, J.M., & Kaplan, G.A. (1989). Predictors of health aging: prospective evidence from the Alameda County study. The American Journal of Public Health, 79(6), 703-708.

Hanlon, J.T., Schmader, K.E., Samsa, G.P., Weinberger, M., Uttech, K.M., Lewis, I.K., … Feussner, J.R. (1992). A method for assessing drug therapy appropriateness. Journal of Clinical Epidemiology, 45(10), 1045-1051.

Harris, T., Kovar, M.G., Suzman, R., Kleinman, J.C., & Feldman, J.J. (1989). Longitudinal study of physical ability in the oldest old. American Journal of Public Health, 79(6), 698-702.

Hepler, C.D., & Strand, L.M. (1990). Opportunities and responsibilities in pharmaceutical care. American Journal of Hospital Pharmacy, 47(3):533-543.

Hogan, D.B., Macnight, C., & Bergman, H. (2003). Models, definitions, and criteria of frailty. Aging Clinical and Experimental Research, 15(3):1-29.

Jones, D., Song, X., Mitnitski, A., & Rockwood, K. (2005). Evaluation of a frailty index based on a comprehensive geriatric assessment in a population based study of elderly Canadians. Aging Clinical and Experimental Research, 17(6), 465-471.

Leendertse, A.J., Egberts, A.C.G., Stoker, L.J. & van den Bent, P.M.L.A. (2008). Frequency of and risk factors for preventable medication-related hospital admissions in the Netherlands. Archives of Internal Medicine, 168(17), 1890-1896.

Levey, A.S., Bosch, J.P., Lewis, J.B., Greene, T., Rogers, N., & Roth, D. (1999). A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Annals of Internal Medicine, 130(6), 461-470.

Lund, B.C., Carnahan, R.M., Egge, J.A., Chrischilles, E.A. & Kaboli, P.J. (2010). Inappropriate prescribing predicts adverse drug events in older adults. The Annals of Pharmacotherapy, 44(6), 957-963.

Merle, L., Laroche, M.L., Dantoine, T., & Charmes, J.P. (2005). Predicting and preventing adverse drug reaction in the very old. Drugs and Aging, 22(5), 375-392.

Millar, W. (1998). Multiple medication use among seniors. Health Reports (Statistics Canada, Catalogue 82-003), 9(4), 11-17.

Mitnitski, A., Song, X., Skoog, I., Broe, G.A., Cox, J.L., … Rockwood, K. (2005). Relative fitness and frailty of elderly men and women in developed countries and their relationship with mortality. The Journal of the American Geriatrics Society, 53(12), 2184-2189.

Naranjo, C.A., Busto, U., Sellers, E.M., Sandor, P., Ruiz, I., … Greenblatt, D.J. (1981). A method for estimating the probability of adverse drug reactions. Clinical Pharmacology & Therapeutics, 30(2), 239-245.

O'Connor, J. L., Gardner, E. M., Mannheimer, S. B., Lifson, A. R., Esser, S., Telzak, E. E., & Phillips, A. N. (2013). Factors associated with adherence amongst 5295 people receiving antiretroviral therapy as part of an international trial. Journal of Infectious Disease, 208(1), 40-49.

Olivier, P., Bertrand, L., Tubery, M., Lauque, D., Montastruc, J.L., & Lapeyre-Mestre, M. (2009). Hospitalizations because of adverse drug reactions in elderly patients admitted through the emergency department: a prospective survey. Drugs Aging, 26(6), 475-482.

Price, S.D., Holman, C. D. J., Sanfilippo. F. M., & Emery J.D. (2014). Association between potentially inappropriate medication from the Beers criteria and the risk of unplanned hospitalization in elderly patients. Annals of Pharmacotherapy, 48(1),6-16.

Pugh, J.A., Wang, C.P., Espinoza S. E., Noel, P. H., Bollinger, M., Amuan, M., Finley, E., & Pugh M. J. (2014). Influence of frailty-related diagnoses, high-risk prescribing in elderly adults, and primary care use on readmissions in fewer than 30 days for veterans aged 65 and older. Journal of the American Geriatrics Society, 62(2), 291-298.

Ramage-Morin, P.L. (2009). Medication use among senior Canadians. Health Reports, 20(1), 37-44.

Rockwood, K., Song, X., MacKnight, C., Berman, H., Hogan, D.B. … Mitnitski, A. (2005). A Global Clinical Measure of Fitness and Frailty in Elderly People. Canadian Medical Association Journal, 173(5), 489-495.

Rockwood, K., Fox, R.A., Stolee, P., Robertson, D., & Beattie, R.L. (1994). Frailty in elderly people: an evolving concept. The Canadian Medical Association Journal, 150(4), 489-495.

Samoy, L.J., Zed, P.J., Wilbur, K., Balen, R.M., Abu-Laban, R.B., & Roberts, M. (2006). Drug-related hospitalizations in a tertiary care internal medicine service of a Canadian hospital: a prospective study. Pharmacotherapy, 26(11), 1578-1586.

Shahtahmasebi, S., Davies, R., & Wenger, G.C. (1992). A longitudinal analysis of factors related to survival in old age. The Gerontologist, 32(3), 404-413.

Sikdar, K.C., Alaghehbandan, R., Macdonald, D., Barett, B., Collins, K.D., Donnan, J., & Gadag, V. (2010). Adverse drug events in adults leading to emergency department visits. The Annals of Pharmacotherapy, 44(4), 641-649.

Steinman, M.A., Lund, B.C., Miao, Y., Boscardin, W.J., & Kaboli, P.J. (2011). Geriatric conditions, medication use, and risk of adverse drug events in a predominantly male, older veteran population. Journal of the American Geriatrics Society, 59(4), 615-621.

Strand, L.M., Morley, P.C., Cipolle, R.J., Ramsey, R., & Lamsam, G.D. (1990). Drug-related problems: Their structure and function. DICP, The Annals of Pharmacotherapy, 24(11), 1093-1097.

Tipping, B., Kalula, S., & Badri, M. (2006). The burden and risk factors for adverse drug events in older patients – a prospective cross-sectional study. The South African Medical Journal, 96(12), 1255-1259.

Vliet, M.J., Schuurmans, M.J., Grypdonck, M.H.F., & Duijnstee, M.S.H. (2006). Improper intake of medication by elders – insights on contributing factors: a review of the literature. Research and Theory for Nursing Practice: An International Journal, 20(1), 79-93.

vonRenteln-Kruse, W., Thiesemann, N., Thiesemann, R., & Meier-Baumgartner, H.P. (2000). Does frailty predispose to adverse drug reactions in older patients? Age and Aging, 29(5), 461-462.

Wong, C. H., Weiss, D., Sourial, N., Karunananthan, S., Quail, J. M., Wolfson, C., & H. Bergman. (2010). Frailty and its association with disability and comorbidity in a community-dwelling sample of seniors in Montreal: a cross-sectional study. Aging Clinical and Experimental Research, 22(1), 54-62.

Zhan, C., Sangl, J., Bierman, A.S., Miller, M.R., Friedman, B., Wickizer, S.W., & Meyer, G.S. (2001). Potentially inappropriate medication use in the community-dwelling elderly. Journal of the American Medical Association, 286(22), 2823-2829.