2019-04-26

Incidence and Risk Factors for Hyponatremia in Patients Newly Prescribed Citalopram

Shysh, Andrea Christine

UNIVERSITY OF CALGARY

Incidence and Risk Factors for Hyponatremia in Patients Newly Prescribed Citalopram

by

Andrea Christine Shysh

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE

DEGREE OF MASTER OF SCIENCE

GRADUATE PROGRAM IN MEDICAL SCIENCE

CALGARY, ALBERTA

APRIL, 2019

Abstract

Hyponatremia is a common and under-recognized adverse drug reaction of citalopram. This study aims to determine the incidence of hyponatremia and to identify risk factors in a large, population-based cohort initiating new prescriptions for citalopram.

Following approval from the ethics review board, data were obtained from Alberta Information Network databases to identify patients with new citalopram prescriptions from 2010-2017, inclusive. Hyponatremia was defined as serum sodium level <135 mmol/L. Associations were determined by performing Cox regression with time-varying covariate analysis, with the development of hyponatremia as the dependent variable.

This is the first large-scale, population-based study to explore risk factors, based solely on laboratory serum data, for the development of hyponatremia in patients initiating citalopram therapy. We report a 16.7% incidence of hyponatremia after starting citalopram treatment and significant risk factors include lower baseline sodium, concurrent thiazide diuretic use, older age, and male sex.

Preface

This thesis is original, unpublished, independent work by the author, AC Shysh. The experiments in Chapter 2 were covered by the ethics certificate number REB 16-2538, issued by the University of Calgary Conjoint Research Ethics Board on March 20, 2017.

Acknowledgements

This research was made possible by the financial support, in the form of grant funding, from the Canadian Institutes of Health Research.

I would like to express the deepest gratitude to my graduate committee supervisor, Dr. Christopher Naugler, for continually providing me guidance throughout the process of completing this thesis. From offering suggestions on the scope of the research to supplying access to materials that were helpful in the formatting of the manuscript, I appreciate every second of advice!

I would like to thank my committee members, Dr. Davinder Sidhu and Dr. Zahinoor Ismail, for the advice given in directing my research and for providing the expertise in pharmacy and physiology required to appreciate the significance of my findings.

I would also like to extend a huge thanks to the research group under the supervision of Dr. Naugler, Cheryl Lau, Irene Ma, Maggie Guo, Vijay Kandalam, Leonard Nguyen, Jeannine Viczko, Tarah Lynch, and Zane Ramdas, for accepting me amongst your midst. A special thanks is reserved for Maggie Guo, for providing me with the data, and all subsequent corrections, for my thesis and for Leo Nguyen, for tirelessly helping me navigate the beast that is Cox regression with time-varying variables. The friendship and inclusion contributed to the encouragement I felt during my studies and will not be forgotten.

Lastly, I would like to acknowledge and thank my family and loved ones, for the love and support through every step of the process. From offering external opinions and edits on my thesis, to sustaining my wellbeing, this thesis would not have been possible without them.

Dedication

I dedicate this dissertation to my grandfather, Alec Shysh, who studied and practiced pharmacy long before I was born and witnessed the evolution of pharmacy in the 20th century.

Table of Contents

List of Tables

CHAPTER 2

List of Figures

CHAPTER 2

List of Symbols, Abbreviations and Nomenclature

Symbol	Definition
ABC	ATP-binding Cassette
ADH	Anti-diuretic Hormone
CI	Confidence Interval
CMA	Calgary Metropolitan Area
CNS	Central Nervous System
DIN	Drug Identification Number
eGFR	Estimated Glomerular Filtration Rate
HR	Hazard Ratio
ICD-10	International Classification of Diseases, Tenth Revision
IRF7	Interferon Regulatory Factor 7
LDL	Low-density Lipoprotein
MHC	Major Histocompatibility Complex
PET	Positron Emission Topography
PHN	Provincial Health Number
PIN	Pharmaceutical Information Network
SIADH	Syndrome of Inappropriate Anti-diuretic Hormone
SIGLECP3	Sialic Acid-binding Immunoglobulin-like Lectin, Pseudogene 3
SMAD 7	SMA-and MAD-related Protein 7
SSRI	Selective Serotonin Reuptake Inhibitor
V2R	Vasopression Receptor 2
5-HIAA	5-Hydroxyindole-3-Acetic Acid
5HT	5-Hydroxytryptamine

Chapter One: Introduction

1.1 Hyponatremia and SIADH Defined

The preservation of electrolyte homeostasis is crucial for optimal physiological functioning, with hormonal and renal mechanisms regulating the extracellular and intracellular concentrations of each specific electrolyte. Sodium is one of the primary dietary electrolytes with a large influence on the maintenance of blood pressure and fluid equilibrium, plus additional roles in blood pH balance and neuron action potential propagation. While hypernatremia is usually a consequence of dehydration or nephron depletion due to age or disease [1], a reduction in serum sodium is equally detrimental to the health of the individual.

Three classifications of hyponatremia exist and are distinguished on the basis of serum osmolality. Isotonic and hypertonic hyponatremia occur due to the presence of plasma proteins or other osmotically-active solutes that reduce the fraction of plasma water in the total plasma volume [2]. Since sodium is water-soluble, the proportion of sodium in terms of total plasma volume is decreased even if the plasma water concentration of sodium is unchanged. True hyponatremia is an electrolyte deficiency defined as a serum sodium concentration less than 135 mmol/L and occurs with the condition of low serum osmolality (hypotonic hyponatremia) [3, 4]. The symptoms of mild to moderate hyponatremia (<132 mmol/L and <128 mmol/L serum sodium, respectively) include nausea, fatigue, confusion, cramping, unsteadiness, dizziness, and depressed reflexes while severe hyponatremia (<125 mmol/L serum sodium) can result in delirium, seizures, coma, and death [5]. Furthermore, the development of hyponatremia in hospitalized patients results in increased mortality, which is correlated with the severity of plasma sodium depletion [6]. Clinical consequences of hyponatremia include an increased

incidence of hospitalization, length of hospital stay, and an increased financial burden on the healthcare system [5].

It is important to determine the etiology of hyponatremia in order to administer effective treatment and reduce continued exposure to suboptimal electrolyte conditions. The etiology of reduced sodium levels is divided into three conditions: hypovolemic, hypervolemic, and euvolemic hyponatremia. Hypovolemic hyponatremia occurs alongside the loss of water via renal or other mechanisms, including vomiting, diarrhea, or diuretic use, while hypervolemic hyponatremia is suggestive of heart or renal failure. Euvolemic hyponatremia may indicate primary polydipsia or hypothyroidism, but most notably arises as a result of the syndrome of inappropriate anti-diuretic hormone (SIADH) [3].

SIADH, the increased production of antidiuretic hormone (ADH), may be caused by a multitude of malignant and non-malignant conditions. ADH, synthesized by the hypothalamus, is normally released by the posterior pituitary gland in response to osmolality changes. It then binds to the kidney vasopressin receptor 2 (V2R) and increases water reabsorption in the collecting ducts of the kidney. Cancerous tumors may induce ADH secretion via paraneoplastic secretion while central nervous system (CNS) disorders, pulmonary diseases and infections may provoke ADH stimuli unrelated to osmotic homeostasis [7, 8]. In terms of adverse drug effects, certain medications may cause hyponatremia through SIADH, or may heighten the V2R response to ADH, which is classified as the nephrogenic syndrome of antidiuresis [9]. Hyponatremia due to SIADH is a known side effect of antidepressants, including that of serotonin selective reuptake inhibitors (SSRI).

1.2 Serotonin Selective Reuptake Inhibitors

In the past two decades, worldwide use of antidepressants has increased, though the frequency of antidepressant use in Canada has stabilized over the past 5 years [10]. A recent study among older adults in Manitoba, Canada reports an overall decrease in the incidence of new antidepressant prescriptions in the last decade, although the use of newer antidepressants is prevailing over older classes [11]. SSRI are one of the newer classes of antidepressants that contain some of the most commonly prescribed drugs for the treatment of depressive and anxiety disorders. As described by its name, the SSRI mechanism of action in the brain involves binding to the presynaptic serotonin reuptake transporter. This binding decreases the affinity of the transporter for serotonin, thereby extending the presence of the neurotransmitter in the synaptic cleft. As a result of the specificity for the serotonin pathway, SSRI have reduced effects on dopamine and norepinephrine activity, which is a marked advantage over older antidepressants that caused effects on a variety of pathways involving many different neurotransmitters.

Significant differences in depression rates between women and men exist and may be explained by sex differences in the serotonin system. Women have twice the rate of depression, as well as higher rates of recurring depression in comparison with men [12, 13]. Higher concentrations of the serotonin metabolite 5-hydroxyindole-3-acetic acid (5-HIAA) were found in the cerebral spinal fluid of female rats than male rats [14], and postmortem studies in humans also confirm higher 5-HIAA presence in female hypothalamus, lobus occipitalis, and hippocampus tissues [15]. Positron Emission Topography (PET) studies using radioligands for the 5-hydroxytryptamine (5HT) receptor 5HT1A and the serotonin reuptake transporter revealed higher 5HT1A receptor binding and lower serotonin reuptake transporter binding in depressed women than in men [16]. Women have lower levels of serotonin synthesis, confirmed with another PET study [17], which may also result in the internalization of the serotonin reuptake

transporter [18].

The downstream effect of serotonin is dependent on the receptor type present in the postsynaptic membrane. Among the different subtypes of the 5HT receptor, the 5HT1A and the 5HT2 receptors have the largest influence on mood and anxiety [19]. It is thought that serotonin mediation elevates the concentration of circulating ADH to increase the reabsorption of water, regardless of declining sodium levels [5, 6, 9]. Extensive studies on rats show that serotonin stimulates ADH secretion from the posterior pituitary [19-24]. 5HT receptors present on neurohypophyseal tissue facilitate ADH secretion into the hypophyseal portal system and also into the peripheral circulation upon serotonergic stimulation. The action of serotonin on ADH is mediated by brain angiotensin in the CNS. Since SSRI antidepressants increase the amount of serotonin present in the synapse, the effect is a similar increase in ADH secretion [20, 23].

1.3 Citalopram

Citalopram, one of the six SSRI antidepressants, had the most significant increase in use among older adults in Canada from 1997 to 2013 [11]. The prevalence of citalopram use over other SSRIs is presumably a result of fewer drug interactions and side effects [11], although its use has been implicated in QT interval prolongation [25]. Citalopram exists as a racemic mixture of two enantiomers, (R)-(-)-citalopram and (S)-(+)-citalopram, which attach to two different binding sites on the serotonin reuptake transporter and induce the internalization of the transporter. S-citalopram, otherwise known as escitalopram, binds to the high-affinity orthosteric binding site while R-citalopram binds to the low-affinity allosteric site on the transporter and noncompetitively inhibits S-citalopram action on the high-affinity binding site [26, 27]. Cytochrome P450 enzymes in the liver metabolize the citalopram enantiomers, but the breakdown and excretion of R-citalopram occurs at a slower rate than that of its racemic counterpart [26, 28].

A differential response in citalopram treatment efficacy exists due to age, the severity of the depressive disorder, comorbidities, and several pharmacogenomic factors. Differences between variants in the liver CYP2C19 and CYP2D6 genes result in altered citalopram clearance, which has a direct influence on the efficacy and toxicity of the citalopram treatment [29]. The down regulation of SMA-and MAD-related protein 7 (SMAD 7) and sialic acid-binding immunoglobulin-like lectin, pseudogene 3 (SIGLECP3) genes and the up regulation of interferon regulatory factor 7 (IRF7) gene seem to have a beneficial effect on citalopram treatment [30, 31]. Polymorphisms in the 5HTR1Dβ gene is suggested to cause agitation in children treated with citalopram [32] and a RS17135437 single-nucleotide polymorphism in the EMID2 gene is also significantly correlated with visual and auditory side effects of citalopram treatment [33], to name just a few of the genes implicated in citalopram treatment and adverse effects.

1.4 Existing Research

Existing research is mostly comprised of individual case studies detailing the hospitalization, diagnosis, and subsequent treatment of a hyponatremic patient on citalopram [34-38]. In these case studies, the patient was either admitted to hospital, or already an inpatient who presented symptoms of hyponatremia within two weeks of initiating citalopram treatment. Following formal hyponatremia diagnosis, electrolyte infusion and cessation of citalopram successfully restored serum sodium concentrations to pre-antidepressant levels within one week.

A handful of retrospective, population-based cohort studies studying antidepressant-induced hyponatremia reinforce the trends seen in the case studies. In a Swedish study of adults admitted to the hospital, a correlation between new antidepressant treatment and the likeliness of hospitalization for hyponatremia was found [39] and several studies have compared the incidence of hyponatremia between antidepressant classes, with varying results [5, 39-41].

However, research examining an entire adult population based primarily on laboratory serum data rather than International Classification of Diseases, Tenth Revision (ICD-10) codes is scarce.

1.5 Study objectives

This study explores the relationship between the initiation of citalopram use and the development of hyponatremia in the adult population of Calgary, Canada. The first part of this thesis includes an update on the incidence of hyponatremia among all adult age groups and the identification of risk factors for the development of hyponatremia following new citalopram treatment. An investigation of current hyponatremia rates stemming from citalopram or SSRI treatment, along with information from existing literature, is given in Chapter 2.

The second part of this study considers the application of risk factor analysis with potential expansion into personalized medicine. A discussion into the risk factors that can be analyzed to determine patterns useful in establishing precision health is given in Chapter 3, with emphasis on geo-mapping and the creation of clinical guidelines. These preventative medicine techniques are intended for physician, administrative, and hospital use for improved patient care and, thus, a reduction in hospitalizations due to SIADH.

Chapter Two: Risk Factors for Hyponatremia in Patients Newly Prescribed Citalopram: a Retrospective Observational Study

2.1 Abstract

Hyponatremia is a common and under-recognized adverse drug reaction of SSRI antidepressants. Despite its clinical importance, there are few large-scale studies on the risk factors associated with this adverse reaction. This study aims to determine the incidence of hyponatremia and to identify risk factors in a large, population-based cohort initiating new prescriptions for citalopram.

Following approval from the ethics review board, data were obtained from an Alberta Health Pharmacy database to identify new citalopram prescriptions from 2010-2017, inclusive. Patients with new prescriptions were linked with Calgary Laboratory Services data to identify patients who developed hyponatremia following prescription initiation. Hyponatremia was defined as serum sodium level <135 mmol/L. Associations were determined by performing Cox regression with time-varying covariate analysis, with the development of hyponatremia as the dependent variable.

A total of 19,679 patients with new prescriptions were identified; 12,842 females and 6,837 males. The mean age was 55.48 years with a standard deviation of 21.35 years. 3,250 (16.5%) of these patients developed hyponatremia, 1996 (15.5% of) females and 1254 (18.3% of) males. Cox regression showed significant associations of hyponatremia with lower baseline sodium (HR = 0.788), older age (HR = 1.029), diuretic use (HR = 1.141) and male sex (HR = 1.168). Pharmaceutical manufacturer or strength of citalopram did not have significant effects on the development of hyponatremia.

This is the first large-scale, population-based study to explore risk factors, based solely on laboratory serum data, for the development of hyponatremia in patients initiating citalopram

therapy. We report a 16.7% incidence of hyponatremia after starting citalopram treatment, and significant new findings include a higher incidence in males. This is the first published incidence of hyponatremia following the initiation of citalopram treatment across all ages in Canada.

2.2 Introduction

The global increase in antidepressant use over the last two decades has been attributed to the rise in SSRI antidepressants, of which citalopram is the most prevalent [9, 11, 39, 42]. Antidepressant use increased over all age groups from the 1990s to the 2000s in the United States, United Kingdom, and the Netherlands [43-45]. In each case, the increase was mainly due to the rise in SSRI use, particularly among the elderly [42, 45]. Despite the global increase in antidepressant use, the frequency of antidepressant treatment in Canada has stabilized over the last five years [10], with the exception of citalopram, which quadrupled in use [11]. Additionally, citalopram is the most common SSRI used in Sweden, Denmark, and American nursing homes [9, 39, 44]. The dominance of citalopram over other SSRIs and non-SSRI antidepressants is presumably a result of fewer drug interactions and side effects [46], although its use has been implicated in QT interval prolongation and hyponatremia [18, 47].

Hyponatremia occurs as a result of disease or adverse drug reactions, and impacts patient health and healthcare systems. Hyponatremia is an electrolyte deficiency defined as serum sodium concentration <135 mmol/L. While a reduction in serum sodium can arise from preexisting medical conditions, most notably congestive heart failure and chronic kidney disease, hyponatremia is also a common side effect of SSRI antidepressants. The development of hyponatremia in hospitalized patients results in increased mortality, correlated with the severity of plasma sodium depletion [6]. The symptoms of mild to moderate hyponatremia, <132 mmol/L and <128 mmol/L serum sodium, respectively, include nausea, fatigue, confusion, cramping,

unsteadiness, dizziness, and depressed reflexes while severe hyponatremia, <125 mmol/L serum sodium, can result in delirium, seizures, coma, and death [5]. The clinical consequences of hyponatremia include increased incidence of hospitalization, longer length of hospital stay, and larger financial burden on the healthcare system [5].

Despite the clinical importance of citalopram and other SSRI antidepressants, there are few large-scale studies on the risk factors for hyponatremia. Existing research is mostly comprised of individual case studies detailing the hospitalization, diagnosis, and subsequent treatment of a hyponatremic patient on citalopram treatment [34-38]. These studies reported that the risk of hyponatremia was greater in females and also increased with age and thiazide diuretic use [5]. Naturally, those with lower baseline serum sodium levels were at a higher risk for hyponatremia on citalopram treatment as well [5]. Symptoms of renal, cardiac, or metabolic disease, such as hypertension, hypothyroidism, or the use of calcium channel blockers or other, non-thiazide diuretics, have also been significantly associated with the risk of hyponatremia [5]. A handful of retrospective, population-based cohort studies assessing antidepressant-induced hyponatremia reinforce the trends seen in the case studies, but are either partially or wholly based on ICD-10 codes instead of concrete serum data, characterize instances of hyponatremia between different antidepressants, and tend to focus on adults over the age of 65 instead of the whole population [5, 9, 39-41].

The goal of this study is to provide the incidence of hyponatremia and to identify risk factors in a large, population-based cohort with new prescriptions for citalopram. This study is based on patient data from 2010-2017 collected at hospitals and patient service centres in Calgary, Alberta. Analysis was limited to the Calgary Metropolitan Area (CMA) population of over 1.3 million residents.

2.3 Study Design

2.3.1 Ethics Statement

Ethics approval for this study was obtained from the University of Calgary Conjoint Research Ethics Board (REB 16-2538).

2.3.2 Source of Data

Data were obtained from the Alberta Health Pharmacy Information Network (PIN) database to identify all new citalopram prescriptions from 2010-2017, inclusive. A handful of databases linked by a unique patient identifier, the Alberta Provincial Health Number (PHN), were used to generate the patient demographics and collect diagnostic laboratory data. The PIN database, part of the Alberta Netcare Electronic Health Record system, provided access to patient medication profiles and basic demographic information. The PHN was matched to the postal code using the Provincial registry, for use as a geographical control. Lastly, access to Cerner Millennium, the software used by Calgary Laboratory Services, provided diagnostic data on blood tests collected within the established time frame. Calgary Laboratory Services is a regionalized laboratory providing diagnostic services to Calgary and surrounding area in Southern Alberta.

2.3.3 Case Inclusion

Inclusion of patient data was restricted to those residing in the Calgary Metropolitan Area with a new prescription for citalopram, regardless of strength, dosage, or Drug Identification Number (DIN) from 2010 to 2017. A new prescription was defined as no previous antidepressant treatment six months prior to citalopram initiation. Patients with new prescriptions were linked with Calgary Laboratory Services data to identify those who developed hyponatremia following citalopram treatment. Hyponatremia was defined as a serum sodium level <135 mmol/L. A

baseline serum sodium concentration, to a maximum of six months pre-treatment, was required. The baseline values were compared to serum laboratory data collected up to 365 days after the start of citalopram treatment. The first instance of a serum sodium level <135 mmol/L was considered a hyponatremic event, in cases with multiple, sequential serum laboratory collections.

2.3.4 Statistical Analyses

Summary statistics were performed to measure baseline characteristics, such as means and proportions. Associations were then determined by performing Cox regression with time-varying covariates with the development of hyponatremia as the dependent variable. Sex, age, baseline sodium, pharmaceutical manufacturer, citalopram strength, and thiazide diuretic use were the covariates examined. Thiazide diuretic use was defined as treatment with thiazide diuretics within six months before starting the citalopram prescription. All data analyses and calculations were done in R Studio [48] using R version 3.5.1 [49].

2.4 Results

We identified 19,679 patients with new citalopram prescriptions from 2010 – 2017 who met the inclusion criteria for this study (Figure 2-1). The baseline characteristics of the study population are described in Table 2-1. Citalopram users were predominantly female, with an average age (standard deviation) of 54.63 (21.94) years. Thiazide diuretic use was documented in 2,327 cases (11.8%), and the average age of diuretic users was 69.38 (14.33) years, compared to that of non- diuretic users, which was 53.61 (21.45) years old. Baseline sodium measurements were similar between females and males, and were also similar between diuretic and non-diuretic users, 138.78 (3.70) mmol/L and 139.52 (3.07) mmol/L, respectively.

Of patients on new citalopram treatment, 3,250 (16.5%) developed hyponatremia: 1996 (15.5% of) females and 1254 (18.3% of) males. The average age of those who developed

hyponatremia was 67.75 (18.74) years, greater than the average age of 53.05 (20.99) years in those who did not. 662 (28.4% of) patients on concurrent thiazide diuretic use developed hyponatremia, as compared to 2,588 (14.9% of) patients who developed hyponatremia but were not using diuretic medications. The baseline sodium levels averaged 136.76 (4.16) mmol/L in those that developed hyponatremia, lower than the baseline sodium levels for those who did not develop hyponatremia was 139.96 (2.62) mmol/L.

Pharmascience, Sanis, Actavis, Apotex, and Mint manufactured the most common citalopram formulations, with at least 1,000 prescriptions per company. Several formulations were less frequently prescribed, with less than 500 prescriptions for 10 of the manufacturers. Although more than 20% of ECL and Acceleron citalopram formulations resulted in hyponatremia, the results were not statistically significant ($p>0.05$).

The 20mg strength of citalopram was the most common strength prescribed and was dispensed to more than 13,000 patients. Fewer than 6,000 patients were prescribed citalopram 10mg, with the 40mg and 30mg strengths only treating less than 700 and 100 patients, respectively. Since so few individuals were treated by the 30mg strength, these patients were grouped together with those on 40mg citalopram for subsequent analyses. Almost 20% of patients on citalopram 10mg developed hyponatremia, however this result was not statistically significant ($p>0.05$).

Results from the risk factor analysis are summarized in Table 2-2, with a total cumulative hazard risk shown in Figure 2-2. Baseline sodium and age violated the proportional hazard assumption and were corrected to satisfy the global goodness-of-fit. Sex, diuretic use, age, and baseline sodium were all significant risk factors for the development of hyponatremia ($p<0.05$), further illustrated in the respective hazard curves (Figures 2-2 to 2-6). Males and concurrent

diuretic use had hazard ratios of 1.168 [95% CI 1.088 – 1.254] and 1.141 [95% CI 1.045 – 1.246], respectively. Age had a hazard ratio of 1.029 [95% CI 1.027 – 1.032] for the development of hyponatremia and baseline sodium level (mmol/L) had a hazard ratio of 0.788 [95% CI 0.780 – 0.796]. The strength of citalopram was not a significant risk factor for hyponatremia events ($p>0.05$). The manufacturer Pharmascience was chosen as the reference group for the manufacturer analysis since the highest proportion of the population (5,747/19,679 [29%]) was treated with a pms-citalopram formula. The only manufacturers with a significant risk of hyponatremia on citalopram treatment compared to Pharmascience were Jamp and Ranbaxy, although relatively few patients were treated with Jamp-citalopram or Ran-citalopram, 221 and 492, respectively.

Table 2-1. The baseline characteristics of patients on citalopram treatment. Age and baseline sodium are represented as mean (S.D), and thiazide diuretic use is expressed as a percentage of the population.

	Sex		Total (n = 19,679)
	Female (n = 12,842)	Male (n = 6,837)	
Age (years)	54.63 (21.94)	57.08 (20.10)	55.48 (21.35)
Thiazide diuretic use (percentage)	12.3	10.9	11.8
Baseline sodium (mmol/L)	139.39 (3.15)	139.52 (3.19)	139.43 (3.16)

Table 2-2. Risk factors for the development of hyponatremia in patients starting a new citalopram prescription.

Covariate		Hazard ratio	95% Confidence Interval	Probability
Sex (Male)		1.168	1.088 – 1.254	<0.000*
Age		1.029	1.027 – 1.032	<0.000*
Diuretic Use		1.141	1.045 – 1.246	0.003
Baseline Sodium		0.788	0.780 – 0.796	<0.000*
Strength	20mg	0.929	0.835 – 1.034	0.180
	40mg	1.056	0.853 – 1.306	0.619
Manufacturer	Acceleron	1.063	0.900 – 1.256	0.469
	Actavis	1.083	0.951 – 1.233	0.232
	Apotex	1.028	0.893 – 1.183	0.702
	Celexa	0.839	0.634 – 1.110	0.219
	Ecl	1.924	0.959 – 3.360	0.065
	Jamp	1.524	1.094 – 2.122	0.013*
	Marcan	0.781	0.292 – 2.088	0.623
	Mint	0.949	0.827 – 1.090	0.460
	Mylan	1.133	0.905 – 1.418	0.278
	Natco	0.653	0.271 – 1.572	0.342
	Ran	1.303	1.043 – 1.629	0.020*
	Sandoz	1.025	0.734 – 1.431	0.886
	Sanis	0.995	0.862 – 1.148	0.941
	Septa	<0.000	<0.000 – >9999	0.970
	Sivem	1.138	0.847 – 1.529	0.390
	Sunovion	0.875	0.479 – 1.599	0.664
	Teva	1.076	0.866 – 1.336	0.509

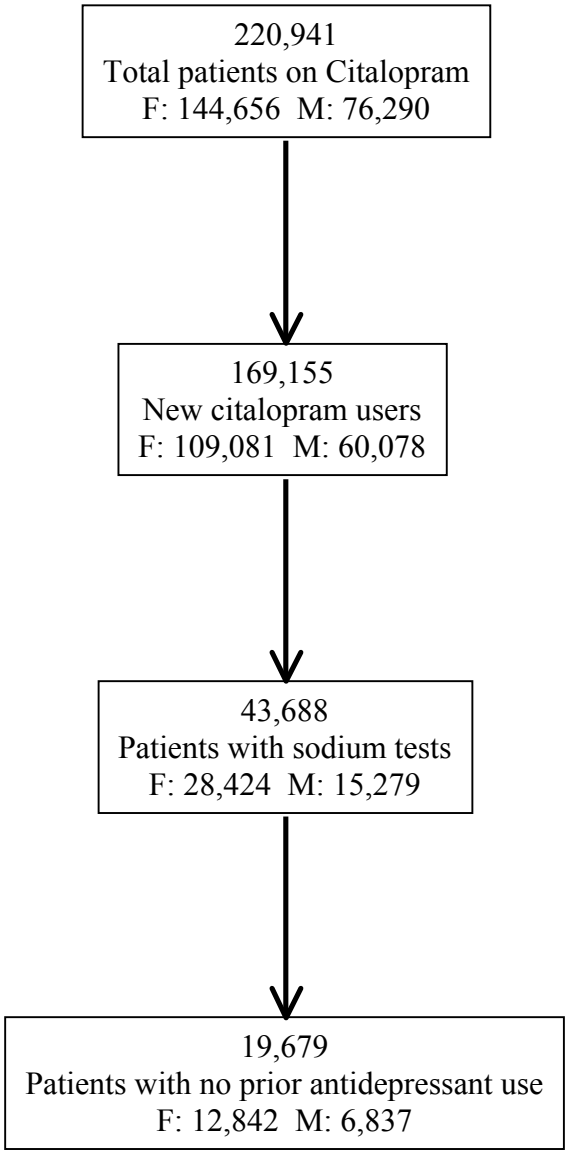

Figure 2.1. Case selection. Cases were limited to residents of the Calgary Metropolitan Area from 2010-2017, inclusive.

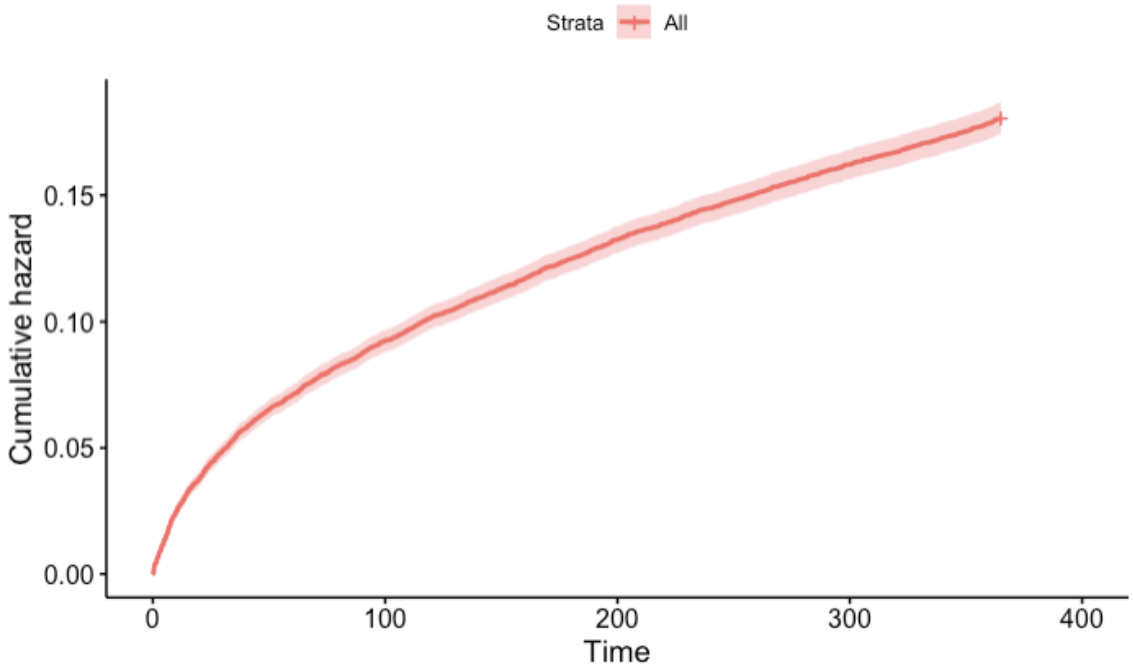

Figure 2-2. The total cumulative hazard of hyponatremia following citalopram treatment over time.

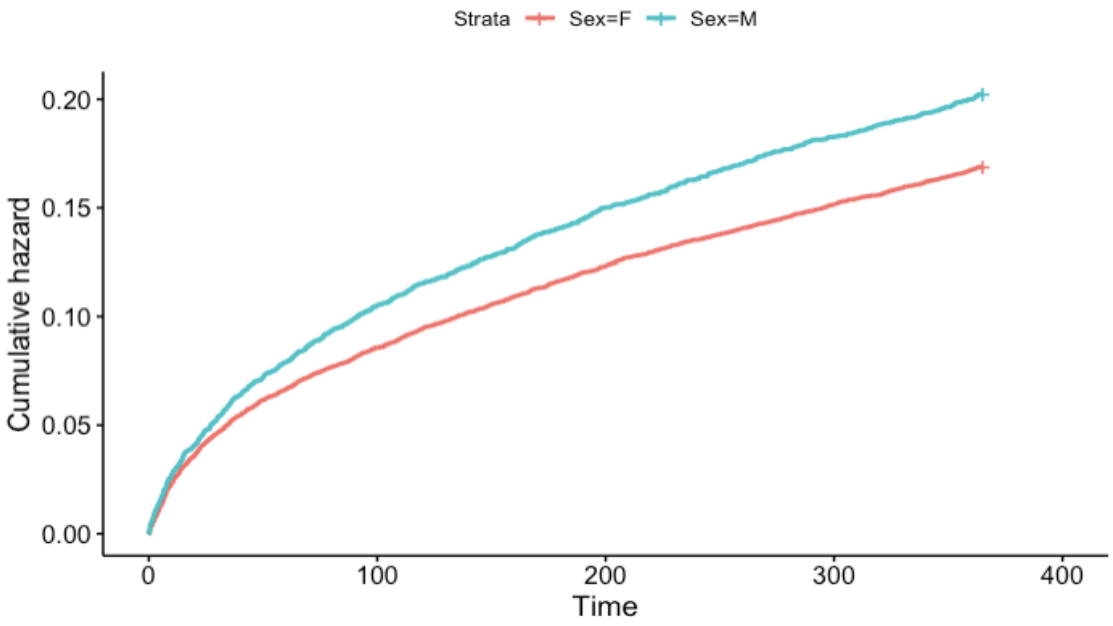

Figure 2-3. The cumulative hazard of hyponatremia following citalopram treatment over time, stratified by sex.

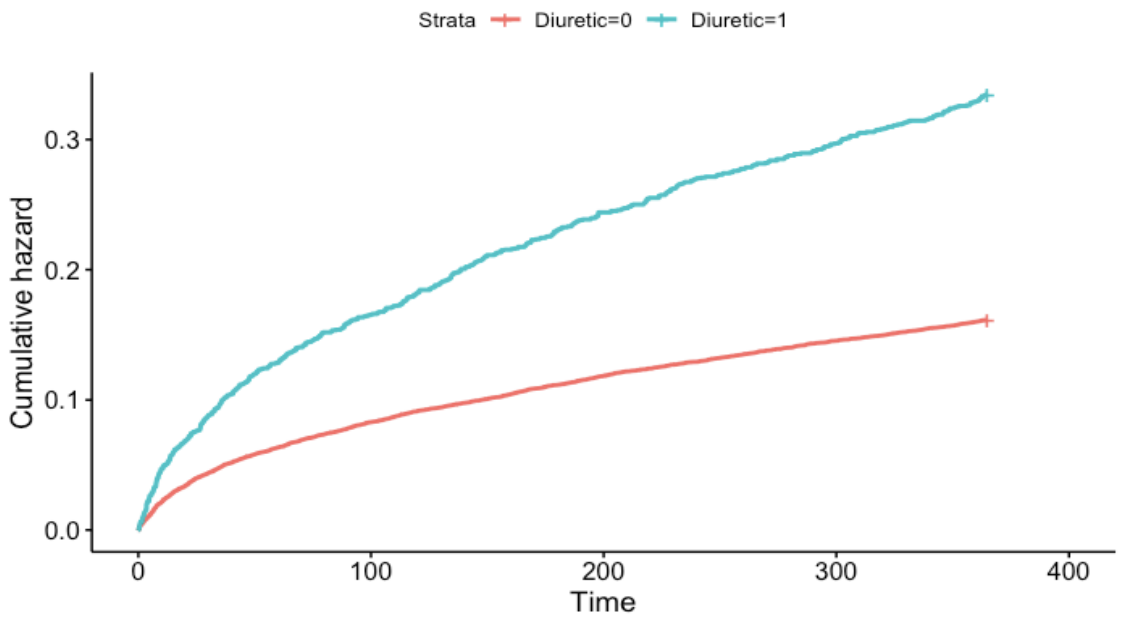

Figure 2-4. The cumulative hazard of hyponatremia following citalopram treatment over time, stratified by diuretic use.

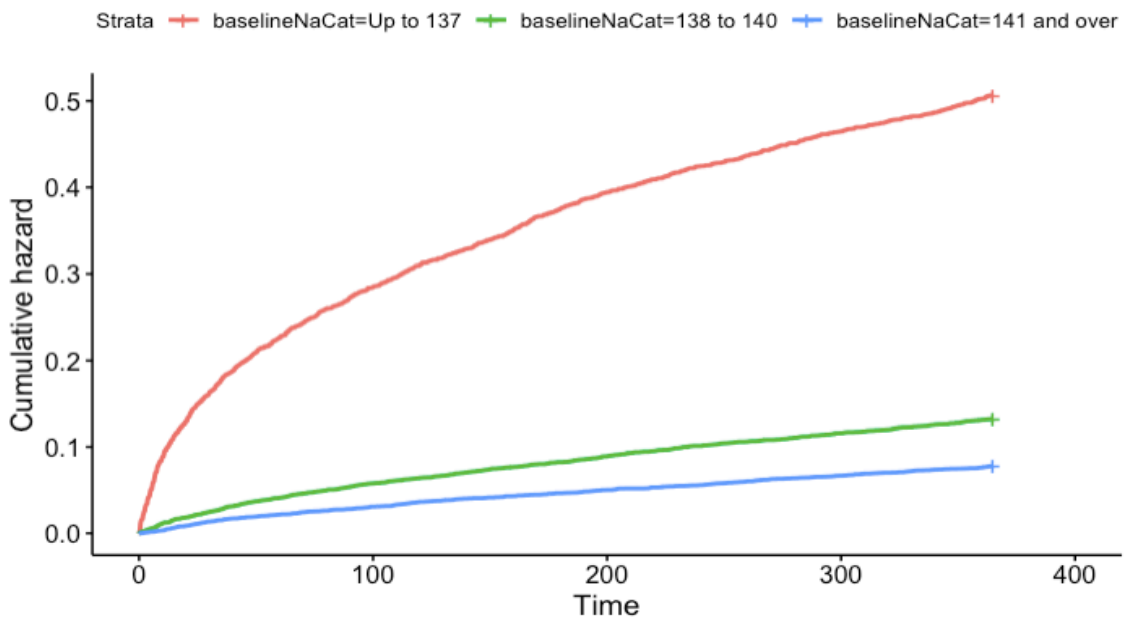

Figure 2-5. The cumulative hazard of hyponatremia following citalopram treatment over time, stratified by baseline sodium categories (mmol/L).

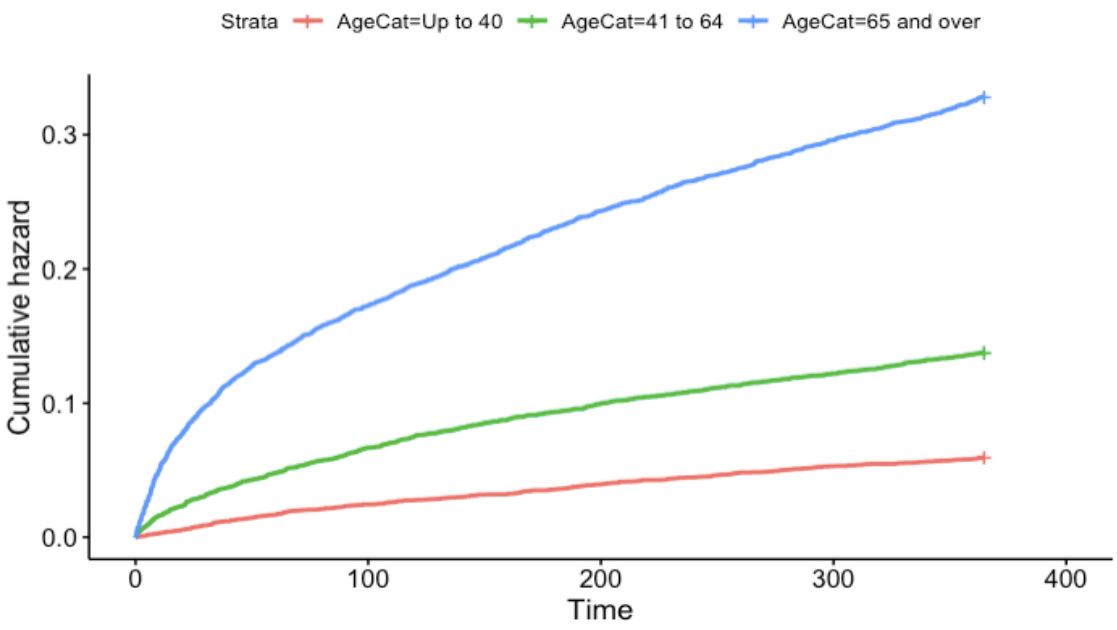

Figure 2-6. The cumulative hazard of hyponatremia following citalopram treatment over time, stratified by age (years).

2.5 Discussion

This study is the first to provide population-based incidence data and risk factor analysis for the development of hyponatremia using serum laboratory data, following the initiation of citalopram treatment, inclusive of all ages. The reported prevalence of hyponatremia after SSRI use ranged between 0.06 – 40% in existing literature, however this incidence range was based on case reports and case-controlled studies of less than 1000 individuals [50]. Additionally, older case studies defined hyponatremia as a serum sodium level <130 mmol/L, while more recent studies use serum sodium levels of 135 mmol/L as the cutoff diagnostic value [50-55]. Repeating the analysis using 130 mmol/L as the definition of hyponatremia resulted in an incidence of 4.8%, with only age and baseline sodium as significant risk factors.

The significance of age as a risk factor for the development of hyponatremia is a well-documented outcome, based on the increased likelihood of physiological deficits and disease with age. Existing studies are predominantly focused on elderly populations [5, 40, 41, 51, 56, 57], since hyponatremia is more prevalent in aging populations [5, 58]. Older individuals tend to have more comorbid conditions and are generally treated with a higher number of prescriptions, which may favour the event of an adverse drug reaction [5, 57]. Physiological changes associated with age, such as kidney volume loss and a decreased ability to regulate electrolyte concentration, result in a reduced ability to cope with the stress of drug-induced hyponatremia [5, 57, 59]. It is important to note that the risk of hyponatremia may not be equal in all elderly patients, with possible influence from genetic polymorphisms in the cytochrome P450 enzymes [55].

Unsurprisingly, lower baseline serum sodium levels were associated with a greater risk of hyponatremia since a smaller reduction in serum sodium was required to reach hyponatremic levels [59]. Although hyponatremia is the most common electrolyte disorder, with an even

higher prevalence in older and hospitalized groups [58], it is often under-reported [60]. The clinical features of low serum sodium are often nonspecific, ranging from nausea and cramping to confusion and delirium, and can easily be mistaken for symptoms of the underlying illness [5]. However, even pre-existing, asymptomatic hyponatremia is associated with changes in mental status and mortality, especially in the elderly population [59], and the long-term risks of undiagnosed, asymptomatic hyponatremia are unknown.

Simultaneous thiazide diuretic use on citalopram treatment was another expected risk factor in the development of hyponatremia, since the pathway of thiazide-induced hyponatremia is well understood. Diuretic use, even without concurrent citalopram treatment, has a reported incidence of hyponatremia ranging between 4-14%, with risk factors including age and female sex as well [61]. Thiazide-induced increases in fluid ingestion and impaired water excretion, mediated by ADH or urea mechanisms, are known to result in hyponatremia [61]. Although the exact mechanism of SSRI-stimulated hyponatremia are not confirmed, it is thought that serotonin mediation elevates the concentration of circulating ADH to increase the reabsorption of water, regardless of declining sodium levels [5, 6, 9]. In terms of hyponatremia, a synergistic effect hinging on inappropriate ADH release may exist between thiazide diuretics and SSRIs [62].

The increased risk of hyponatremia on citalopram in males, in comparison to females, is unique to this study and unsupported in the literature. Although some studies did not find an association between sex and the risk of hyponatremia, the majority of research identified female sex as a significant risk factor [40, 50-55]. However, these findings were either based on a review of case reports or small, case-controlled studies, and thus had a limited number of patients eligible for inclusion in the analysis. Since the majority of citalopram users were elderly and female, the instances of hyponatremia in the smaller studies may inadvertently bias the risk analysis reviews. The prevalence of female antidepressant use is possibly due to a greater

willingness to perceive and explore treatment for depression from their physicians, or the longer life expectancy of females, as compared to men [63]. The large patient population included in this study, coupled with robust statistical analysis, circumvented the problem of inclusion bias present in analyzing case reports and smaller case-control studies and may more accurately reflect the increased risk of hyponatremia in males.

The mechanism behind the difference in risk between sexes is unknown, but likely related to the still-uncertain mechanism of citalopram-induced hyponatremia. The average serum sodium level is lower in females than in men, except for those aged 50-70 [64], and potential differences in intracellular sodium pathways and metabolism is thought to increase the risk of hyponatremia for females [5]. Sexual dimorphism in renal transporters were reported in mice and resulted in differences in water and electrolyte homeostasis [65]. Females also tend to have lower body weight, which is another published risk factor for the development of hyponatremia on SSRI treatment [50, 51, 55]. Since males experience greater serotonin reuptake transporter binding than depressed women [16], it is possible that differences in the serotonin pathway itself may contribute to the increased burden of hyponatremia seen in males. Nevertheless, further insight into the pathway(s) responsible for drug-induced hyponatremia may yield information on the differences seen between sexes.

The increased hyponatremia risk of Jamp and Ranbaxy formulations, as compared to the Pharmascience reference group, cannot be conclusive considering the variance in treatment size and an unexplored effect on the pharmaceutical manufacturer on adverse drug effects in the literature. Since five companies, Pharmascience, Sanis, Actavis, Apotex, and Mint, treated the vast majority of the population, a comparison with much less frequent formulations may be skewed. The manufacturer results depended on which pharmaceutical company was chosen as the reference group, suggesting a more complicated relationship between generic and brand

citalopram forms. Although all forms of citalopram are considered bioequivalent at each respective strength, the Food and Drug Administration accepts a bioavailability range of 80-125% compared with the original Celexa formula [66]. Additionally, variations between product batches have been reported in cases of adverse drug reactions [66].

The dose of citalopram treatment did not have significant effects on the risk of developing hyponatremia, which may be a result of the wide therapeutic range of citalopram and clinical dose titration. The therapeutic efficacy of citalopram ranges from 10mg/day to 60mg/day [67]. Since plasma serotonin concentrations are significantly decreased at 4 and 8 weeks of therapy [68], any therapeutic and adverse effects are likely to occur in that time. Dose titration is not essential for SSRI use, however clinicians may choose to gradually increase the dose to effective levels in order to reduce the incidence of adverse reactions [67].

A selection bias in this study exists since the incidence and risk factor analysis was based on the patients that complete more frequent diagnostic laboratory testing. Overall, females represent the majority of tested population in Calgary [69]. If an increased rate of testing in males had been observed, it may have offered an explanation for the higher incidence of hyponatremia compared to that of females. However the proportion of patients with sodium tests within the new citalopram user population was about 25% for both males and females (Figure 2-1). The frequency of diagnostic laboratory testing increases with age, since the likelihood of comorbidity and polypharmacy also increase with age. Older patients tend to have more contact with their healthcare providers, and thus are more likely to complete laboratory testing than those younger in age [70]. Polypharmacy further increases the risk of adverse drug interactions; therefore patients on high-risk medications, and also those on thiazide diuretics, are significantly more likely to complete regular testing as well [70, 71]. However, new medication users are less likely to complete ordered tests, and a study on elderly hypertensive patients without

comorbidities revealed that two-thirds of the patients had no serum electrolyte measurements before or after therapy initiation [71]. Since the older patients, especially those on thiazide diuretics, were more likely to complete regular laboratory testing, the incidence rate of hyponatremia may overestimate the true occurrence. However, since only 25% of the total number of new citalopram users in our study had baseline and follow-up sodium tests (Figure 2-1), the instance of hyponatremia may have been missed in the majority of patients. Given the high incidence rate of hyponatremia provided by this study, and the low percentage of patients with regular serum sodium values available, regular sodium testing on patients starting citalopram treatment should be considered by healthcare practitioners.

The limitations of this study include the lack of patient clinical data on the details of citalopram or thiazide treatment and other concomitant causes of hyponatremia. Changes in citalopram or thiazide diuretic treatment, such as dose increase, decrease, or cessation, may impact the occurrence of hyponatremia. Existing research has identified other possible risk factors of hyponatremia on citalopram treatment, such as low body weight and psychosis [40, 50, 51, 54], the data for which were not available for this study. Preexisting conditions or diseases that may independently induce hyponatremia were not identified in our patient population and may skew the results – especially for those patients presenting with a hyponatremic serum baseline value.

Future studies into the risk of hyponatremia with compliant citalopram use, as well as other SSRIs and concurrent use of other diuretic classes, may provide insight into an adverse drug reaction of two, highly prevalent treatments. Particular focus should be given to the risk factors associated with escitalopram use, given its enantiomeric relationship with citalopram. Although not a major finding in this study, quantifying the difference in risks between pharmaceutical manufacturers may be significant in understanding the etiology behind

hyponatremia and other adverse drug reactions. Lastly, analysis into the mechanism behind citalopram-induced hyponatremia and the effect of sex on the pathway should be explored, especially since the results of this study contradict existing literature.

2.6 Conclusion

This is the first large-scale, population-based study to explore the incidence and risk factors, based solely on laboratory serum data, for development of hyponatremia in patients initiating citalopram therapy. We report a 16.5% incidence of hyponatremia after starting citalopram treatment and significant new findings, including a higher incidence in males. The risk factors identified by previous research were largely confirmed in this study, with a notable exception in the effect of sex. Knowledge of the risk factors of hyponatremia following the initiation of citalopram will aid in the prevention of undiagnosed hyponatremia and improve the safety of antidepressant treatment.

Chapter Three: Applications of Risk Factor Analysis

3.1 Risk Factor Analysis

Adverse drug reactions exist as a subset of drug-related problems, which also encompasses medication errors [72]. In Europe, up to 63% of hospital patients discharged with a prescription experienced a drug-related problem [72] and half of prescription-related hospital admissions were preventable [72]. The preventability of adverse drug reactions, one of the leading causes of death in the USA [73], highlights the importance of risk factor analysis for adverse drug reactions.

The risk factors for adverse drug reactions can be categorized into those relating to the patient, disease, genetic, health-service, and drug [73], though this schema can be applied to study other unfavorable conditions as well. Among patient-related risk factors, age and gender are the most commonly considered, along with certain lifestyle factors such as alcohol or smoking habits [73]. In terms of disease- and genetic-related factors, patients with comorbidities, especially those suffering from genitourinary, circulatory, and immune disorders carry the highest number of risk factors and genetic mutations in the major histocompatibility complex (MHC) class I, ATP-binding cassette (ABC) transporter, and cytochrome P450 genes are the most frequently studied [73]. Insufficient information transfer and cost barriers to healthcare access are important health-service-related risk factors, and the use of cardiovascular or CNS medications have a higher risk of adverse drug reactions [72, 73]. However, polypharmacy is the most reported risk factor for an adverse drug reaction and carries the greatest risk, since it increases the potential for harmful drug interactions [73-75].

3.2 Prevention of Adverse Drug Reactions

It is important to identify the risk factors for adverse drug reactions in order to enact and improve preventative measures. By recognizing avoidable risk factors, such as lifestyle factors or the number of concurrent medications, and unavoidable factors, such as age or genetic markers, methods in the administration and supervision of medication therapy can be tailored to the individual patient. An assortment of interventions, ranging from personal to institutional, may then be implemented to direct patient action and enable effective clinical procedures in reducing risk factors for adverse drug reactions.

The individual patient usually has a significant amount of control over lifestyle factors and treatment compliance that, when managed effectively, may reduce the risk factors for disease and adverse drug reactions. However, many patients perpetuate behaviour, such as an unhealthy diet, lack of physical activity, or treatment noncompliance, even after receiving education about the significance of healthy changes on the reduction of their risk factors [76]. Self-management programs are aimed at bridging the gap between sharing information and achieving behavioural change. These programs directly involve the patient in the improvement of behavioural habits over time through a system of education, empowerment, and support [76]. In a study on stroke prevention, self-management interventions had a significant effect on improving lifestyle behaviour risk factors, most notably in medication adherence, and reducing the overall risk of stroke [76]. Useful in the management of chronic illnesses as well, the skills learned through self-management programs promote the sustainability of healthy lifestyle changes by focusing on patient-centred needs and care [76, 77].

Improvements in the communication between healthcare providers and patients can be facilitated by regular medical history and medication reviews. In the hospital, patients are not

always able to quickly and accurately relay their long-term medical and medication history, which may hide relevant risk factors for further treatment [72]. Similarly, patients may be discharged with a change in medication treatment without adequate communication to the patient and their primary healthcare provider [72]. This can negatively impact patient care by increasing the number of concurrent medications, a drug-related risk factor, and promoting confusion regarding the treatment [72]. Periodic medication and history reviews with the patient, either by a medication manager or a pharmacist, are recommended by several studies [72, 73, 75]. In an analysis of risk factors in critically ill patients, the inclusion of a pharmacist in the intensive care unit rounds decreased preventable adverse drug reactions by 66% [75]. The medication and medical history review can identify the risk factors present in each case and consider the possible adverse drug reactions, with an emphasis on patient comprehension of their condition and treatment plan [72, 73].

At an organizational level, risk factor analysis can be used to create and modify clinical guidelines for patient screening techniques. Patients at risk for a specific adverse drug reaction or disease may be identified by clinicians and then informed of the risk with monitoring for symptoms, or offered alternative treatment options. Such a risk-assessment pattern is used to screen for patients at high risk for primary cutaneous melanoma and provides follow-up guidelines for lesion monitoring [78]. However, high-risk patients should not be the only consideration for screening guidelines; surprising trends can emerge when analyzing the population for risk factors. While increasing age is usually associated with the risk factors for cardiovascular disease, a German population study actually discovered a high incidence of unreported hypertension and high low-density lipoprotein (LDL) levels in a young cohort, aged 30-39.” [79]. Diligent monitoring of abnormal diagnostic values, both through manual or

algorithmic methods, is also effective in preventing adverse drug reactions, and can be implemented to catch new trends in population risk factors [75]. Population-level risk analysis in Spain determined that a high proportion of adults aged 40-65 years were likely at a moderate risk for cardiovascular disease [80]. Since most cardiovascular events occurred in patients with moderate risk factors, due to the large size of the risk-group, the modification of public prevention strategies, which preferentially targeted high-risk individuals, were recommended [80]. Patients at a high risk for disease or adverse drug reactions should certainly be targeted by risk factor analysis for clinical guidelines, however comprehensive clinical guidelines, inclusive of possible risk factors and risk-levels, may best manage the occurrence of adverse drug reactions.

3.3 Geo-mapping Population Risk Factors

The distribution of risk factors likely varies over space and time, since populations are rarely static and evenly dispersed. Differences between regions may be explored by visually geo-mapping risk factor patterns within the population. Mapping risk factors may also supplement personalized medicine by detecting environmental and socioeconomic factors for adverse events. Furthermore, public health authorities may use this information for the creation of tailored strategies to mitigate the risk factors of affected communities.

Typically used to elucidate national and international health trends, geo-mapping has the potential to determine geospatial patterns in the risk factors of local populations. The characterization of regional risk factors may provide more detailed, and useful information for local health institutions in establishing trends in adverse reactions. Likewise, mapping the rates of abnormal conditions or disease may identify relevant nonclinical, or patient-related, risk factors for the respective conditions. A Canadian study combined public census and secondary

laboratory data within a city population to visually represent statistically significant geographic differences in abnormal estimated glomerular filtration rate (eGFR), a measure of chronic kidney disease [81]. Sociodemographic risk factors were then inferred from the census data, confirming significant associations through statistical analysis [81]. A risk factor analysis and visual representation of vitamin D status in Dublin, Ireland was achieved using similar geo-mapping techniques [82]. Additionally, Laird *et al.* determined significant seasonal changes in vitamin D status among age, district, and sex groups [82].

The identification of population-level risk factor trends is necessary to ascertain the underlying contributions to health, particularly those that relate to social and environmental aspects. Many patterns are based on known, patient-related risk factors, such as older age, low income, and low educational level, and tend to cluster in low socioeconomic status individuals [83]. Regions of social economic disadvantage had higher rates of vitamin D deficiency [82] and abnormal eGFR [81], in their respective studies. Individuals with low socioeconomic status also have reduced access to healthcare and healthier lifestyle alternatives, possibly due to poor neighborhood environment and an unequal opportunity for quality healthcare [83].

Public health divisions can use the information gained by geo-mapping risk factors to enact targeted community interventions. Increased screening and treatment services in areas with a greater proportion of risk factors may reduce the instance of disease or adverse reactions [83]. The collaboration of health, social, and educational sciences may serve to address the needs of disadvantaged communities, lessening the number or severity of patient-related risk factors [83]. In fact, the combination of clinical and nonclinical data best predicted re-hospitalization or death in patients with acute heart failure, further supporting the use of risk factor analysis for preventative medicine [84]. As an expansion of risk factor analysis, geo-mapping may become a

useful tool in modifying public health policies to effectively manage regional differences in risk and predict temporal changes in the likeliness of adverse reactions.

Chapter 4: Summary and Conclusion

4.1 Summary of Findings

The main objective of this thesis was to investigate the relationship between the initiation of citalopram use and the development of hyponatremia in the adult population of Calgary, Canada. The incidence of hyponatremia, among adults, in the first year following initial citalopram use was 16.5%. Of the covariates examined, male sex (HR = 1.168), older age (HR = 1.029), lower baseline sodium (HR = 0.788), and concurrent thiazide diuretic (HR = 1.141) were significant risk factors for the development of hyponatremia following new citalopram treatment. Pharmaceutical manufacturer or citalopram strength did not have significant associations with hyponatremia. The risk factors identified by previous research were confirmed except for that of male sex, which is a novel finding unique to this thesis.

The secondary goal of this study was to consider the application of risk factor analysis in personalized and preventative medicine. The classification of risk factors could be used in a variety of programs that direct patient action, based on patient-centred needs, and create effective clinical guidelines for the screening and treatment of patients. Expansion of spatial and temporal risk analysis, using geo-mapping, can further promote targeted interventions.

4.2 Strengths

Access to the regionalized pharmacy and diagnostic laboratory services provided the patient medication profiles and basic demographic information of almost 20,000 patients that started citalopram treatment from 2010-2017. The wide range of reported hyponatremia incidence following SSRI use in existing literature, 0.06 – 40%, was based on case reports and case-controlled studies of less than 1000 individuals [50]. Additionally, the identification of female sex as a significant risk factor in the literature was based on reviews of the same case

reports and small, case-controlled studies mentioned above [40, 50-55]. The large population sample studied in this thesis, coupled with the robust Cox regression with time-varying covariate analysis, was able to provide updated and accurate information regarding the incidence and risk factors of hyponatremia on citalopram treatment. The use of concrete laboratory serum values, rather than ICD-10 codes, better captured the incidence of even mild hyponatremia.

4.3 Limitations

Several limitations of this thesis were worth considering. The patient data for some published risk factors for the development of hyponatremia upon initiating citalopram treatment, such as low body weight and psychosis [40, 50, 51, 54], were not available for analysis. Additionally, preexisting conditions or diseases that may have independently induced hyponatremia, such as renal failure, were not identified in our patient population. Data on the temporal changes in citalopram or thiazide diuretic use, such as dose modification, noncompliance, or treatment cessation, were also not available in the databases used.

4.4 Future Direction

Research into the risk of hyponatremia with compliant citalopram use, especially with regular serum sodium level monitoring, might be useful in determining more reliable rates of hyponatremia as well as defining the timeline of adverse events. The incidence and risk factors of hyponatremia following the use of other SSRIs, replicating the methods of this thesis, should be examined and compared to citalopram. Particular focus should be given to the risk factors associated with escitalopram use, given its enantiomeric relationship with citalopram and therapeutic differences. Analysis into the biochemical pathway of citalopram-induced hyponatremia may provide insight into the observed incidence levels and the effect of sex on the mechanism, especially since the results of this study contradict existing literature. Lastly, clinical

researchers and practitioners should consider risk factor studies as a relatively easy method of expanding the awareness of factors that may affect patient health and treatment.

4.5 Conclusion

Risk factor analysis is crucial in maintaining patient health by reducing the likeliness of adverse drug reactions. This is especially important considering increase in global antidepressant use and the prevalence of citalopram as an SSRI treatment. Awareness gained from this thesis may aid in the prevention of undiagnosed hyponatremia and improve the safety of antidepressant treatment.

Bibliography

1. Shah MK, Workeneh B, Taffet GE. Hypernatremia in the geriatric population. *Clin Interv Aging.* 2014;9:1987-1992.

2. Sahay M, Sahay R. Hyponatremia: a practical approach. *Indian J Endocrinol Metab.* 2014;18(6):760-771.

3. Braun MM, Barstow CH, Pyzocha NJ. Diagnosis and management of sodium disorders: hyponatremia and hypernatremia. Am Fam Physician 2015;91(5):299-307.

4. Morley JE. Dehydration, hypernatremia, and hyponatremia. *Clin Geriatr Med.* 2015;31(3):389-399.

5. Gandhi S. Risk of hyponatremia in older adults receiving psychotropic drug treatment. Electronic Thesis and Dissertation Repository 2016.

6. Hannon MJ, Thompson CJ. The syndrome of inappropriate antidiuretic hormone: prevalence, causes and consequences. *Eur J Endocrinol.* 2010;162:S5-S12.

7. Zerbe R, Stropes L, Robertson G. Vasopressin function in the syndrome of inappropriate antidiuresis. *Ann Rev Med.* 1980;31:315-327.

8. Shepshelovich D, Leibovitch C, Klein A, Zoldan S, Milo G, Shochat T, Rozen-zvi B, Gafter-Gvili A, Lahav M. The syndrome of inappropriate antidiuretic hormone secretion: distribution and characterization according to etiologies. *Eur J Intern Med.* 2015;26(10):819-824.

9. Leth-Moller KB, Hansen AH, Torstensson M, Andersen SE, Odum L, Gislasson G, Torp-Pedersen C, Holm EA. Antidepressants and the risk of hyponatremia: a Danish register-based population study. *BMJ Open.* 2016;6(5):e011200.

10. Patten SB, Williams JVA, Lavorato DH, Fiest KM, Bulloch AGM, Wang J. Antidepressant use in Canada has stopped increasing. *Can J Psychiatry.* 2014;59(11):609-614.

11. Leong C, Enns MW, Sareen J, Alessi-Severini S, Bolton J, Prior HJ, Chateau D. New antidepressant use in older adults: a Canadian population-based study (1997-2013). *Aging Ment Health.* 2016;21(7):720-729.

12. Ernst C, Angst J. The Zurich Study. XII. Sex differences in depression. Evidence from longitudinal epidemiological data. *Eur Arch Psychiatry Clin Neurosci.* 1992;241(4):222-230.

13. Kendler KS, Thornton LM, Gardner CO. Stressful like events and previous episodes in the etiology of major depression in women: an evaluation of the "kindling" hypothesis. *Am J Psychiatry.* 2000;157(8):1243-1251.

14. Rosecrans JA. Differences in brain area 5-hydroxytryptamine turnover and rearing behavior in rats and mice of both sexes. *Eur J Pharmacol.* 1970;9(3):379-382.

15. Gottfries CG, Roos BE, Winblad B. Determination of 5-hydroxytryptamine, 5-hydroxyindoleacetic acid and homovanillic acid in brain tissue from an autopsy material. *Acta Psychiatr Scand.* 1974;50:496-507.

16. Jovanovic H, Lundberg J, Karlsson P, Cerin A, Saijo T, Varrone A, Halldin C, Nordström AL. Sex differences in the serotonin 1A receptor and serotonin transporter binding in the human brain measured by PET. *NeuroImage.* 2008;39(3):1408-1419.

17. Sakai Y, Nishikawa M, Leyton M, Benkelfat C, Young SN, Diksic M. Cortical trapping of alpha-[(11)C]methyl-l-tryptophan, an index of serotonin synthesis, is lower in females than males. *NeuroImage.* 2006;33(3):815-824.

18. Ramamoorthy S, Blakely RD. Phosphorylation and sequestration of serotonin transporters differentially modulated by psychostimulants. *Science.* 1999;285(5428):763-766.

19. Stahl SM. Mechanism of action of serotonin selective reuptake inhibitors: serotonin receptors and pathways mediate therapeutic effects and side effects. *J Affect Disord*. 1998;51(3):215-235.

20. Gibbs DM, Vale W. Effect of the serotonin reuptake inhibitor fluoxetine on corticotropin-releasing factor and vasopressin secretion into hypophysial portal blood. *Brain Res.* 1983;280:176-179.

21. Saydoff JA, Rittenhouse PA, Carnes M, Armstrong J, Van De Kar LD, Brownfield MS. Neuroendocrine and cardiovascular effects of serotonin: selective role of brain angiotensin on vasopressin. *Am J Physiol.* 1996;270(3 Pt 1):E513-521.

22. Galfi M, Radacs M, Juhasz A, Laszlo F, Molnar A, Laszlo FA. Serotonin-induced enhancement of vasopressin and oxytocin secretion in rat neurohypophyseal tissue culture. *Regul Pept.* 2005;127(1-3):225-231.

23. Faull CM, Charlton JA, Phillips E, Thornton S, Butler T, Baylis PH. The effect of modulation of central serotonin neurotransmission on osmoregulated vasopressin release in rats. *Ann N Y Acad Sci.* 1993;689:484-488.

24. Bagdy G, Sved AF, Murphy DL, Szemeredi K. Pharmacological characterization of serotonin receptor subtypes involved in vasopressin and plasma renin activity responses to serotonin agonists. *Eur J Pharmacol.* 1992;210:285-289.

25. Castro VM, Clements CC, Murphy SN, Gainer VS, Fava M, Weilburg JB, Erb JL, Churchill SE, Kohane IS, Iosifescu DV, Smoller JW, Perlis RH. QT interval and antidepressant use: a cross sectional study of electronic health records. *BMJ.*

2013;346:f288.

26. Kasper S, Sacher J, Klein N, Mossaheb N, Attarbaschi-Steiner T, Lanzenberger R, Spindelegger C, Asenbaum S, Holik A, Dudczak R. Differences in the dynamics of serotonin reuptake transporter occupancy may explain superior clinical efficacy of escitalopram versus citalopram. *Int Clin Psychopharmacol.* 2009;24(3):119-125.

27. Matthaus F, Haddjeri N, Sanchez C, Marti Y, Bahri S, Rovera R, Schloss P, Lau T. The allosteric citalopram binding site differentially interferes with neuronal firing rate and SERT trafficking in serotonergic neurons. *Eur Neuropsychopharmacol.* 2016;26(11):1806-1817.

28. Olesen OV, Linnet K. Studies on the stereoselective metabolism of citalopram by human liver microsomes and cDNA-expressed cytochrome P450 enzymes. *Pharmacology.* 1999;59:298-309.

29. Sangkuhl K, Klein TE, Altman RB. PharmGKB summary: citalopram pharmacokinetics pathway. *Pharmacogenet Genomics*. 2011;21(11):769-772.

30. Mamdani F, Berlim M, Beaulieu M-M, Turecki G. Pharmacogenomic predictors of citalopram treatment outcome in major depressive disorder. *World J Biol Psychiatry*. 2014;15(2):135-144.

31. Mamdani F, Berlim MT, Beaulieu M-M, Labbe A, Merette C, Turecki G. Gene expression biomarkers of response to citalopram treatment in major depressive disorder. *Transl Psychiatry.* 2011;1(6):e13.

32. Amitai M, Kronenberg S, Carmel M, Michaelovsky E, Frisch A, Brent D, Apter A, Chen A, Weizman A, Fennig S. Pharmacogenetics of citalopram-related side effects in children with depression and/or anxiety disorders. *J Neural Transm.* 2016;123(11):1347-1354.

33. Adkins DE, Clark SL, Aberg K, Hettema JM, Bukszar J, McClay JL, Souza RP, van den Oord EJCG. Genome-wide pharmacogenomics study of citalopram-induced side effects in STAR*D. *Transl Psychiatry.* 2012;2(7):e129.

34. Bourgeois JA, Babine SE, Bahadur N. A case of SIADH and hyponatremia associated with citalopram. *Psychosomatics*. 2002;43(3):241-242.

35. Dirks AC, van Hyfte DM. Recurrent hyponatremia after substitution of citalopram with duloxetine. *J Clin Psychopharmacol.* 2007;27(3):313.

36. Flores G, Perez-Patrigeon S, Cobos-Ayala C, Vergara J. Severe symptomatic hyponatremia during citalopram therapy – a case report. BMC Nephrol 2004;5:2.

37. Holland S, Townley S, Summerfield R. Citalopram – a risk factor for postoperative hyponatremia. *Anaesthesia.* 2003;58(5):491-492.

38. Iraqi A, Baickle E. A case report of hyponatremia with citalopram use. *J Am Med Dir Assoc*. 2004;5(1):64-65.

39. Farmand S, Lindh JD, Calissendorff J, Skov J, Falhammar H, Nathanson D, Mannheimer B. Differences in associations of antidepressants and hospitalization due to hyponatremia. *Am J Med.* 2018;131(1):56-63.

40. Mannesse CK, Jansen PA, Van Marum RJ, Sival RC, Kok RM, Haffmans PM, Egberts TC. Characteristics, prevalence, risk factors, and underlying mechanism of hyponatremia in elderly patients treated with antidepressants: a cross-sectional study. *Maturitas.* 2013;76(4):357-363.

41. Gandhi S, Shariff SZ, Al-Jaishi A, Reiss JP, Mamdani M-M, Hackam DG, Li L, McArthur E, Weir MA, Garg AX. Second-generation antidepressants and hyponatremia risk: a population-based cohort study of older adults. *Am J Kidney Dis.* 2017;69(1):87-96.

42. Karkare SU, Bhattacharjee S, Kamble P, Aparasu R. Prevalence and predictors of antidepressant prescribing in nursing home residents in the United States. *Am J Geriatr Pharmacother.* 2011 Apr;9(2):109-119.

43. Phillips, JA, Nugent CN. Antidepressant use and method of suicide in the Unites States: variation by age and sex, 1998-2007. *Arch Suicide Res.* 2013;17(4):360-372.

44. Mars B, Heron J, Kessler D, Davies NM, Martin RM, Thomas KH, Gunnell D. Influences on antidepressant prescribing trends in the UK: 1995-2011. *Soc Psychiatry Psychiatr Epidemiol.* 2017 Feb;52(2):193-200.

45. Sonnenberg CM, Deeg DJ, Comijs HC, van Tilburg W, Beekman AT. Trends in antidepressant use in the older population: results from the LASA-study over a period of 10 years. *J Affect Disord.* 2008 Dec;111(2-3):299-305.

46. Solai LK, Mulsant BH, Pollock BG. Selective serotonin reuptake inhibitors for late-life depression: a comparative review. *Drugs Aging.* 2001;18(5):355-368.

47. Porsteinsson AP, Drye LT, Pollock BG, Devanand DP, Frangakis C, Ismail Z, Marano C, Meinert C, Meinert CL, Mintzer JE, Munro CA, Pelton G, Rabins PV, Rosenberg PB, Schneider LS, Shade DM, Weintraub D, Yesavage J, Lyketsos CG, CitAD Research Group. Effect of citalopram on agitation in Alzheimer disease: the CitAD randomized clinical trial. *JAMA.* 2014;311(7):682-691.

48. RStudio Team: RStudio: Integrated Develoment for R. RStudio, Inc. Boston, MA; 2018 [http://www.rstudio.com/].

49. R Core Team: R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria; 2018 [https://www.R-project.org/].

50. De Picker L, Van Den Eede F, Dumont G, Moorkens G, Sabbe BGC. Antidepressants

and the risk of hyponatremia: a class-by-class review of literature. *Psychosomatics.* 2014;55(6):536-547.

51. Jacob S, Spinler SA. Hyponatremia associated with selective serotonin-reuptake inhibitors in older adults. *Ann Pharmacother.* 2006;40(9):1618-1622.

52. Liu BA, Mittmann N, Knowles SR, Shear NH. Hyponatremia and the syndrome of inappropriate secretion of antidiuretic hormone associated with the use of selective serotonin reuptake inhibitorsL a review of spontaneous reports. *CMAJ.* 1996;155(5):519-527.

53. Strachan J, Shepherd J. Hyponatremia associated with the use of selective serotonin re-uptake inhibitors. *Aust N Z J Psychiatry.* 1998;32(2):295-298.

54. Wee R, Lim WK. Selective serotonin re-uptake inhibitors (SSRIs) and hyponatremia in the elderly. *Int J Geriatr Psychiatry.* 2004;19(6):590-591.

55. Greenblatt HK, Greenblatt DJ. Antidepressant-associated hyponatremia in the elderly. *J Clin Psychopharmacol.* 2016;36(6):545-549.

56. Coupland C, Dhiman P, Morriss R, Arthur A, Barton G, Hippisley-Cox J. Antidepressant use and risk of adverse outcomes in older people: population based cohort study. *BMJ.* 2011;343:d4551.

57. Bowen PD. Use of selective serotonin reuptake inhibitors in the treatment of depression in older adults: identifying and managing potential risk for hyponatremia. *Geriatr Nurs.* 2009;30(2):85-89.

58. Filippatos TD, Makri A, Elisaf MS, Liamis G. Hyponatremia in the elderly: challenges and solutions. *Clin Interv Aging.* 2017;12:1957-1965.

59. Bissram M, Scott FD. Risk factors for symptomatic hyponatremia: the role of pre-existing asymptomatic hyponatremia. *Intern Med J.* 2007;37(3):149-155.

60. Nagler EV, Vanmassenhove J, Van der Veer SN, Nistor I, Van Biesen W, Webster AC, Vanholder R. Diagnosis and treatment of hyponatremia: a systematic review of clinical practice guidelines and consensus statements. *BMC Med.* 2014;12:1.

61. Burst V, Grundmann F, Kubacki T, Greenberg A, Becker I, Rudolf D, Verbalis J. Thiazide-associated hyponatremia, report of the hyponatremia registry: an observational multicenter international study. *Am J Nephrol.* 2017;45(5):420-430.

62. Rosner MH. Severe hyponatremia associated with the combined use of thiazide diuretics and selective serotonin reuptake inhibitors. *Am J Med Sci.* 2004;327(2):109-111.

63. Voyer P, Cohen D, Lauzon S, Collin J. Factors associated with psychotropic drug use amonf community-dwelling older persons: a review of empirical studies. *BMC Nurs.* 2004;3(1):3.

64. Sun H, Sun M. Age- and gender- dependent associations of blood pressure and serum sodium and potassium – renal and extrarenal regulations. *J Am Soc Hypertens.* 2018;12(5):392-401.

65. Veiras LC, Girardi ACC, Curry J, Pei L, Ralph DL, Tran A, Castelo-Branco RC, Pastor-Soler N, Arranz CT, Yu ASL, McDonough AA. Sexual dimorphism pattern of renal transporters and electrolyte homeostasis. *JASN.* 2017;28(12):3504-3517.

66. Dunne S, Shannon B, Dunna C, Cullen W, A review of the differences and similarities between generic drugs and their original counterparts, including economic benefits associated with usage of generic medicines, using Ireland as a case study. *BMC Pharmacol Toxicol.* 2013;14:1.

67. Bech R, Tanghøj P, Andersen HF, Overø K. Citalopram dose-response revisited using an alternative psychometric approach to evaluate clinical effects of four fixed

citalopram doses compared to placebo in patients with major depression. *Psychopharmacology (Berl)*. 2002;163(1):20-25.

68. Gupta M, Neavin D, Liu D, Biernacka J, Hall-Flavin D, Bobo WV, Frye MA, Skime M, Jenkins GD, Batzler A, Kalari K, Matson W, Bhasin SS, Zhu H, Mushiroda T, Nakamura Y, Kubo M, Wang L, Kaddurah-Daouk R, Weinshilboum RM. TSPAN5, ERICH3 and selective serotonin reuptake inhibitors in major depressive disorder: pharmacometabolomics-informed pharmacogenomics. *Mol Psychiatry*. 2016;21(12):1717-1725.

69. Barber J, Guo M, Nguyen LT, Thomas R, Turin TC, Vaska M, Naugler C, COAPT (Collaboration On Assessing Physician Testing). Sociodemographic correlated of clinical laboratory test expenditures in a major Canadian city. *Am J Clin Pathol*. 2017;148(1):91-96.

70. Fischer SH, Field TS, Gagne SJ, Mazor KM, Preusse P, Reed G, Peterson D, Gurwitz JH, Tjia J. Patient completion of laboratory tests to monitor medication therapy: a mixed-methods study. *J Gen Intern Med.* 2013;28(4):513-521.

71. McAlister FA, Tu K, Majumdar SR, Padwal R, Chen Z, Campbell NR. Laboratory testing in newly treated elderly hypertensive patients without co-morbidities: a population-based cohort study. *Open Med.* 2007;1(2):e60-67.

72. Kaufmann CP, Stampfli D, Hersberger KE, Lampert ML. Determination of risk factors for drug-related problems: a multidisciplinary triangulation process. *BMJ Open.* 2015;(5)3:e006376.

73. Zhou L, Rupa AP. Categorization and association analysis of risk factors for adverse drug events. *Eur J Clin Pharmacol.* 2018;74(4):389-404.

74. Saedder EA, Lisby M, Nielsen LP, Bonnerup DK, Brock B. Number of drugs most

frequently found to be independent risk factors for serious adverse reactions: a systematic literature review. *Br J Clin Charmacol.* 2015;80(4):808-817.

75. Kane-Gill SL, Kirisci L, Verrico MM, Rothschild JM. Analysis of risk factors for adverse drug events in critically ill patients. Crit Care Med 2012;40(3):823-828.

76. Sakakibara BM, Kim AJ, Eng JJ. A systematic review and meta-analysis on self-management for improving risk factor control in stroke patients. *Int J Behav Med.* 2017;24(1):42-53.

77. Ko D, Bratzke LC, Roberts T. Self-management assessment in multiple chronic conditions: a narrative review of literature. *Int J Nurs Stud.* 2018;83:83-90.

78. Watts CG, Dieng M, Morton RL, Mann GJ, Menzies SW, Cust AE. Clinical practice guidelines for identification, screening and follow-up of individuals at high risk of primary cutaneous melanoma: a systemic review. *Br J Dermatol.* 2015;172(1):33-47.

79. Tiffe T, Wagner M, Rücker V, Morbach C, Gelbrich G, Störk S, Heuschmann PU. Control of cardiovascular risk factors and its determinants in the general population-findings from the STAAB cohort study. *BMC Cardiovasc Disord.* 2017;17(1):276.

80. Amor AJ, Masana L, Soriguer F, Goday A, Calle-Pascual A, Gaztambide S, Rojo-Martinez G, Valdés S, Gomis R, Ortega E. Estimating cardiovascular risk in Spain by the European guidelines on cardiovascular disease prevention in clinical practice. *Rev Esp Cardiol (Engl Ed).* 2015;68(5):417-425.

81. Ma I, Guo M, Muruve D, Benediktsson H, Naugler C. Sociodemographic associations with abnormal estimated glomerular filtration rate (eGFR) in a large Canadian city: a cross-sectional observational study. *BMC Nephrol.* 2018;19(1):198.

82. Laird E, Shannon T, Crowley VEF, Healy M. The benefits of utilizing geo-mapping for visualizing the vitamin D status of Dublin city and the surrounding urban districts.

Ir J Med Sci. 2017;186(4):807-813.

83. Schultz WM, Kelli HM, Lisko JC, Varghese T, Shen J, Sandesara P, Quyyumi AA, Taylor HA, Gulati M, Harold JG, Mieres JH, Ferdinand KC, Mensah GA, Sperling LS. Socioeconomic status and cardiovascular outcomes: challenges and interventions. *Circulation.* 2018;137(20):2166-2178.

84. Huynh QL, Saito M, Blizzard, CL, Eskandari M, Johnson B, Adabi G, Hawson J, Negishi K, Marwick TH. Roles of nonclinical and clinical data in prediction of 30-day rehospitalization or death among heart failure patients. *J Card Fail.* 2015;21(5):374-381.