

Pharmacotherapies in Parkinson Disease:
Investigating Trends and Adverse Health Outcomes

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AAN	American Academy of Neurology
ADR	adverse drug reaction
AHR	adjusted hazard ratio
AMSTAR	Assessment of the Methodological Quality of Systematic Reviews
AOR	adjusted odds ratio
ARS	Anticholinergic Risk Scale
B-HCH	beta-hexachlorocyclohexane
CENTRAL	Cochrane Central Register of Controlled Trials
CI	confidence interval
CIHR	Canadian Institutes of Health Research
CINAHL	Cumulative Index to Nursing and Allied Health
CME	continuing medical education
COMT	catechol-O-methyltransferase
DA	dopamine agonist
ED	emergency department
EMR	electronic medical record
FAERS	FDA Adverse Event Reporting System
FDA	Food and Drug Administration
GAD	generalized anxiety disorder
HF	heart failure (throughout) or high-frequency (in appendix II)
HR	hazard ratio
hs-CRP	high-sensitivity c-reactive protein
ICD	impulse control disorder
ICD-9	International Classification of Diseases, Ninth Revision
IL-6	Interlukin-6
IRR	incident rate ratio
LF	low frequency
LR	likelihood ratio
MAO-B	monoamine oxidase-B
MD	mean difference
MDD	major depressive disorder
MDS	International Parkinson and Movement Disorder Society
MeSH	Medical Subject Heading
MHI-5	five-item mental health inventory
MU	methamphetamine use
NRS	non-randomized studies
NSERC	National Sciences and Engineering Council of Canada
OR	odds ratio
PD	Parkinson disease or Parkinson's disease
RBD	REM sleep behaviour disorder
RCT	randomized clinical trial or randomized controlled trial
REM	rapid eye movement
RO	research objective

ROS	reactive oxygen species
RQ	research question
RR	relative risk or risk ratio
SMD	standardized mean difference
SNP	single nucleotide polymorphism
TNF	tumor necrosis factor
UK	United Kingdom
US	United States of America
USA	United States of America
WBC	white blood cell
WHO	World Health Organization

ABSTRACT

Parkinson disease (PD) is the second most common neurodegenerative disease worldwide, with estimates suggesting that PD prevalence and incidence will increase with aging populations. Therapeutic options and clinical guidelines for PD have significantly changed over the past 15 years; however, pharmacoepidemiology data in PD are lacking, especially regarding adverse effects of non-ergot dopamine agonists (DAs) and outcomes associated with anticholinergic burden. The objectives of this doctoral research are threefold: 1) examine patterns of antiparkinson drug use in relation to clinical guideline publication, drug availability, and emerging safety concerns; 2) determine whether PD patients treated with non-ergot DAs are at increased risk of adverse cardiovascular or cerebrovascular outcomes; and 3) determine whether anticholinergic burden is associated with adverse outcomes in PD. Specific research questions were investigated using epidemiological methods and electronic health data from Cerner Health Facts®, an electronic medical record database that stores time-stamped patient records for more than 300 Cerner subscribing facilities across the United States. Findings from this work are reported in a series of manuscripts, all of which have been published. Key findings include: 1) DA use began declining in 2007, from 34% to 27% in 2012. The decline followed publication of the American Academy of Neurology's practice parameter refuting levodopa toxicity, pergolide withdrawal, and pramipexole label revisions; 2) heart failure was the only adverse cardiovascular or cerebrovascular outcome that demonstrated a significant association with non-ergot DA use, mainly pramipexole; and 3) anticholinergic burden in PD was associated with the diagnosis of fracture and delirium, and significantly increased the risk of emergency department visit and readmission post inpatient discharge. Reported antiparkinson prescribing trends suggest that safety and best practice information may be communicated effectively in PD. Although findings warrant replication, individuals with PD and independent risk factors for or a history of heart failure may benefit from limited use of pramipexole. Similarly, individuals with PD may benefit from substituting non-PD medications with anticholinergic effects for equally effective non-anticholinergic agents. Additional pharmacovigilance studies are needed to better understand health risks and the impact of population health interventions in PD.

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“Do not go where the path may lead, go instead where there is no path and leave a trail.”

–Ralph Waldo Emerson

Dedicated to my loving grandmother, Ms. Alice Nykyforak
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CHAPTER 1: Introduction

Parkinson disease (PD) is an increasingly prevalent chronic and progressive neurological disorder that is characterized by motor and non-motor symptoms. There is no cure for PD; however, both pharmacological and non-pharmacological therapies are effective at treating PD symptoms and improving patient quality of life. Considerable advances in pharmacotherapy-based interventions for PD have been made in the first part of the twenty-first century, including changes in the availability of medications for PD and increased knowledge of adverse events associated with best medical care. Similarly, technological developments, decreasing costs of storing personal health information, and regulatory changes have contributed to the implementation of electronic record keeping systems by care facilities to better manage health data. These actions have given rise to the availability of electronic health record databases that may be used to study health services and medication use, associated health outcomes, and healthcare costs. Knowledge of treatment utilization, effectiveness, and safety gained from the analysis of large databases of health records provide necessary data to support evidence-based regulatory decisions and interventions that impact public and population health. The following sections briefly review the epidemiology, etiology, and treatment of PD, as well as discuss PD pharmacoepidemiology and existing knowledge gaps. Information presented provide context for the research questions and objectives that are put-forth and examined in this doctoral thesis using population-based health data from the United States of America (US).

PARKINSON DISEASE

Clinical features

Parkinson disease was first described by Dr. James Parkinson in 1817 as a shaking palsy:

“Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to a running pace: the senses and intellects being un- injured.” [1]. Since that time, considerable gains have been made in our understanding and treatment of this complex neurodegenerative disorder. Motor symptoms, including tremor, muscle stiffness or rigidity, slow movement, and difficulties walking and maintaining balance are the hallmark clinical features of PD [2]. Non-motor symptoms are common in PD and may contribute to significant patient disability by imposing difficulties sleeping and autonomic dysfunction [3]. In recent years, there has been growing interest in the prodromal features of PD, presymptomatic characteristics indicative of neuronal degradation that may be used to better predict PD onset [4-6]. Since PD is frequently first detected in primary care settings, it is imperative that primary care clinicians practice sound diagnostic techniques and know when to refer individuals suspected of having PD to specialty care [7]. A confirmed PD diagnosis is generally based on expert (neurologist or movement disorder specialist) clinical assessment according to explicit criteria outlined in one the of validated rating scales used to evaluate motor impairment and overall level of disability [8].

Motor features

The cardinal features of PD are the presence of one or more of the following clinical signs, summarized by the mnemonic ‘TRAP’: Tremor at rest, Rigidity, Akinesia (or bradykinesia), and Postural instability [2]. A rest tremor is one of the most common and noticeable PD symptoms, experienced by approximately 69% of individuals at PD diagnosis and occurring in roughly 75% of individuals throughout the disease course [9]. They often occur at a frequency of 4 to 6 Hz in the distal part of a resting limb, are unilateral, and are suppressed when sleeping or initiating movement [10]. Rest tremors are not restricted to the limbs and may affect the lips, chin, and jaw [2]. Rigidity in PD is characterized by the existence of increased resistance to passive joint movement that is not exclusively attributed to the inability to relax [10], while akinesia and bradykinesia respectively refer to loss of movement and slowness of movement with decreased amplitude or speed [10, 11]. Freezing, described as abrupt and brief blocks of movement and occurring in nearly half of all individuals with PD, is a form of akinesia that may significantly interfere with activities of daily living, increase individual risk of falling, and contribute to decreased quality of life [12]. The loss of postural reflexes over time in PD frequently leads to postural instability [13]. Although a cardinal feature of PD, the presence of postural instability in early disease stages may be indicative of a condition other than PD [10]. Together, freezing and postural instability are the most common causes of fall-related injuries in PD, particularly hip fracture, with a large cohort study estimating that median time to first fall is 9 years [13]. Authors also reported that women with PD fall more frequently and at earlier stages of disease compared to men [13]. A systematic review on recurrent falling in PD identified increased motor impairment,

increased disease severity and duration, freezing of gait, impaired mobility, and pharmacotherapy regimen as being associated with an increased risk of falling [14].

Non-motor features

Until recently, the non-motor features of PD have traditionally been overlooked and undertreated as a consequence. The most prevalent non-motor features of PD include difficulties sleeping (such as insomnia (54-60%), excessive daytime somnolence (51%), and rapid eye movement (REM) sleep behaviour disorder (RBD; 15-40%)), autonomic dysfunction (such as constipation (28-61%), urinary incontinence (30-70%), and orthostatic hypotension (20-58%)), reduced ability to detect odors (hyposmia; 90%), psychiatric issues (such as depression (36-50%), anxiety (40%), hallucinations (40%), and dementia (30-40%)), and painful sensations unrelated to osteoarthritis or neuropathy (40-50%) [10, 15-20]. They are universal features of PD and occur at all stages of disease, with evidence suggesting that select non-motor symptoms, such as olfactory loss, constipation, RBD, and depression, may precede the diagnosis of PD by many years [15, 16, 21]. Cognitive impairment is common in PD, with more than one third of individuals having deficits at the time of PD diagnosis [22]. Dementia becomes increasingly prevalent in the later stages of disease, affecting over 80% of individuals with PD for 20 or more years [23]. If detected, the treatment of non-motor PD symptoms may contribute to increased quality of life; however, a large international survey of 242 individuals with PD found that 31.8-65.2% of non-motor PD symptoms (such as apathy, sexual dysfunction, incontinence, and RBD) were unreported to clinicians - a likely result of embarrassment or not knowing that the symptoms are associated with PD [24]. In addition to improving patient quality of life, the detection and treatment of non-motor PD

symptoms has shown to reduce hospitalizations, institutionalizations, reduce care partner distress, and dramatically lower costs associated with delivering care to those with PD [15, 25-28].

Prodromal features

The failure of early PD neuroprotective trials suggests that the initiation of pharmacological interventions may be too late in the degenerative disease process to result in significant clinical benefit [29]. This is supported by evidence of more than 50% deficit in key dopaminergic pathways implicated in PD in the earliest stage of classical disease where motor symptoms are present [29, 30]. Studies on pre-motor markers of PD, including the Honolulu-Asia Aging Study [31], have provided strong evidence to support that non-motor features such as olfactory loss, constipation, depression, and RBD may be prodromal markers of PD onset [5, 6, 32]. Together, these issues have prompted discussions and additional research on better defining and diagnosing early PD, with hopes that this may support the identification of early pharmacological interventions that slow disease progression. In 2014, a task force of the International Parkinson and Movement Disorders Society (MDS) published a proposed classification of early PD: 1) preclinical PD - neurodegeneration without signs or symptoms, 2) prodromal PD - neurodegeneration with signs and symptoms that are insufficient to diagnose classical PD, and 3) clinical PD – early diagnosis of PD based on cardinal motor features [33].

Prodromal markers are distinct from traditional risk factors (personal or environmental characteristics that increase likelihood of disease), since they may arise from underlying PD-

specific pathology within populations that do not satisfy explicit PD diagnostic criteria [34]. Moreover, prodromal markers may precede a PD diagnosis by several years, during which time neuronal degradation is occurring without immediate impacts to motor function [4]. To date, RBD is the single greatest prodromal marker for PD onset, with 38% of individuals diagnosed with RBD developing PD within 5 years and more than 80% of individuals being diagnosed with a neurodegenerative disease within 16 years [35, 36]. Despite the absence of a validated approach to clinically diagnose prodromal PD and no known neuroprotective intervention, recently published MDS research criteria for prodromal PD provide the initial foundation for delineating early disease stages [21]. Using an estimated prevalence of prodromal PD (2%) and literature searches to identify true risk factors and likely prodromal markers of PD, MDS task force investigators calculated likelihood ratios (LRs) to determine how test results (positive or negative) impact PD disease probability [21]. They subsequently demonstrated how an overall post-test probability of prodromal PD for distinct individuals may be calculated by multiplying all LRs for risk and prodromal factors together, acknowledging that the addition of missing information into overall calculations may significantly impact derived estimates. The strongest clinical non-motor prodromal markers of PD identified by the task force and their corresponding computed LRs include: 1) polysomnogram-proven idiopathic RBD (LR+ 130, LR- 0.62), 2) olfactory loss (LR+ 4.0, LR- 0.43), 3) constipation (LR+ 2.2, LR- 0.80), 4) excessive daytime somnolence (LR+ 2.2, LR- 0.88), 5) symptomatic hypotension (LR+ 2.1, LR- 0.87), 6) severe erectile dysfunction (LR+ 2.0, LR- 0.90), 7) urinary dysfunction (LR+ 1.9, LR- 0.90), and 8) depression (+/- anxiety) (LR+ 1.8, LR- 0.85) [21].

Risk factors

For the purposes of this review, risk factors for PD onset are considered to be individual or environmental characteristics that are separate from prodromal markers and alter the likelihood of disease [34]. They may be used in conjunction with prodromal markers to estimate the overall probability of prodromal PD; however, are insufficient at diagnosing disease alone [21]. Unsurprisingly, the majority of recent population-based studies of PD risk factors examine associations between single nucleotide polymorphisms (SNPs) and PD diagnosis [37-39]. In addition to specific SNPs, many other PD risk factors have been described. A recent systematic review of meta-analyses identified numerous environmental factors that modify the risk of PD, including but not limited to alcohol and coffee consumption (decrease), smoking (decrease), outdoor work (decrease), pesticide exposure (increase), and beta-blocker use (increase) [40]. Despite much evidence of associations between examined risk factors and PD, substantial heterogeneity among compared studies led investigators to conclude that reverse causation, confounding, and sponsor conflicts likely biased estimates of association reported by included meta-analyses [40]. Nevertheless, it remains possible that the heterogeneity could have resulted from genuine population differences across compared studies. It is important to note that investigators of this review only searched PubMed for systematic reviews and meta-analyses that examined associations between non-genetic factors and biomarkers with PD, and that their search strategy excluded studies reporting on more recent PD risk factors and factors that have not yet been summarized by systematic review or meta-analysis. Other non-genetic factors reported to modify PD risk include statin use (decrease) [41], male sex (increase) [42], head injury (increase) [43], and dairy intake (increase) [44]. Additional research is required to elucidate

the extent to which identified factors modify PD risk, as well as to determine if there are individual or environmental factors that modify the risk of disease progression (refer to Appendix II).

Epidemiology

Parkinson disease affects all populations; however, global estimates of PD incidence and prevalence vary considerably, with crude incidence and prevalence ranging from 4.5-20+ cases per 100,000 individuals per year and 18-300+ cases per 100,000 individuals, respectively [45]. Differences in regional estimates of PD likely reflect variations in measurement methods, case definitions, and age distributions of studied populations [45]. Additionally, differences in genetic susceptibility, exposure to environmental risk factors, life expectancy, and access to medical specialists may account for observed differences in estimated PD incidence and prevalence between regions [45]. Overall, epidemiological studies have persistently shown that both the incidence and prevalence of PD increase with age, and that men are more likely than women to have PD [42, 46]. Using data from the 2010/11 Canadian Community Health Survey, the 2011/12 Survey of Neurological Conditions in Institutions in Canada, and the 2011 Survey of Living with Neurological Conditions in Canada, it is estimated that there are more than 77,500 individuals living with PD in Canada, 4.9% (12,500) of who reside in residential institutions [46]. Consistent with other populations of individuals with PD, Canadians living with PD are most often older adults (79% of those living at home and 97% of those living in institutions are 65 years of age or older, respectively), with a mean age of diagnosis of 66.2 years of age [46]. Within the US, estimates of PD prevalence vary greatly, with extrapolated estimates of PD prevalence

for individuals age 40 or more years ranging from approximately 400,000 to more than one million [47-49]. Moreover, using Medicare beneficiary data for individuals age 65 to 95 years, Willis and colleagues (2010) demonstrated that PD prevalence is unequally distributed across US states and that Whites are more likely to have PD [49]. A recent meta-analysis investigated the prevalence of PD by age, sex, and global region [50]. Investigators found that PD prevalence increases with age worldwide, with a significant difference in prevalence by sex only observed among individuals age 50-59 (greater in men). PD prevalence was similar across regions, with one exception: a significantly lower proportion of individuals age 70-79 had PD in Asia compared to other global regions [50]. Although these findings suggest demographic differences in the worldwide prevalence of PD, methodological limitations of individual studies may partially account for observed inequalities. In light of rapidly aging North American populations, there is an imminent need to more precisely estimate PD prevalence and incidence, as this may inform future healthcare priorities, policies, and project the appropriate distribution of resources required to support necessary PD interventions. Long-term prospective studies will assist in better understanding PD burden, including whether there are significant inequalities in PD measures by demographic characteristics.

Pathophysiology

Overall, the etiology of PD remains poorly understood; however, in-vitro, in-vivo, and clinical studies have shed light on the causative factors and molecular mechanisms involved in this chronic and progressive neurodegenerative disorder [51]. Idiopathic PD results from the death of dopaminergic neurons in the substantia nigra (midbrain), with classical motor

and non-motor symptoms only appearing after substantial degradation of more than 50% of implicated neuronal pathways [29, 52]. Growing evidence suggests that oxidative stress, intracellular accumulation of misfolded proteins, and disruptions to the ubiquitin-proteasome system contribute to the pathogenesis of PD [53]. Oxidative damage to lipids, proteins, and DNA has consistently been observed in post-mortem analyses of affected PD brains [53]. The source of excess reactive oxygen species (ROS) is unclear, though studies point to increased catecholamine metabolism, impaired ROS scavenging, and mitochondrial dysfunction [53]. The histological hallmark of Parkinson's disease is the Lewy body, a cytoplasmic inclusion comprised of the protein α -synuclein found within dopaminergic neurons [54]. Studies have repeatedly shown that misfolded α -synuclein and the deposition of Lewy bodies within midbrain neurons are significant contributors to neuronal damage and death [51]. Future studies are needed to better understand the pathophysiology of PD.

PHARMACOLOGIC TREATMENT OF PARKINSON DISEASE

There is no cure for PD; however, many pharmacological interventions have proven to be effective at increasing dopamine levels and reducing debilitating disease symptoms [55]. Since dopamine is unable to cross the blood-brain barrier to reach affected brain regions, dopamine precursors, agonists, and/or catecholamine degrading enzyme inhibitors, alone or in combination, are essential to the treatment of PD [56]. Levodopa, a dopamine precursor, was first introduced in the 1960's as a drug to treat idiopathic PD and continues to be the most widely used and effective PD medication [55]. Levodopa is administered together with a dopa-decarboxylase enzyme inhibitor, which helps minimize movement-related adverse effects arising from its conversion to dopamine in the periphery [57]. Dopamine receptor

agonists are compounds with structures that allow them to mimic the effects of dopamine in the brain [55]. They may be used alone or in combination with other PD drugs and may be an effective therapy for individuals who develop motor complications while taking levodopa [55]. Dopamine receptor agonists are divided into two categories: ergot-derived (from fungi) and non-ergot derived agents, each having distinct therapeutic and adverse effect profiles [58]. Often used with levodopa, catecholamine degrading enzyme inhibitors are medications that improve the bioavailability of intracellular dopamine by inhibiting its breakdown by catecholamine degrading enzymes, monoamine oxidase-B (MAO-B) and catechol-O-methyltransferase (COMT) [55, 57]. No pharmacological intervention for PD has shown to be neuroprotective and prior notions that levodopa, the most potent PD medication, accelerates disease progression have been rejected [59]. Table 1 describes the most common PD medications, including adverse events reported with their use.

Drug Class	Generic Name(s)	Reported Adverse Event(s) [60-66]
Dopamine Precursor	levodopa	Motor fluctuations, dyskinesia, nausea, somnolence, dizziness, headache, confusion, hallucinations, delusions, agitation, psychosis, and orthostatic hypotension.
Dopamine Agonist (ergot)	bromocriptine cabergoline pergolide lisuride	Peripheral edema, nausea, vomiting, somnolence and “sleep attacks”, orthostatic hypotension, confusion, hallucinations, impulse control disorders (i.e. hypersexuality, pathologic gambling, and compulsive shopping), valvular heart disease, and skin reactions.
Dopamine Agonist (non-ergot)	apomorphine piribidil pramipexole ropinirole rotigotine	
Monoamine Oxidase B (MOA-B) Inhibitor	rasagiline selegiline	Nausea, headache, confusion, and impulse control disorders.
Catechol-o-methyltransferase (COMT) Inhibitor	entacapone tolcapone	Hepatotoxicity, dyskinesia, nausea, confusion, hallucinations, and orthostatic hypotension.
Antiviral	amantadine	Peripheral edema, confusion, and hallucinations.

Table 1. The most common medications used to treat Parkinson disease.

**Anticholinergic medications are intentionally omitted from the above table due to the large number of medications used in the treatment of PD that have anticholinergic effects. Chapter V of this thesis identifies medications with anticholinergic properties and examines associations between anticholinergic burden and adverse outcomes in PD.*

PHARMACOEPIDEMOLOGY

Pharmacoepidemiology serves as the bridge between clinical pharmacology and epidemiology, and is defined as the study of medication use and effects in large populations [67]. The dynamic field dates back to the 1960s and has evolved from simple descriptive studies to the use of increasingly large population-based electronic health databases and complex analytical methods to examine the use, effectiveness, and safety of pharmacological interventions [67, 68]. As predicted in 1990 by Strom and Tugwell, interest in pharmacoepidemiology has dramatically increased over the last decades and has had positive

impacts on clinical medicine by improving risk-based decision making capacities pertaining to the use of drugs. Advancements in the field are largely owed to: 1) the growth (in overall number and size) of anonymized publicly and privately available electronic health databases with in-depth information to study medication use and outcomes in large populations; 2) hardware and software computing developments that support the storage and timely analysis of these large datasets; and 3) the evolution of methodological approaches, including the now common use of propensity scores, to address confounding [69]. Currently, inherent limitations of randomized clinical trials (RCTs) (such as small samples sizes, non-representative patient populations, short duration, etc.) necessitate post-market pharmacoepidemiology research to better understand the use and effects of approved medications in representative patient populations [70, 71]. The following sections broadly introduce the study of drug utilization and safety using information from large databases and discuss these aspects in the context of PD.

Drug utilization

Medication use by populations may differ across and within geographic regions according to multiple determinants, such as household income, education, insurance status, drug pricing, advertising, and access to care [72, 73], and may serve as a predictor of health risks and an indicator of quality of medical care received. Drug utilization research, a hallmark of pharmacoepidemiology, enables stakeholders (such as regulators, clinicians, patients, and manufacturers) to gain a greater understanding of the usage of medications (prescription and over-the-counter) outside of RCTs, which may subsequently influence care and policy decisions. Such research may increase knowledge of drug utilization patterns, serve as a

preliminary indicator of irrational drug use, and provide valuable evidence in the assessment of interventions designed to improve drug use/prescribing [74]. Drug utilization research is primarily divided into two distinct categories: descriptive and analytical studies [67], while data sources used to conduct these studies include and are not limited to: patient reports, manufacturer wholesale information, provider prescribing records, and pharmacy dispensing data [70, 71]. Descriptive studies generally focus on temporal patterns of medication use in relation to drug availability or knowledge of safety and effectiveness, while analytical studies often link utilization data to other datasets for the purposes of examining medication use in relation to provider characteristics, health outcomes, and/or quality of care [67, 70]. Analytical studies may also serve to partially explain observed patterns of drug use and to determine whether pharmacotherapy choices are appropriate [67]. Drug utilization research has largely shifted over the course of the last decade, with many studies focusing on health outcomes and quality of medical care associated with prescribing [75-77], opposed to descriptive accounts of drug use within a defined population. Information derived from utilization studies, including the prevalence, incidence, and duration of medication use allows regulators to assess whether medications are being prescribed according to clinical guidelines and can assist with health system planning [70]. Comparisons of derived measures by individual drugs or drug classes in the same population permit a more thorough understanding of how medications are being used in that population, as well as possible reasons for therapy choice. Results of drug utilization research may also identify care setting and physician characteristics that predict appropriate or inappropriate prescribing, which may prompt targeted communications such as Dear Healthcare Professional Letters and further research aimed at more thoroughly understanding observed prescribing. Ultimately,

conclusions drawn from drug utilization studies are limited by the quality of analyzed data (i.e. patient reports vs. dispensed or sales data), as well as necessary research assumptions made (i.e. all dispensed medications are ingested). Nevertheless, well-conducted and reasonably interpreted drug utilization research provides valuable information on the clinical appropriateness of prescribed medications, predictors of therapy choice, and associations with select outcomes and quality of care [67].

Drug safety

Pharmacovigilance, often referred to as drug safety, adverse event reporting, or post-market surveillance, is a subfield of pharmacoepidemiology that primarily focuses on observing and assessing adverse outcomes associated with medication use outside of RCTs [78]. Such studies are essential to understanding the safety of marketed pharmaceutical products, particularly in regards to the identification of rare but potentially serious adverse events that may be linked to prolonged medication exposure, drug-drug interactions, or changes in disease status that may go unobserved during pre-marketing trials [69, 78]. Serious adverse events may go undetected in clinical studies that serve as the basis for drug approval for many reasons, including: 1) few participants, 2) omission or underrepresentation of select populations (such as the elderly, pregnant women, and children), 3) use comparators (such as placebos) that do not reflect realistic treatment approaches, 4) short durations, even for medications that are intended to be used for extended periods, and 5) the assessment of interventions and outcomes in non-conventional ways [69, 78]. As a result, pharmacovigilance studies, or phase IV studies, may provide valuable knowledge on the safety of marketed pharmaceutical products.

Historically, worldwide post-market drug safety surveillance has largely relied on data originating from voluntary reporting systems, such as the US Food and Drug Administration's (FDA) Adverse Event Reporting System (FAERS) and the World Health Organization's (WHO) Programme for International Drug Monitoring [79]. Surveillance activities such as these are considered passive drug safety initiatives since they lack in-depth information on medication use within the entire population of interest, especially those who do not experience any adverse reactions [79]. Despite their ability to potentially identify early adverse event signals, several limitations of passive pharmacovigilance systems exist and need to be considered when interpreting suspected medication risks, including: 1) often no or incomplete demographic (such as age, sex, and race) and clinical data (such as length and dose of drug exposure, other medications being used, comorbidities, measures of outcome severity) within reports, 2) underreporting of events that are perceived as being less severe or hypothesized to be unrelated to medication use, and 3) source of report (physician, patient, manufacturer, lawyer) [79-81]. Unfortunately, numerous studies have erroneously reported on drug-related adverse events, ranging from movement disorders to cardiac toxicity, based on the incorrect use and interpretation of spontaneous reports [78]. As a result, the term "Pharmacovigilance Syndrome" was coined to describe the inappropriate use of spontaneous event data to: 1) conclude causal relationships between medication use and adverse outcomes, 2) estimate the prevalence or incidence of adverse outcomes in a population, and 3) to compare the risk of adverse outcome between different drugs [78]. To minimize future instances of the Pharmacovigilance Syndrome, investigators must recognize that systems such as FAERS and the WHO's Programme for International Drug Monitoring are tools for signal detection and hypothesis generation, and that identified safety signals

should be further investigated and refined using the best available pharmacoepidemiology data and methods [78].

In recent years, regulatory agencies have shifted their attention to more “active” approaches to post-market drug safety surveillance, whereby suspected drug-associated adverse event signals identified from passive data are studied using administrative claims or electronic health records [79]. Active pharmacovigilance approaches may employ prospective or retrospective study designs to examine adverse events among pre-defined groups of users and non-users of specific medications, while taking medication dose and duration of exposure into consideration and making statistical adjustments for other demographic and clinical factor that may bias generated estimates of risk [82, 83]. Although active approaches to pharmacovigilance are superior to studies that solely rely on spontaneous reports of adverse event, their reliance on secondary health data make them prone to bias, particularly confounding, selection, and misclassification of exposures and outcomes [84]. However, increasing awareness of potential study biases and the development of advanced analytical methods to study drug safety, including the use of instrumental variables [85] and propensity scores [86] to minimize confounding, have strengthened the ability to draw meaningful conclusions from well-executed pharmacovigilance studies [67, 87].

Many national and multinational pharmacovigilance initiatives have been implemented over the course of the last decade, most notably of which is the US FDA’s Sentinel Initiative, which was announced in 2008 and realized in 2012 [69, 88]. The Sentinel Initiative’s primary objective is to actively leverage electronic health information from more than one

hundred million distinct individuals receiving care across the US for the purposes of monitoring the safety of marketed medical products [69, 88]. Other preeminent initiatives with similar objectives include the Canadian Drug Safety and Effectiveness Network, the Patient Centered Outcomes Research Institute in the US, the Exploring and Understanding Adverse Drug Reactions initiative in Europe, and the Asian Pharmacoepidemiology Network in Asia and Australia [69, 84]. Over time, multinational pharmacoepidemiologic initiatives will provide greater insight on the use and safety of marketed pharmaceuticals within and between regions, which may support clinical decision-making capacities and mitigate health risks to individuals receiving medical care.

Parkinson disease pharmacoepidemiology

Interest in the post-market use and safety of antiparkinson drugs and other medications used by individuals with PD has steadily increased with the discovery of symptomatic benefits of levodopa for PD and the birth of pharmacoepidemiology in the 1960s [67, 89, 90]. The introduction of new therapies for early and advanced PD over the last two decades, including the approval of DAs, entacapone, rasagiline, and deep brain stimulation, has led to numerous studies on the use and safety of interventions used to treat PD [91-94]. Collectively, these studies have provided key findings to support evidence-based decisions by clinicians, regulators, and manufacturers.

Many studies have examined the use of levodopa, the most potent and frequently prescribed antiparkinson medication. Using a Swedish referent population, a Cuban study examined levodopa use as a marker of PD prevalence and concluded that underutilized levodopa likely

reflected the absence of reliable screening methods and undiagnosed PD [95]. Consistent with a progressively aging population and a projected increasing prevalence of PD, Spanish investigators observed a more than 50% increase in dispensed orders of dopaminergic medications between 1992 and 2004 in the Basque Autonomous Community, with levodopa and non-ergot DA use increasing the most [96]. Similarly, a study from Southern Italy found that the overall prevalence of antiparkinson use was stable between 2003 and 2005, but that both levodopa and DA use dramatically increased among elderly individuals (≥ 70 years of age) during the same period [97].

A recent Japanese study used a large medical claims database to investigate antiparkinson drug use (2005 to 2010) in a cohort of individuals with PD in relation to mandated revisions to pergolide and cabergoline labels (2007) warning of cardiac valvulopathy risks [98]. Investigators observed a marked decrease in ergot DA use and an increase in non-ergot DA use post regulatory actions; however, were unable to attribute changes in prescribing behaviour to regulatory actions alone. Additionally, investigators reported that anticholinergic medications (such as trihexyphenidyl and biperiden) were frequently prescribed (~30% of individuals) as a first-line pharmacotherapy for PD, which was projected to decrease with revised guidelines that excluded these medications as initial therapies to treat PD due to concerns of their ability to worsen cognition [98, 99]. Similar patterns of anticholinergic prescribing for PD were observed among veterans with incident PD in the US (1998 to 2004), whereby mental health providers were more likely (odds ratio (OR) 76; 95% confidence interval (CI): 31.7 to 181.7) than other clinicians to prescribe anticholinergic medications instead of DAs as initial therapies [99]. Primary care physicians

were found to most frequently prescribe initial PD medications, specifically levodopa (OR 1.7; 95% CI: 1.1 to 2.5), compared to neurologists and movement disorder specialists - who favoured DAs as initial therapies [99]. As seen in Japan, an Australian study found that the use of ergot DAs declined (1995 to 2009) following increasing concerns of cardiovascular risks with these medications and that pramipexole was preferred over ropinirole, two approved non-ergot DAs [100]. Investigators also observed a decrease in the use of medications with anticholinergic properties by individuals with PD, which was attributed to atypical antipsychotics becoming the preferred treatment option for psychotic illness [100]. Decreasing use of typical antipsychotics was also reported by a Canadian study that examined medication use (1998 to 2002) in a large cohort of older adults with PD; however, prescriptions for typical antipsychotics were still common (9% in 2002) considering the associated risk of extrapyramidal adverse effects with their use [101].

Despite similar health insurance status, disparities in access and utilization of PD medications have been reported in the US, with African-Americans being four times less likely than whites to receive necessary PD treatment [102]. In addition, the effects of antiparkinson medication nonadherence has been extensively studied among Medicare beneficiaries in the US, revealing that nonadherence to PD treatment regimens in the prior month is significantly associated with changes in treatment regimens in the current month [103-105]. Findings also demonstrated that all-cause and PD-specific hospitalizations, as well as total all-cause health expenditures, increased in the following three months for individuals who underwent changes in treatment regimens compared to those without changes to their treatment plan [104, 105].

Clinical trials and subsequent observational studies on the safety of marketed antiparkinson medications have increased knowledge of potential adverse events associated with these necessary interventions, ranging from nausea, vomiting, and impulse control disorders with the use of DAs to motor fluctuations and hypotension with levodopa treatment [60-66]. Table 1 outlines adverse events that have been reported with the use of PD medications. The most profound example of pharmacovigilance influencing care for PD may be the post-market withdrawal of pergolide in some countries due to overwhelming evidence of cardiotoxicity that was not identified during pre-market trials. Post-market case reports and observational studies consistently showed an increased risk of heart valve damage with pergolide use [106-108], with a large United Kingdom-based study reporting a significantly elevated risk of cardiac valve regurgitation with high-dose (Incident Rate Ratio (IRR) 37.1; 95% CI: 5.1 to 270.6) and extended use (≥ 6 months; IRR 9.8; 95% CI: 2.9 to 33.1) of pergolide, compared to no current or recent use of DAs [109]. These studies ultimately led to the voluntary withdrawal of pergolide from US and Canadian markets in 2007 [110]. Pergolide continues to be available in some regions worldwide; however, is rarely prescribed due to its known cardiotoxicity [110]. Increasing popularity of non-ergot DAs as initial and less potent interventions for PD has led to in-depth post-market surveillance of these medications, with studies suggesting a potential risk of heart failure with pramipexole use [111-113]. However, biases in existing studies on this topic preclude regulators from drawing strict conclusions on the cardiac safety of pramipexole. Therefore, additional studies on the cardiac safety of pramipexole in homogenous populations of individuals with PD are required to support evidence-based decisions pertaining to the use of pramipexole for PD.

Recent reports have raised important questions about the potential impacts of anticholinergic burden, defined as the cumulative anticholinergic potential resulting from polypharmacy, in PD [114-116]. Medication with anticholinergic properties are commonly used to treat a wide range of indications, including urinary incontinence, allergies, gastrointestinal issues, pain, hypertension, respiratory disorders, and psychiatric illness [117]. Moreover, essential PD therapies such as levodopa, pramipexole, selegiline, entacapone, and amantadine have moderate to strong anticholinergic properties, which contribute to an individual's overall anticholinergic burden and risk of experiencing associated adverse outcomes [118]. Prior reports have shown that anticholinergic burden is associated with an increased risk of falls [119], delirium [120, 121], and cognitive impairment [122] in older adult populations; however, studies of similar exposures and associated adverse events in PD are lacking. A recent study of the use of anticholinergic medications by PD inpatient in Spain found that more than 50% of individuals were prescribed medications with moderate anticholinergic effects, while more than 10% of individuals received medications with very strong anticholinergic effects [115]. Investigators also found that anticholinergic burden was primarily attributed to the use of non-PD medications, suggesting that anticholinergic burden may be lessened by replacing these therapies with equally effective drugs without anticholinergic properties [115]. A second study on this topic examined cognitive scores within a cohort of individuals with PD in the United Kingdom and found no significant difference in cognitive outcomes across multiple validated scales [116]. As acknowledged by study authors, these findings are contrary to reports in other older adult populations and may be due to numerous factors, including a younger study population and low overall

anticholinergic burden within the studied cohort [116]. Future studies are required to better understand the effects of anticholinergic burden, if any, among populations with PD.

THESIS FRAMEWORK

Knowledge gaps

In consideration of the current state of knowledge pertaining to PD pharmacoepidemiology, known limitations in existing observational studies on the utilization and safety of medications used in the treatment of PD, and the availability of Cerner Health Facts® electronic medical records from the US to support population health research, the following knowledge gaps have been identified as key priorities to be investigated by the research embodied within this thesis.

1. There is a limited understanding of national trends in the utilization of PD medications in the US, especially following changes in the availability of PD treatments over the course of the last two decades and significant revisions to best practice guidelines for PD care.
2. Recent observational studies suggest that non-ergot DAs, particularly pramipexole, may be associated with adverse cardiovascular outcomes such as heart failure; however, biases in existing studies presently limit the ability to make definitive conclusions on this topic.
3. Although the effects of anticholinergic burden have been previously investigated in older adult populations, there is limited data on anticholinergic burden and its effects, if any, in subpopulations that are more likely to be prescribed medications with anticholinergic properties, such as those with PD.

Research questions

Inspired by PD pharmacoepidemiology knowledge gaps, the research questions (RQ) that this thesis aims to address are:

- RQ1.** How has the availability of new medications and changes to best practice guidelines for PD care influenced the use of antiparkinson medications in the US over time?
- RQ2.** Compared to other drugs, is the use of non-ergot DAs for PD associated with adverse cardiovascular reactions such as heart failure?
- RQ3.** Is anticholinergic burden common among individuals receiving treatment for PD?
- RQ4.** Compared to no anticholinergic burden, is anticholinergic burden in PD associated with an increased risk of clinical and healthcare utilization outcomes?

Research objectives

Based on the above-defined RQs, the specific research objectives (RO) of this thesis are to:

RQ1

- RO1.** Describe patterns of antiparkinson drug use in the US between 2001 and 2012 in relation to clinical guideline publication, drug introduction/withdrawal, and emerging safety concerns.
- RO2.** Examine temporal trends and relative differences in the pharmacological management of PD by age and sex.

RQ2

- RO3.** Explore whether non-ergot DA use is associated with the diagnosis of adverse cardiovascular (acute myocardial infarction, heart failure, hypotension, and

valvulopathy) and cerebrovascular events (cerebrovascular accident and ischemic stroke).

- RO4.** Examine whether significant non-ergot DA-outcome (cardiovascular and cerebrovascular) relationships differ by patient demographic characteristics.

RQ3 & RQ4

- RO5.** Assess the magnitude of anticholinergic burden among individuals with PD.

- RO6.** Determine whether anticholinergic burden is associated with the diagnosis of clinical (fracture and delirium) and healthcare utilization (emergency department visit and inpatient readmission within 30-days of inpatient discharge) outcomes.

All research questions will be investigated using accepted pharmacoepidemiological methods, retrospective study designs, and data available from the Cerner Health Facts® database. Detailed descriptions of study methods are provided in subsequent chapters.

Conceptual framework

The fields of population health and risk science have largely evolved independently over the last 40 years; however, each have proposed theories, guiding principles, and frameworks to support the development and implementation of evidence-based health policies [123].

Growing interests in the field of population health has led to a more thorough understanding of how inequities in the determinants of health (such as biology, personal health practices, and physical, social, and economic environments) may contribute to disparities in physical, mental, and social outcomes within and between populations [124, 125]. In essence, the population health approach to understanding and addressing health issues is broader than traditional notions that environmental risk and lifestyle factors influence disease, which have

been the primary focus of public health and health promotion, respectively [124, 125]. Evolution of risk science has led to increasingly dynamic ways to research, assess, and manage risk issues, while emphasizing the need to think broadly about risk mitigation opportunities and the importance of involving all stakeholders in each step [123].

Population health advocates for beneficial determinants of health, while risk sciences aims to avoid unhealthy risk factors [123]. Krewski and colleagues (2007) highlighted the complementarity of these concepts in their proposed *Integrated Framework for Risk Management and Population Health* (Figure 1), which serves to guide the research and discussions presented within this thesis. Essential to the framework are the determinants of health, which are divided into three categories (biology and genetics, environmental and occupational factors, and social and behavioural factors; as well as their interactions) and may influence outcomes of examined health risks, which are subsequently characterized using a multidisciplinary approach and available data (qualitative and/or quantitative) [123]. Similar to the identification of risk management options in other frameworks, health risk policy analysis is evidence-based and informs regulators of potential management strategies, as well as their feasibility, costs/benefits, and cultural/social impacts [123, 126]. As noted in the framework, the acronym “REACT” highlights that population health risk management interventions (regulatory, economic, advisory, community action, and technological) may be implemented simultaneously and across multiple sectors [123].

In the context of this project, quantitative methods will be used to describe medication use and characterize associated health risks (such as adverse cardiovascular reactions and

inpatient readmission) among individuals with PD receiving care in the US, while taking into consideration differences in the distribution of the determinants of health. Findings from these analyses will provide preliminary data to support evidence-based policy analyses and recommendations of interventions aimed at improving PD care, outcomes, and quality of life.

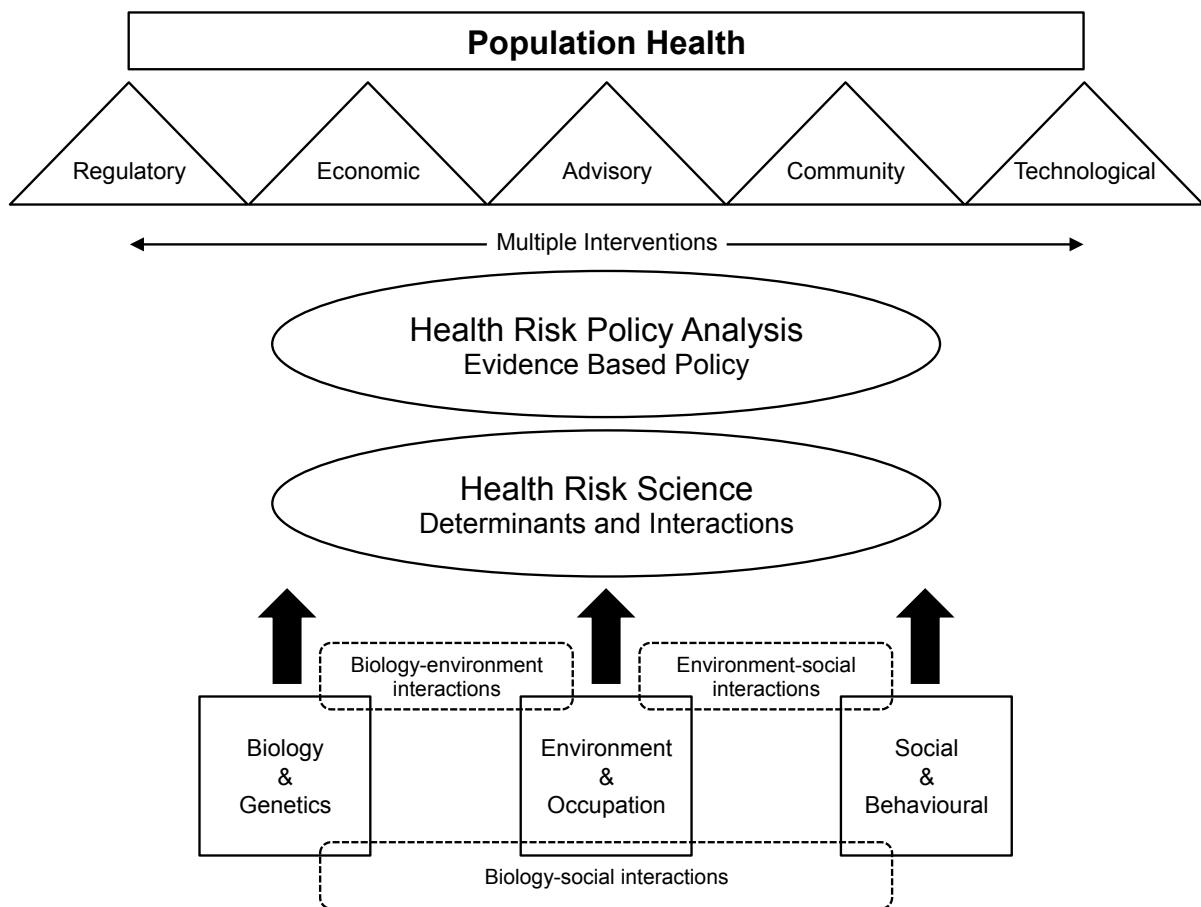


Figure 1. Integrated Framework for Risk Management and Population Health (adapted from Krewski et al., 2007).

Subsequent chapters and appendices

The following chapters describe studies that were undertaken to generate knowledge specific to the RQs and ROs put forward by this thesis.

- Chapter II, titled “*Trends in inpatient antiparkinson drug use in the United States, 2001-2012*” and published in the *European Journal of Clinical Pharmacology*, addresses RO1 and RO2 (antiparkinson drug use trends in the US).
- Chapter III, titled “*Associations between cardiovascular events and non-ergot dopamine agonists in Parkinson disease*” and published in *Movement Disorders Clinical Practice*, addresses RO3 and RO4 (associations between non-ergot DA use and the diagnosis of adverse cardiovascular and cerebrovascular events).
- Chapter IV, titled “*Non-ergot dopamine agonists and the risk of heart failure and other adverse cardiovascular reactions in Parkinson disease*” and published in *The Cochrane Library*, also addresses RO3 and RO4 (associations between non-ergot DA use and the diagnosis of adverse cardiovascular events). This article is the developed protocol for a Cochrane systematic review on the topic of cardiovascular safety of non-ergot dopamine agonists in PD. This work is ongoing and is expected to be complete and published in *The Cochrane Library* as a separate full-length systematic review in 2017.
- Chapter V, titled “*Associations between anticholinergic burden and adverse health outcomes in Parkinson disease*” and published in *PLOS ONE*, addresses RO5 and RO6 (associations between anticholinergic burden and adverse clinical and healthcare outcomes).

- Chapter VI is a general discussion of the main findings presented throughout this thesis in the context of the population health and the *Integrated Framework for Risk Management and Population Health* [123].

Appendices I and II describe works relevant to this thesis that were completed in collaboration with other research groups. The RQs and ROs of these studies were formulated by other investigators.

- Appendix I, titled “*Risk of heart failure following treatment with dopamine agonists in Parkinson’s disease patients*” was published in *Expert Opinion on Drug Safety*.
- Appendix II, titled “*Onset and progression factors in Parkinson’s disease: a systematic review*” was published in *NeuroToxicology*.

Due to page constraints in the (published) manuscripts that comprise this thesis, additional information on the studies presented in Chapters II, III, and V is provided in Appendix III.

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CHAPTER II: Trends in inpatient antiparkinson drug use in the USA, 2001-2012

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ABSTRACT

Purpose: Although therapeutic options and clinical guidelines for Parkinson disease (PD) have changed significantly in the past 15 years, prescribing trends in the USA remain unknown. The purpose of this population-based cohort study was to examine patterns of inpatient antiparkinson drug use between January 2001 and December 2012 in relation to clinical guideline publication, drug introduction/withdrawal, and emerging safety concerns.

Methods: A total of 16,785 inpatients receiving pharmacological treatment for PD were identified in the Cerner Health Facts database. Our primary outcome was standardized (age, sex, race, and census region) annual prevalence of antiparkinson drug use. We also examined antiparkinson medication trends and polypharmacy by age and sex.

Results: The most frequently prescribed antiparkinson drugs between 2001 and 2012 were levodopa (85%) and dopamine agonists (28%). Dopamine agonist use began declining in 2007, from 34% to 27% in 2012. The decline followed publication of the American Academy of Neurology's practice parameter refuting levodopa toxicity, pergolide withdrawal, and pramipexole label revisions. Despite safety concerns for cognitive impairment and falls, individuals ≥ 80 years of age demonstrated stable rates of dopamine agonist use from 2001 to 2012. Polypharmacy was most common in younger patients.

Conclusions: Dopamine agonist use declined from 2007 to 2012, suggesting that increased awareness of safety issues and practice guidelines influenced prescribing. These events appear to have minimally influenced treatment provided to older PD patients. Antiparkinson prescribing trends indicate that safety and best practice information may be communicated effectively.

INTRODUCTION

Treatment options for both early and advanced Parkinson disease (PD) have expanded considerably over the last 15 years. The introduction of dopamine agonists (DAs) to treat PD in the late 1990's, USA Food and Drug Administration approval of deep brain stimulation for PD in 2002, and approval of other antiparkinson drugs such as entacapone and rasagiline reflect the substantial public and private investment in improving the lives of those affected by PD. Increasing knowledge of antiparkinson drug safety (including reports of DA-associated impulse control disorders [1,2] and cardiotoxicity [3-9]) and efficacy, findings that PD progression is not accelerated by levodopa [10,11], and the failures of selegiline and rasagiline to demonstrate neuroprotection [11,12] have the potential to influence clinical practice.

Ideally, prescribing practices reflect known risks and benefits, which can change over time. Evidence-based clinical guidelines are routinely published and updated by professional organizations such as the International Parkinson and Movement Disorder Society and the American Academy of Neurology (AAN) to reflect changes in scientific knowledge [11,13-15]. Additionally, treatment availability and adverse drug event reporting may also contribute to changing antiparkinson drug prescribing practices over time. Previous USA PD drug utilization studies have consistently demonstrated sociodemographic disparities in PD treatment [16-18]; however, prescribing trends are unreported. Furthermore, the impact of evidence-based guideline publication, drug availability, and safety concerns on antiparkinson drug prescribing has been investigated in Europe, Asia, and Australia [19-22], but not in the USA. Previous studies have shown that levodopa is the most commonly prescribed

antiparkinson drug [19-22], that prescribing of DAs may be influenced by safety concerns [20], and that despite safety concerns, DAs may be routinely prescribed to older adults [22]. Nevertheless, changes in antiparkinson drug use in relation to practice guideline publication, drug availability, and emerging safety concerns remain unknown in the USA.

To address this knowledge gap, we performed a 12-year retrospective analysis of electronic medical records (EMRs) from more than 16,000 individuals with PD in Cerner Health Facts®, an EMR database comprised of complete encounter data for patients who received care at any USA health center subscribed to Cerner EMR services. The primary objective of our study was to describe patterns of antiparkinson drug use between January 2001 and December 2012 in relation to clinical guideline publication, drug introduction/withdrawal, and emerging safety concerns. PD prevalence increases sharply with age [23], and yet older adults are also most vulnerable to side effects from PD medications [2,6,24]. Our secondary objectives were therefore to examine temporal trends and relative differences in the pharmacological management of PD by age and sex.

MATERIALS AND METHODS

This study was approved by the Health Sciences and Science Research Ethics Board at the University of Ottawa, Ottawa, ON, Canada.

Data source

Study data were derived from the Cerner Corporation's (Kansas City, Missouri) Health Facts® data warehouse. Launched in January 2000, Health Facts® is an electronic medical

record system that stores time-stamped patient records, including sociodemographic, geographical, clinical, laboratory, pharmacy, and billing data for clients. As of 2014, there were over 300 contributing subscribers to the Health Facts®, and data from more than 230 million patient encounters, representing over 41 million distinct patients. Health Facts® subscribers are situated in all USA census regions: Northeast (40%), Midwest (27%), South (21%), and West (11%). The majority of subscribers are academic medical centers, which contribute approximately 65% of all encounters. Health Facts® is well suited for studying responses to changing practice guidelines, specifically among inpatients, since pharmacy data are most complete for inpatient populations.

Study population

We searched all encounters from January 1, 2000 to December 31, 2012 to identify individuals with a primary or secondary diagnosis of PD according to the International Classification of Diseases, Ninth Revision (ICD-9; code 332 for PD, or code 332.0 for Paralysis Agitans). Information from all encounters within the study period was extracted for individuals with one or more PD diagnoses (n=40,609). We excluded individuals diagnosed at any time with a primary or secondary diagnosis of secondary parkinsonism (ICD-9, code 332.1) or other degenerative diseases of the basal ganglia (ICD-9, code 333.0) (n=1,450, 3.6%). In effort to exclude individuals with atypical PD and cases of PD misclassification, we also excluded those who were diagnosed with PD prior to age 40 (n=375, 0.96%) and those without a recorded age at time of PD diagnosis (n=18, 0.05 %). Because all outpatient physicians do not use Health Facts®, we further restricted the cohort to inpatients who were prescribed one or more antiparkinson drugs between January 1, 2001 and December 31, 2012

(n=17,375, 45%). Finally, to accommodate direct standardization, we restricted the cohort to individuals with complete demographic information (age, sex, and race) recorded (n=16,785, 97%).

Demographic data and care setting characteristics

Demographic data collected from encounters included patient age, sex (male or female), and race (Caucasian, African American, Asian, Hispanic, or other). Patient age at time of first recorded PD diagnosis, defined as the study-qualifying encounter, was categorized into the following age strata: 40-64, 65-79, and 80+ years. The principal diagnosis for each study encounter was identified and classified according to commonly used ICD-9 categories. Care setting characteristics collected from study-qualifying encounters included location type (urban or rural), teaching status (teaching or non-teaching), and census region (Northeast, South, Midwest, or West).

Drug utilization

Our primary outcome was standardized (age, sex, race, and census region) annual prevalence of antiparkinson drug use among inpatients with PD who were prescribed one or more antiparkinson drugs. Antiparkinson drugs were identified by searching hospital formularies for generic names of interest and classified according to the following categories: (1) levodopa, (2) DA (ergot (bromocriptine, cabergoline, and pergolide) and non-ergot (pramipexole, ropinirole, and rotigotine)), (3) monoamine oxidase-B (MAO-B) inhibitor (selegiline and rasagiline), (4) catechol-o-methyltransferase (COMT) inhibitor (tolcapone and entacapone), (5) amantadine, and (6) anticholinergic (benztropine, biperiden,

procyclidine, and trihexyphenidyl). After excluding drug orders that were cancelled or not dispensed, the number of inpatients with an antiparkinson prescription was calculated annually by drug class from January 1, 2001 through December 31, 2012. Using data from the 2005 American Community Survey (USA Census Bureau), we calculated annual standardized (age, sex, race, and census region) antiparkinson drug use to examine prescribing trends over time. Subgroup analyses contrasted prescribing trends by age and sex. We defined PD drug complexity as the sum of unique drug classes prescribed to an individual patient in one calendar year, categorized as 1, 2, 3, and 4+ drugs.

Factors affecting prescribing practice

Our *a priori* hypothesis was that the greatest changes in the most commonly prescribed drug classes - levodopa and DAs - would be temporally related to (1) practice guideline publication, (2) official safety concerns (such as market withdrawal), and (3) the 2008 pramipexole (Mirapex) label revisions warning of the risk of impulse control issues (urges to gamble and increased sexual urges). To test this hypothesis, we examined the change in levodopa and DA use between the event year and 1, 2, and 3 years after (1) publication of the April 2006 AAN practice parameter reporting that levodopa does not accelerate PD progression and that no pharmacological intervention is neuroprotective, (2) the voluntary withdrawal of pergolide (an ergot-derived DA) from the market in 2007 due to concerns about cardiotoxicity, and (3) the December 2008 pramipexole label revisions which added precautions about uncontrollable urges to the label. We used a Wilcoxon-Mann-Whitney test to examine whether standardized annual prevalence of levodopa and DA use significantly changed after events of interest. In order to ensure independence of the data between the two

years being compared, individuals appearing in both years (6-25% of sample depending on the particular comparison) were excluded from the analyses. Two-tailed p values less than 0.0015 were considered statistically significant.

RESULTS

Demographics and care setting characteristics

We identified 16,785 individuals with PD from the Cerner Health Facts® data warehouse who satisfied our inclusion/exclusion criteria between January 1, 2001 and December 31, 2012 (Table 1). The demographic characteristics of our population were similar to previously published epidemiological studies of PD in the USA [23,25]. Caucasians comprised 91.2% of the population; the remaining individuals were African American (6.1%), Asian (0.7%), Hispanic (1.0%), and other races (1.0%). Men (54.9%) were more prevalent than women (45.1%) (Table 1). The majority (88.4%) of individuals were aged 65 years or older at the time of their first recorded PD diagnosis in Health Facts®, which agrees with published data on age-stratified PD prevalence [23,25]. Care centers were most likely located in urban areas (99.6%), academic medical centers (64.9%), and in the Northeast USA (49.2%).

Supplementary Table 1 shows that study cohort demographics and care setting census regions were similar across study years. Supplementary Table 2 demonstrates that individuals within our study cohort were primarily admitted to hospital for diseases of the circulatory system, diseases of the respiratory systems, and symptoms, signs, and ill-defined conditions, which is consistent with reasons for inpatient admission among older USA adults [26].

Characteristic	Population	
	n (16,785)	%
Age at diagnosis ^a		
40-64	1,943	11.6
65-79	7,574	45.1
80+	7,268	43.3
Sex		
Male	9,211	54.9
Female	7,574	45.1
Race		
Caucasian	15,314	91.2
African American	1,026	6.1
Asian	114	0.7
Hispanic	167	1.0
Other	164	1.0
Care Setting		
Urban	16,726	99.6
Rural	57	0.3
Teaching status		
Teaching	10,899	64.9
Non-Teaching	5,886	35.1
Census region		
Northeast	8,254	49.2
South	4,225	25.2
Midwest	3,007	17.9
West	1,299	7.7

Table 1. Demographics of inpatients with PD and care setting characteristics.
Abbreviation: PD, Parkinson disease.

^aAge at first recorded diagnosis in Health Facts.

Changes in drug utilization in relation to AAN practice guidelines

As shown in Figure 1 and Table 2, use of levodopa was stable prior to and after the 2006 publication of the AAN's evidence-based review of neuroprotective strategies and alternative therapies in PD, which put forth that there was no advantage to initiating therapy with levodopa alternatives. DAs were the most commonly used levodopa alternatives at that time, and DA utilization steadily increased from 21.7% (2001) to 31.2% (2006) during the same pre-guideline period. Use of non-ergot DAs was significantly higher (+3.2%; $p < 0.0015$) in the year immediately following release of the AAN practice guideline; however, did not further increase in subsequent years (Table 2). Prevalent use of ergot DAs agonists significantly declined 2 (-0.6%; $p < 0.0015$) and 3 (-0.8%; $p < 0.0015$) years after AAN practice guideline publication (Table 2).

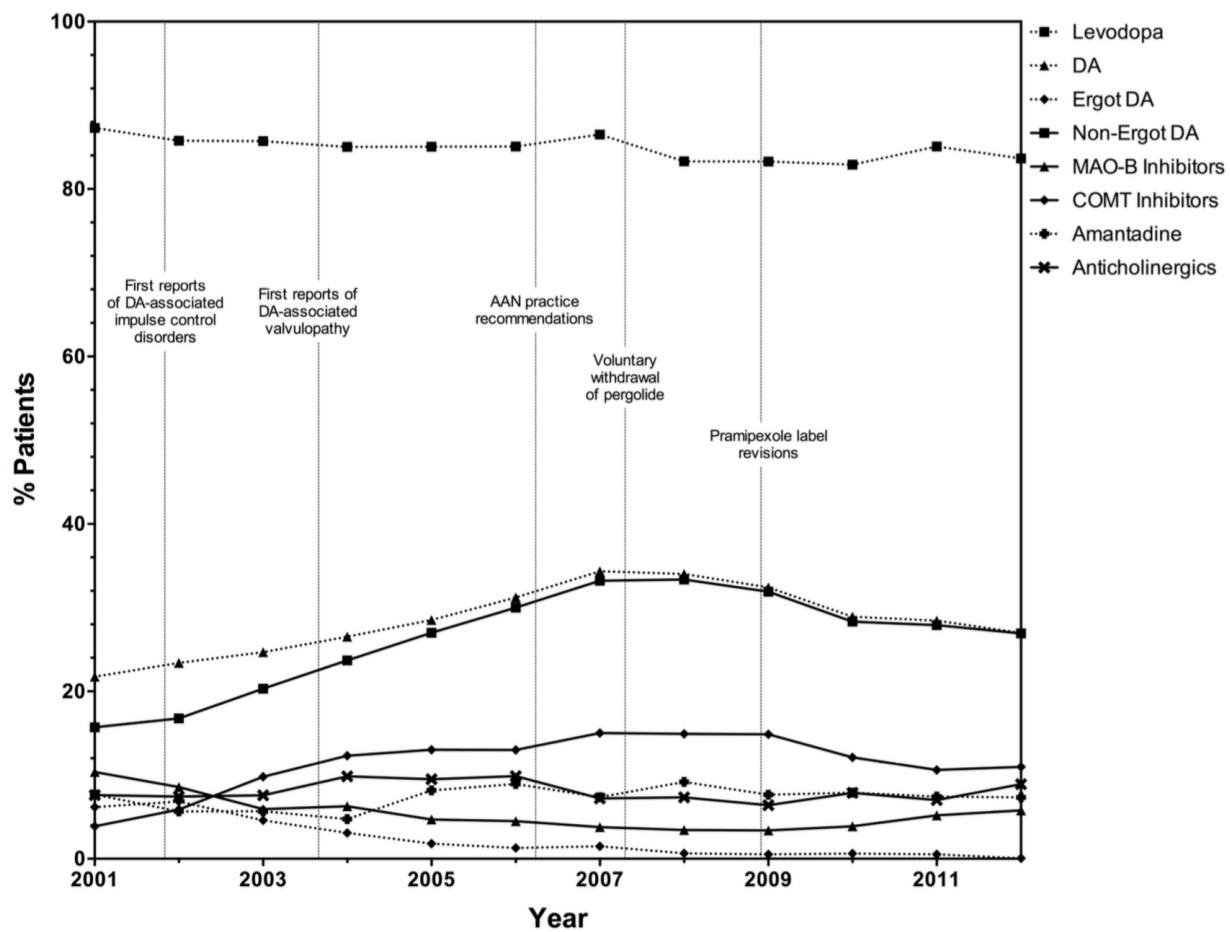


Figure 1. Standardized prevalence of antiparkinson drug use over time. Abbreviations: AAN, American Academy of Neurology; COMT, catechol-o-methyltransferase; DA, dopamine agonist; MAO-B, monoamine oxidase-B.

Event	Event Year (%) ^a	Year After (%) ^a	% Change ^a	2 Years After (%) ^a	% Change ^a	3 Years After (%) ^a	% Change ^a
AAN Practice Recommendations (2006)							
Levodopa	85.1	86.5	+1.4	83.3	-1.8	83.3	-1.8
Dopamine Agonists	31.2	34.4	+3.2	34.0	+2.8	32.4	+1.2
Ergot	1.3	1.5	+0.2	0.7	-0.6*	0.5	-0.8*
Non-ergot	30.0	33.2	+3.2*	33.4	+3.4	31.9	+1.9
Pergolide Withdrawal (2007)							
Levodopa	86.5	83.3	-3.2	83.3	-3.2	82.9	-3.6
Dopamine Agonists	34.4	34.0	-0.4	32.4	-2.0	28.9	-5.5*
Ergot	1.5	0.7	-0.8	0.5	-1.0	0.6	-0.9
Non-ergot	33.2	33.4	+0.2	31.9	-1.3	28.3	-4.9*
Pramipexole Label Revisions (2008)							
Levodopa	83.3	83.3	0.0	82.9	-0.4	85.1	+1.8
Dopamine Agonists	34.0	32.4	-1.6	28.9	-5.1	28.5	-5.5*
Ergot	0.7	0.5	-0.2	0.6	-0.1	0.5	-0.2
Non-ergot	33.4	31.9	-1.5	28.3	-5.1	27.9	-5.5*

Table 2. Change in levodopa and dopamine agonist utilization in relation to guideline publication, pergolide withdrawal, and emerging safety concerns.

Abbreviation: AAN, American Academy of Neurology.

^aStandardized annual prevalent use expressed as a percentage.

*Significant at $p=0.0015 \approx 0.05/36$, using a Bonferroni adjustment to control for the 36 individual tests conducted.

Due to polypharmacy, the sum of the standardized annual prevalent use for antiparkinson drugs studied may exceed 100% in a given year.

Changes in drug utilization in relation to pergolide withdrawal

In March 2007, pergolide (an ergot DA) was withdrawn from the USA market over mounting evidence of cardiotoxicity, specifically valvular disease [27]. Use of DAs (mainly non-ergot DAs) surged prior to the withdrawal of pergolide, increasing from 21.7% in 2001 to a maximum of 34.3% in 2007 (Figure 1). At the time of withdrawal, approximately 1.5% of inpatients receiving pharmacotherapy for PD were treated with ergot DAs. Levodopa use was not impacted by the withdrawal of pergolide (Table 2). Similarly, the withdrawal of one of its class members had little immediate impact on DA use; however, DA (-5.5%; $p < 0.0015$) and non-ergot DA (-4.9%; $p < 0.0015$) use significantly declined 3 years following pergolide's withdrawal (Table 2).

Changes in drug utilization in relation to pramipexole label revisions

In-depth precautions about uncontrollable urges were added to the pramipexole (Mirapex) label in 2008 [28]. Moreover, 2008 was a focal year in the use trend of DAs, as it was the first year in our sample where DA use decreased (-1.6%; $p > 0.0015$) from the previous year (Figure 1 and Table 2). A significant decrease (-5.5%; $p < 0.0015$) in the use of non-ergot DAs was observed 3 years following the pramipexole label revisions, while use of levodopa remained unchanged (Table 2).

Prescribing trends by age and sex

No discernable differences according to age or sex were observed in the use trends of levodopa or DAs following (1) publication of the 2006 AAN practice parameter, (2) the 2007 withdrawal of pergolide from the USA market, and (3) the 2008 pramipexole labeling

revisions (Figure 2). We observed differences in levodopa (Figure 2a) and DA (Figure 2c) use within older adult PD populations (80+ years of age). On average, 73.4% of adults aged 40-64 years used levodopa, which rose to 90.1% for individuals aged 80+ years. Younger patients (40-64 years of age) were uncommon and were more likely to be prescribed DAs, which decreased with increasing age (Figure 2c). Adults aged 65-79 years had intermediate rates of DA and levodopa use, with levodopa favored over DAs. As shown in Figure 2, year-to-year trends in levodopa and DA use were more volatile for younger patients, while the pharmacological management of PD proved to be more resistant to change among older patients. Despite emerging safety concerns pertaining to the use of DAs in older populations, use of DAs did not decrease over time in the oldest (80+ years of age) population, 20.2% of who were prescribed a DA. Polypharmacy (two or more PD drugs) was most common in patients 40-64 years of age (42.2%), and decreased with increasing age (38.6% and 25.5% among patients 65-79 and 80+ years of age, respectively). Annual prevalence of levodopa (Figure 2b) and DA (Figure 2d) use was similar among men and women.

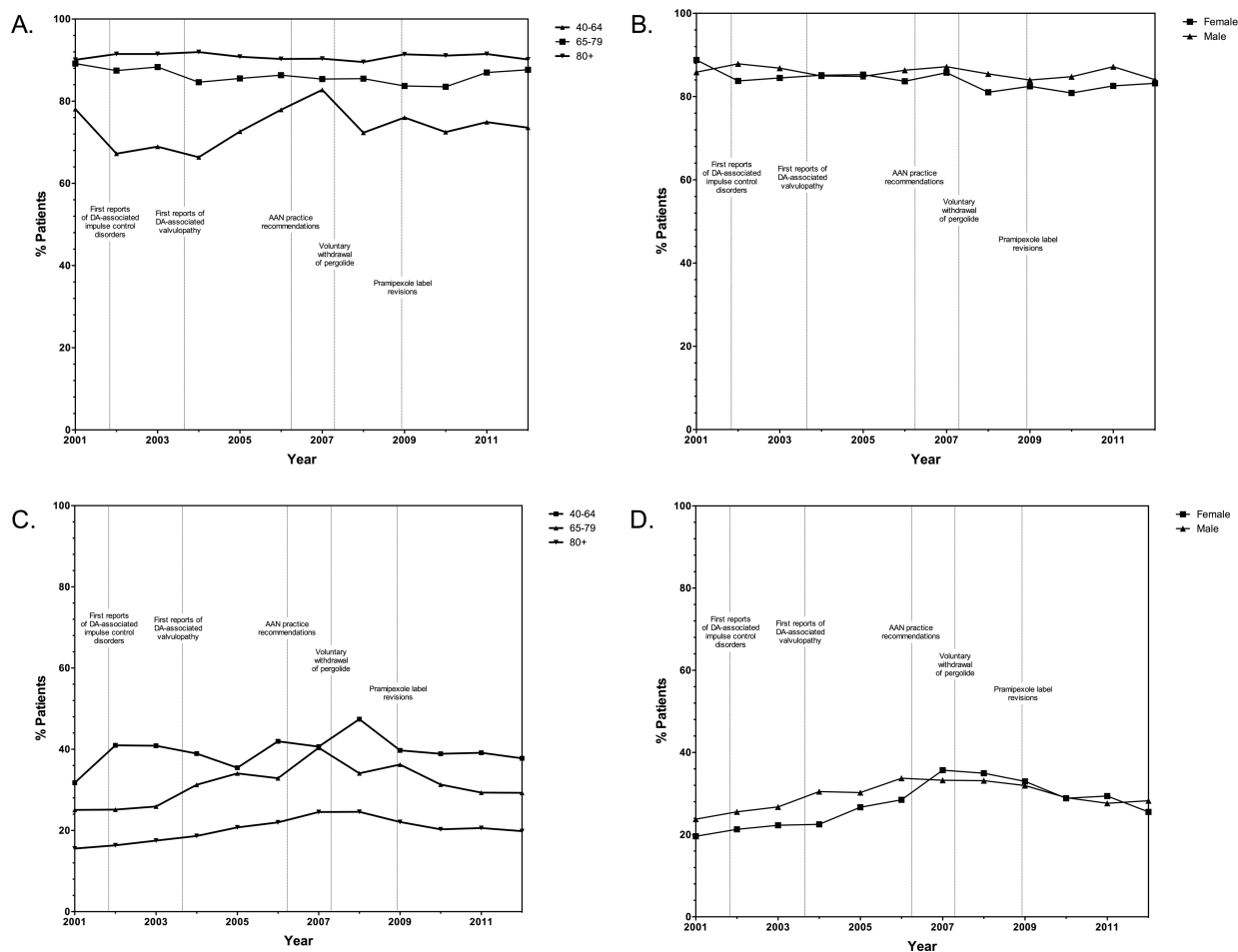


Figure 2. Standardized prevalence of antiparkinson drug use over time by age and sex. Levodopa use over time by age (a) and sex (b); dopamine agonist use over time by age (c) and sex (d).

Abbreviations: AAN, American Academy of Neurology; DA, dopamine agonist.

Trends were not standardized by the stratification variable for analyses of annual prevalence of antiparkinson drug use by age and sex.

DISCUSSION

While unpublished data may regularly be used by the pharmaceutical industry to inform marketing decisions, there are significant benefits to publicly reporting such information. Prescribing patterns serve as markers of practice parameter adherence and response to new scientific evidence. Real-world prescription studies may also identify deviations from standard practice in the form of age, sex, race, or socioeconomic treatment disparities. Our retrospective analyses of inpatients with PD who received pharmacological treatment between January 1, 2001 and December 31, 2012 is, to our knowledge, the first national analysis of trends in PD medication use in the USA. Our primary finding is that there has been a shift in prescribing practices for PD in the USA, and that these changes are due in part to emerging safety concerns and evidence of efficacy. Secondary analyses revealed that (1) despite safety concerns, older PD patients were persistently prescribed DAs, (2) use of levodopa and DAs did not greatly differ between men and women over time, and (3) antiparkinson drug polypharmacy was most common in younger PD patients.

DAs gained popularity as the initial pharmacotherapy for PD in the early 2000's because of concerns over levodopa neurotoxicity and that motor fluctuations in PD were due to levodopa treatment duration [29,30]. Published in April 2006, the world's largest professional association of neurologists, the AAN, completed an evidence-based review of the therapies purported to delay the onset of motor fluctuations or decrease motor progression in PD [11]. The expert review reported that levodopa did not accelerate PD progression and that no pharmacological intervention was neuroprotective. Our findings show that USA prescribing trends of antiparkinson drugs, notably DAs, did not immediately

change as a result of the AAN's practice parameter publication. There are several possible reasons for this finding. Continued disagreement regarding the toxicity of levodopa likely contributed to the observed delay in response. The notion that DAs are less toxic (rather than simply less potent) continues to have a strong footing in the scientific literature and lay press [31,32]. Notwithstanding any disagreement, recent evidence reaffirms the AAN's finding that levodopa is not toxic [10,33-35]. Lack of prescriber awareness is another possible reason as to why there was little immediate response to the practice parameter. There is currently no mandate for specialty care for PD, as exists for equally complicated conditions such as cancer. The majority of individuals diagnosed with PD do not have neurologist care, especially in the years immediately following diagnosis [36,37]. Primary care physician continuing medical education (CME) training may not include specialty practice parameter updates in a timely fashion. Whether lack of awareness of paradigm shifts in PD treatments is associated with worse outcomes will need to be considered in future studies. Finally, despite knowledge of the latest guidelines, sound clinical judgment may have dictated that switching some patients from a DA to levodopa was contraindicated, particularly in patients responding well to a DA or those who had previously experienced intolerable side effects with levodopa.

We next examined inpatient antiparkinson drug use in relation to increasing concerns of adverse events such as cardiovascular complications and impulse control disorders (ICDs). Studies have demonstrated that DAs, specifically ergot derivatives, are associated with the development of cardiac fibrosis and valvular heart disease [3,6,8,9]. Although the majority of DAs prescribed within our study period were non-ergot derivatives, it is possible that

decreasing use of DAs reflects emerging concerns of cardiac safety with all DAs. Recent reports of increased risk of heart failure with non-ergot DAs suggest that researchers are beginning to examine this phenomenon carefully, hopefully providing guidelines that better enable informed use of DAs in patients with cardiovascular disease [4-7]. In addition to cardiovascular concerns, reports of DA-associated ICDs have surged in the last decade [1,2,38]. ICDs are characterized by problems in self-control despite personal repercussions and may include pathological gambling, compulsive buying, hypersexuality, binge eating, and punting [1,2]. While there is currently no black box warning of ICDs with DAs, the precautions section of the pramipexole (Mirapex) label was revised in December 2008 to include information about uncontrollable urges while taking pramipexole, including intense urges to gamble, increased sexual urges, and other intense urges [28]. Increasing knowledge of these risks by clinicians may have contributed in part to the reduced use of DAs after 2007.

Although most physicians avoid DAs in adults >60 years of age over concerns of cognitive impairment [39,40], a large proportion of individuals >65 years of age in our dataset were prescribed DAs. There was also little change in levodopa or DA use in the most elderly patients. These data may reflect differences in care structure for the oldest PD patients, who are more likely to reside in nursing homes and are least likely to utilize specialty care [41]. Alternatively, older patients or the physicians who care for them may be more averse to the risks of known levodopa-induced side effects (nausea, hallucinations, dyskinesias, and orthostatic hypotension) and instead rely on DAs and other therapies for symptomatic PD. It is also possible that older PD patient populations have a lower susceptibility to ICDs or have

more social support to prevent personal and financial consequences of mild dopamine-associated impulsivity, reducing the need to change medications. However, differences in care quality must be considered, as studies have found that older PD patients are undertreated on examination and have undertreatment-related disability [42,43].

Our study has a number of strengths. Data for this study were derived from a large number of patients spanning multiple treatment centers over 10+ years, with relatively complete pharmacy data. While other studies have investigated antiparkinson drug use cross-sectionally [22,44], within a single center [16], or within smaller patient populations [20,22,44], our study offers broader insight on the influence of practice parameter publication, drug introduction/withdrawal, and increasing knowledge of drug efficacy and safety on prescribing patterns. Since the majority of our study data are derived from urban teaching centers, they are assumed to be highly sensitive to detecting modifications to clinical practice, including changing prescribing patterns in response to new guidelines or evidence.

There are a number of limitations to our study. Due to lacking outpatient drug information, our study was restricted to inpatients prescribed one or more antiparkinson drugs during the study period. This was done to minimize false negatives for antiparkinson treatment.

However, because PD is rarely the principal reason for hospital admission [45,46], we could not account for radical changes in PD regimen that accompanied an admission. Moreover, since differences may exist in the identification and treatment of PD among inpatients and individuals receiving care at academic centers; our findings may not reflect antiparkinson

prescribing trends in the general USA PD patient population. Nevertheless, our reported trends provide valuable information on antiparkinson drug use by the oldest and sickest individuals with PD who are hospitalized, many of who (those <65 years of age) are not represented in other large national databases such as Medicare. We could not account for PD disease severity and did not take comorbidities and the use of other medications into account, which may impact prescribing at the individual level. However, our study examined all PD cases over time (rather than a fixed cohort), reducing the potential impact of individual disease progression, comorbidities, and use of other drugs on our results. Unmeasured factors, including drug pricing and pharmaceutical company promotional activity, have certainly influenced antiparkinson drug utilization over time. Therefore, our observed trends in antiparkinson drug use may only be explained in part by examined events. Finally, there are also limitations to our statistical approach. Calculated p values from the Wilcoxon-Mann-Whitney test may overstate the significance of changes in drug utilization over time in the presence of clustering in the data, such as might occur if there were a tendency for differences in prescribing practices among hospitals. Percent changes in Table 2, which represent changes in levodopa and DA use for the entire population under study, could mask differential changes by population subgroup; however, trends by age, sex, race, and census region shown in Supplementary Table 1 did not generally show marked differences among these subgroups.

Despite study limitations, we demonstrate that changes in the use of antiparkinson drugs in the USA have occurred over time and that these changes may reflect increasing knowledge of drug safety and efficacy. Future studies that examine the impact of care structure and

quality on prescribing practices, particularly with regard to barriers to the dissemination, acceptance, and adoption clinical guidelines, as well as studies which investigate outcomes associated with drug choice in select PD populations are needed.

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Authors' roles

Study concept and design: JAGC, LMB, DEK, DM, AWW, DK. Data analysis and drafting of the manuscript: JAGC, AWW. Interpretation of data, critical review, and critique of manuscript: JAGC, YF, DPT, ME, LMB, DEK, SPL, DM, AWW, and DK. Final approval of the manuscript: JAGC, YF, ME, LMB, DEK, SPL, DM, AWW, and DK.

Conflict of interest

Mr. Crispo, Mr. Fortin, Mr. Thibault, Dr. Bjerre, Dr. Kohen, and Dr. Willis have no potential conflicts of interest to disclose. Dr. Perez Lloret served as a consultant for Aguetant Laboratories in 2014. Dr. Emons is employed by the Cerner Corporation. Dr. Mattison serves as Chief Medical Officer of Risk Sciences International, a Canadian company formed in partnership with the University of Ottawa in 2006 (www.risksciences.com) that conducts risk assessment work for public and private sector clients in Canada and internationally. To date, RSI has not conducted work on the subject of the present research paper. Dr. Krewski serves as Chief Risk Scientist and CEO of Risk Sciences International. From 2009 to 2014, Dr.

Krewski held a Natural Sciences and Engineering Council of Canada (NSERC) Industrial Research Chair in Risk Science, through a peer-reviewed university-industry partnerships program administered by NSERC. None of the industrial partners in this program were from the pharmaceutical industry.

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Characteristic	2001 Population n (1,006)	%	2002 Population n (1,198)	%	2003 Population n (1,290)	%	2004 Population n (1,080)	%	2005 Population n (1,491)	%	2006 Population n (1,845)	%	2007 Population n (1,977)	%	2008 Population n (2,239)	%	2009 Population n (2,384)	%	2010 Population n (2,344)	%	2011 Population n (2,932)	%	2012 Population n (2,899)	%	
Age																									
40-64	71	7.1	72	6.0	76	6.0	75	6.9	116	7.8	196	10.6	202	10.2	233	10.4	266	11.2	315	11.1	354	12.1	363	12.5	
64-79	476	47.3	557	46.5	576	45.7	480	44.4	658	44.1	777	42.1	819	41.4	950	42.4	1,013	42.5	1,249	43.9	1,218	41.5	1,292	44.6	
80+	459	45.6	569	47.5	608	48.3	525	48.6	717	48.1	872	47.3	956	48.4	1,056	47.2	1,105	46.4	1,280	45.0	1,360	46.4	1,244	42.9	
Sex																									
Female	471	46.8	571	47.7	556	44.1	511	47.3	774	48.1	863	46.8	892	45.1	1,039	46.4	1,317	44.8	1,305	45.9	1,289	44.0	1,323	45.6	
Male	535	53.2	627	52.3	704	55.9	569	52.7	717	51.9	982	53.2	1,085	54.9	1,200	53.6	1,067	55.2	1,539	54.1	1,689	56.0	1,576	54.4	
Race																									
Caucasian	958	95.2	1,137	94.9	1,173	93.1	1,014	93.9	1,401	94.0	1,740	94.3	1,853	93.7	2,041	91.2	2,179	91.4	2,559	90.0	2,635	89.9	2,563	88.4	
African American	34	3.4	34	2.8	49	3.9	36	3.3	65	4.4	82	4.4	91	4.6	153	6.8	161	6.8	202	7.1	208	7.1	242	8.3	
Hispanic	*	*	16	1.3	23	1.8	12	1.1	*	*	*	*	20	1.0	17	0.8	19	0.8	27	0.9	32	1.1	24	0.8	
Asian	*	*	*	*	11	0.9	12	1.1	*	0.8	*	*	*	*	12	0.5	13	0.5	24	0.8	32	1.1	23	0.8	
Other	*	*	*	*	*	*	*	*	12	0.8	*	*	*	*	16	0.7	12	0.5	32	1.1	41	1.4	47	1.6	
Census region																									
Midwest	197	19.6	244	20.4	378	30.0	310	28.7	257	17.2	382	20.7	470	23.8	391	17.5	402	16.9	453	15.9	344	11.7	399	13.8	
Northeast	635	63.1	750	62.6	650	51.6	550	50.9	859	57.6	1,024	55.5	1,040	52.6	1,035	46.2	1,193	50.0	1,283	45.1	1,335	45.5	1,349	46.5	
South	126	12.5	73	6.1	44	3.5	92	8.5	314	21.1	404	21.9	397	20.1	628	28.0	654	27.4	933	32.8	1,024	34.9	861	29.7	
West	48	4.8	131	10.9	188	14.9	128	11.9	61	4.1	35	1.9	70	3.5	185	8.3	135	5.7	175	6.2	229	7.8	290	10.0	
Anti-PD Drugs																									
Levodopa	896	89.1	1,063	88.7	1,113	88.3	942	87.2	*	*	1,612	87.4	1,729	87.5	1,922	85.8	2,074	87.0	2,451	86.2	2,577	87.9	2,556	87.1	
Dopamine agonist	214	21.3	264	22.0	291	23.1	272	25.2	405	27.2	506	27.4	639	32.3	678	30.3	687	28.8	743	26.1	740	25.2	726	25.0	
Ergot	66	6.6	71	5.9	43	3.4	36	3.3	28	1.9	29	1.6	19	1.0	*	*	12	0.5	14	0.5	*	*	*	*	
Bromocriptine	29	2.9	28	2.3	*	*	16	1.5	13	0.9	15	0.8	14	0.7	*	*	12	0.5	14	0.5	*	*	*	*	
Carergoline	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Pergolide	37	3.7	43	3.6	33	2.6	20	1.9	15	1.0	14	0.8	*	*	*	*	*	*	731	25.7	732	25.0	721	24.9	
Non-ergot	150	14.9	196	16.4	251	19.9	239	22.1	381	25.6	479	26.0	625	31.6	668	29.8	676	28.4	731	25.7	732	25.0	721	24.9	
Apomorphine	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Ropinirole	127	12.6	155	12.9	178	14.1	157	14.5	234	15.7	252	13.7	277	14.0	363	16.2	347	14.6	336	11.8	321	10.9	308	10.6	
Pramipexole	23	2.3	43	3.6	74	5.9	83	7.7	149	10.0	235	12.7	277	14.0	313	14.0	338	14.2	411	14.5	418	14.3	418	14.4	
Rosiglitone	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
MAO-B inhibitor	99	9.8	105	8.8	75	6.0	61	5.6	67	4.5	80	4.3	82	4.1	79	3.5	92	3.9	103	3.6	158	5.4	169	5.8	
Selagine	99	9.8	105	8.8	75	6.0	61	5.6	67	4.5	77	4.2	69	3.5	63	2.8	54	2.3	49	1.7	75	2.6	76	2.6	
Reserpine	*	*	*	*	*	*	*	*	*	*	*	*	13	0.7	16	0.7	38	1.6	56	2.0	83	2.8	93	3.2	
COMT inhibitor	29	2.9	68	5.7	110	8.7	111	10.3	167	11.2	232	12.6	266	13.5	302	13.5	320	13.4	312	11.0	295	10.1	307	10.6	
Tetraopone	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Entacapone	28	2.8	66	5.5	104	8.3	109	10.1	166	11.1	231	12.5	264	13.4	298	13.3	315	13.2	310	10.9	290	9.9	302	10.4	
Amantadine	62	6.2	59	4.9	53	4.2	48	4.4	114	7.6	148	8.0	116	5.9	160	7.1	146	6.1	186	6.5	177	6.0	197	6.8	
Amphetamine	67	6.7	73	6.1	78	6.2	80	7.4	95	6.4	117	6.3	106	5.4	126	5.6	123	5.2	173	6.1	159	5.4	177	6.1	
Benzotropine	30	3.0	24	2.0	46	3.7	47	4.4	50	3.4	60	3.3	55	2.8	65	2.9	80	3.4	111	3.9	102	3.5	110	3.8	
Biperiden	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Procyclidine	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Trihexyphenidyl	37	3.7	51	4.3	30	2.4	36	3.3	47	3.2	60	3.3	53	2.7	62	2.8	43	1.8	64	2.3	58	2.0	69	2.4	

Supplementary Table 1. Study cohort demographics, care setting census regions, and prevalence of antiparkinson drug use by study year.

Abbreviations: COMT, catechol-o-methyltransferase; MAO-B, monoamine oxidase-B; PD, Parkinson disease.

*To reduce the risk of individual identification of persons, results for cells where tabulated data is less than or equal to 100 are not shown.

Principal Diagnosis (by ICD-9 category)	Frequency*	
	n (54,345)	%
Infectious and parasitic diseases (001-139)	2,505	4.6
Neoplasms (140-239)	804	1.5
Endocrine, nutritional and metabolic diseases, and immunity disorders (240-279)	1,967	3.6
Diseases of the blood and blood-forming organs (280-289)	469	0.9
Mental disorders (290-319)	1,958	3.6
Diseases of the nervous system (320-359)	3,745	6.9
Diseases of the sense organs (360-389)	107	0.2
Diseases of the circulatory system (390-459)	8,359	15.4
Diseases of the respiratory system (460-519)	6,201	11.4
Diseases of the digestive system (520-579)	3,229	5.9
Diseases of the genitourinary system (580-629)	3,639	6.7
Complications of pregnancy, childbirth, and the puerperium (630-679)	*	*
Diseases of the skin and subcutaneous tissue (680-709)	943	1.7
Diseases of the musculoskeletal system and connective tissue (710-739)	2,438	4.5
Congenital anomalies (740-759)	*	*
Certain conditions originating in the perinatal period (760-779)	*	*
Symptoms, signs, and ill-defined conditions (780-799)	6,752	12.4
Injury and poisoning (800-999)	4,526	8.3
E Codes (all codes)	*	*
V Codes (all codes)	1,989	3.7
Missing	4,588	8.4

Supplementary Table 2. Reasons for hospitalization of individuals with Parkinson disease, 2001-2012

Abbreviations: ICD-9, International Classification of Diseases, Ninth Revision.

*To reduce the risk of individual identification of persons, results for cells where tabulated data is less than or equal to 100 are not shown. Individuals may have more than one recorded principal diagnosis per inpatient encounter.

CHAPTER III: Associations between cardiovascular events and non-ergot dopamine agonists in Parkinson disease

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ABSTRACT

Objective: Knowledge of possible cardiovascular risks from Parkinson disease (PD) medications is critical to informing safe and effective treatment decisions. The objective of our study was to determine whether PD patients treated with non-ergot dopamine agonists (DAs) are at increased risk of adverse cardiovascular or cerebrovascular outcomes, relative to PD patients receiving other treatments.

Methods: Matched case-control studies were conducted within a cohort of 14,122 inpatients receiving treatment for PD who were identified in the Cerner Health Facts database. Primary outcomes were associations between non-ergot DA use and diagnosis of adverse cardiovascular events (acute myocardial infarction, heart failure (HF), hypotension, and valvulopathy). Secondary outcomes included associations between non-ergot DA use and diagnosis of adverse cerebrovascular events (cerebrovascular accident and ischemic stroke), and odds of significant exposure-outcome relationships by patient factors.

Results: HF was the only adverse event that demonstrated a significant association with non-ergot DA use. Individuals treated with pramipexole were more likely to be diagnosed with HF, relative to no-use (adjusted odds ratio (AOR): 1.28, 95% CI: 1.07-1.53). The association between pramipexole and HF was greater among individuals treated with pramipexole monotherapy (relative to levodopa monotherapy) (AOR: 1.50, 95% CI: 1.09-2.06). Compared to non-users, men and older individuals treated with pramipexole were more likely to be diagnosed with HF.

Conclusions: Results from our study suggest an association between pramipexole use and HF. Findings warrant replication; however, individuals with PD and independent risk factors for or a history of HF may benefit from limited use of this drug.

INTRODUCTION

After levodopa, dopamine agonists (DAs) are drugs most frequently used in the treatment of Parkinson disease (PD). They are classified as ergot-derivatives (bromocriptine, cabergoline, lisuride, and pergolide) or non-ergot derivatives (apomorphine, priribedil, pramipexole, ropinirole, and rotigotine) and may be used alone or as adjunct therapy.¹

Several studies demonstrated that pergolide was associated with valvulopathy prior to its voluntary withdrawal from the United States market.²⁻⁵ Recently, attention has shifted to non-ergot DAs and possible risks of adverse cardiovascular outcomes such as heart failure (HF).⁶⁻⁹ Following a review of phase II/III clinical trial data for pramipexole, investigators found that, compared to placebo, HF was more frequently diagnosed among pramipexole users.⁹ Although these results serve as useful preliminary data, they do not reflect real world prescribing conditions. Additionally, levodopa users may represent a more appropriate reference group when investigating associations between DAs and cardiovascular events, since levodopa users are more likely to be older and presumably have more severe PD.¹⁰ Signals detected from such analyses are less likely to overestimate the level of patient risk due to low baseline risk in the referent group.

To investigate non-ergot DA safety, we examined the relationship between non-ergot DAs and adverse cardiovascular events in a PD inpatient population. Our primary objective was to determine whether non-ergot DA use was associated with the diagnosis of adverse cardiovascular events. Secondary objectives were to investigate the relationship between

non-ergot DA use and the diagnosis of adverse cerebrovascular events, and to examine significant exposure-outcome relationships by patient demographic characteristics.

METHODS

This study was approved by the Health Sciences and Science Research Ethics Board at the University of Ottawa, Ottawa, Ontario, Canada.

Data source

Data were obtained from the Cerner Corporation's (Kansas City, Missouri) Health Facts® database, which contains over 230 million time-stamped encounters for over 41 million unique patients who received care between 2000 and 2012. The electronic medical records in this database include demographic, clinical, laboratory, pharmacy, hospital, and billing data for more than 300 subscribing medical centers across the United States. Roughly 65% of all data is gathered from academic medical centers. Although Health Facts® contains outpatient encounters, pharmacy data is most complete for inpatient encounters, therefore the inpatient population is preferred for drug use studies.

Inpatient PD cohort definition

The study cohort consisted of hospitalized individuals with a diagnosis of PD who were prescribed an antiparkinson drug during their encounter. To assemble the cohort, we first searched all encounters from January 1, 2000 to December 31, 2012 to identify individuals diagnosed with PD according to the International Classification of Diseases, Ninth Revision (ICD-9: code 332 for PD, or code 332.0 for Paralysis Agitans) (n=40,609). We excluded

individuals who had diagnoses (in any setting) of secondary parkinsonism (ICD-9, code 332.1) or other degenerative diseases of the basal ganglia (ICD-9, code 333.0) (n=1,450, 3.6%), those under the age of 40 years of age (n=375, 0.9%), or without a documented age at first PD diagnosis (n=18, 0.04%). We then excluded individuals with missing or unknown demographic (sex and race) data (n=1,536, 4.0%), only outpatient encounters (and therefore limited drug data) (n=10,374, 27.9%), and all inpatient encounters occurring prior to their PD diagnosis (n=1,779, 6.6%). Since home medications may not be dispensed by the hospital pharmacy for shorter stays, such as day surgeries or diagnostic procedures, or may not be provided to individuals with clear catastrophic or terminal events upon arrival, we excluded encounters where the inpatient stay was less than 3 days due to discharge or death (3,954 individuals, 15.8%). To minimize selection bias, we selected the earliest inpatient encounter for each patient where an antiparkinson drug was prescribed (n=14,122, 66.8%). A flow diagram showing cohort selection is provided in Figure 1.

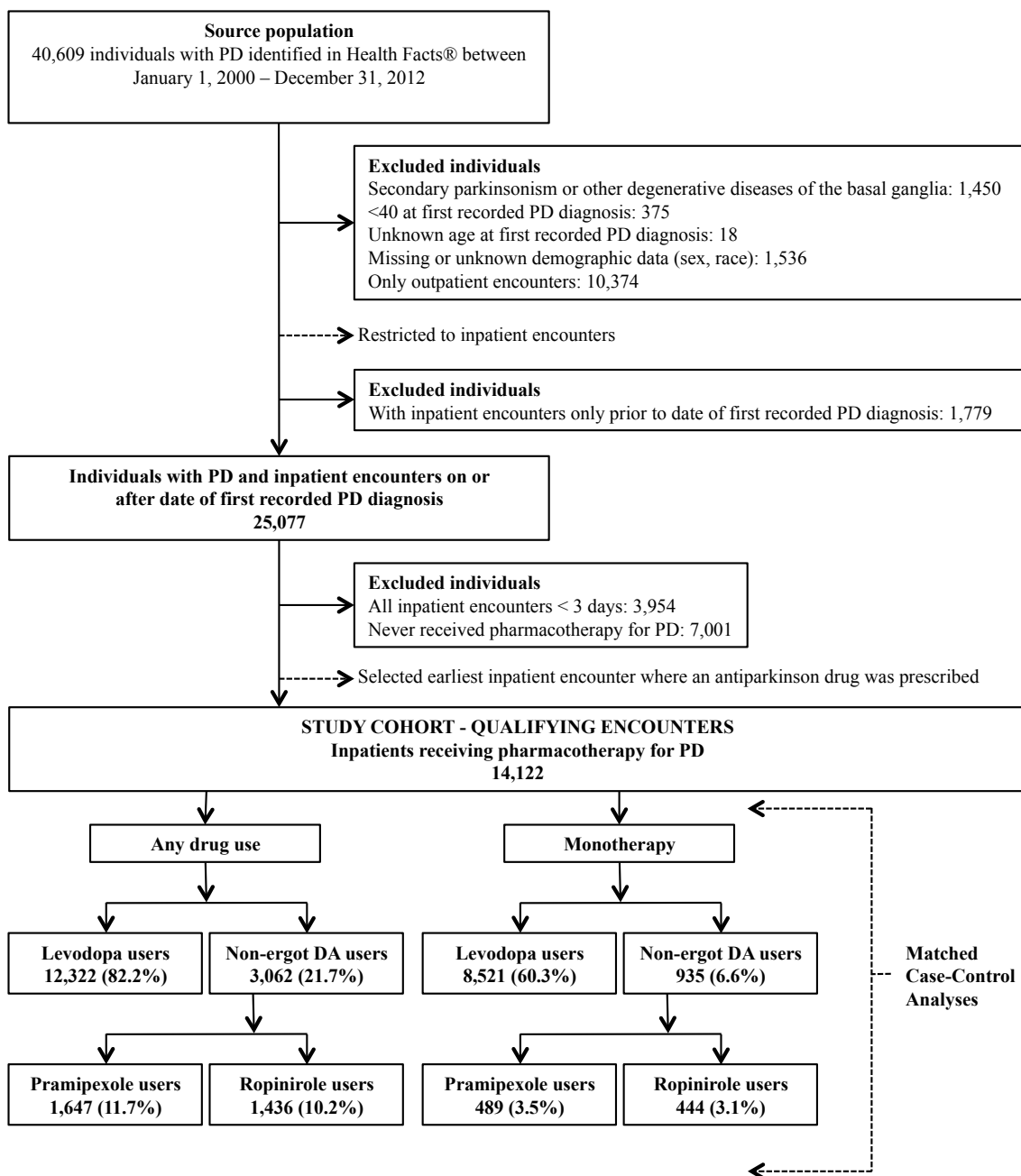


Figure 1. Cohort selection.

Abbreviations: DA, dopamine agonist; PD, Parkinson disease.

Demographic and care setting characteristics

We examined and reported the following demographic data for the study cohort and for all matched case-control analyses: race (Caucasian, African American, Hispanic, Asian, or other), sex (female or male), and age at admission. Age at admission was categorized into 5-year age strata from 40-44 to 90+ years. Care setting characteristics collected from study-qualifying encounters included: teaching status (teaching or non-teaching), number of beds (<5, 6-99, 100-199, 200-299, 300-499, 500+), census region (Northeast, South, Midwest, or West), and location (urban or rural). We also determined the length of stay for each patient's study-qualifying encounter.

Inpatient diagnoses

In this study, cases were hospitalized individuals who were diagnosed with a specific cardiovascular or cerebrovascular clinical event during the first inpatient encounter where they received pharmacotherapy for PD. Controls were hospitalized individuals not diagnosed with the clinical event of interest during the first inpatient encounter where they received pharmacotherapy for PD. Cardiovascular diagnoses of interest (acute myocardial infarction, HF, hypotension, and valvulopathy) were events that, based on previous reports, may be associated with non-ergot DA use.^{5,7,8,11-14} Cerebrovascular diagnoses of interest (cerebrovascular accident, and ischemic stroke) were events that were hypothesized to be associated with non-ergot DA use.¹⁵⁻¹⁷ Diagnoses were identified from study-qualifying encounter data by ICD-9 diagnosis code and were defined as: acute myocardial infarction (410.xx), HF (428.xx), hypotension (458.xx), valvulopathy (394, 394.0, 394.2, 394.9, 396.xx, 397, 397.0, and 424.xx), cerebrovascular accident (430.xx, 431.xx, 432.xx, 433.xx,

434.xx, 435.xx, 436.xx), and ischemic stroke (434.xx, 436.xx). All outcome definitions were reviewed and approved by a clinician.

Matching

Demographic characteristics may modify or confound the relationship between PD treatment and cardiovascular disease.¹⁸ Therefore, controls from the study-qualifying cohort were matched to each case at a 3:1 ratio on age, race, and sex, using a variable optimal matching macro.¹⁹ Controls could only be matched to a single case for each event; however, individual patients could serve as cases or controls for other primary and secondary analyses.

Medication use

Antiparkinson drug use was identified using dispensed hospital pharmacy orders and categorized as follows: (1) levodopa, (2) non-ergot DA (apomorphine, piribedil, pramipexole, ropinirole, or rotigotine), (3) ergot DA (bromocriptine, cabergoline, lisuride, or pergolide), (4) monoamine oxidase-B inhibitor (selegiline or rasagiline), (5) catechol-o-methyltransferase inhibitor (tolcapone or entacapone), (6) amantadine, and (7) anticholinergic (benztropine, biperiden, procyclidine, or trihexyphenidyl). Individuals were classified as receiving monotherapy or polypharmacy for PD. Antiparkinson medications dispensed in inpatient settings were assumed to be probable continuations of outpatient treatment regimens.

Statistical analyses

To determine the association between non-ergot DA use with inpatient diagnosis of a specific adverse event, we constructed conditional logistic regression models that determined the adjusted odds of non-ergot DA use compared to a reference group for each of the previously described cardiovascular and cerebrovascular events. For the first set of models, we examined the association between the use of non-ergot DAs and diagnosis of cardiovascular or cerebrovascular events, with individual patients being categorized as users or non-users of non-ergot DAs, pramipexole, and ropinirole respectively. Non-users served as the reference drug group for all comparisons.

A second set of models was constructed to account for potential bias in risk estimates due to use of multiple medications and possible confounding by disease severity. These models were limited to individuals from the study-qualifying cohort who received monotherapy for PD, either levodopa (n=8,521, 60.3%) or a non-ergot DA (n=935, 6.6%). Individuals receiving levodopa monotherapy served as the reference drug group for these comparisons.

A third set of models examined whether the association between non-ergot DA use and inpatient diagnosis of adverse cardiovascular and cerebrovascular events differed by patient demographics (effect modification). We completed sex, race (white and non-white), and age (60-69 years, 70-79 years, and 80+ years) stratified analyses of all event-exposure relationships that were statistically significant in our primary analyses. For these analyses, eligible controls were sampled from the study-qualifying cohort and re-matched to cases at a 3:1 ratio on two of three (age, race, and sex) demographic factors.

To identify adjustment covariates for our models, we first examined potential confounders in univariate analyses to test for their effect on the cardiovascular or cerebrovascular event. Potential confounders included: demographic information (age, race, and sex), length of stay, number of antiparkinson drugs dispensed, care setting characteristics (census category, number of beds, teaching status, and urban/rural location), and the following comorbidities defined according to the enhanced ICD-9-CM coding algorithms for Elixhauser comorbidities: congestive HF, cardiac arrhythmia, valvular disease, pulmonary circulation disorders, peripheral vascular disorders, hypertension uncomplicated, hypertension complicated, paralysis, other neurological disorders (excluding PD), chronic pulmonary disease, diabetes uncomplicated, diabetes complicated, hypothyroidism, renal failure, liver disease, peptic ulcer disease - excluding bleeding, lymphoma, metastatic cancer, solid tumor without metastasis, rheumatoid arthritis/collagen, coagulopathy, obesity, weight loss, fluid and electrolyte disorders, blood loss anemia, deficiency anemia, alcohol abuse, drug abuse, psychoses, and depression.²⁰ All covariates that were independently associated ($p < 0.05$) with a specific event were included in the final model for that event. All analyses were conducted using SAS v9.4 (SAS Institute Inc., Cary, NC, USA).

Sensitivity analyses

Sensitivity analyses were performed to examine whether the association between pramipexole use and HF would remain after excluding individuals diagnosed with HF prior to the study-qualifying encounter. To do so, we repeated primary and stratified analyses after excluding 1) individuals with 5 or fewer encounters (in any setting) prior to the study-

qualifying encounter and 2) individuals diagnosed with HF prior to the study-qualifying encounter.

RESULTS

Cohort characteristics

A total of 14,122 individuals with treated PD met our inclusion criteria between January 1, 2000 and December 31, 2012 (Table 1). The demographic characteristics of this inpatient cohort were similar to those reported by other large population-based studies of PD in the U.S.^{21,22} The majority of individuals were Caucasian (n=12,881, 91.2%), while remaining individuals were African American (n=891, 6.3%), Hispanic (n=138, 1.0%), Asian (n=87, 0.6%), or other (n=125, 0.9%) races. Men (n=7,632, 54.0%) were more common than women (n=6,490, 46.0%) and the majority of individuals were 65 years of age or older (90.3%) at admission.

The most frequently prescribed antiparkinson drugs were levodopa (n=12,322, 87.3%) and non-ergot DAs (n=3,062, 21.7%). Pramipexole (n=1,647, 11.7%) and ropinirole (n=1,436, 10.2%) use was similar, while rotigotine (n=5, 0.0%) use was negligible and there were no users of apomorphine. Monotherapy for PD was common (n=10,133, 71.8%). HF (n=2,318, 16.4%) and cerebrovascular accident (n=971, 6.9%) were the most frequently diagnosed cardiovascular and cerebrovascular events, respectively. Demographic characteristics of cases and matched controls for each cardiovascular and cerebrovascular event studied are shown in Supplementary Table 1. Cases and controls for each event had very similar distributions of sex, race, and age after matching.

Characteristic	Study Population n= 14,122 (%)
Race	
Caucasian	12,881 (91.2)
African American	891 (6.3)
Hispanic	138 (1.0)
Asian	87 (0.6)
Other	125 (0.9)
Sex	
Female	6,490 (46.0)
Male	7,632 (54.0)
Age at admission	
40-44	22 (0.2)
45-49	66 (0.5)
50-54	179 (1.3)
55-59	355 (2.5)
60-64	744 (5.3)
65-69	1,154 (8.2)
70-74	1,996 (14.1)
75-79	2,919 (20.7)
80-84	3,434 (24.3)
85-89	2,361 (16.7)
90+	892 (6.3)
Anti-PD drugs used	
Monotherapy	10,133 (71.8)
Levodopa	12,322 (87.3)
Non-ergot DA	3,062 (21.7)
Pramipexole	1,647 (11.7)
Ropinirole	1,436 (10.2)
Rotigotine	5 (0.0)
Diagnosed Outcome	
Acute MI	482 (3.4)
Heart Failure	2,318 (16.4)
Hypotension	869 (6.2)
Valvulopathy	981 (6.9)
CVA	971 (6.9)
Ischemic Stroke	478 (3.4)
Old Stroke	488 (3.5)
Length of stay	
<7 days	8,865 (62.8)
7-30 days	5,121 (36.3)
31+ days	136 (1.0)
Teaching status	
Teaching	9,107 (64.5)
Non-teaching	5,015 (35.5)
Number of beds	
< 5	50 (0.4)
6-99	1,047 (7.4)
100-199	1,886 (13.4)
200-299	4,453 (31.5)
300-499	3,014 (21.3)
500+	3,672 (26.0)
Census region	
Northeast	7,112 (50.4)
South	3,483 (24.7)
Midwest	2,481 (17.6)
West	1,046 (7.4)
Care Setting Location	
Urban	14,079 (99.7)
Rural	43 (0.3)

Table 1. Demographics of the study cohort. Abbreviations: CVA, cerebrovascular accident; DA, dopamine agonist; MI, myocardial infarction; PD, Parkinson disease.

Case-control analyses

Associations between non-ergot DA use for PD and the inpatient diagnosis of cardiovascular events (acute myocardial infarction, HF, hypotension, and valvulopathy) are shown in Table 2. HF was the only cardiovascular event that demonstrated a significant association with concurrent and probable prior non-ergot DA use. Individuals treated with a non-ergot DA were more likely to be diagnosed with HF, relative to no-use (adjusted odds ratio (AOR): 1.19, 95% CI: 1.02-1.38). Class-level findings were attributed to an association between pramipexole use and HF (relative to no-use) (AOR: 1.28, 95% CI: 1.07-1.53), which was not observed among ropinirole users (AOR 0.99, 95% CI: 0.82-1.20). Estimates of the risk of HF with non-ergot DA use were greater in comparisons of individuals receiving monotherapy for PD, with individuals receiving pramipexole monotherapy being more likely to be diagnosed with HF (relative to levodopa monotherapy) (AOR: 1.50, 95% CI: 1.09-2.06). Estimates of the risk of cerebrovascular events (cerebrovascular accident and ischemic stroke) in relation to non-ergot DA use for PD are shown in Table 3. Diagnosis of either cerebrovascular event was not associated with non-ergot DA use.

Acute MI ^a				
	Cases n = 482 (%)	Controls* n = 1,446 (%)	AOR (95% CI)	p value
DA use vs. no use				
Any non-ergot	94 (19.5)	320 (22.1)	0.80 (0.60 - 1.08)	0.14
Pramipexole	41 (8.5)	173 (12.0)	0.68 (0.46 - 1.01)	0.06
Ropinirole	53 (11.0)	149 (10.3)	0.98 (0.68 - 1.42)	0.90
DA only use vs. LD only use				
Levodopa	306 (63.5)	888 (61.4)	ref	-
Any non-ergot	35 (7.3)	102 (7.1)	1.03 (0.62 - 1.73)	0.91
Pramipexole	18 (3.7)	61 (4.2)	0.88 (0.44 - 1.77)	0.72
Ropinirole	17 (3.5)	41 (2.8)	1.09 (0.52 - 2.29)	0.82
Heart Failure ^b				
	Cases n = 2,318 (%)	Controls* n = 6,954 (%)	AOR (95% CI)	p value
DA use vs. no use				
Any non-ergot	488 (21.1)	1,370 (19.7)	1.19 (1.02 - 1.38)	0.02
Pramipexole	263 (11.3)	729 (10.5)	1.28 (1.07 - 1.53)	0.01
Ropinirole	229 (9.9)	654 (9.4)	0.99 (0.82 - 1.20)	0.94
DA only use vs. LD only use				
Levodopa	1,523 (65.7)	4,420 (63.6)	ref	-
Any non-ergot	180 (7.8)	409 (5.9)	1.31 (1.04 - 1.66)	0.02
Pramipexole	96 (4.1)	212 (3.0)	1.50 (1.09 - 2.06)	0.01
Ropinirole	84 (3.6)	197 (2.8)	1.13 (0.81 - 1.59)	0.48
Hypotension ^c				
	Cases n = 869 (%)	Controls* n = 2,607 (%)	AOR (95% CI)	p value
DA use vs. no use				
Any non-ergot	201 (23.1)	568 (21.8)	1.09 (0.90 - 1.32)	0.39
Pramipexole	102 (11.7)	297 (11.4)	1.12 (0.87 - 1.44)	0.37
Ropinirole	100 (11.5)	276 (10.6)	1.02 (0.79 - 1.32)	0.88
DA only use vs. LD only use				
Levodopa	517 (59.5)	1,591 (61.0)	ref	-
Any non-ergot	50 (5.8)	167 (6.4)	0.94 (0.64 - 1.39)	0.75
Pramipexole	22 (2.5)	74 (2.8)	1.09 (0.61 - 1.96)	0.77
Ropinirole	28 (3.2)	93 (3.6)	0.81 (0.49 - 1.35)	0.42
Valvulopathy ^d				
	Cases n = 981 (%)	Controls* n = 2,943 (%)	AOR (95% CI)	p value
DA use vs. no use				
Any non-ergot	206 (21.0)	584 (19.8)	1.11 (0.91 - 1.36)	0.30
Pramipexole	112 (11.4)	327 (11.1)	1.11 (0.86 - 1.42)	0.44
Ropinirole	96 (9.8)	262 (8.9)	1.08 (0.82 - 1.43)	0.59
DA only use vs. LD only use				
Levodopa	622 (63.4)	1,882 (63.9)	ref	-
Any non-ergot	67 (6.8)	183 (6.2)	1.31 (0.91 - 1.88)	0.15
Pramipexole	37 (3.8)	104 (3.5)	1.09 (0.68 - 1.75)	0.71
Ropinirole	30 (3.1)	79 (2.7)	1.73 (0.98 - 3.08)	0.06

Table 2. Adjusted risk estimates for the association between non-ergot DA use and inpatient diagnosis of cardiovascular outcomes.

*Controls matched to cases at 3:1 ratio by age, race, and sex.

^aAdjusted for length of stay, census category, hospital teaching status, congestive HF, cardiac arrhythmia, valvular disease, pulmonary circulation disorders, hypertension complicated, chronic pulmonary disease, diabetes uncomplicated, renal failure, metastatic cancer, solid tumor without metastasis, obesity, and depression.

^bAdjusted for length of stay, number of antiparkinson drugs dispensed, census category, cardiac arrhythmia, valvular disease, pulmonary circulation disorders, peripheral vascular disorders, hypertension uncomplicated, hypertension complicated, chronic pulmonary disease, diabetes uncomplicated, diabetes complicated, hypothyroidism, renal failure, coagulopathy, obesity, fluid and electrolyte disorders, drug abuse, psychoses, and depression.

^cAdjusted for census category, hospital teaching status, congestive HF, cardiac arrhythmia, valvular disease, pulmonary circulation disorders, hypertension complicated, hypothyroidism, renal failure, peptic ulcer disease - excluding bleeding, coagulopathy, weight loss, fluid and electrolyte disorders, and blood loss anemia.

^dAdjusted for census category, hospital teaching status, congestive HF, cardiac arrhythmia, pulmonary circulation disorders, peripheral vascular disorders, hypertension uncomplicated, hypertension complicated, paralysis, chronic pulmonary disease, renal failure, liver disease, coagulopathy, obesity, and depression.

Abbreviations: AOR, adjusted odds ratio; CVA, cerebrovascular accident; DA, dopamine agonist; LD, levodopa; MI, myocardial infarction.

CVA ^a				
	Cases n = 971 (%)	Controls* n = 2,913 (%)	AOR (95% CI)	p value
DA use vs. no use				
Any non-ergot	201 (20.7)	609 (20.9)	1.02 (0.81 - 1.29)	0.87
Pramipexole	107 (11.0)	353 (12.1)	0.97 (0.74 - 1.27)	0.82
Ropinirole	98 (10.1)	260 (8.9)	1.12 (0.83 - 1.49)	0.46
DA only use vs. LD only use				
Levodopa	627 (64.6)	1,774 (60.9)	ref	-
Any non-ergot	69 (7.1)	190 (6.5)	1.06 (0.74 - 1.51)	0.77
Pramipexole	41 (4.2)	105 (3.6)	1.13 (0.71 - 1.79)	0.61
Ropinirole	28 (2.9)	85 (2.9)	0.89 (0.51 - 1.54)	0.67
Ischemic Stroke ^b				
	Cases n = 478 (%)	Controls* n = 1,434 (%)	AOR (95% CI)	p value
DA use vs. no use				
Any non-ergot	85 (17.8)	299 (20.9)	0.85 (0.59 - 1.21)	0.36
Pramipexole	48 (10.0)	159 (11.1)	1.09 (0.72 - 1.66)	0.67
Ropinirole	38 (7.9)	140 (9.8)	0.67 (0.41 - 1.09)	0.11
DA only use vs. LD only use				
Levodopa	323 (67.6)	875 (61.0)	ref	-
Any non-ergot	30 (6.3)	94 (6.6)	0.81 (0.44 - 1.47)	0.48
Pramipexole	20 (4.2)	54 (3.8)	1.08 (0.50 - 2.30)	0.85
Ropinirole	10 (2.1)	39 (2.7)	0.52 (0.20 - 1.36)	0.18

Table 3. Adjusted risk estimates for the association between non-ergot DA use and inpatient diagnosis of cerebrovascular outcomes.

*Controls matched to cases at 3:1 ratio by age, race, and sex.

^aAdjusted for number of antiparkinson drugs dispensed, hospital teaching status, congestive HF, cardiac arrhythmia, pulmonary circulation disorders, peripheral vascular disorders, hypertension uncomplicated, paralysis, other neurological disorders, chronic pulmonary disease, lymphoma, fluid and electrolyte disorders, and psychoses.

^bAdjusted for number of antiparkinson drugs dispensed, cardiac arrhythmia, valvular disease, hypertension uncomplicated, paralysis, other neurological disorders, chronic pulmonary disease, and fluid and electrolyte disorders.

Abbreviations: AOR, adjusted odds ratio; CVA, cerebrovascular accident; DA, dopamine agonist; LD, levodopa; MI, myocardial infarction.

Stratified analyses – sex, race, and age effects

To investigate the possibility of effect modification, associations between pramipexole use and HF stratified by demographic characteristics (sex, race, and age) were examined (Table 4A). Men (AOR: 1.46, 95% CI: 1.09-1.95) and individuals 70-79 years of age (AOR: 1.69, 95% CI: 1.10-2.61) treated with pramipexole were at significantly higher risk of HF, relative to no use. The association between pramipexole monotherapy and HF (relative to levodopa monotherapy) was more pronounced for men (AOR: 1.90, 95% CI: 1.05-3.45) and septuagenarians (AOR: 4.30, 95% CI: 1.64-11.26). Small sample sizes precluded us from calculating estimates of the risk of HF following pramipexole use for non-white populations.

A		Heart Failure ^e				B		Heart Failure ^e			
Cases		Controls		AOR (95% CI)	p value	Cases		Controls		AOR (95% CI)	p value
n = 2,318 (%)		n = 6,954 (%)				n = 483 (%)		n = 1,449 (%)			
		DA use vs. no use				DA use vs. no use					
Pramipexole ^a	263 (11.35)	729 (10.48)	0 [†]	0.00	Pramipexole ^a	61 (12.6)	145 (10.0)	1.37 (0.94 - 1.98)	0.10		
Female ^b	113 (4.9)	367 (5.3)	1.06 (0.75 - 1.48)	0.76	Female ^b	29 (6.0)	73 (5.0)	1.48 (0.67 - 3.25)	0.33		
Male ^b	150 (6.5)	366 (5.3)	1.46 (1.09 - 1.95)	0.01	Male ^b	32 (6.6)	68 (4.7)	1.57 (0.83 - 2.95)	0.16		
White ^c	239 (10.3)	675 (9.7)	1.18 (0.98 - 1.42)	0.08	White ^c	56 (11.6)	135 (9.3)	1.40 (0.94 - 2.06)	0.10		
Non-White ^c	24 (1.0)	44 (0.6)	**	**	Non-White ^c	5 (1.0)	8 (0.6)	**	**		
60-69 ^d	33 (1.4)	175 (2.5)	0.61 (0.13 - 2.95)	0.54	60-69 ^d	8 (1.7)	26 (1.8)	**	**		
70-79 ^d	91 (3.9)	322 (4.6)	1.69 (1.10 - 2.61)	0.02	70-79 ^d	22 (4.6)	78 (5.4)	0.73 (0.25 - 2.17)	0.57		
80+ ^d	132 (5.7)	263 (3.8)	1.34 (0.97 - 1.86)	0.08	80+ ^d	31 (6.4)	50 (3.5)	2.19 (1.07 - 4.47)	0.03		
DA only use vs. LD only use											
Pramipexole ^a	96 (4.14)	212 (3.05)	0 [†]	0.00	Pramipexole ^a	22 (4.6)	53 (3.7)	1.71 (0.90 - 3.25)	0.10		
Female ^b	43 (1.9)	117 (1.7)	1.15 (0.64 - 2.09)	0.64	Female ^b	7 (1.4)	24 (1.7)	3.51 (0.50 - 24.71)	0.21		
Male ^b	53 (2.3)	109 (1.6)	1.90 (1.05 - 3.45)	0.03	Male ^b	15 (3.1)	22 (1.5)	1.82 (0.50 - 6.58)	0.36		
White ^c	86 (3.7)	202 (2.9)	0.93 (0.67 - 1.28)	0.65	White ^c	20 (4.1)	41 (2.8)	2.40 (1.12 - 5.14)	0.02		
Non-White ^c	10 (.4)	14 (.2)	**	**	Non-White ^c	2 (0.4)	4 (0.3)	**	**		
60-69 ^d	9 (.4)	38 (.5)	**	**	60-69 ^d	2 (0.4)	8 (0.6)	**	**		
70-79 ^d	41 (1.8)	81 (1.2)	4.30 (1.64 - 11.26)	0.00	70-79 ^d	8 (1.7)	22 (1.5)	**	**		
80+ ^d	45 (1.9)	75 (1.1)	1.25 (0.72 - 2.18)	0.44	80+ ^d	12 (2.5)	15 (1.0)	1.27 (0.33 - 4.88)	0.73		

Table 4. Stratified risk estimates for the association between pramipexole use and HF (A). Sensitivity analysis (B).

^aControls matched to cases at 3:1 ratio by age, race, and sex. ^bControls matched to cases at 3:1 ratio by age and race. ^cControls matched to cases at 3:1 ratio by age and sex. ^dControls matched to cases at 3:1 ratio by race and sex. ^eAdjusted for length of stay, number of antiparkinson drugs dispensed, census category, cardiac arrhythmia, valvular disease, pulmonary circulation disorders, peripheral vascular disorders, hypertension uncomplicated, hypertension complicated, chronic pulmonary disease, diabetes uncomplicated, diabetes complicated, hypothyroidism, renal failure, coagulopathy, obesity, fluid and electrolyte disorders, drug abuse, psychoses, and depression.

Abbreviations: AOR, adjusted odds ratio; DA, dopamine agonist; LD, levodopa.

Sensitivity analyses

Associations between both pramipexole use (relative to no use) (AOR: 1.29, 95% CI: 1.02-1.38) and pramipexole monotherapy (relative to levodopa monotherapy) (AOR: 1.50, 95% CI: 1.09-2.06) and HF were similar in direction to those observed in the primary and secondary analyses (Table 4B). Stratified analyses revealed that older individuals (80+ years of age) (AOR: 2.19, 95% CI: 1.07-4.47) treated with pramipexole (relative to no use) were at higher risk of HF, as were whites (AOR: 2.40, 95% CI: 1.12-5.14) receiving pramipexole monotherapy (relative to levodopa monotherapy) for PD.

DISCUSSION

Dopaminergic medications reduce symptom burden/disability, improve quality of life, and increase survival in PD.²³⁻²⁵ In addition, individuals with PD who adhere to antiparkinson treatment regimens utilize health services less often and have lower health care expenditures.²⁶ The benefits of treating PD are clear; knowledge of potential risks from PD medications allows physicians to make individualized treatment recommendations based on motor symptoms, comorbid diseases, and patient preferences. Because randomized controlled trials (RCTs) are designed to maximize internal validity, active pharmacovigilance using real world data is key to identifying potential health risks associated with medications in the general/intended population.²⁷ Using a matched case-control study design and data from more than 14,000 inpatients receiving pharmacotherapy for PD, we investigated whether non-ergot DA use is associated with specific cardiovascular outcomes. Our primary finding is that inpatients treated with pramipexole are more likely to be diagnosed with HF than those not receiving this drug. Secondary findings include: (1) non-ergot DA use was not

associated with the inpatient diagnosis of cerebrovascular events and (2) men and older individuals using pramipexole were at increased risk of HF, compared to those not receiving pramipexole.

Non-ergot DAs are commonly used as monotherapy in younger and mildly symptomatic PD patients.^{1,28,29} Impulsivity, cognitive impairment, and somnolence are known adverse events associated with non-ergot DAs.^{1,30-32} Our data add to the growing body of pharmacovigilance literature that suggests cardiac diagnoses may be more common among DA users. Phase II/III clinical trial data demonstrated a higher frequency of HF among pramipexole users vs. placebo, but this difference was not statistically significant.⁹ Using the United Kingdom General Practice Research Database, a subsequent study demonstrated an increased risk of outpatient diagnosis of HF associated with the use of any DA (vs. no use) (RR: 1.58, 1.26-1.96), and that this risk was greatest for users of pramipexole and cabergoline.⁸ Similarly, a study utilizing pooled outpatient data from the United Kingdom, Italy, and the Netherlands reported an increased risk of HF associated with pramipexole (RR: 1.61, 1.09-2.38) use relative to levodopa.⁷ While it may be more appropriate to use levodopa users over non-users of non-ergot DAs as a referent group when examining associations between non-ergot DA use and adverse cardiovascular events, estimates of the risk of HF associated with pramipexole use were similar between prior studies using European data.^{7,8} Additionally, findings from our monotherapy models for the association between pramipexole and HF (AOR: 1.50, 95% CI: 1.09-2.06 relative to levodopa) are congruent in magnitude and direction with previously reported results.

Investigators of the most recent study to examine the association between non-ergot DAs and HF used data from Taiwan's National Health Insurance research database to conduct a large case-control study nested within a cohort of new users of antiparkinson drugs.⁶ They compared the risk of HF among DA users to non-DA users and found a non-significant increased HF risk with both ropinirole (AOR 1.22, 95 % CI 0.76–1.95) and pramipexole (AOR 1.40, 95 % CI 0.75–2.61). Using a similar study design, we report similar findings for ropinirole (AOR: 1.13, 95% CI: 0.81-1.59 relative to no use) and show a significant risk of HF with pramipexole (AOR: 1.28, 95% CI: 1.07-1.53 relative to no use). As Hsieh and Hsiao (2013) discuss, differences in reported associations between non-ergot DA use and HF may in large part be attributed to population-level differences, including but not limited to differences in prescribing practices between countries. Our study builds upon these findings by examining associations between non-ergot DA use and cardiovascular and cerebrovascular events in a large U.S. patient population. Moreover, our study is the first to investigate associations between pramipexole and HF in patient subpopulations defined by specific demographic characteristics (age, race, and sex).

Although biological mechanisms by which pramipexole could potentially cause HF remain unclear, a recent phase I clinical trial suggests that drug-induced supraphysiologic increases in vital signs underly the associations between D2 receptor agonists and HF.³³ In this trial, pramipexole was administered to 52 healthy male subjects in escalating doses over 13 days and serial measurements of blood pressure and heart rate were analyzed. Statistically significant increases in mean systolic blood pressure, heart rate, pulse pressure, and resting pulse pressure were observed in a dose dependent fashion. Moreover, authors suggest that

non-physiologic increased chronic pulsatile stress (equal to pulse pressure * heart rate) may result in endothelial cell dysfunction through a variety of pathophysiologic mechanisms.³³⁻³⁵

Our findings that men and older individuals treated with pramipexole were more likely than those not receiving pramipexole to be diagnosed with HF have several possible explanations. HF is more prevalent in men than women at all ages, even after adjusting for common HF risk factors such as obesity and diabetes.³⁶ If a medication were to increase the risk of HF, men may be more susceptible to adverse effects of the drug. The increased association between pramipexole use and HF observed in older populations may reflect prolonged pramipexole use by older individuals with less severe PD or by older individuals who are intolerant of the autonomic/cognitive side effects of levodopa.

Our study has a number of strengths. Data were derived from a large cohort of individuals with PD who received care from many health facilities across the United States during the 13-year study period. Because the majority of the study data originate from neurologist-rich urban teaching centers, observed treatment regimens for PD likely reflect best practice guidelines at the time of admission. Our study also included older individuals with PD, a group that is underrepresented in RCTs, and vulnerable to adverse outcomes. Our primary findings are congruent with existing pharmacovigilance data, are supported by plausible pathogenic mechanisms, and were robust to several sensitivity/secondary analyses.

Despite these strengths, making causal inferences based on these data is inappropriate for several reasons. We were unable to calculate the dose-adverse event relationship or lifetime

risk estimates for cardiovascular and cerebrovascular events studied, as medication dose was difficult to assess in quantitative terms and our data had limited information on outpatient drug use and prescription adherence. Although our data did not permit us to take dose of dopamine agonist treatment into account in our statistical models, results from similar analyses in non-US populations suggest that our primary finding of an increased risk of heart failure in relation to pramipexole use may have been minimally impacted by this limitation. Prior studies found no association between the dose of pramipexole and the risk of heart failure.^{7,8} While we assumed that antiparkinson medications dispensed in inpatient settings were probable continuations of outpatient treatment regimens, we could not verify this nor length of drug exposure. Nevertheless, the effect of pramipexole exposure duration on heart failure risk remains controversial, with two studies showing no effect,^{6,8} and a single study suggesting that there may be significant risk of heart failure in the first three months of pramipexole exposure that diminishes, rather than increases, with continued use.⁷ Although, we used statistical matching and covariate adjustment techniques to decrease the effects of case mix and possible confounding in our analyses, the possibility of bias from unmeasured confounders, such as smoking, remains. The strong association between smoking and HF is well-documented,^{37,38} however, the association between smoking behavior and PD diagnosis remains unclear,^{39,40} and there is no data which suggests that smoking history impacts antiparkinson medication choice or response. Despite incomplete data on smoking history in Health Facts®, 15.5% (n = 2,187) of individuals in our study cohort were identified as having smoked. Univariate analyses demonstrated that smoking history, defined by categorizing individuals as ever- or never-smokers, was independently associated with the diagnosis of heart failure, but not with pramipexole use, suggesting that our reported

associations between pramipexole use and inpatient diagnosis of heart failure are not confounded by smoking history. Furthermore, inclusion of smoking history as a covariate in our adjusted statistical models had no effect on estimates of the risk of heart failure in relation pramipexole use (data not shown). Coding errors may have resulted in misclassification of diagnoses and drug use that we could not detect in sensitivity analyses or account for using statistical methods of adjustment. Additionally, our multiple case-control study design resulted in our analyses being better powered to detect associations between non-ergot DAs and more common outcomes, such as HF and ischemic stroke. While analyses of inpatients with PD may impose limitations to external validity, we have previously reported that inpatients with PD are hospitalized for reasons that are consistent with inpatient admissions among older adults in the United States.⁴¹ Lastly, the present analysis involved a large number of statistical tests based on four cardiovascular and two cerebrovascular outcomes, as well as different classes of non-ergot DAs (pramipexole and ropinirole) and different referent groups (no use or levodopa monotherapy). A formal adjustment for multiple comparisons was not made, as our analyses are considered largely exploratory. However, our most significant findings (use of non-ergot DAs and the risk of HF) are consistent with the strongest associations previously reported in the literature.⁶⁻⁸

In conclusion, we found a positive association between pramipexole use and inpatient diagnosis of HF in a large population-based dataset comprised largely of academic medical centers. Our data add to the growing literature on cardiovascular risks associated with non-ergot DA use. This evidence is not sufficient to contraindicate the use of a specific medication, but may support monitoring for signs/symptoms of HF, including shortness of

breath, edema, and increased heart rate (especially in older adults and men) and demands replication and additional investigation. Moreover, our findings support the need for future prospective studies to examine the association between pramipexole use and heart failure and whether identified associations, if any, are clinically important. If dose dependent exposure-outcome relationships are confirmed, clinical guidelines and/or drug packaging may be modified to monitor/limit non-ergot DA exposure in individuals with a history of HF or with independent risk factors for HF.

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Mr. Crispo, Dr. Willis, Mr. Thibault, Mr. Fortin, Dr. Bjerre, and Dr. Kohen report no disclosures. Dr. Perez Lloret served as a consultant for Aguetant Laboratories in 2014. Dr. Emons was employed by the Cerner Corporation at the time this study was conducted. Dr. Mattison serves as Chief Medical Officer of Risk Sciences International, a Canadian company formed in partnership with the University of Ottawa in 2006 (www.risksciences.com) that conducts risk assessment work for public and private sector clients in Canada and internationally. To date, RSI has not conducted work on the subject of the present research paper. Dr. Krewski serves as Chief Risk Scientist and CEO of Risk Sciences International. From 2009- 2014, Dr. Krewski held a Natural Sciences and Engineering Council of Canada (NSERC) Industrial Research Chair in Risk Science, through a peer-reviewed university-industry partnerships program administered by NSERC. None of the industrial partners in this program were from the pharmaceutical industry.

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Characteristic	Acute MI		Heart Failure		Hypertension		Valvulopathy		CVA		Ischemic Stroke	
	Cases n (%)	Controls n (%)	Cases n (%)	Controls n (%)	Cases n (%)	Controls n (%)	Cases n (%)	Controls n (%)	Cases n (%)	Controls n (%)	Cases n (%)	Controls n (%)
Study Population	n = 14,122	n = 1,482	n = 1,446	n = 2,318	n = 869	n = 2,607	n = 981	n = 2,943	n = 971	n = 2,913	n = 478	n = 1,434
Race												
Caucasian	12,881 (91.2)	449 (93.2)	1,347 (93.2)	2,136 (92.1)	786 (90.4)	2,360 (90.5)	920 (93.8)	2,761 (93.8)	879 (90.5)	2,640 (90.6)	423 (88.5)	1,269 (88.5)
African American	891 (6.3)	20 (4.1)	66 (4.6)	141 (6.1)	66 (7.6)	203 (7.8)	48 (4.9)	148 (5.0)	68 (7.0)	208 (7.1)	40 (8.4)	127 (8.9)
Hispanic	138 (1.0)	6 (1.2)	13 (0.9)	13 (0.6)	7 (0.8)	15 (0.6)	5 (0.5)	10 (0.3)	7 (0.7)	18 (0.6)	5 (1.0)	9 (0.6)
Asian	87 (0.6)	2 (0.4)	5 (0.3)	31 (0.4)	5 (0.6)	14 (0.5)	4 (0.4)	12 (0.4)	4 (0.4)	8 (0.3)	2 (0.4)	5 (0.3)
Other	125 (0.9)	5 (1.0)	15 (1.0)	16 (0.7)	5 (0.6)	15 (0.6)	4 (0.4)	12 (0.4)	13 (1.3)	39 (1.3)	8 (1.7)	24 (1.7)
Sex												
Female	6,490 (46.0)	206 (42.5)	614 (42.5)	1,040 (44.9)	372 (42.8)	1,115 (42.8)	472 (48.1)	1,418 (48.2)	442 (45.5)	1,328 (45.6)	228 (47.7)	683 (47.6)
Male	7,632 (54.0)	277 (57.5)	832 (57.5)	1,278 (55.1)	497 (57.2)	1,492 (57.2)	509 (51.9)	1,525 (51.8)	529 (54.5)	1,585 (54.4)	250 (52.3)	751 (52.4)
Age at admission												
40-44	22 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	3 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
45-49	66 (0.5)	1 (0.2)	3 (0.2)	0 (0.0)	2 (0.2)	6 (0.2)	2 (0.2)	6 (0.2)	3 (0.3)	9 (0.3)	1 (0.2)	3 (0.2)
50-54	179 (1.3)	1 (0.2)	3 (0.2)	11 (0.5)	8 (0.9)	24 (0.9)	4 (0.4)	12 (0.4)	8 (0.8)	25 (0.9)	3 (0.6)	10 (0.7)
55-59	355 (2.5)	7 (1.5)	3 (0.2)	25 (1.1)	14 (1.6)	42 (1.6)	6 (0.6)	18 (0.6)	12 (1.2)	35 (1.2)	7 (1.5)	20 (1.4)
60-64	744 (5.3)	13 (2.7)	21 (1.5)	75 (3.2)	49 (5.6)	147 (5.6)	28 (2.9)	84 (2.9)	42 (4.3)	126 (4.3)	32 (6.7)	87 (6.1)
65-69	1,154 (8.2)	35 (7.3)	39 (2.7)	127 (5.5)	67 (7.7)	200 (7.7)	49 (5.0)	146 (5.0)	63 (6.5)	189 (6.5)	39 (8.2)	96 (6.7)
70-74	1,996 (14.1)	61 (12.7)	105 (7.3)	263 (11.3)	122 (14.0)	367 (14.1)	114 (11.6)	343 (11.7)	111 (11.4)	333 (11.4)	60 (12.6)	179 (12.5)
75-79	2,919 (20.7)	108 (22.4)	324 (22.4)	454 (18.7)	193 (22.2)	579 (22.2)	212 (21.6)	636 (21.6)	209 (21.5)	627 (21.5)	106 (22.2)	319 (22.2)
80-84	3,434 (24.3)	126 (26.1)	378 (26.1)	643 (27.7)	216 (24.9)	648 (24.9)	270 (27.5)	810 (27.5)	271 (27.9)	815 (28.0)	126 (26.4)	377 (26.5)
85-89	2,361 (16.7)	95 (19.7)	285 (19.7)	495 (21.4)	157 (18.1)	471 (18.1)	211 (21.5)	632 (21.5)	184 (18.9)	550 (18.9)	81 (16.9)	244 (17.0)
90+	892 (6.3)	35 (7.3)	105 (7.3)	243 (10.5)	40 (4.6)	120 (4.6)	85 (8.7)	256 (8.7)	68 (7.0)	204 (7.0)	33 (6.9)	99 (6.9)
Anti-PD drugs used												
Monotherapy	10,133 (71.8)	363 (75.3)	1,047 (72.4)	1,791 (77.3)	603 (69.4)	1,879 (72.1)	722 (73.6)	2,182 (74.1)	732 (75.4)	2,088 (71.7)	371 (77.6)	1,035 (72.2)
Levodopa	12,322 (87.5)	420 (87.1)	1,265 (87.5)	2,028 (87.5)	770 (88.6)	2,292 (87.9)	876 (89.3)	2,605 (88.5)	858 (88.4)	2,554 (87.7)	426 (89.1)	1,253 (87.4)
Non-ergot DA	3,062 (21.7)	94 (19.5)	320 (22.1)	488 (21.1)	201 (23.1)	568 (21.8)	206 (21.0)	584 (19.8)	201 (20.7)	609 (20.9)	85 (17.8)	299 (20.9)
Pramipexole	1,647 (11.7)	41 (8.5)	173 (12.0)	263 (11.3)	102 (11.4)	297 (11.4)	102 (11.4)	327 (11.1)	107 (11.0)	353 (12.1)	48 (10.0)	159 (11.1)
Ropinirole	1,436 (10.2)	53 (11.0)	149 (10.3)	229 (9.9)	100 (11.5)	276 (10.6)	96 (9.9)	262 (8.9)	98 (10.1)	260 (8.9)	38 (7.9)	140 (9.8)
Rosiglitone	5 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	1 (0.2)	1 (0.1)
Length of stay												
<7 days	8,865 (62.8)	239 (49.6)	904 (62.5)	1,302 (56.2)	542 (62.4)	1,598 (61.3)	599 (61.1)	1,839 (63.2)	601 (61.9)	1,814 (62.3)	288 (60.3)	893 (62.3)
7-30 days	5,121 (36.3)	239 (49.6)	527 (36.4)	992 (42.8)	322 (37.1)	979 (37.6)	377 (38.4)	1,062 (36.1)	360 (37.1)	1,077 (37.0)	182 (38.1)	523 (36.5)
31+ days	136 (1.0)	4 (0.8)	15 (1.0)	24 (1.0)	5 (0.6)	30 (1.2)	5 (0.5)	22 (0.7)	10 (1.0)	22 (0.8)	8 (1.7)	18 (1.3)
Teaching status												
Teaching	9,107 (64.5)	334 (69.3)	927 (64.1)	1,529 (66.0)	592 (68.1)	1,660 (63.3)	684 (69.7)	1,860 (63.2)	671 (69.1)	1,881 (64.6)	329 (68.8)	928 (64.7)
Non-teaching	5,015 (35.5)	148 (30.7)	519 (35.9)	789 (34.0)	277 (31.9)	947 (35.7)	297 (30.3)	1,083 (36.8)	300 (30.9)	1,032 (35.4)	149 (31.2)	506 (35.3)
Number of beds												
< 5	50 (0.4)	0 (0.0)	2 (0.1)	4 (0.2)	0 (0.0)	9 (0.3)	1 (0.1)	6 (0.2)	0 (0.0)	6 (0.2)	0 (0.0)	8 (0.6)
6-99	1,047 (7.4)	24 (5.0)	116 (8.0)	187 (8.1)	68 (7.8)	203 (7.8)	42 (4.3)	245 (8.3)	60 (6.2)	231 (7.9)	23 (4.8)	117 (8.2)
100-199	1,886 (13.4)	57 (11.8)	200 (13.8)	298 (12.9)	104 (12.0)	324 (12.4)	101 (10.3)	406 (13.8)	130 (13.4)	334 (11.5)	65 (13.6)	169 (11.8)
200-299	4,453 (31.5)	161 (33.4)	446 (30.8)	738 (31.8)	248 (28.5)	807 (31.0)	271 (27.6)	947 (32.2)	283 (29.1)	947 (32.1)	143 (29.9)	419 (29.2)
300-499	3,014 (21.3)	102 (21.2)	279 (19.3)	476 (20.5)	191 (22.0)	520 (19.9)	217 (22.1)	572 (19.4)	213 (21.9)	589 (20.2)	98 (20.5)	276 (19.2)
500+	3,672 (26.0)	138 (28.6)	403 (27.9)	615 (26.5)	258 (29.7)	744 (28.5)	349 (35.6)	767 (26.1)	285 (29.4)	819 (28.1)	149 (31.2)	445 (31.0)
Census region												
Northeast	7,112 (50.4)	273 (56.6)	720 (49.8)	1,174 (50.6)	394 (45.3)	1,290 (49.5)	530 (56.1)	1,525 (51.8)	514 (52.9)	1,476 (50.7)	247 (51.7)	692 (48.3)
South	3,483 (24.7)	113 (23.4)	383 (26.5)	597 (25.8)	264 (30.4)	680 (26.1)	223 (22.7)	752 (25.6)	242 (24.9)	761 (26.1)	122 (25.5)	420 (29.3)
Midwest	2,481 (17.6)	59 (12.2)	243 (16.8)	404 (17.4)	150 (17.3)	442 (17.0)	150 (15.3)	487 (16.5)	163 (16.8)	474 (16.3)	82 (17.2)	226 (15.8)
West	1,046 (7.4)	37 (7.7)	100 (6.9)	143 (6.2)	61 (7.0)	195 (7.5)	58 (5.9)	179 (6.1)	52 (5.4)	202 (6.9)	27 (5.6)	96 (6.7)
Care Setting Location												
Urban	14,079 (99.7)	480 (99.6)	1,441 (99.7)	2,316 (99.9)	869 (100.0)	2,599 (99.7)	979 (99.8)	2,931 (99.6)	969 (99.8)	2,901 (99.6)	476 (99.6)	1,429 (99.7)
Rural	43 (0.3)	2 (0.0)	5 (0.3)	2 (0.1)	0 (0.0)	8 (0.3)	2 (0.2)	12 (0.4)	2 (0.2)	12 (0.4)	2 (0.4)	5 (0.3)

Supplementary Table 1. Demographic characteristics of cases and controls after matching on age, race, and sex. Abbreviations: CVA, cerebrovascular accident; DA, dopamine agonist; MI, myocardial infarction; PD, Parkinson disease.

CHAPTER IV: Non-ergot dopamine agonists and the risk of heart failure and other adverse cardiovascular reactions in Parkinson disease

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BACKGROUND

Description of the condition

Idiopathic Parkinson disease (PD), a condition characterized by the progressive degeneration of dopaminergic neurons in the substantia nigra pars compacta, is the second most common neurodegenerative disorder worldwide (Lang 1998; Muangpaisan 2011). PD is a disease of aging; therefore a growing fraction of older adults in a population will cause the prevalence and incidence of PD to increase (de Lau 2006; Van Den Eeden 2003; Wright Willis 2010). The worldwide prevalence of PD in the general population ranges from 57 to 371 per 100,000 population, with an incidence rate of 5 to 24 cases per 100,000 individuals per year, with men demonstrating consistently higher incidence rates than women (Tarazi 2007; Wooten 2004). However, PD is most prevalent in older adult populations and is diagnosed in 1-2 % of adults over the age of 60 (Wright Willis 2010).

The first motor symptoms of PD typically include tremor, rigidity, bradykinesia, and difficulties walking and maintaining balance (Casey 2013). Patients may develop depression, sleep disorders, and autonomic dysfunction (such as constipation, urinary dysfunction, and orthostatic hypotension), cognitive impairment, either as initial symptoms or as the disorder progresses (Grimes 2012; Merims 2008).

Although there is no known cure for PD, many pharmacological and non-pharmacological interventions are effective at managing PD symptoms and improving patient quality of life. Medications used alone or in combination in the treatment of PD include: levodopa, dopamine agonists, enzyme inhibitors (monoamine oxidase B and catechol-o-

methyltransferase inhibitors), anticholinergics, and amantadine (Grimes 2012). Non-pharmacological interventions include: physical and exercise therapies, occupational therapy, and speech and language therapy (Grimes 2012). Disease progression is associated with “motor fluctuation”, temporal shortening of medication response, and drug-related involuntary movements. Deep brain stimulation surgery is efficacious for those with PD who suffer from non-responsive motor fluctuations (Bronstein 2011).

Levodopa remains the gold standard for the treatment of PD, it is potent, and associated with side effects such as nausea, dopa-induced chorea or dystonia, and hypotension (Lieberman 2013; Perez-Lloret 2014). Consequently, other anti-PD drugs are often incorporated into the management of milder PD symptoms, including dopamine agonists (Sprenger 2013).

Description of the intervention

First developed in the 1970’s, dopamine receptor agonists are primarily indicated for the treatment of neurologic diseases, such as PD and restless legs syndrome, and non-neurologic conditions, such as hyperprolactinemia (Bonuccelli 2009; Majumdar 2013; Nirenberg 2013).

Dopamine receptor agonists are classified into two pharmacological categories: (1) ergot derivatives (bromocriptine, cabergoline, pergolide, and lisuride) and (2) non-ergot derivatives (apomorphine, pramipexole, ropinirole, and rotigotine) (Perez-Lloret 2014). Possible adverse effects associated with dopamine agonist use may be related to dopaminergic stimulation or to idiosyncratic reactions (Perez-Lloret 2010). These effects include impulse control disorders (pathological gambling, hypersexuality, compulsive shopping), addiction/substance abuse, cognitive slowing/confusion, sleep attacks, cardiac

valve fibrosis, pleuropulmonary fibrosis, retroperitoneal fibrosis, psychosis, nausea, vomiting, dizziness, postural hypotension, and peripheral edema (Bonuccelli 2009; Möller 2008; Vilas 2012).

How the intervention might work

The mechanism of action for dopamine agonists is reliant on the activation of dopamine receptors, with some agonists also stimulating nondopaminergic receptors, such as α -adrenergic and serotonergic receptors (Perez-Lloret 2014). Ergot derivatives stimulate both D1-like and D2-like receptors, while non-ergot derivatives selectively stimulate D2-like receptors (Katsuki 2012; Perez-Lloret 2014)

In addition to providing another alternative to levodopa, evidence from *in-vitro* and *in-vivo* experimental models suggests that non-ergot derivatives may be neuroprotective; however, this remains to be substantiated in clinical practice (Möller 2008; Radad 2005).

Why is it important to do this review?

Dopamine agonists, specifically ergot derivatives, have attracted attention over the course of the last decade for their association with adverse cardiovascular events other than orthostatic hypotension, such as valvulopathy and heart failure (Junghanns 2007; Mokhles 2012; Peralta 2006; Renoux 2012; Steiger 2009; Zadikoff 2008). Mounting evidence of the risk of serious damage to heart valves led to the withdrawal of pergolide from the market in some countries, including Canada and the United States (Grossman, 2007; U.S. Food and Drug Administration [FDA] 2007). Although ergot derivatives are still used worldwide, they are

not recommended as a first-line pharmacological intervention for PD due to their associated risk of fibrotic reactions (Bonuccelli 2009).

More recently, safety concerns have shifted to the risk of adverse cardiovascular reactions following the use of non-ergot dopamine agonists, with two large observational studies reporting an increased risk of heart failure with pramipexole use (Mokhles 2012; Renoux 2012). Based on these reports, the FDA released a safety announcement in September 2012 informing the public of the potential risk of heart failure associated with pramipexole use (FDA 2012).

This review will increase our understanding of the cardiac events associated with non-ergot dopamine agonists and will serve to identify knowledge gaps and further research priorities.

OBJECTIVES

To evaluate the risk of heart failure and other adverse cardiovascular reactions in Parkinson disease patients treated with non-ergot dopamine agonists, compared to other anti-Parkinson pharmacological interventions, placebo, or no intervention.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs) where exposure to one or more non-ergot dopamine agonists are included in the intervention or comparison group(s) will be eligible for

inclusion. Cross-over trials will be excluded. Since serious adverse cardiovascular reactions are thought to be rare outcomes in the treatment of Parkinson disease with non-ergot dopamine agonists, non-randomized studies (NRS), including cohort and case-control studies, satisfying our inclusion criteria will also be eligible for inclusion. To limit the potential for residual confounding and other biases, case, case series, controlled before-and-after, quasi-randomized, and interrupted-time-series studies will be excluded (Reeves 2011).

Types of participants

Participants diagnosed with idiopathic PD according to study investigators will be eligible for inclusion. Participants will not be restricted according to age, gender, disease duration, disease severity, or history of pre-existing cardiovascular disease; however, subgroup analyses will investigate differences in treatment effects by these characteristics, as appropriate.

Types of interventions

Any dose of a non-ergot dopamine agonist (apomorphine, pramipexole, ropinirole, or rotigotine) compared to other anti-Parkinson pharmacological intervention(s), placebo, or no intervention.

Types of outcomes measures

Since this systematic review focuses on harms, specifically the risk of heart failure and other adverse cardiovascular reactions in Parkinson disease, all cardiovascular outcome data will be collected and reported separately. Moreover, reporting of cardiovascular outcomes will

rely on study-specific outcome definitions. This may include investigator reports, events confirmed by clinical tests and/or hospital admission, or cardiovascular events recorded in a health administrative record or an electronic health record. Self-reports of adverse cardiovascular reactions will be excluded.

Primary outcomes

- Heart failure, as defined by individual studies

Secondary outcomes

- Blood pressure disorders, including hypertension and hypotension
- Valvulopathy
- Pleural effusion
- Peripheral edema
- Myocardial infarction
- Arrhythmias
- Cardiovascular death
- Use of cardiac drugs, including angiotensin-converting enzyme inhibitors or adrenergic beta-antagonists
- Use of artificial pacemakers or implantable defibrillators
- Syncope
- Stroke

Search methods for identification of studies

Electronic searches

The following databases will be searched for articles reporting the use of non-ergot dopamine agonists and adverse cardiovascular reactions in Parkinson disease: the Cochrane Central Register of Controlled Trials (CENTRAL; all dates), MEDLINE (from 1946 to present), Embase (from 1980 to present), the Cumulative Index to Nursing and Allied Health (CINAHL; all dates), PsycINFO (from 1806 to present), and PubMed (all dates). No language restrictions will be applied to our searches.

The Medline search strategy is provided in Appendix 1.

Searching other resources

In an effort to identify further published, unpublished, and ongoing studies, we will:

- screen the reference lists of relevant articles and textbooks;
- identify and hand search relevant conference proceedings;
- contact authors of relevant studies;
- search trial registries such as ClinicalTrials.gov (<http://www.clinicaltrials.gov>) and the World Health Organization (WHO) International Clinical Trials Registry Platform (<http://apps.who.int/trialsearch/>); and
- perform Google searches.

Data collection and analysis

Selection of studies

Two review authors (JAGC and YF) will independently screen the titles and abstracts of all studies identified through the literature searches described above and will exclude studies that do not meet our inclusion criteria. JAGC and YF will then review the full text of remaining studies and assess eligibility according to our inclusion criteria. Disagreements will be resolved through discussion or, if necessary, through input from a third review author. We will contact study authors if additional information is required to resolve a disagreement. DistillerSR (Evidence Partners, Ottawa, Ontario, Canada) software will be used for study screening, as well as for data extraction and management.

Data extraction and management

A standardized data abstraction form will be developed and tested prior to extracting data from included studies. Once validated, two review authors (JAGC and YF) will independently extract data from included studies using the abstraction form. Data will be extracted on the following items:

- study participants (such as sample size, age, gender, country, ethnicity, who diagnosed PD, stage of PD (Hoehn & Yahr, UPDRS, MDS-UPDRS ADL, and/or motor score), disease duration, presence of dyskinesia and/or motor fluctuations, and comorbid conditions);
- methods (such as randomization, allocation concealment, and blinding of participants, personnel, and outcome assessors);

- pharmacological exposures and control interventions (such as a description of the pharmacological intervention, dosage, frequency, route of administration, and duration of exposure);
- outcome measures (such as a description of the outcome measures, including how and when diagnoses were made); and
- study results (such as frequency counts, risk estimates, measures of variance, and timing of adverse events).

If required, we will contact the authors of included studies to obtain information about data that is unclear or not reported. Disagreements will be resolved through discussion or, if necessary, through input from another review author. Once data extraction is complete, JAGC will enter the extracted data into Review Manager 5.2 (version 5.2.7, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

Assessment of risk of bias in included studies

Using Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions*, two review authors (JAGC and YF) will independently assess the risk of bias in included RCTs (Higgins 2011a). For these studies, JAGC and YF will assess the risk of bias for each of the following domains as “low risk of bias”, “high risk of bias”, or “unclear risk of bias”:

- sequence generation;
- allocation concealment;
- blinding of participants and personnel (for each outcome);
- blinding of outcome assessors (for each outcome);
- incomplete outcome data (for each outcome);

- selective outcome reporting; and
- other sources of bias.

For included cohort and case-control studies, JAGC and YF will assess study bias using the Newcastle-Ottawa quality assessment scale for observational studies, a scale that judges selection of study groups, the comparability of groups, and ascertainment of the exposure (case-control) or outcome (cohort) of interest (Wells 2000). Although cohort and case-control studies are prone to biases, the Newcastle-Ottawa quality assessment scale for observational studies has successfully been used by other Cochrane reviews to assess potential biases (Loke 2007). We will contact study authors if additional information is required to assess the risk of bias. Disagreements will be resolved through discussion or, if necessary, through input from another review author.

The Newcastle-Ottawa quality assessment scale for observational studies is provided in Appendix 2.

Measures of treatment effect

For dichotomous outcomes, such as the occurrence or non-occurrence of heart failure, we will report measures of treatment effect as risk estimates (such as risk ratios (RR), odds ratios (OR), hazard ratios (HR), and incidence rate ratios (IRR)) with 95% confidence intervals.

For continuous outcomes, such as blood pressure, we will report mean differences (MD) or standardized mean differences (SMD), as appropriate, with 95% confidence intervals.

Unit of analysis issues

We do not anticipate identifying any cluster-randomized trials that meet our inclusion criteria. However, should one or more cluster-randomized trials be included after screening, we will use chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* as a guide for dealing with unit of analysis issues (Higgins 2011b). We will describe in detail how we have handled data from these studies, as necessary.

Dealing with missing data

We will contact study authors by email in an attempt to acquire any missing data. If study authors do not respond to our request for missing data, we will not impute the missing information. However, we will discuss the possible impact of missing data on the findings of our systematic review.

Assessment of heterogeneity

Heterogeneity will be assessed using the I^2 statistic and the *Cochrane Handbook for Systematic Reviews of Interventions*' recommended thresholds for interpreting the variability in intervention effects between studies, which are:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity; and
- 75% to 100%: considerable heterogeneity.

In instances where I^2 is greater than 50%, reflecting substantial heterogeneity, we will not report the results of a meta-analysis. In such cases, we will discuss factors believed to

contribute to either the clinical or methodological diversity, or both, among compared studies with substantial heterogeneity.

Assessment of reporting biases

We will examine the symmetry of funnel plots in order to assess reporting biases. In instances where funnel plots are asymmetrical, we will discuss sources that may be contributing to small-study effects, including selection biases, poor methodological quality, true heterogeneity, sampling variation, and chance (Egger 1997).

Data synthesis

We will adopt a two-level approach to data synthesis. We will first combine comparable data, including risk estimates (such as RRs, ORs, HRs, and IRRs), MDs, and SMDs (where I^2 is 50% or less), from RCTs and NRS separately in meta-analyses to estimate the risk of primary and secondary outcomes. When combining estimates of effect from NRS, we will use estimates identified as the primary adjusted models by study authors in our meta-analyses. If authors fail to explicitly identify the primary adjusted model, we will use estimates from models that are adjusted for the maximum number of covariates in our meta-analyses. Inverse variance weighting and random-effects modeling will be used in all meta-analyses, irrespective of heterogeneity. In instances where heterogeneity is high (I^2 is greater than 50%), or where there is only a single study identified, findings will be excluded from meta-analyses and will be qualitatively described.

Although the *Cochrane Handbook for Systematic Reviews of Interventions* does not recommend combining RCT and NRS data in a meta-analysis due to varying effects of different sources of bias on distinct study designs (Reeves 2011), empirical evidence suggests that it is advantageous to do so when estimating the risk of adverse effect of an intervention (Golder 2011; Hutton 2012; Shrier 2007). Therefore, in instances where comparable data (where I^2 is 50% or less) from both RCTs and NRS are available for the same cardiovascular outcome, RCT and NRS data will be combined in a single meta-analysis to estimate an overall risk of adverse cardiovascular reaction attributed to non-ergot dopamine agonist use.

Subgroup analysis and investigation of heterogeneity

Where possible, we will complete subgroup analyses to evaluate the risk of heart failure and other adverse cardiovascular reactions with individual non-ergot dopamine agonists to determine whether our findings vary according to:

1. age;
2. gender;
3. PD disease duration;
4. PD disease severity;
5. history of pre-existing cardiovascular disease; and
6. timing of adverse cardiovascular reaction (short term, medium term, long term).

Sensitivity analysis

RCTs will be considered to be at high risk of bias if a high risk of bias is identified in any of the assessed domains (sequence generation; allocation concealment; blinding of participants and personnel (for each outcome); blinding of outcome assessors (for each outcome); incomplete outcome data (for each outcome); selective outcome reporting; and other sources of bias). NRS will be considered to be at high risk of bias if they have a score <7 stars (of 9) on the Newcastle-Ottawa quality assessment scale for observational studies. Data permitting, we will perform the following sensitivity analyses to assess the robustness of our results:

- 1) exclude RCTs identified as having a high risk of bias (in any of the assessed domains) from meta-analyses of RCT data;
- 2) exclude NRS identified as having a high risk of bias (score <7 stars (of 9) on the Newcastle-Ottawa quality assessment scale for observational studies) from meta-analyses of NRS data; and
- 3) 1 and 2 for meta-analyses of combined RCT and NRS data.

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CONTRIBUTIONS OF AUTHORS

All authors contributed to writing and reviewing the study protocol.

DECLARATIONS OF INTEREST

JAGC, YF, LS, DEK, LMB, SPL, RCH, AWW have no conflicts of interest to declare.

DRM serves as Chief Medical Officer and Senior Vice President at Risk Sciences

International (www.risksciences.com), which has conducted work on other pharmaceutical products for federal government clients. DK serves as Chief Risk Scientist and CEO at Risk Sciences International.

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APPENDICES**APPENDIX 1.****MEDLINE search strategy via Ovid SP (to be modified for the search in other databases)**

1. Parkinson Disease/
2. parkinson*.tw.
3. (paralysis adj2 agitans).tw.
4. or/1-3
5. Piribedil/
6. Apomorphine/
7. apomorphine.tw.
8. p#ribedil.tw.
9. pramipexole.tw.
10. ropinirole.tw.
11. rotigotine.tw.
12. or/5-11
13. (ae or co or de).fs. or (safe or safety or side effect* or undesirable effect* or treatment emergent or tolerability or toxicity or adrs or (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes))).ti,ab.
14. exp Cardiovascular Diseases/
15. exp Cerebrovascular Disorders/
16. Defibrillators, Implantable/
17. exp Pacemaker, Artificial/
18. exp Syncope/
19. exp Angiotensin-Converting Enzyme Inhibitors/
20. exp Adrenergic beta-Antagonists/
21. Pleural Effusion/
22. (cardiovasc* adj2 dis*).tw.
23. (cerebrovasc* adj2 dis*).tw.
24. (heart adj2 failure).tw.
25. (edema or oedema).tw.
26. (pleura* adj1 effusion*).tw.
27. (valv* adj2 dis*).tw.
28. regurgitation.tw.
29. hypertension.tw.
30. hypotension.tw.
31. (myocardial adj2 infarction*).tw.
32. (heart adj2 attack*).tw.

33. arrhythmia*.tw.
34. (implant* adj1 cardiovert* adj1 defib*).tw.
35. (cardiac adj1 resynchroni?ation* adj1 therap*).tw.
36. syncop*.tw.
37. stroke.tw.
38. ACE.tw.
39. (beta adj1 blocker*).tw.
40. (cardiovasc* adj2 death*).tw.
41. or/14-40
42. 4 and 12 and 13 and 41

This search strategy has been edited by the Trials Search Coordinator for the Cochrane Movement Disorders Group.

APPENDIX 2.

Newcastle-Ottawa quality assessment scale for observational studies

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE CASE CONTROL STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Selection

- 1) Is the case definition adequate?
 - a) yes, with independent validation *
 - b) yes, eg record linkage or based on self reports
 - c) no description

- 2) Representativeness of the cases
 - a) consecutive or obviously representative series of cases *
 - b) potential for selection biases or not stated

- 3) Selection of Controls
 - a) community controls *
 - b) hospital controls
 - c) no description

- 4) Definition of Controls
 - a) no history of disease (endpoint) *
 - b) no description of source

Comparability

- 1) Comparability of cases and controls on the basis of the design or analysis
 - a) study controls for _____ (Select the most important factor.) *
 - b) study controls for any additional factor * (This criteria could be modified to indicate specific control for a second important factor.)

Exposure

- 1) Ascertainment of exposure
 - a) secure record (eg surgical records) *
 - b) structured interview where blind to case/control status *
 - c) interview not blinded to case/control status
 - d) written self report or medical record only
 - e) no description
- 2) Same method of ascertainment for cases and controls
 - a) yes *
 - b) no
- 3) Non-Response rate
 - a) same rate for both groups *
 - b) non respondents described
 - c) rate different and no designation

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE COHORT STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

- 1) Representativeness of the exposed cohort
 - a) truly representative of the average _____ (describe) in the community *
 - b) somewhat representative of the average _____ in the community *
 - c) selected group of users eg nurses, volunteers
 - d) no description of the derivation of the cohort
- 2) Selection of the non exposed cohort
 - a) drawn from the same community as the exposed cohort *
 - b) drawn from a different source c) no description of the derivation of the non exposed cohort
- 3) Ascertainment of exposure
 - a) secure record (eg surgical records) *
 - b) structured interview *
 - c) written self report
 - d) no description

- 4) Demonstration that outcome of interest was not present at start of study
 a) yes *
 b) no

Comparability

- 1) Comparability of cohorts on the basis of the design or analysis
 a) study controls for _____ (select the most important factor) *
 b) study controls for any additional factor * (This criteria could be modified to indicate specific control for a second important factor.)

Outcome

- 1) Assessment of outcome
 a) independent blind assessment *
 b) record linkage *
 c) self report
 d) no description
- 2) Was follow-up long enough for outcomes to occur
 a) yes (select an adequate follow up period for outcome of interest) *
 b) no
- 3) Adequacy of follow up of cohorts
 a) complete follow up - all subjects accounted for *
 b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ %
 (select an adequate %) follow up, or description provided of those lost) *
 c) follow up rate < ____% (select an adequate %) and no description of those lost
 d) no statement

CHAPTER V: Associations between anticholinergic burden and adverse health outcomes in Parkinson disease

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ABSTRACT

Background: Elderly adults should avoid medications with anticholinergic effects since they may increase the risk of adverse events, including falls, delirium, and cognitive impairment. However, data on anticholinergic burden are limited in subpopulations, such as individuals with Parkinson disease (PD). The objective of this study was to determine whether anticholinergic burden was associated with adverse outcomes in a PD inpatient population.

Methods: Using the Cerner Health Facts® database, we retrospectively examined anticholinergic medication use, diagnoses, and hospital revisits within a cohort of 16,302 PD inpatients admitted to a Cerner hospital between 2000 and 2011. Anticholinergic burden was computed using the Anticholinergic Risk Scale (ARS). Primary outcomes were associations between ARS score and diagnosis of fracture and delirium. Secondary outcomes included associations between ARS score and 30-day hospital revisits.

Results: Many individuals (57.8%) were prescribed non-PD medications with moderate to very strong anticholinergic potential. Individuals with the greatest ARS score (≥ 4) were more likely to be diagnosed with fractures (adjusted odds ratio (AOR): 1.56, 95% CI: 1.29-1.88) and delirium (AOR: 1.61, 95% CI: 1.08-2.40) relative to those with no anticholinergic burden. Similarly, inpatients with the greatest ARS score were more likely to visit the emergency department (adjusted hazard ratio (AHR): 1.32, 95% CI: 1.10-1.58) and be readmitted (AHR: 1.16, 95% CI: 1.01-1.33) within 30-days of discharge.

Conclusions: We found a positive association between increased anticholinergic burden and adverse outcomes among individuals with PD. Additional pharmacovigilance studies are needed to better understand risks associated with anticholinergic medication use in PD.

INTRODUCTION

Anticholinergic medications belong to a class of drugs that block muscarinic receptors and are used to treat a wide range of indications that more frequently present in elderly populations, including urinary incontinence, hypertension, respiratory disorders, and depression [1, 2]. Studies have found anticholinergic burden, defined as the cumulative anticholinergic potential resulting from polypharmacy [3], to be a significant risk factor for falls and fractures [4-7], delirium [6, 8], and cognitive impairment in elderly populations [9, 10]. Anticholinergic burden is also associated with hospital readmission among older adults [7, 11-13], which may be preventable. Knowledge of adverse outcomes associated with medications having anticholinergic properties has contributed to the development of numerous scales to quantify anticholinergic burden [13-15]. Validation studies have consistently shown that a higher anticholinergic burden score on any scale increases the risk of experiencing adverse events [15].

Disease-related disruptions to central cholinergic pathways may cause individuals with PD who have elevated anticholinergic burden to be more vulnerable to adverse effects compared to individuals with PD who are treated with fewer or less potent anticholinergic medications [16, 17]. Levodopa, pramipexole, selegiline, entacapone, and amantadine have mild anticholinergic effects, but are essential medications in the treatment of PD [18]. Common

cardiac, gastrointestinal, allergy, pain, and psychiatric medications have anticholinergic effects as well, but these medications generally have alternatives. In order to develop clinical guidelines that may reduce preventable adverse events in PD, basic information on anticholinergic burden and its impact, if any, on the health and care of individuals with PD is required.

To address this important data gap, we used electronic health records from the Cerner Health Facts® database to determine non-PD anticholinergic medication use and examine the relationship between anticholinergic burden and adverse outcomes in a PD inpatient population. Our primary objectives were to determine whether anticholinergic burden was associated with the diagnosis of clinical outcomes, specifically fracture and delirium. Anticholinergic burden has been demonstrated to increase healthcare utilization among elderly adults [11]; however, its impact on the care of individuals with PD remains unknown. Our secondary objectives were therefore to examine whether anticholinergic burden was associated with emergency department (ED) visit and inpatient readmission within 30-days of inpatient discharge.

METHODS

This study was approved by the Health Sciences and Science Research Ethics Board at the University of Ottawa, Ottawa, Ontario, Canada (H05-13-24). Informed consent was not required from individuals included in this study, as all health records were anonymized and de-identified prior to our analyses.

Data source

Data for this study was obtained from the Cerner Corporation's (Kansas City, Missouri) Health Facts® database. First implemented in subscribing care centers in January 2000, Health Facts® is a time-stamped electronic health record that contains in-depth patient demographic, encounter, clinical, laboratory, pharmacy, and billing data. To date, Health Facts® contains encounter-level health information on over 47 million individuals who have received care at any of the more than 600 subscribing centers. Approximately 65% of all data in Health Facts® originate from academic medical centers. Most outpatient pharmacy data is missing in Health Facts®; therefore, the database is best suited for inpatient drug-association studies and health services research.

Cohort and index encounter selection

The study cohort was comprised of hospitalized individuals with PD between January 2000 and December 2011. To be eligible for cohort entry, individuals had to have: 1) a recorded diagnosis of PD (in any setting) according to the International Classification of Diseases, Ninth Revision (ICD-9: code 332 for PD, or code 332.0 for Paralysis Agitans) and 2) one or more inpatient encounters > 2 days at or after the time of PD diagnosis in which diagnoses were recorded and medications were dispensed. Eligible encounters were restricted to those > 2 days in order to more accurately approximate outpatient pharmacotherapy, since outpatient medications may not be dispensed by hospital pharmacies for shorter stays (such as day surgeries) or to individuals admitted for fatal events. Individuals were excluded from our study if 1) they had a diagnosis (in any setting) of secondary parkinsonism (ICD-9, code 332.1) or other degenerative diseases of the basal ganglia (ICD-9, code 333.0) or 2) their age

was undocumented or less than 40 years at first PD diagnosis, thus reducing the number of individuals with atypical PD or cases of incorrectly diagnosed PD from the cohort. The earliest qualifying inpatient encounter was then selected as the index encounter for each individual from the eligible study cohort (n = 17,337). Since our secondary objectives focused on 30-day hospital revisits, individuals who died during their index encounter were excluded from the cohort (n = 512). Lastly, to accommodate adjustment for *a priori* defined covariates, we restricted the cohort to individuals with complete sex and race data (n=16,302).

Demographics, care setting characteristics, and comorbidity

Demographic data examined and reported from index encounters were age at admission, sex (female or male), and race (Caucasian, African American, Hispanic, Asian, or other). Age at admission was categorized into 10-year age strata from 40-49 to 90+ years. Care setting characteristics derived and reported from index encounters included location (urban or rural), teaching status (teaching or non-teaching), census region (Northeast, South, Midwest, or West), and number of beds (<6, 6-99, 100-199, 200-299, 300-499, 500+). Length of stay of each index encounter was categorized as 3-6, 7-30, or 31+ days. Comorbidity was assessed at the index encounters using enhanced ICD-9-CM coding algorithms for Elixhauser comorbidities [19]. A weighted comorbidity summary score was then calculated for each individual using data from their index encounter [20].

Anticholinergic exposure

The Anticholinergic Risk Scale (ARS), a validated and pharmacist-developed weighted list of frequently prescribed medications that have anticholinergic potential, was used to calculate anticholinergic burden [18]. To appraise anticholinergic burden, we first reconciled medications dispensed during index encounters and examined the prevalent use of each ARS drug. Each individual's ARS score was calculated as the weighted sum of ARS drugs dispensed during their index encounter and classified as 0, 1, 2-3, or 4+. Since the Cerner Health Facts® database does not contain detailed outpatient pharmacy data, information on the use of over-the-counter medications, or prescription adherence data, the ARS score was solely derived using data on medications dispensed in inpatient settings. We made the assumption that medications that were prescribed in the inpatient setting and not marked as canceled or not dispensed were actually administered to the patient.

Outcomes data

Our primary outcomes were inpatient diagnosis of fracture and delirium, with secondary outcomes being 30-day ED visit and inpatient readmission. Outcomes were selected based on prior reports of associations between anticholinergic burden and clinical and health service utilization outcomes in large cohorts of elderly adults [4-10]. Primary outcomes were defined as a recorded primary or secondary ICD-9 diagnosis of fracture (800.x - 829.x) and delirium (293.x), respectively, during the index encounter. As it is not possible to follow individual patients across different Health Facts® subscribing care centers, secondary outcomes were defined as ED visit or inpatient readmission at the same care center within 30-days of index encounter discharge. Prior to examining hospital revisits, we confirmed that all index

encounter care centers were still active subscribers to Health Facts® 30-days post individual inpatient discharge. Thirty-day ED visit and inpatient readmission post index encounter discharge was then coded as a binary variable, with the minimum time to hospital return recorded for all events.

Statistical analyses

Descriptive statistics were used to report demographic, clinical, and care setting characteristic, as well as the prevalent use of individual ARS drugs. To determine the association between anticholinergic burden and inpatient diagnosis of adverse events (fracture or delirium), we constructed unconditional logistic regression models that computed unadjusted and adjusted odds of adverse event compared to a reference group (ARS score = 0, no anticholinergic burden) for each category of anticholinergic burden (ARS score = 1, 2-3, and 4+). For secondary outcomes, we calculated the risk of 30-day ER visit and inpatient readmission using a time-to-event analysis. Cox proportional hazard models were constructed to determine the unadjusted and adjusted risk of 30-day ED visit and inpatient readmission relative to a reference group (ARS score = 0) for each category of anticholinergic burden (ARS score = 1, 2-3, and 4+). Multivariable logistic regression and Cox proportional hazard models included the following demographic, clinical, and care setting characteristics that were hypothesized *a priori* to be potential confounders: age (continuous), sex, race, length of stay, comorbidity score, census region, urban/rural status, hospital size (number of beds), and hospital teaching status. All analyses were completed using SAS v9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Cohort characteristics

There were 16,302 individuals with PD who satisfied our inclusion criteria and were admitted to hospital between January 1, 2000 and December 31, 2011 (Table 1). Consistent with the demographics of other large PD populations, men (52.3%) comprised the majority of our study cohort and individuals were older (82.3% were 70 years of age or older) at admission [21, 22]. Individuals were predominantly Caucasian (91.2%), while others identified as African American (n = 1,061; 6.5%), Hispanic (1.0%), Asian (0.6%), or other (0.8%) races. Nearly all (99.1%) inpatient encounters were 30 days or less. Most study encounters took place at large (300+ beds, 46.8%), urban (99.8%), academic (64.1%), Northeast (49.0%) care centers.

Characteristic	Study Cohort n (%)	Characteristic	Study Cohort n (%)
Age		Payer status	
40-49	125 (0.8)	Medicare	7,228 (44.3)
50-59	630 (3.9)	Public	377 (2.3)
60-69	2,121 (13.0)	Private	799 (4.9)
70-79	5,486 (33.7)	Uninsured	258 (1.6)
80-89	6,753 (41.4)	Missing	7,640 (46.9)
90+	1,187 (7.3)	Care setting location	
Sex		Urban	16,266 (99.8)
Female	7,730 (47.4)	Rural	36 (0.2)
Male	8,572 (52.6)	Teaching status	
Race		Non-teaching	5,848 (35.9)
Caucasian	14,861 (91.2)	Teaching	10,454 (64.1)
African American	1,061 (6.5)	Census region	
Hispanic	164 (1.0)	Northeast	7,984 (49.0)
Asian	91 (0.6)	South	4,007 (24.6)
Other	125 (0.8)	Midwest	3,220 (19.8)
Length of stay		West	1,091 (6.7)
3-6 days	10,362 (63.6)	Number of beds	
7-30 days	5,799 (35.6)	<5	53 (0.3)
31+ days	141 (0.9)	6-99	1,193 (7.3)
ARS score		100-199	2,365 (14.5)
0	2,463 (15.1)	200-299	5,065 (31.1)
1	4,280 (26.3)	300-499	3,418 (21.0)
2-3	4,762 (29.2)	500+	4,208 (25.8)
4+	4,797 (29.4)	Mean Comorbidity Score^a	6.1 ± 6.7

Table 1. Demographic characteristics of study cohort (n = 16,302).

Abbreviation: ARS, anticholinergic risk scale.

^aMean ± standard deviation.

Anticholinergic exposure

The majority (57.8%) of individuals included in our study were prescribed one or more non-PD medications with anticholinergic effects. Any use of medications with anticholinergic properties was common among individuals in our study, with similar proportions of individuals in examined ARS score strata (ARS score 1: 26.3%; 2-3: 29.2%; 4+: 29.4%) (Table 1). Individuals were frequently prescribed one or more medications with a moderate anticholinergic potential (1 point, 77.1%), which were primarily antiparkinson agents (levodopa, 60.7%; pramipexole, 8.4%; entacapone, 6.3%; and selegiline, 2.5%) (Table 2).

Medications with strong (2 points) and very strong (3 points) anticholinergic potential were prescribed to 19.9% and 25.4% of inpatients, respectively.

1 Point	n (%)	3 Points	n (%)
Any 1 point ARS drug	12,570 (77.1)	Any 3 point ARS drug	4,135 (25.4)
carbidopa-levodopa ^a	9,900 (60.7)	diphenhydramine hydrochloride	1,241 (7.6)
quetiapine fumarate	1,563 (9.6)	promethazine hydrochloride	1,002 (6.1)
metoclopramide hydrochloride	1,426 (8.7)	oxybutynin chloride	552 (3.4)
pramipexole dihydrochloride ^a	1,374 (8.4)	atropine products	417 (2.6)
haloperidol	1,041 (6.4)	hydroxyzine hydrochloride or hydroxyzine pamoate	391 (2.4)
entacapone ^a	1,021 (6.3)	benztropine mesylate	358 (2.2)
risperidone	839 (5.1)	amitriptyline hydrochloride	284 (1.7)
mirtazapine	799 (4.9)	meclizine hydrochloride	245 (1.5)
paroxetine hydrochloride	714 (4.4)	hyoscyamine products	104 (0.6)
trazodone hydrochloride	669 (4.1)	dicyclomine hydrochloride	92 (0.6)
ranitidine hydrochloride	566 (3.5)	tizanidine hydrochloride	53 (0.3)
selegiline hydrochloride ^a	411 (2.5)	chlorpromazine hydrochloride	51 (0.3)
ziprasidone hydrochloride	148 (0.9)	perphenazine	43 (0.3)
methocarbamol	90 (0.6)	cyproheptadine hydrochloride	42 (0.3)
2 Points	n (%)	imipramine hydrochloride	37 (0.2)
Any 2 point ARS drug	3,252 (19.9)	carisoprodol	33 (0.2)
olanzapine	750 (4.6)	thioridazine hydrochloride	19 (0.1)
amantadine hydrochloride ^a	663 (4.1)	chlorpheniramine maleate	16 (0.1)
tolterodine tartrate	543 (3.3)	fluphenazine hydrochloride	16 (0.1)
loratadine	348 (2.1)	trifluoperazine hydrochloride	13 (0.1)
prochlorperazine maleate	341 (2.1)	thiothixene	12 (0.1)
loperamide hydrochloride	300 (1.8)		
cyclobenzaprine hydrochloride	211 (1.3)		
baclofen	153 (0.9)		
nortriptyline hydrochloride	92 (0.6)		
cetirizine hydrochloride	82 (0.5)		
clozapine	68 (0.4)		
cimetidine	52 (0.3)		
desipramine hydrochloride	9 (0.1)		
pseudoephedrine hydrochloride-	1 (0.0)		
triprolidine hydrochloride			

Table 2. Prevalent use of individual ARS medications by anticholinergic potential in study cohort (n = 16,302).

Abbreviation: ARS, anticholinergic risk scale.

^aAntiparkinson medication.

Inpatient diagnosis of fracture and delirium

Associations between anticholinergic burden and inpatient diagnosis of fracture and delirium are shown in Table 3A and 3B, respectively. Unadjusted models demonstrated a significant association between each strata of anticholinergic burden and fracture diagnosis (compared to individuals with ARS score = 0), with the association being greatest for individuals with the highest ARS scores (odds ratio (OR): 1.66, 95% CI: 1.38-1.99). Individuals with ARS scores > 1 were significantly more likely to be diagnosed with delirium compared to those prescribed medications without anticholinergic effects. Adjustment for relevant covariates, including potential confounders, weakened the observed associations only slightly. Results revealed that individuals with the highest ARS scores (≥ 4) had the greatest statistically significant risk of fracture (adjusted odds ratio (AOR): 1.56, 95% CI: 1.29-1.88) and that individuals with high to very high ARS scores were at significant risk of delirium compared to individuals with no anticholinergic burden (ARS score 2-3: AOR: 2.14, 95% CI: 1.46-3.15; 4+: AOR: 1.61, 95% CI: 1.08-2.40).

A. Fractures		Yes	No				
ARS Score	n = 1,452 (%)	n = 14,850 (%)	OR (95% CI)	p value	AOR ^a (95% CI)	p value	
0	169 (11.6)	2,294 (15.4)	REF	-	REF	-	
1	360 (24.8)	3,920 (26.4)	1.25 (1.03 - 1.51)	0.02	1.15 (0.95 - 1.39)	0.16	
2-3	401 (27.6)	4,361 (29.4)	1.25 (1.04 - 1.50)	0.02	1.17 (0.97 - 1.42)	0.11	
4+	522 (36.0)	4,275 (28.8)	1.66 (1.38 - 1.99)	<0.01	1.56 (1.29 - 1.88)	<0.01	
B. Delirium		Yes	No				
ARS Score	n = 362 (%)	n = 15,940 (%)	OR (95% CI)	p value	AOR ^a (95% CI)	p value	
0	33 (9.1)	2,430 (15.2)	REF	-	REF	-	
1	65 (18.0)	4,215 (26.4)	1.14 (0.75 - 1.73)	0.55	1.05 (0.69 - 1.61)	0.81	
2-3	149 (41.2)	4,613 (28.9)	2.38 (1.63 - 3.48)	<0.01	2.14 (1.46 - 3.15)	<0.01	
4+	115 (31.8)	4,682 (29.4)	1.81 (1.22 - 2.67)	<0.01	1.61 (1.08 - 2.40)	0.02	

Table 3. Associations between ARS score and clinical outcomes.

^aAdjusted for age, sex, race, length of stay, Elixhauser comorbidity score, census region, urban/rural status, hospital size (number of beds), and hospital teaching status.

Abbreviations: ARS, anticholinergic risk scale; AOR, adjusted odds ratio; CI, confidence interval; OR, odds ratio; REF, referent group.

ED visit and inpatient readmission

Estimates of associations between ARS score and 30-day ED visit and inpatient readmission are given in Tables 4A and 4B, respectively. Unadjusted Cox results showed that individuals with the greatest ARS score (≥ 4) were significantly more likely to visit the ED within 30-days of inpatient discharge compared to those not prescribed medications with anticholinergic effects (hazard ratio (HR): 1.29, 95% CI: 1.08-1.54). Prior to covariate adjustment, no association between anticholinergic burden and 30-day inpatient readmission was observed. Hazard ratios slightly increased after covariate adjustment, showing that individuals with high to very high ARS scores were at significant risk of visiting the ED within 30 days of inpatient discharge compared to those without anticholinergic burden (ARS score 2-3: adjusted hazard ratio (AHR): 1.22, 95% CI: 1.02-1.46; 4+: AHR: 1.32, 95% CI: 1.10-1.58). Similarly, compared to individuals not prescribed anticholinergic medications (ARS score = 0), individuals with the greatest anticholinergic burden (ARS score ≥ 4) had a 16% greater risk of being readmitted to an inpatient setting within 30 days of inpatient discharge (AHR: 1.16, 95% CI: 1.01-1.33).

A. 30-Day ED Visit						
ARS Score	Visits / patients (%)	HR (95% CI)	p value	AHR ^a (95% CI)	p value	
0	171 / 2,463 (6.9)	REF	-	REF	-	
1	300 / 4,280 (7.0)	1.01 (0.84 - 1.22)	0.89	1.04 (0.86 - 1.26)	0.66	
2-3	390 / 4,762 (8.2)	1.19 (1.00 - 1.43)	0.05	1.22 (1.02 - 1.46)	0.03	
4+	423 / 4,797 (8.8)	1.29 (1.08 - 1.54)	0.01	1.32 (1.10 - 1.58)	<0.01	
B. 30-Day Readmission						
ARS Score	Visits / patients (%)	HR (95% CI)	p value	AHR ^a (95% CI)	p value	
0	312 / 2,463 (12.7)	REF	-	REF	-	
1	545 / 4,280 (12.7)	1.01 (0.88 - 1.16)	0.92	1.04 (0.90 - 1.19)	0.60	
2-3	652 / 4,762 (13.7)	1.09 (0.95 - 1.25)	0.21	1.12 (0.98 - 1.29)	0.10	
4+	671 / 4,797 (14.0)	1.11 (0.97 - 1.27)	0.11	1.16 (1.01 - 1.33)	0.04	

Table 4. Associations between ARS score and healthcare utilization outcomes.

^aAdjusted for age, sex, race, length of stay, Elixhauser comorbidity score, census region, urban/rural status, hospital size (number of beds), and hospital teaching status.

Abbreviations: ARS, anticholinergic risk scale; AHR, adjusted hazard ratio; CI, confidence interval; ED, emergency department; HR, hazard ratio; REF, referent group.

DISCUSSION

Many cardiac, gastrointestinal, allergy and psychiatric medications exhibit anticholinergic potential. Multiple studies have demonstrated risks associated with anticholinergic burden in the older adult population, including falls, fractures, cognitive impairment, pneumonia, and hospital readmission [4-12, 23]. Individuals with PD may be susceptible to anticholinergic effects due to cholinergic dysfunction as part of the disease process, and the exposure to anticholinergic substances in the form of antiparkinson medications. Overall, there is need for more studies to examine anticholinergic effects in PD, both among PD populations with varying exposure to anticholinergic medications and between PD and non-PD populations with comparable exposures to these medications. Such studies will be essential to informing future best practice guidelines, as well as public health policies. Using data from a large cohort of more than 16,000 individuals with PD admitted to hospital between 2000 and 2011, we examined anticholinergic use and the extent to which anticholinergic burden was associated with adverse clinical and health service utilization outcomes.

Despite known risks of prescribing medications with anticholinergic effects to older adults, estimates suggest that over one-third of medications prescribed to the elderly have anticholinergic properties [24]. Our findings show that even after excluding PD medications, anticholinergic medications were prescribed to more than half of our PD inpatient cohort, which is consistent with a prior report that anticholinergic burden in PD is largely attributed to the use of non-PD medications [25]. We also found that patients with the highest anticholinergic burden were more likely to be diagnosed with a fracture and delirium compared to those not taking medications with anticholinergic effects. Previous studies have

demonstrated that traumatic injuries are prevalent and a leading cause of morbidity, mortality, and disability in PD. One study found that a PD diagnosis was four times more common in a sample of 1,066,404 hospitalizations for acute hip fractures (age- sex-adjusted prevalence ratio 4.02, 4.00- 4.03) than in the general population [26]. Post hip fracture mortality is increased in Medicare beneficiaries diagnosed with PD compared to the general Medicare population (AHR 2.41, 2.37-2.46) [27]. Hip fracture is also an independent predictor of nursing home residence (AOR 2.10, 2.04-2.15) [27-30].

In PD, as in the general older adult population, acute metabolic or infection insults can precipitate delirium. Multiple studies have found an association between anticholinergic medication use and delirium [31-33], resulting in prolonged hospitalization and rehabilitation [34]. However, in PD, acute delirium may lead to loss of motor function. A recent study of 80 individuals with PD examined risk factors for persistent significant motor deterioration (e.g. going from walking independently to requiring an assist device) after an acute inflammatory process (such as a respiratory tract infection). Individuals with PD who had delirium were 15 times more likely to have persistent PD motor disability six months after the acute illness resolved (AOR 15.89, 3.23-78.14) [35]. Both cross-sectional and longitudinal studies suggest that cognitive impairment is the most commonly observed non-motor feature of PD; however, the determinants of cognitive dysfunction, particularly early in disease, are not clear. An international, multi-site study of 423 individuals with PD recently reported that approximately 10% of newly diagnosed cases of PD had measurable cognitive impairment at disease presentation [36]. Most recently, a large cohort study examined anticholinergic burden in PD and found that there were no differences in global

cognition or assessments of attention, memory, and executive function at 1.5 years in groups of users and non-user of anticholinergic medications [37]. This is in contrast to other studies that found executive dysfunction and attentional deficits in individuals with PD exposed to anticholinergic medications, even in subclinical doses [38], and in contrast to multiple studies that relate anticholinergic drug exposure to incident dementia [39-41]. Our data raise important questions about the extent to which traumatic injuries, motor decline, and cognitive dysfunction are preventable in PD. The potential public health impact of these initial data, if confirmed, is substantial.

Our findings that PD inpatients with high anticholinergic burden were significantly more likely than those not treated with anticholinergic acting medications to visit the ED and be readmitted within 30 days of discharge are congruent with prior reports of adverse events in other elderly populations [7, 11-13]. Non-PD medications with anticholinergic effects may often be substituted for equally effective non-anticholinergic agents: a portion of the ED visits and inpatient readmissions we observed are thus potentially preventable. If replicated using other data sources, our findings may serve to inform care center policies and practices pertaining to prescribing, adverse event reporting, and reimbursement.

Although there are published lists of drugs that should be avoided by elderly populations (such as Beers Criteria [42]), inappropriate prescribing stills occurs and is a contributor to preventable adverse health outcomes [2, 43, 44]. Many care centers have implemented computerized provider order entry systems to improve the quality of care while reducing variable operating costs. These systems are designed to leverage patient data and pre-

programmed drug information to warn clinicians if ordered medications are potentially contraindicated on a case-by-case basis [45]. Prompted warnings based on anticholinergic burden may prove beneficial in PD, as this would allow care providers who may otherwise prescribe anticholinergic acting medications to reevaluate their decisions and make medication substitutions where appropriate. However, current warning systems for antidopaminergic medication use in PD have not always produced adequate physician response [46]. In instances where individuals are diagnosed with outcomes believed to result from anticholinergic burden, mandatory in-hospital reporting and medication reconciliation may be necessary to improve future quality of care.

Our study has several strengths. Study data originated from multiple care centers in the United States and include information on individuals with PD from multiple payers. Academic centers were overrepresented in our dataset and are more likely to have providers with PD expertise available on-site. In-depth data for each index encounter enabled us to adjust multivariable models for *a priori* defined covariates that may modify or confound the association between anticholinergic burden and adverse outcomes in PD. We accounted for differences in health status across compared groups by including a weighted comorbidity summary score in our multivariable logistic regression and Cox proportional hazard models, which has shown to be statistically superior compared to adjustment for individual comorbidity counts [47]. Finally, our results are congruous with previous studies of other older adult populations.

In spite of these strengths, limitations in our study design should be considered when interpreting these initial data. Confounding by indication or protopathic bias may affect our risk estimates, as we did not have information on PD severity or access to outpatient prescription history, nor were we able to perform time-lag analyses. Although comorbidity summary scores may effectively summarize health status and predict in-hospital mortality [20, 47], it is possible that differences in factors that could not be accounted for by our study, including outpatient use of prescribed or over-the-counter central nervous system acting medications not documented upon admission, contributed to individuals with the greatest anticholinergic burden returning to hospital at a higher rate than those with no anticholinergic burden. Moreover, we did not have any validation data available to perform external adjustment to reduce possible residual confounding bias [48]. It is possible that antidepressants and hypnotics with anticholinergic potential were prescribed for early symptoms of dementia or palliative treatment of advanced PD, conditions that independently predict admission to hospital for falls and altered mental status [49, 50]. Additionally, we could not account for significant medication changes post inpatient discharge that could impact anticholinergic burden, nor measure ED visits or readmissions to care centers that were not subscribed to Health Facts®, which could lead to possible over or underestimation of reported risks. Our choice to use the ARS, a popular anticholinergic burden measurement tool that has been validated in other United States health databases, may be responsible in part for observed associations between anticholinergic burden and clinical and healthcare utilization outcomes. Currently, there are many distinct drug lists used to measure anticholinergic burden, with considerable disagreement among developed scales [51-55]. Anticholinergic measurement tools should not be used in settings that dramatically differ

from those in which the scales were developed, as differences in drug availability may adversely impact measured anticholinergic exposure [51, 56]. A recent systematic review on the use of anticholinergic scales found that cumulative exposure to anticholinergic medications measured using the ARS was associated with cognitive and functional disorders [57]. Furthermore, a New Zealand-based study of older adults examined whether nine published anticholinergic burden scales, including the ARS, were associated with adverse health outcomes [13]. Investigators found that scores derived from all nine scales were independently associated with an increased risk of hospital admission, including admission for falls [13]. To date, no scale has demonstrated a clear relationship with mortality [57]. Although our findings are supported by some studies that used the ARS to investigate associations between anticholinergic medication exposure and the diagnosis of adverse outcomes in older adult populations [13, 18, 58, 59], our study is the first to use the ARS to examine these associations among individuals with PD. Future work is needed to examine how differences in anticholinergic burden measurement impact the predictive validity of clinically relevant outcomes in Cerner Health Facts® and other health databases, both in older adult populations and in subpopulations that may be most sensitive to anticholinergic effects.

It is important to note that medications included in the ARS, such as haloperidol and metoclopramide, possess central antidopaminergic activity in addition to anticholinergic properties and that these medications are independent predictors of adverse outcomes in inpatients with PD [60, 61]. There is also growing evidence that exposure to the most potent dopamine receptor blocking agents is associated with increased risk of mortality, both in the

general population and among individuals with PD [62-64]. Since there are no widely accepted standards for assessing dopamine receptor blocking activity of medication included in the ARS, we were unable to account for differences in antidopaminergic activity, if any, within compared groups in our study. Future studies that examine how prescribed medications with both anticholinergic and antidopaminergic properties may contribute to adverse events in older adult populations, especially those with PD, are required.

Although medications dispensed in inpatient settings were presumed continuations of outpatient treatment, lacking outpatient pharmacy data in Health Facts® limited our ability to ascertain whether anticholinergic burden was temporally associated with examined clinical outcomes. This is particularly true for anticholinergic burden and the diagnosis of delirium, since haloperidol and quetiapine may have been prescribed for acute changes in the mental status [65, 66]. To better understand possible confounding by indication in this context, future studies that compare use of a particular drug for the same indication among individuals with PD and varying degrees of anticholinergic burden are needed. Finally, we did not make adjustments for multiple comparisons, as our analyses are exploratory. Despite study limitations, prior reports of adverse outcomes with anticholinergic burden in older adults support an apparent association between ARS medications use and the diagnosis of adverse clinical and health service utilization outcomes in PD [4-7].

In conclusion, we found a positive association between anticholinergic burden and adverse clinical (fracture and delirium) and health service (30-day ED visit and inpatient readmission) outcomes in a large cohort of inpatients with PD. Anticholinergic burden was primarily attributed to the use of non-PD medications. Although study replication is

warranted, initial findings suggest that older adults with PD may benefit from limited use of non-PD medications with anticholinergic effects.

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CHAPTER VI: General Discussion

Parkinson disease (PD) is an increasingly prevalent chronic neurodegenerative disorder that if left untreated may lead to significant disability and subsequently result in profoundly negative impacts to quality of life [1-3]. The introduction of new therapeutic options for early and advanced PD over the course of the last two decades offers patients the ability to more effectively manage debilitating motor and non-motor symptoms that are characteristic of their disorder [4-8]. While randomized clinical trials (RCTs) and observational studies have provided valuable knowledge of PD medication safety and efficacy [6, 9-13], studies examining utilization trends of marketed drugs are essential to understanding changes in prescribing practices. Moreover, it is imperative that post-market surveillance of approved PD medications occurs to identify and mitigate risks of adverse events that were not observed during pre-marketing trials. Motivations for the research embodied within this thesis were prior knowledge gaps in PD pharmacoepidemiology pertaining to trends in PD medication use, risks of adverse cardiovascular events with non-ergot dopamine agonist (DA) use, and outcomes associated with anticholinergic burden. Therefore, using data from Cerner Health Facts®, a large database of electronic medical records (EMRs) in the United States (US), the objectives of this doctoral research were threefold: to 1) examine patterns of antiparkinson drug use from 2001 to 2012 in relation to clinical guideline publication, drug availability, and emerging safety concerns; 2) determine whether PD patients treated with non-ergot DAs are at increased risk of adverse cardiovascular or cerebrovascular outcomes; and 3) assess whether anticholinergic burden is associated with adverse outcomes in PD. The following sections briefly summarize completed studies and their key findings, and discuss study implications in the context of population health using the *Integrated Framework for*

Risk Management and Population Health [14]. Strengths and limitations of using Cerner Health Facts® data to conduct PD pharmacoepidemiology are presented prior to drawing general conclusions and proposing future areas of research.

SUMMARY OF RESEARCH AND KEY FINDINGS

Trends in inpatient antiparkinson drug use

Population-based studies of longitudinal drug utilization (synonymous with prescribing in the context of this thesis) provide important information about the use of medications in real world settings, as they may indicate whether clinical guidelines are being followed, determine if interventions are accessible, and serve as preliminary markers of adverse event issues. Using a retrospective cohort study design and dispensed prescription data from 16,785 PD inpatients between January 2001 and December 2012, standardized temporal trends in medication use were examined and reported in *Chapter 2*, which was published in the *European Journal of Clinical Pharmacology* [15]. Since ideal prescribing practices reflect known risks and benefits, which vary over time, changes in antiparkinson medication use were assessed 1, 2, and 3 years after events hypothesized to have the greatest impact on use of the most commonly prescribed PD drug classes (levodopa and DAs). Examined events included (1) publication of the April 2006 AAN practice parameter reporting that levodopa does not accelerate PD progression and that no pharmacological intervention is neuroprotective, (2) the voluntary withdrawal of pergolide (an ergot-derived DA) from the market in 2007 due to concerns about cardiotoxicity, and (3) the December 2008 pramipexole label revisions which added precautions about uncontrollable urges to the label. Utilization patterns for levodopa and DAs were stratified by age and sex to examine how

therapy choice differed in relation to demographic characteristics that may independently predict treatment risks and benefits.

The primary finding of this study was that there has been a shift in prescribing practices for PD in the US, and that these changes are due in part to emerging safety concerns and evidence of efficacy. The most frequently prescribed antiparkinson drugs between 2001 and 2012 were levodopa (85%) and DAs (28%), with DA use starting to decline in 2007, from 34% to 27% in 2012. Levodopa use remained constant across all study years. Secondary analyses revealed that (1) despite safety concerns, older adults with PD were persistently prescribed DAs, (2) use of levodopa and DAs did not greatly differ between men and women over time, and (3) simultaneous use of multiple antiparkinson drugs was most common among younger populations with PD. An in-depth discussion that proposes reasons for observed antiparkinson utilization patterns is presented in *Chapter 2*. Although we did not account for all factors that may precipitate changes in antiparkinson medication use, such as drug pricing, pharmaceutical company promotional activity, and disease severity, this study provides the basis for future research that investigates the effects of care structure, clinical guideline adoption, and treatment adherence on prescribing in PD.

Non-ergot dopamine agonists and the risk of cardiovascular and cerebrovascular outcomes

A pooled analysis of randomized clinical trial data by the US Food and Drug Administration (FDA) found that users of the non-ergot DA pramipexole were more likely to be diagnosed with heart failure compared to individuals treated with a placebo, prompting a 2012 FDA

safety announcement on possible cardiovascular risks (such as heart failure) associated with the use of pramipexole for PD. Since then, observational studies have investigated associations between non-ergot DA use and the subsequent diagnosis of heart failure [16-18]; however, heterogeneity within and between studies have limited the ability to deduce conclusions on risks of heart failure among PD patients using non-ergot DAs. Therefore, as presented in *Chapter 3* and published in *Movement Disorders Clinical Practice* [19], we completed a study to examine whether PD patients treated with non-ergot DAs are at increased risk of adverse cardiovascular (acute myocardial infarction, heart failure, hypotension, and valvulopathy) or cerebrovascular (cerebrovascular accident and ischemic stroke) outcomes relative to PD patients receiving other treatments. We constructed the following conditional logistic regression models to estimate the unadjusted and adjusted odds of non-ergot DA use compared to a reference group for each cardiovascular and cerebrovascular outcome of interest: 1) all individuals were categorized as users or non-users of non-ergot DAs (pramipexole, and ropinirole), with non-users serving as the referent drug group for all comparisons; 2) analyses restricted to individuals receiving levodopa or non-ergot DA monotherapy for PD, with levodopa monotherapy users serving as the referent drug group for all comparisons; and 3) sex, race (white and non-white), and age (60-69 years, 70-79 years, and 80+ years) stratified analyses of all event-exposure relationships that were statistically significant in our primary analyses. Demographic, clinical, and care setting covariates that were independently associated ($p < 0.05$) with study outcomes in a univariate analysis were included in the final adjusted model for that event. Sensitivity analyses sought to examine whether observed associations would remain after excluding recurrent cases of heart failures.

Completed analyses revealed that heart failure was the only adverse outcome to be significantly associated with non-ergot DA use. Individuals treated with pramipexole were more likely to be diagnosed with heart failure, relative to no-use (adjusted odds ratio (AOR): 1.28, 95% CI: 1.07-1.53). Furthermore, the association between pramipexole and heart failure was greatest among individuals receiving pramipexole monotherapy (relative to levodopa monotherapy) (AOR: 1.50, 95% CI: 1.09-2.06). Compared to non-users, men and older adults treated with pramipexole were more likely to be diagnosed with heart failure. Taking into consideration plausible biological mechanisms, study strengths, and the limitations of working with EHR data, a detailed interpretation of our findings is presented in *Chapter 3*. While our findings should be interpreted with caution and are insufficient alone to contraindicate the use of select antiparkinson medications, they add to the growing weight of evidence on cardiovascular risks associated with necessary PD interventions.

To supplement our assessment of adverse cardiovascular outcomes associated with select antiparkinson medications and support evidence-based decision making regarding the use of non-ergot DAs for PD, we developed a comprehensive systematic review protocol to evaluate the cardiac safety of this PD drug class. Our protocol is presented in *Chapter 4* and was published in the *Cochrane Library* [20]. The objective of our systematic review is to evaluate the risk of heart failure and other adverse cardiovascular reactions in PD patients treated with non-ergot dopamine agonists, compared to other antiparkinson pharmacological interventions, placebo, or no intervention. This review greatly differs from traditional Cochrane systematic reviews since its focus is solely on safety outcomes and not effectiveness, which requires that both RCTs and observational studies be considered for

inclusion. Challenges arising from the inclusion of observational studies in a systematic review lead to lengthy discussions about review methods with collaborators and a longer than usual methodology review by Cochrane's Movement Disorders Group. This work is ongoing and expected to be published as a full-length systematic review in the *Cochrane Library* in 2017. Completion of this review will increase understanding of the cardiac safety of non-ergot DAs and may serve to identify knowledge gaps and future research priorities specific to the safe and effective of pharmacotherapies for PD.

Associations between anticholinergic burden and adverse health outcomes

Anticholinergic burden is defined as the cumulative anticholinergic potential resulting from polypharmacy [21], and has been demonstrated to be associated with many adverse outcomes among elderly populations that may be preventable, including but not limited to fractures, delirium, cognitive impairment, and hospital readmission [22-30]. Although the effects of anticholinergic burden have been extensively studied in elderly populations, few studies have examined the prevalence of anticholinergic burden in PD, nor its impacts. Studies that have examined these phenomena have been inconsistent [31, 32], which is thought to be attributed to heterogeneity in studied populations and differences in care setting practices. The most frequently prescribed antiparkinson medications are not generally thought of as anticholinergics; however, some of these medications exhibit mild anticholinergic properties (levodopa, pramipexole, selegiline, entacapone, and amantadine), which may contribute to clinicians underestimating anticholinergic burden [33]. Moreover, disease-related disruptions to central cholinergic pathways may cause individuals with PD to have increased susceptibility to the effects of cumulative anticholinergic potential. We therefore

hypothesized that individuals with PD may be vulnerable to anticholinergic burden and its effects. To address knowledge gaps specific to anticholinergic burden in PD, we conducted a retrospective cohort study in which we examined associations between anticholinergic burden and clinical (diagnosis of fracture and delirium) and healthcare utilization (emergency department visit or readmission) outcomes. This study is presented in *Chapter 5* and was published in *PLOS ONE* [34]. The Anticholinergic Risk Scale (ARS), a validated and pharmacist-developed weighted list of frequently prescribed medications that have anticholinergic potential [33], was used to calculate anticholinergic burden among individuals included in our study. To assess the association between anticholinergic burden and the diagnosis of adverse clinical events (fracture or delirium), we constructed unconditional logistic regression models that computed unadjusted and adjusted odds of adverse event compared to a reference group for each category of anticholinergic burden. For healthcare utilization outcomes, Cox proportional hazard models were constructed to determine the unadjusted and adjusted risk of 30-day ED visit and inpatient readmission relative to a reference group for each category of anticholinergic burden. All multivariable models included demographic, clinical, and care setting characteristics that were hypothesized *a priori* to be potential confounders.

Findings from our analyses demonstrated that more than half (57.8%) of individuals included in our study were prescribed non-PD medications with moderate to very strong anticholinergic potential. Additionally, individuals with the greatest ARS score were more likely to be diagnosed with fractures (AOR: 1.56, 95% CI: 1.29-1.88) and delirium (AOR: 1.61, 95% CI: 1.08-2.40), and visit the emergency department (adjusted hazard ratio (AHR):

1.32, 95% CI: 1.10-1.58) and be readmitted (AHR: 1.16, 95% CI: 1.01-1.33) within 30-days of discharge, relative to those with no anticholinergic burden. While study replication is necessary, our findings suggest that individuals with PD may benefit from substitution of non-PD medications with anticholinergic properties for equally effective medications that lack anticholinergic activity. Reaffirming this notion are findings from a study that was published shortly after our manuscript, which investigated anticholinergic burden in PD in southwestern France using adverse drug reaction reports recorded in the Midi-Pyrénées Pharmacovigilance DataBase [35]. While investigators did not examine the effects of anticholinergic burden, they did find that medications with anticholinergic properties are commonly prescribed to individuals with PD (nearly 3 of every 5 prescriptions), 17% of individuals were categorized within the highest group of anticholinergic burden, and that prescribed anticholinergics were primarily for the management of non-motor symptoms. Together, the growing weight of evidence of anticholinergic burden in PD and its effects may provide the basis for future population-based interventions that seek to mitigate avoidable health risks, thereby improving patient quality of life.

PARKINSON DISEASE PHARMACOEPIDEMIOLOGY AND POPULATION

HEALTH: THE BIG PICTURE

Studies completed as part of this thesis increase knowledge regarding the use and safety of medications that are commonly prescribed to individuals with PD. Together, our findings inform health risk science, which is the basis for implementing multiple evidence-based interventions that aim to reduce health inequalities and inequities within and between populations. Using the *Integrated Framework for Risk Management and Population Health*

(Chapter 1, Figure 1) as a guide, our study findings are broadly discussed in subsequent paragraphs in relation to the determinants of health, health risk science, health risk policy analysis, and risk management.

Determinants of health

Population health focuses on 1) health outcomes among groups of individuals, 2) the distributions of health outcomes within studied groups, and 3) ways in which the determinants health contribute to health outcomes, including physical, mental, and social wellbeing [36, 37]. In this context, determinants of health are most commonly thought of as upstream factors, such as socioeconomic status and physical environments, that contribute to future health outcomes; however, may also include downstream factors that are more proximal contributors to individual health status, such as smoking and alcohol consumption [36, 37]. For these reasons, the determinants of health are routinely referred to as “the causes of the causes” [38]. The determinants of health serve as the *Integrated Framework for Risk Management and Population Health’s* foundation, and are categorized as follows: 1) biology and genetics, which may include genetic endowment, biomolecular pathways and systems, and development and again; 2) environment and occupation, which may include all physical environments and workplace conditions; and 3) social and behavioural, which may include socioeconomic status, social capital, culture, and health-related practices) [14]. Categories of determinants of health in the framework are intentionally broad, which enables the majority of factors believed to influence the health of populations to be considered when characterizing and attempting to mitigate health risks [14]. Interactions between the determinants of health should be defined (based on empirical evidence or hypotheses) prior

to proposing risk management strategies, as they may modify health risks. Furthermore, examining multiple determinants of health simultaneously offers the potential to estimate which interventions will be most cost-effective when implemented for the population of interest [14].

In our assessment of antiparkinson utilization trends, we leveraged inpatient prescription and demographic data, as well as health determinant data (age, sex, race, and census region) from the 2005 American Community Survey, to calculate annual standardized medication use. This allowed us to examine temporal changes in antiparkinson prescribing in relation to clinically important events, speculate reasons for observed trends, and propose future areas of study. Select determinants of health, including the effects of medication adherence on treatment regimen and care provider specialty, were not assessed by our study and should be considered prior to implementing interventions intended to modify the prevalent use of antiparkinson medications. Our secondary analyses examined temporal changes in the standardized prevalent use of antiparkinson medication by age and sex, two biological determinants of health. Findings revealed that the oldest individuals with PD (80+ years of age) were consistently prescribed DAs despite emerging safety concerns pertaining to their use and that PD treatment did not vary by sex. Additional research on whether such prescribing contributes to avoidable adverse health outcomes within older adult populations would aid to inform risk management options.

Associations between non-ergot DA use and adverse cardiovascular and cerebrovascular outcomes were examined in Chapter 3, which provides data for our ongoing systematic

review described in Chapter 4. Primary analyses utilized traditional risk assessment methods whereby a single risk factor (use of a non-ergot DA relative to non-use) was considered to influence specific cardiovascular and cerebrovascular outcomes. Construction of conditional multivariable logistic regression models enabled us to estimate exposure-outcome associations while taking into account the impact of other health determinants (such as demographic, clinical and care setting characteristics) on the overall level of risk of each outcome. Secondary analyses stratified significant findings for heart failure risk by available biological (age, sex) and social/behavioural (race) determinants of health, which identified subpopulations that may be at greatest risk of developing heart failure with the use of pramipexole. Although small sample sizes and suspected residual bias necessitate that these analyses be repeated using other health data from a similar population, initial findings suggest that men and septuagenarians may be at increased risk of heart failure when treated with pramipexole for PD. In Chapter 5, we again used risk assessment methods to ascertain whether anticholinergic burden was associated with adverse clinical and healthcare utilization outcomes. Due to the limited number of individuals with examined outcomes within each strata of anticholinergic burden, we did not stratify exposure-outcome associations by individual or care setting characteristics. Nevertheless, our analyses included health determinants as covariates in statistical models and demonstrated that anticholinergic burden was associated with potentially avoidable adverse events within a population of PD inpatients. If confirmed, findings from our pharmacoepidemiological studies will provide empirical data upon which broad and population-specific interventions may be proposed.

Finally, there are many determinants of health that may independently predict medication use and/or associated adverse outcomes for individuals with PD that could not be examined by our studies. These include PD severity and genetic susceptibilities to adverse outcomes (biological & genetics); access to specialty care (environment & occupation); and access to drug-based therapies, personal health practices, and individual involvement in making decisions about health (social and behavioural). Elucidating the role of these determinants and their interaction in contributing to medication use and adverse events in PD may identify more effective risk management opportunities, as deemed necessary.

Health risk science

Within the *Integrated Framework for Risk Management and Population Health*, health risk science represent risk assessment activities, specifically characterizing risks to the health of a population using qualitative or quantitative methods that allow for the impact of health determinants and their interactions on the level of risk to be considered [14]. Ideally, health risk science leverages advanced analytical methods and data from transdisciplinary sources to generate comprehensive estimates of health risks that are minimally biased [14]. In the context of PD pharmacoepidemiology, this includes making use of instrumental variables [39] and propensity scores [40] where possible, as well as available health, genetic, environmental, and behavioural data to characterize the risk of adverse outcomes associated with specific medication exposures. This may also include systematic searches of the literature for studies on a specific PD drug for the purposes of using reported data to generate overall population-based estimates of safety and effectiveness. Ultimately, health risk science

provides necessary data for evidence-based health risk policy analysis and the implementation of population-based health interventions [14].

All studies completed as part of this thesis utilized in-depth EMR data, including information on biological (such as age, sex, and level of comorbidity), environmental (such as care setting location and teaching status), and social and behavioural (such as race and smoking history) health determinants, to conduct health risk science and address important questions related to the use and safety of pharmacotherapies prescribed to older adults with PD.

Findings from this work, which are summarized in prior sections, provide benchmark data that may be used to support the implementation of evidence-based policies and interventions to better prescribing practices in PD and improve patient outcomes.

Health risk policy analysis and risk management interventions

Implementation of effective health risk policies and population-based interventions are essential to reducing health inequalities and inequities that are identified through health risk science activities. The consideration and implementation of health policies and interventions form the risk management component of the *Integrated Framework for Risk Management and Population Health*. Health policies should be evidence-based and take into consideration the health needs of the population intended to benefit from such policies, including projected changes in population dynamics and future requirements to live healthy lives [14].

Implemented policies may govern activities ranging from vehicle emission standards to regulating the marketing of pharmaceutical products; however, must be transparent and incorporate both prevention and treatment approaches to health [14]. In recent years, the

population approach to risk management has gained considerable attention. Contrary to classic top-down government health policies, the population health approach favours the implementation of multiple non-regulatory interventions that may operate along a continuum, either upstream, midstream, or downstream of the health issue of interest [36-38]. As outlined in the *Integrated Framework for Risk Management and Population Health*, efficient and effective interventions may involve Regulatory, Economic, Advisory, Community action, and Technological (REACT) components to achieve health equity. Interventions may be implemented at community, provincial or territorial, national, or international levels, and should balance top-down (politicians and policy makers) and bottom-up (civil society) actions [41]. Finally, open communication between all stakeholders and periodical evaluations of the effectiveness of implemented interventions (with ensuing changes as required) are key to the success of the overarching risk management strategy.

While our findings alone may be insufficient to justify the implementation of population-based health interventions, they provide valuable information that may be taken into account when weighing evidence regarding the appropriateness of antiparkinson prescribing practices and risks of adverse outcomes to necessary treatments. If future studies reproduce our findings and affected stakeholders determine that interventions are warranted, the following risk management strategies may be contemplated as efficient and effective solutions to the health concerns in question. The proposed risk management strategies are for the purposes of discussion only, based on the present state of knowledge of antiparkinson medication use and safety, and were not developed in consultation with relevant stakeholders.

- **Economic incentives:** Clinician and care setting incentives based on favourable patient outcomes (such as not returning to hospital for a suspected adverse event within 30-days and having minimal anticholinergic burden) offers potential to increase awareness of medication risks and limit inappropriate prescribing in PD.
- **Community outreach and engagement programs:** Community-based programs that aim to increase patient and care partner awareness of the benefits and risks of available PD therapies may facilitate increased patient participation in shared decision making processes specific to PD treatment.
- **EMR or pharmacy-based warning systems:** Clinical warning systems based on risk of adverse cardiovascular outcomes and total anticholinergic burden may prove beneficial in PD, since they may alert clinicians to prescribing risks and equally effective drug substitutions.
- **Remote health monitoring systems:** Use of wearable health monitoring devices may assist in detecting and monitoring signs of tremor, unsteady gait, cognitive impairment, and heart failure, which may be indicative of necessary changes to an individual's PD treatment regimen.

STRENGTHS & LIMITATIONS

Studies completed as part of this doctoral research have a number of strengths and limitations, which are individually acknowledged and discussed in prior study-specific

chapters. The following paragraphs broadly describe general strengths and limitations of using Cerner Health Facts® data to conduct pharmacoepidemiology studies in PD.

There are several strengths to our studies. Data were derived from large populations of PD inpatients who received care at multiple facilities throughout the US over more than 10 years. This may render our findings more generalizable compared to smaller, single center, or studies of shorter duration. Additionally, since the pharmacologic management of PD is similar across developed countries, our findings may be applicable to PD care and health systems outside of the United States, including Canada and Europe. Our analyses were largely comprised of older adults with PD, a group that is frequently underrepresented in RCTs and may be most vulnerable to adverse outcomes. In-depth pharmacy data enabled analyses of antiparkinson trends and estimates of association between medication use and adverse health outcomes. Examined exposures are presumed to reflect best practice guidelines, since individuals in our studies primarily sought care at urban teaching centers that are more likely to offer specialty care on-site. Lastly, detailed demographic, clinical, and care setting data for each encounter permitted multivariable models to include many *a priori* defined covariates that were hypothesized to modify or confound associations between examined exposures and outcomes.

Despite highlighted strengths, there are a number of limitations to our studies. Lacking outpatient pharmacy data required that all studies be restricted to PD inpatients, the majority of who were admitted for durations shorter than 30 days. Hospital admission among elderly individuals with PD is common and individuals in our studies were admitted for reasons that

are consistent with admissions among older adults in the US [42-44]. Therefore, dispensed medications in inpatient settings may accurately reflect outpatient treatment regimens and our findings may be generalizable to older adult outpatient populations with PD. The majority of individuals included in our studies received care at large teaching hospitals where PD diagnostic and management approaches may vary compared to those in other care settings, which may limit the external validity of our findings. We were unable to take medication dose, exposure time, and prescription adherence into consideration in our analyses. As such, we could not ascertain whether medication use was temporally associated with examined clinical outcomes, nor explore possible confounding by indication. Unmeasured factors such as PD severity, lifestyle habits, and disease duration may have contributed to residual bias in our reported estimates of association. Moreover, medical coding errors and misclassification of both exposures and outcomes may have contributed to over or underestimations of reported associations. This is particularly true for inpatient diagnoses of delirium, as less severe episodes may have gone undocumented in the EMR. Our studies of adverse outcomes examined associations between drug exposures and multiple adverse events, and are therefore considered exploratory. As such, adjustments for multiple comparisons were not made. Although our analyses should be replicated using other population-based datasets, our findings are supported by prior drug safety reports and plausible biomolecular mechanisms.

CONCLUSIONS AND FUTURE DIRECTIONS

In conclusion, research completed as part of this thesis serves to address knowledge gaps pertaining to the use and safety of medications that are commonly utilized by individuals

with PD. Leveraging data from Cerner Health Facts® and advanced pharmacoepidemiology methods, study findings demonstrate that 1) there have been temporal changes in the use of antiparkinson drugs in the US between 2001 and 2012 and that changes in prescribing practices may reflect increasing knowledge of drug safety and efficacy; 2) use of pramipexole for PD is associated with the inpatient diagnosis of heart failure, particularly among older adults and men; and that 3) anticholinergic burden attributed to the use of non-PD medications is associated with clinical and health service utilization outcomes, which may be preventable. Although replication of these studies is warranted, initial evidence suggests that individuals with PD and a history of heart failure or independent risk factors for heart failure may benefit from limited use of pramipexole. Consistent with prior studies of older adults, individuals with PD may benefit from limited use of non-PD medications with anticholinergic properties. In the context of the *Integrated Framework for Risk Management and Population Health*, these findings provide much needed benchmark data that may be used to inform future health risk assessments and risk management strategies.

Future studies that examine 1) care structure effects on prescribing practices in PD; 2) barriers to dissemination and adoption of best clinical PD practices; 3) the risk of heart failure among individuals with incident PD who are new-users of pramipexole; 4) the clinical significance of pramipexole-related heart failure in PD; 5) whether anticholinergic burden quantified according to other validated measurement scales is also associated with adverse health outcomes in PD; 6) how medications with both anticholinergic and antidopaminergic properties affect the risk of adverse outcomes in PD; and 7) whether our findings are relevant to health systems and the management of PD outside of the United States, will provide

necessary information on the use and safety of medications utilized by individuals with PD and assist in determining whether population-based interventions are justified.

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APPENDIX I: Risk of heart failure following treatment with dopamine agonists in Parkinson's disease patients

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ABSTRACT

Introduction: Dopamine agonists are frequently used in the treatment of early or advanced Parkinson's disease (PD) patients. They have been shown to be efficacious for the treatment of motor symptoms and for delaying levodopa-induced dyskinesias. However, their utilization is limited by the risk of adverse drug reactions, some of which affect the cardiovascular system. Recently, the U.S. Food and Drug Administration identified a possible association between exposure to pramipexole and the risk of heart failure.

Areas covered: This article begins by reviewing the pharmacodynamic and cardiovascular effects of dopamine agonists in PD patients. Pharmacoepidemiological studies about the association between dopamine agonists and heart failure are then evaluated.

Expert Opinion: Four nested case-control studies were reviewed. In general, results showed higher heart failure risk following use of pramipexole or cabergoline. Although the effects of cabergoline may be explained by the induction of cardiac valve fibrosis, the basis for the significantly increased risk associated with pramipexole is not clear. It remains to be determined if these are dose-related effects, at what point they occur during the course of treatment, and if the risk is the same for all patients irrespective of other potential modifying factors, such as age and sex.

INTRODUCTION

Levodopa remains the ‘gold standard’ for treating Parkinson’s disease (PD) [1].

Nevertheless, its initial impressive therapeutic efficacy is frequently limited within a few years by the emergence of motor complications (such as fluctuations or abnormal movements) and other neurological problems [2, 3]. As a consequence, the treatment of patients with PD has expanded to incorporate additional pharmacologic approaches, including the use of dopamine receptor agonists and inhibitors of the monoamine oxidase-B (MAO-B) and/or catechol-O-methyltransferase (COMT) enzymes.

Bromocriptine was the first dopamine agonist (DA) to be used as an adjunct to levodopa therapy for PD patients experiencing motor fluctuations [4]. Presently, nine different DAs are available worldwide for the treatment of PD, four of which are ergot derivatives (bromocriptine, cabergoline, pergolide, lisuride), while the remaining five are not (apomorphine, pramipexole, ropinirole, and rotigotine). Pergolide was withdrawn from the U.S. and Canadian markets because of concerns about adverse cardiovascular events in 2007 [5, 6], although it is still available in Europe [7]. Piribedil and lisuride are not available in North America.

Multiple randomized controlled trials and a large body of clinical experience support the efficacy of DAs with respect to symptomatic control of motor symptoms in both early and advanced PD [8]. DAs also delay the occurrence of levodopa-induced motor complications, reduce off-time in patients with wearing-off [8], and can be used to ameliorate some non-motor symptoms such as depression [9].

Adverse drug reactions (ADRs) of dopaminergic and non-dopaminergic origin often complicate the treatment of PD with DAs. The former can be classified as peripheral (including gastro-intestinal reactions such as nausea and vomiting, or cardiovascular reactions such as orthostatic hypotension and leg edema) or central (psychotic or behavioral syndromes and sedative reactions) [8]. The most frequent non-dopaminergic ADRs include fibrotic reactions with ergot derivatives, application site reactions with subcutaneous apomorphine or rotigotine transdermal patches, skin reactions with bromocriptine, and ocular disturbances with cabergoline [8].

Recently, the U.S. Food and Drug Administration (FDA) evaluated the risk of heart failure by a pooled analysis of randomized clinical trials [10]. All randomized, placebo-controlled, phase 2 and 3 clinical trials of pramipexole submitted by the manufacturer (Mirapex®, Boehringer Ingelheim) were analyzed. Results showed that the frequency of newly diagnosed heart failure was non-significantly higher with pramipexole (0.29%) as compared to placebo (0.14 %) [10].

The objectives of the present paper are to review the general pharmacodynamic characteristics and cardiovascular effects of DAs and to evaluate the evidence linking exposure to DAs with heart failure. With this in mind, literature searches were conducted in PubMed to identify publications about the relationship between heart failure and exposure to DAs. Only four articles on this topic were found, which will be reviewed in Section 4. Therefore, we took the opportunity to review their cardiovascular effects and

pharmacodynamic bases for such effects, aiming to identify clues about the possible mechanisms of heart failure with DAs.

PHARMACODYNAMIC CHARACTERISTICS OF DOPAMINE AGONISTS

We begin by reviewing the localization and actions of dopamine receptors, which are the main targets of DAs. A summary of their localization and effects in the human body is given in Table 1. We will focus on cardiovascular effects resulting from the activation of these receptors. Full discussion of DAs pharmacodynamic properties can be found elsewhere [11, 12].

	D1 family		D2	D2 family	
	D ₁	D ₅		D ₃	D ₄
Function					
Adenylate cyclase	+	+	-	?	?
PIP turnover	+	+	-	?	?
Distribution					
Brain	Striatum Nucleus accumbens	Hypothalamus Hippocampus	Striatum Substantia nigra	Olfactory tubercle Hypothalamus Mesolimbic pathway	Frontal cortex Midbrain
Periphery	Heart Kidney	Vascular Kidney	Vascular Heart Sympathetic ganglia	Vascular Kidney	Heart Kidney
Effects on blood pressure regulation					
Heart rate / contractility	0	?	-	-	-
Natriuresis & diuresis	+	+	+	+	?
Vasodilation	+	+	+	+	?
Other	-	Inhibition of AT1 receptor expression Inhibitory effect on vascular proliferation	Antagonize AngII	Inhibition of AT1 receptor expression and rennin excretion	Antagonize vasopressin- and aldosterone-dependent water and sodium reabsorption

Table 1. Dopamine receptors.

Abbreviations: AngII, angiotensin II; AT1, angiotensin receptor 1; PIP, phosphoinositol phosphate.

The central dopaminergic neuron system is comprised of three main pathways: the nigrostriatal, the mesolimbic/mesocortical, and the tubular-infundibular pathway [11]. The nigrostriatal pathway originates in the substantia nigra pars compacta, projects to the striatum, and is involved in regulating basal ganglia function. The mesolimbic/mesocortical pathways originate in the ventral tegmental area (A10), project to cortical structures, and affect cognitive function and motivation, and are also part of the reward system [13]. The tubular-infundibular pathway originates in the hypothalamus, projects to the hypophysis and other targets, and is involved in neuroendocrine regulation and wake-sleep cycle generation. Activation of dopamine receptors in some of these pathways can produce cardiovascular effects. For example, some studies suggest that the basal ganglia is involved in autonomic regulation of blood pressure and heart rate [14]. In a group of 34 healthy subjects, striatal dopamine D2/D3 receptor binding correlated negatively with supine resting systolic blood pressure and heart rate, and positively with supine resting heart rate variability [15].

Dopamine also inhibits prolactin secretion [16]. Prolactin increases heart rate and vascular tone [17, 18], and induces endothelial dysfunction leading to inflammation and altered function [19]. In the heart, D₁-, D₃-, and D₄- agonists show no major effects, while D₂-agonists decrease heart rate and left ventricular contractility [20].

Dopamine also exerts pronounced cardiovascular and renal effects by activating both D1-like and D2-like dopamine receptors located at various sites within the cardiac, vascular, and renal regions [11, 21, 22]. For example, stimulation of D1-like receptors induces vasodilatation and natriuresis, whereas stimulation of D2-like receptors results in inhibition

of norepinephrine release and inhibition of aldosterone secretion, contributing to vasodilatation and sodium excretion. Effects on vessel walls are mediated by post-junctional D1-like and pre-junctional D2-like receptors. Interestingly, intravenous administration of apomorphine to dogs resulted in blood pressure fall due to vasodilation, which in turn led to increased heart rate, stroke volume, and cardiac output [23].

The kidney, a target of dopamine, expresses both D1-like and D2-like receptors [11, 21]. Renal D1-like receptors exhibit vascular and tubular localization. Acting on these receptors, dopamine inhibits renal sodium-potassium pump activity and the Na^+/H^+ exchanger, which produces a salt-losing effect. On the other hand, D2-like receptors have been shown to inhibit renin release. Dysfunction of the renal dopaminergic system has been proposed as a pathogenetic factor in some forms of hypertension [24].

Dopamine receptors are also expressed in sympathetic ganglia [25]. For example, in anesthetized dogs and in-vitro studies on arterial preparations, D_2 receptor agonists inhibited norepinephrine release. Furthermore, D_2 receptors have also been found in the adrenal medulla and in isolated chromaffin cell preparations. In a recent study, quinpirole-induced inhibition of the sympathetic vasopressor outflow was primarily mediated by activation of dopamine D_2 -like receptors [26]. A similar effect has been observed with D_5 receptors [21].

Dopamine has been hypothesized to affect insulin secretion based on findings of hyperinsulinemia following administration of neuroleptics to normal subjects and reduced insulin secretion in PD patients treated with levodopa [27, 28]. In-vitro studies performed in

isolated pancreatic islets further suggest the participation of D₂ receptors in insulin secretion. Interestingly, D₂R knockout mice demonstrate impairment of insulin response to glucose, high fasting glucose levels, and glucose intolerance [27, 28]. Bromocriptine has also recently been shown to be effective for the treatment of type 2 diabetes mellitus, probably by reducing insulin resistance when administered at appropriate circadian moments [29, 30]. Finally, it has been shown that dopamine inhibits histamine-induced endothelial exocytosis by activating D₂-like receptors, thus reducing Von Willebrand factor secretion [31].

DAs differ in their affinities for dopamine receptors. As demonstrated in Table 2, bromocriptine is a D₂-like receptor agonist and a weak D₁-like receptor antagonist, while apomorphine and pergolide are mixed D₁- and D₂-like receptor agonists. Ropinirole and pramipexole bind selectively to D₂-like receptors [12, 32, 33], with pramipexole being most selective. Within the D₂-like receptor family, these agonists have higher affinity for the D₃ receptor compared with D₂, with pramipexole again showing higher selectivity.

Agonists	D1-like	D2-like	5HT1	5HT2	Alpha-1	Alpha-2
<i>Ergolinic derivatives</i>						
Bromocriptine	0	++	++	+++	++	++
Cabergoline	0/+	+++	++	++	++	++
Pergolide	+	+++	+	+++	++	++
<i>Non-ergolinic compounds</i>						
Apomorphine	++	++	0/+	0/+	0/+	++
Piribedil	0/+	+++	0	0/+	0/+	++
Pramipexole	0/+	+++	0/+	0/+	0/+	++
Ropinirole	0	+++	0	0/+	0/+	+
Rotigotine	0	+++	+	?	+	+

Table 2. Binding affinity of DAs for dopaminergic and non-dopaminergic receptors. Abbreviations: +++, strong; ++, moderate; +, mild; 0, no effect.

DAs also bind to non-dopaminergic receptors (Table 2). For example, ergolinic derivatives demonstrate high to moderate affinity for a variety of non-dopaminergic receptors such as alpha-adrenergic (alpha 1 and alpha 2) and serotonergic (5HT1 and 5HT2) receptors [12, 32, 34-36]. Non-ergolinic receptors are devoid of appreciable effects on 5HT or alpha1-adrenergic receptors, but retain considerable activity on alpha2-adrenergic receptors.

Alpha2-adrenoceptors belong to the superfamily of G-protein coupled receptors [37, 38]. On one hand, they bind to the inhibitory G proteins Gi and Go and decrease adenylyclase activity; however, they are also coupled to Gs-proteins, thus increasing adenylyclase activity. Activation of these receptors could decrease cellular cAMP levels at low agonist concentrations, while at higher concentrations cAMP may be increased. There are 3 main receptor subtypes, referred to as receptors A-C, respectively. A fourth originally described subtype, the adrenoceptor (receptor D), is now accepted as an A-subtype receptor.

The A-subtype receptor is the major autoreceptor in sympathetic neurons, where it inhibits the release of norepinephrine. The C-subtype also functions as an autoreceptor, but it is expressed in sympathetic nerve endings more than in central adrenergic neurons. It has been suggested that C subtype receptors may control norepinephrine release at low action potential frequencies. In contrast, the A-subtype seems to operate primarily at high stimulation frequencies in sympathetic nerves, and may thus be responsible for controlling noradrenaline release during maximal sympathetic activation. In contrast, alpha2-B adrenoceptors are found mainly post-synaptically throughout the body.

In summary, based on their pharmacodynamic profile, dopamine agonists may be expected to 1) reduce sympathetic tone and sodium retention, thus leading to reduced blood pressure; 2) reduce heart rate and contractility, thus leading to reduced cardiac oxygen consumption; 3) reduce insulin resistance, leading to improved metabolic functioning; and 4) reduce Von Willebrand Factor secretion thus leading to reduced coagulability potential. Interestingly, all of these effects should theoretically lead to cardioprotection. In the following section, the cardiovascular effects of dopamine agonists observed experimentally will be reviewed.

CARDIOVASCULAR EFFECTS OF DOPAMINE AGONISTS

Short-term cardiovascular responses to bromocriptine administration were previously explored in healthy subjects [39]. Ten healthy subjects 31 ± 2 years of age were evaluated following administration of bromocriptine (2.5 mg) alone and after blocking peripheral D₂-like receptors by domperidone. An electrocardiogram was performed in the supine and sitting positions and the low-frequency (LF) component, high-frequency (HF) component, and LF/HF ratio were calculated. The latter is used as an index of sympathovagal balance, while the HF component is thought to represent the vagal cardiac influence. Change from the supine and sitting positions induced an increase in the LF/HF ratio, a reduction in the HF component, and increased norepinephrine release. Administration of bromocriptine led to a reduction of blood pressure, a reduction in norepinephrine release, and an increase in the LF/HF ratio. These effects were not completely blocked by pre-administration of domperidone, a peripheral blocker of dopamine receptors. Indeed, a decrease in diastolic blood pressure was still observed. Norepinephrine release was not altered and the LF/HF ratio (a marker of sympathetic tone) decreased. These results suggest that blood pressure

reduction after treatment with bromocriptine occurs by peripheral and central mechanisms. The peripheral mechanisms involve inhibition of norepinephrine release, which induces a reflex increase in the sympathetic cardiac influence. Peripheral blockade of dopamine receptors did not mitigate bromocriptine's hypotensive effects, although a reduction of sympathetic tone was seen in this case.

The effects of bromocriptine on blood pressure and pulse rate was also studied in 20 untreated PD patients in whom bromocriptine monotherapy was initiated [40]. Results showed a dose-dependent reduction in supine systolic and diastolic blood pressure, offset by a small increase in heart rate. In a group of untreated PD patients, administration of a D1 agonist significantly decreased blood pressure and peripheral norepinephrine release in the supine position, and caused orthostatic hypotension [41].

Cardiovascular effects of extended treatment with pergolide were studied in 40 patients, in whom treatment was initiated after inclusion in the study [42]. During the course of treatment with pergolide, 7 patients experienced arrhythmias, 2 experienced syncope, and 8 of them orthostatic hypotension. Critical atrial fibrillation has also been observed with ropinirole [43].

Recently, cardiovascular effects of rotigotine were explored in 34 de novo PD patients [44]. Rotigotine is a non-ergolinic agent with low affinity for the alpha2-adrenergic receptors (Table 1). Results showed that drug administration did not modify cardiovascular

parameters, including orthostatic blood response or cardiac responses to the Valsalva maneuver or to deep breathing.

Treatment with ergot and non-ergot DAs induces leg edema more frequently than levodopa [8]. In different clinical trials, frequency of edemas with pramipexole was 42% vs. 15% with levodopa and 16% with ropinirole or cabergoline vs. 3% in control groups treated with levodopa [8]. Risk factors for peripheral edema include female sex and cardiovascular comorbidities. A recent study reported that edemas were more frequent with DAs as compared to levodopa, with no statistically significant differences among the different DAs [45].

Ergot-derived DAs can induce pleuropulmonary, pericardiac, and/or retroperitoneal fibrosis [8]. Indeed, the risk of valvular fibrosis is significantly higher for these agents compared to non-ergolinic DAs [45]. It has been suggested that this effect is mediated by activation of the 5HT_{2B} receptor [46]. Interestingly, there are no reports on heart valve fibrosis with lisuride, which is a 5HT_{2B} receptor antagonist [47].

Apart from these alterations, ergot-derived compounds do not appear to alter cardiac morphology [48, 49].

ASSOCIATION BETWEEN EXPOSURE TO DOPAMINE AGONISTS AND HEART FAILURE

To the best of our knowledge, four studies have explored the relationship between exposure to DAs and the occurrence of heart failure [50-53]. They provided mixed results. Study protocols – nested case-control studies within cohorts obtained from healthcare databases – are summarized in Table 3. Study databases were comprised of patients of defined ages with prescriptions for dopaminergic drugs used in PD, parkinsonian syndromes, restless leg syndrome, hyperprolactinemia, or acromegaly. Although only one study population was limited to PD patients, patients older than 50 years treated with antiparkinsonian drugs generally represent PD cases. Exposure was defined as one or more prescriptions of a DA, and patients were classified as current or past users of this class of drug. Non-exposure was defined as patients without such a prescription. In one study, however, only subjects on levodopa were included in this group. The outcome was diagnosis of heart failure in the majority of studies based on a review of electronic health records. In one study, the outcome was defined as hospitalization for a coronary, peripheral, or cerebral vascular event.

Author, year	Arbouw et al., 2012	Mokhles et al., 2012	Renoux et al., 2012	Hsieh & Hsiao, 2013
<i>Study design</i>	Nested case-control	Nested case-control	Nested case-control	Nested case-control
<i>Source</i>	PHARMO database	Health Improvement Network (UK), Health Search Database (Italy); Integrated Primary Care Information & PHARMO (Holland)	UK General Practice Research Database	Taiwan's National Health Insurance research database
<i>Study base</i>	at least one prescription for a dopaminergic agent after the age of 55 (1994-2007)	1 yr. of medical history; new users of either DAs or levodopa for PD	Users of antiparkinsonian drugs; 40 to 89 years of age between 1997 - 2009	Users of antiparkinsonian drugs between 2001 and 2010
<i>Definition of exposure</i>	at least one prescription within 1 yr. before the index date	Any prescription for DA or levodopa	Actual or past use of DAs	Actual or past use of DAs
<i>Event definition</i>	hospitalization for a coronary, peripheral, or cerebrovascular event	Incident HF confirmed by review of electronic recordings	Incident HF confirmed by review of electronic recordings	Incident HF
<i>Controls</i>	Matched to case patients on gender, duration of prescription, age (5 yr.)	matched to each case on database, age (± 2 yr.), and sex	drug indication, age, sex, new user status, yr. of entry	age, gender, and cohort entry yr.
<i>Sample size</i>	Study base = 8,094. Cases = 542, controls = 2,155	Study base = 25,459. Cases = 527, controls = 38,641	Study base = 26,814. Cases = 783, controls = 7,454	Study base = 27,135. Cases = 1,707, controls = 3,414
<i>Confounding factors assessed</i>	Prior hospitalization due to ischemic events or other events, co-medication	Concomitant cardiovascular, autoimmune, GI or metabolic disorders, co-medication	Alcohol, smoking, BMI, comorbidities, co-medications	Reason for prescription, comorbidities, co-medications

Table 3. Studies exploring the association between exposure to DAs and the occurrence of heart failure.

Abbreviations: BMI, body mass index; DA, dopamine agonist; GI, gastrointestinal; HF, heart failure.

Such studies are restricted by many of the same limitations, which may explain a number of inconsistencies regarding results, some of which were initially identified by the US FDA [10]. First, the inclusion of non-PD patients, reflecting the use of antiparkinsonian for other indications, may have introduced some heterogeneity in the populations under study. Second, cardiovascular comorbidities were different in exposed and non-exposed groups, being generally more frequent in cases than in controls. Some degree of information bias might have been introduced by the fact that DAs induce peripheral edemas, which might have prompted the search for other cardiovascular diseases, including heart failure. Finally, heart failure diagnosis was not confirmed by an independent review of medical charts. It must also be mentioned that the effect of some DAs, such as rotigotine, priribedil or apomorphine, could not be properly analyzed due to insufficient power.

Results from the three studies that used heart failure as the study outcome will be reviewed. The study from Renoux and colleagues included 26,814 users of antiparkinsonian drugs in whom 787 cases of heart failure (possible or probable) were diagnoses during follow-up (annual rate = 8.7 per 1,000) [53]. Such cases were matched to 7,454 controls (up to 10 per case). Body Mass Index, smoking, alcohol abuse, frequency of cardiovascular and metabolic comorbidities, and frequency of treatment by diuretics were higher in cases compared to controls. Thirty-two heart failure cases (4.1%) were on pramipexole vs. 211 (2.8%) controls (adjusted odds ratio (OR), 95% confidence interval (CI) = 1.86, 1.21-2.85). Ropinirole was used by 40 (5.1%) cases and 385 (2.5%) controls (1.23, 0.85-1.77); cabergoline was used by 36 (4.6%) case and 217 (2.9%) controls (2.07, 1.39-3.07); and pergolide was used by 32 (4.1%) cases and 261 (3.5%) controls (1.42, 0.95-2.12). Increased risk of heart failure with

pramipexole was not modified by dose and therapy duration. Similarly, previous cardiovascular or peripheral edema history and prior levodopa or DA use did not modify the risk of heart failure with pramipexole.

In the study from Mokhles and colleagues, 527 possible or probable heart failure cases were detected in 25,459 levodopa or DA new-users [51]. Finally, 518 heart failure cases were matched to 38,641 cases. Cases had a higher frequency of cardiovascular, metabolic, and respiratory comorbidities. Cabergoline was used by 15 (2.9%) of heart failure cases and 1,159 (3.0%) controls (1.30, 0.76-2.22); pergolide was used by 11 (2.1%) cases and 663 (1.7%) controls (0.78, 0.41-1.46); bromocriptine was used by 2 (0.4%) cases and 155 (0.4%) controls (0.79, 0.19-3.25); pramipexole was used by 31 (6.0%) and 1,806 (4.7%) controls (1.61, 1.09-2.38); and ropinirole was used by 18 (3.5%) cases and 1,720 (4.5%) controls (0.82, 0.50-1.34). There was no dose effect but risk was greater during the first 3 months of pramipexole use and in patients over 80 years of age.

Hsieh and colleagues identified 1,707 heart failure cases among 27,135 users of antiparkinsonian drugs that were matched to 3,414 controls [52]. As observed in previous studies, cardiovascular and metabolic comorbidities and treatments were more frequent among cases. Pramipexole was used by 28 (1.6%) of heart failure cases and 42 (1.2%) controls (1.40, 0.75-2.61); ropinirole was used by 46 (2.7%) cases and 69 (2.0%) controls (1.22, 0.76-1.95); cabergoline was used by 2 (0.1%) cases and 5 (0.2%) controls (2.39, 0.41-14.12); pergolide was used by 33 (1.9%) cases and 47 (1.4%) controls (1.39 (0.77, 2.48); and bromocriptine was used by 45 (2.6%) cases and 60 (1.8%) controls (1.54, 0.93-2.55).

Risk of heart failure with the different DAs as observed by Mokhles and colleagues, Renoux and colleagues, and Hsieh and Hsiao are summarized in Table 4.

	Mokhles et al., 2012	Renoux et al., 2012	Hsieh & Hsiao, 2013
<i>Any dopamine agonist</i>	-	1.58 (1.26–1.96)	1.22 (0.89–1.67)
<i>Ergolinic compounds</i>	1.03 (0.69–1.55)	-	1.46 (1.00–2.12)
Cabergoline	1.30 (0.76–2.22)	2.07 (1.39–3.07)*	2.39 (0.41–14.12)
Bromocriptine	0.79 (0.19–3.25)	-	1.54 (0.93–2.55)
Pergolide	0.78 (0.41–1.46)	1.42 (0.95–2.12)	1.39 (0.77–2.48)
<i>Non-ergolinic compounds</i>	1.18 (0.85–1.62)	-	1.24 (0.84–1.82)
Pramipexole	1.61 (1.09–2.38)*	1.86 (1.21–2.85)*	1.40 (0.75–2.61)
Ropinirole	0.82 (0.50–1.34)	1.23 (0.85–1.77)	1.22 (0.76–1.95)

Table 4. Risk of heart failure with dopamine agonists. Odds ratio as obtained from logistic regression are shown. * p<0.05

Arbouw et al. [50], assessed the relationship between exposure to DAs and the frequency of hospitalizations due to ischemic events in PD patients by analyzing the PHARMO database. Patients with at least one prescription for a medication containing levodopa and age of 55 or more years between 1994 and 2006 were included. Cases were subjects with hospitalizations due to coronary, peripheral, or cerebrovascular events after 1997. Four controls per case were selected, matched for gender, duration of prescription, history available, and age. Risk of hospitalization was non-significantly increased with DAs (OR [95% CI], 1.19 [0.95–1.49]). These results had to be interpreted cautiously, as they did not assess exclusively heart failure, but ischemic effects leading to hospitalization. On one hand, ischemic heart disease is the leading cause of heart failure but not the only one [54]. Furthermore, peripheral or cerebrovascular events were included, which are not related to heart failure.

CONCLUSIONS

DAs have a central role in the treatment of PD. Nonetheless, their use can be complicated by an increased risk of some serious ADRs, some of which are of cardiovascular origin. Among cardiovascular ADRs, one of the most frequent is orthostatic hypotension and the most severe is cardiac valve fibrosis leading to regurgitation, which is only observed with ergolinic compounds. Results from nested case-control studies herein reviewed suggest that pramipexole and cabergoline might increase the risk of heart failure in PD patients. Initial results suggest that this reaction may be more frequent in older subjects and during the first few months after beginning treatment in those treated with pramipexole.

EXPERT OPINION

DAs exert a range of cardiovascular effects related to the activation of dopaminergic and non-dopaminergic receptors. They reduce peripheral resistance, increase salt and water excretion, reduce endothelial activation, and reduce insulin resistance by central and peripheral mechanisms. It is therefore not surprising that DAs have been used experimentally for the treatment of hypertension [55] and have been shown to be efficacious for the treatment of type 2 diabetes [56].

Results suggest that cabergoline and pramipexole appear to increase the risk of heart failure. It was suggested that for cabergoline, cardiac valve fibrosis might lead to heart failure. However, this happens infrequently [57] and might not fully account for the proposed relationship. Mokhles and colleagues performed an exploratory analysis restricted to heart failure cases preceded by new onset cardiac valve regurgitation occurring after the start of

drug use [51]. Results showed that cabergoline but not pramipexole was related to heart failure occurrence. These results, however, do not rule out the possibility that cabergoline increases the risk of both events, which are otherwise not associated to one another.

The link between pramipexole and heart failure, while intriguing, is difficult to explain. One possibility is that pramipexole increases the risk of peripheral edema, which can lead to a false diagnosis of heart failure. Nonetheless, results reported by Renoux and colleagues suggest that the risk of heart failure associated with pramipexole was independent of the presence of peripheral edemas [53].

Pramipexole's effects were more pronounced during the initial months after beginning treatment [51]. Since heart failure is a chronic condition, this may argue in favor of an unmasking effect of pramipexole. In the present context, subjects starting pramipexole may be more closely monitored because of known cardiovascular ADRs, leading to enhanced diagnosis of sub-clinical chronic heart failure. Nonetheless, it is clear that this result need to be confirmed before any firm conclusion is drawn.

It is also possible that pramipexole adversely impacts on the cardiovascular profile, leading to heart failure only in subjects with risk factors, such as male gender, less education, physical inactivity, cigarette smoking, overweight, diabetes, or hypertension [54]. This coincides with the observation that heart failure risk was higher in older subjects and that cases had more cardiovascular antecedents, comorbidities, and co-medications in all studies reported to date [51-53].

Intriguingly, based on its pharmacodynamic properties, a cardioprotective effect of pramipexole may be postulated. Indeed, as discussed in Section 2, it may reduce blood pressure load, heart oxygen consumption, insulin resistance, and hypercoagulability. However, previous experience cautions against such simplified reasoning. For example, milrinone was initially thought to have therapeutic potential for treating heart failure, but was later shown to increase mortality [58]. Ibopamine, a DA, has also been shown to reduce survival in patients with heart failure [59]. Similarly, pramipexole appears to alter cardiovascular function in an adverse way, leading to heart failure. The fact that its pharmacodynamic characteristics might theoretically suggest a cardioprotective effect may indicate that this drug acts on pathways that are not fully elucidated. Therefore, more research on the mechanism of DA of action is warranted.

Interestingly, ropinirole does not appear to lead to an increased risk of heart failure, suggesting a specific effect of pramipexole. The major difference between these drugs is affinity to D₃ receptors, which is higher for pramipexole. At this point, how activation of such receptors might alter cardiac function remains unclear.

Many unanswered questions regarding the risk of heart failure associated with exposure to pramipexole warrant further investigation. First, the cardiovascular effects of pramipexole in PD patients should be investigated, ideally in a comparative study with other DAs. Second, more information is needed to fully characterize the relationship between DAs and heart failure, including the effects of dose, treatment duration, clinical relevance, and if they are modified by co-administration of other antiparkinsonian drugs. Finally, a risk-benefit

analysis should be conducted, focusing on patient groups with higher risk of heart failure. For example, if the risk of heart failure is only increased in pramipexole users above 80 years of age, then its impact in the general population may be less obvious, as these subjects are not frequently treated with DAs due to a higher risk of neuropsychiatric complications [60]. It is also recommended that in future studies, diagnosis of heart failure be based on echocardiography and most importantly on the measure of natriuretic peptide circulating levels [61].

DECLARATION OF INTERESTS

SPLL, MVR, MLM, JC, and JLM have no conflicts of interests to disclose. DK serves as Chief Risk Scientist and CEO at Risk Sciences International (www.risksciences.com), which has conducted work on other pharmaceutical products for federal government clients. OR has acted as an advisor for most drug companies developing antiparkinsonian medications including DAs such as Boehringer-Ingelheim, GSK, Britannia, UCB, and Servier, and has received unrestricted scientific grants from GSK, Novartis, Boehringer-Ingelheim, Faust Pharmaceuticas, Eisai, Lundbeck, TEVA, Euthérapie, and Solvay.

HIGHLIGHTS

- Dopamine agonists are frequently used in the symptomatic treatment of early or advanced Parkinson's disease (PD) patients and delay levodopa-induced dyskinesias.
- Recently, the U.S FDA identified a possible association between exposure to pramipexole and the risk of heart failure.

- Four nested case-control studies were reviewed. In general, results showed higher heart failure risk following use of pramipexole or cabergoline.
- The effects of cabergoline may be explained by the induction of cardiac valve fibrosis. The basis for the significantly increased risk associated with pramipexole remains unknown.
- It remains to be determined if these are dose-related effects, at what point they occur during the course of treatment, and if the risk is the same for all patients, irrespective of other potential modifying factors such as age and sex.

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APPENDIX II: Onset and progression factors in Parkinson's disease: a systematic review

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KEY SCIENTIFIC FACTS

- Parkinson's disease (PD) is a neurodegenerative disorder marked by tremor, muscular rigidity, and slow, imprecise movement mainly affecting individuals over age 65. It is characterized by the death of dopaminergic neurons in the midbrain, which results in dopamine deficiency and impaired motor and non-motor functions.
- PD is the second most common neurodegenerative disorder in the world after Alzheimer's disease, with a prevalence of 1 per 300 people in Canada and incidence increasing with age.
- Pesticide exposure, head injury, rural living, well-water drinking, farming occupation, and family history of PD were identified as risk factors for PD onset.
- Constipation, depression, rapid eye movement (REM) sleep behavior disorder (RBD), erectile dysfunction, hip fracture, and olfaction are recognized as prodromal markers of this disease.
- Interventions aimed at reducing pesticide exposure and head injuries may reduce PD incidence.

ABSTRACT

Current research has identified several factors thought to be associated with the onset and progression of Parkinson's disease (PD); however, whether certain factors contribute to or are protective against PD remains unclear. As such, a systematic search of the literature was performed using variations of MeSH and keyword search terms to identify and summarize systematic reviews and primary studies pertaining to factors associated with the onset and progression of PD. Factors referred to both traditional risk factors and prodromal markers. The following databases were searched: MEDLINE, MEDLINE In-Process, EMBASE, PsycINFO, Scopus, Web of Science, Cochrane Database of Systematic Reviews, Cumulative Index to Nursing and Allied Health Literature (CINAHL), ProQuest Dissertations & Theses, AARP AgeLine, and PDGene. A quality assessment of included systematic reviews was completed using the validated Assessment of the Methodological Quality of Systematic Reviews (AMSTAR) tool. Data extraction targeted reported factors, risk estimates, and 95% confidence intervals. Findings identified 11 systematic reviews of sufficient quality reporting factors for PD onset and no systematic reviews reporting factors for PD progression. In addition, 93 primary articles were identified, of which, 89 articles addressed factors related to PD onset and 4 articles addressed factors related to the PD progression. Pesticide exposure, rural living, well-water drinking, and farming occupation were consistently found to be positively associated with the onset of PD. Moreover, family history and polymorphisms to key genes were also found to be positively associated with the onset of PD. Conversely, coffee consumption, cigarette smoking, and some polymorphisms were consistently found to be negatively associated with the onset of PD. Urate was the only identified factor linked to the progression of PD; it was mostly found to be negatively associated with PD. In sum,

evidence pertaining to factors associated with the onset and progression of PD was systematically found and summarized.

INTRODUCTION

Parkinson's disease (PD) is a common neurological condition, affecting 1 in 300 Canadians (Parkinson Post, 2005). It is particularly prevalent in the elderly as the incidence increases with age (de Lau et al., 2004). In Western Europe's 5 most and the world's 10 most populous nations, the number of individuals with PD over the age of 50 years was 4.1 and 4.6 million in 2005 respectively, and is expected to nearly double by 2030 to 8.7 and 9.3 million respectively (Dorsey et al., 2007). PD is a complex disorder with several subtypes that are classified according to genetic involvement, time of onset, and presence of dementia. Onset may be sporadic or familial, early or late, and with or without dementia (Crosiers et al., 2011; Spatola and Wider, 2014; Wider and Wszolek, 2007). PD is associated with a disorganization of the circuitry of the basal ganglia, which is caused by the loss of dopaminergic neurons in the substantia nigra (Bartels and Leenders, 2009). Physically, this results in timing and scaling problems when the affected individual performs bodily movements (Bartels and Leenders, 2009). The common cardinal motor features of PD include resting tremor, bradykinesia, rigidity, postural instability, stooped posture, and freezing of gait (Savitt et al., 2006). Also, as many as 40% of patients with PD have cognitive impairment or dementia (Braak et al., 2006; Shulman et al., 2001). Together, these motor and non-motor features contribute largely to functional difficulties; thereby, affecting the individual's ability to perform activities of daily living (Weintraub et al., 2004), and eventually increase morbidity and mortality risk (Savitt et al., 2006). As such, individuals with PD have an increasing need

for social and medical care resulting in a potentially large economic burden for them, their families, and their care partners (Hindle, 2010).

Current research has identified several factors associated with PD; however, whether certain factors contribute to or are protective against PD remains unclear. The purpose of this study was to systematically identify literature pertaining to select factors associated with the onset and progression of PD. We targeted factors relating to biology, socioeconomics, environment, psychosocial issues, lifestyle, comorbid conditions, and genetics. We sought to provide a comprehensive review of current literature pertaining to these factors in order to provide a basis for policy makers to identify and implement appropriate measures that will mitigate the burden of PD in Canada.

MATERIALS AND METHODS

The methods utilized have been described in detail (Hersi et al., 2016), and hence are only briefly described herein. Our study had two stages. Stage one included a systematic search of existing systematic reviews and meta-analyses, while stage two included a systematic search of primary studies (case-control, cohort, and cross-sectional).

Locating systematic reviews and meta-analyses: stage one

Identification of studies

To identify eligible systematic reviews and meta-analyses, searches of the following electronic databases were executed, modified appropriately to that used by the central research office in Ottawa following extensive consultation with local library staff at the

University of Toronto: MEDLINE (1946 to September Week 3 2012), MEDLINE In-Process (September 28 2012), EMBASE (1980 to 2012 Week 39), PsycINFO (1806 to September Week 4 2012), Scopus (1960 to October 1 2012), Web of Science (1899 to October 1 2012), Cochrane Database of Systematic Reviews (until September 2012), and CINAHL (1981 to September 2012). Variations of MeSH and keyword search terms were used that related to PD, its risk factors, progression of the disease, and study type such as systematic review and meta-analysis. Refer to *Supplementary Material I* for the complete Medline search strategy.

Inclusion criteria

To be included, eligible studies had to meet all of these inclusion criteria: published in English or French; involved human subjects only; systematic review or meta-analysis; evaluated at least one risk factor in relation to the onset or progression of PD; and provided at least one risk estimate.

Study selection

Two raters independently screened all unique citations (titles and abstracts) for eligibility using DistillerSR software (DistillerSR, Evidence Partners, Ottawa, Canada). Full articles for all eligible citations were then assessed for inclusion by the same two independent raters. Discrepancies between raters were resolved by consensus.

Quality assessment

Two raters independently evaluated the quality of selected systematic reviews and meta-analyses using the validated Assessment of the Methodological Quality of Systematic

Reviews (AMSTAR) tool (Shea et al., 2007) in the DistillerSR software. Reviews that scored low (three or less) were excluded, while reviews that scored moderate (between four and seven) or high (greater than eight) were included in this review. Discrepancies with AMSTAR scores were resolved by consensus with a third rater. Refer to the Methodology paper by Hersi and colleagues (2016) for the AMSTAR tool.

Data collection

Two raters independently extracted the data for the included systematic reviews and meta-analyses using the DistillerSR software. The data extracted included methodological design details such as years of capture, databases utilized, risk factor(s), risk estimates, whether or not publication bias was addressed by the authors, and whether or not a heterogeneity test had been performed for pooled data.

Locating primary studies: stage two

Identification of studies

To identify eligible primary articles, the following electronic databases were searched, once again modified appropriately to that used by the central research office in Ottawa following extensive consultation with local library staff at the University of Toronto: MEDLINE (1946 to February Week 1 2012), MEDLINE In-Process (February 09 2012), EMBASE (1980 to 2012 Week 05), PsycINFO (1806 to February Week 1 2012), Scopus (1960 to February 14 2012), Web of Science (1899 to February 14 2012), Cochrane Library (Until February 2012), CINAHL (1981 to February 2012), ProQuest Dissertations & Theses (1997 to February 10

2012), and AARP AgeLine (1978 to February 10 2012). Refer to *Supplementary Material II* for our complete Medline search strategy.

A systematic search was performed using variations of MeSH and keyword search terms to identify primary studies pertaining to factors associated with the onset and progression of PD. Search terms included factors that might be associated with risk of PD onset and/or progression; namely factors pertaining to biological, lifestyle, socioeconomic, environmental, and psychosocial issues, as well as co-morbidities. Additionally, only articles that used an observational study design were included. Articles utilizing randomized control designs were excluded, as this review was not targeting pharmacological and/or clinical treatment factors.

Inclusion criteria

To be included, eligible articles had to meet all of the following inclusion criteria: published in English or French; involved human subjects only; evaluated at least an onset or progression factor; case-control, cohort, or cross-sectional study; and provided at least one risk estimate.

Study selection

The liberal accelerated method was utilized (Hersi et al., 2016). One reviewer screened the titles and abstracts of all search results, as well as screened all full articles of included studies. A second reviewer only screened studies excluded by the primary reviewer. Articles excluded by the first reviewer, but included by the second reviewer, were discussed until a decision to include or exclude was reached by consensus between the two reviewers. Similar

to the study selection for stage one, study screening was completed using the DistillerSR software.

Data collection

The primary reviewer extracted data from all included articles, while the secondary reviewer randomly extracted data from a five percent sample of included articles. Extracted data was compared and any discrepancies were resolved by consensus. Data extraction was completed using the DistillerSR software. Extracted data included study design, sample size, risk factor(s), and adjusted/unadjusted risk estimates for both the onset and progression of PD.

Review of PDGene “Top Results”

To further identify genetic risk factors associated with PD, our systematic searches of the literature were supplemented with a review of the “Top Results” section of the PDGene database on February 11th 2013, a publicly available, unbiased, and frequently updated collection of PD gene association studies (Lill et al., 2012). The “Top Results” section of PDGene lists polymorphisms most strongly associated with PD based on statistical significance of meta-analyses for that gene (Lill et al., 2012; PDGene, 2013).

Levels of evidence

A three-tiered approach was used to categorize targeted factors based on the available evidence and quality of high-level evidence, as described by Wigle et al. (2008). For details on this approach please refer to Hersi et al. (2016).

RESULTS

The comprehensive searches identified 16 relevant meta-analyses; however, only 11 meta-analyses were determined to be of sufficient quality after critical appraisal and therefore included in this review.

The 11 meta-analyses only reported on factors associated with the onset of PD (Figure 1). In addition, 93 primary articles met the inclusion criteria, of which 89 addressed PD onset and 4 addressed PD progression (Figure 2).

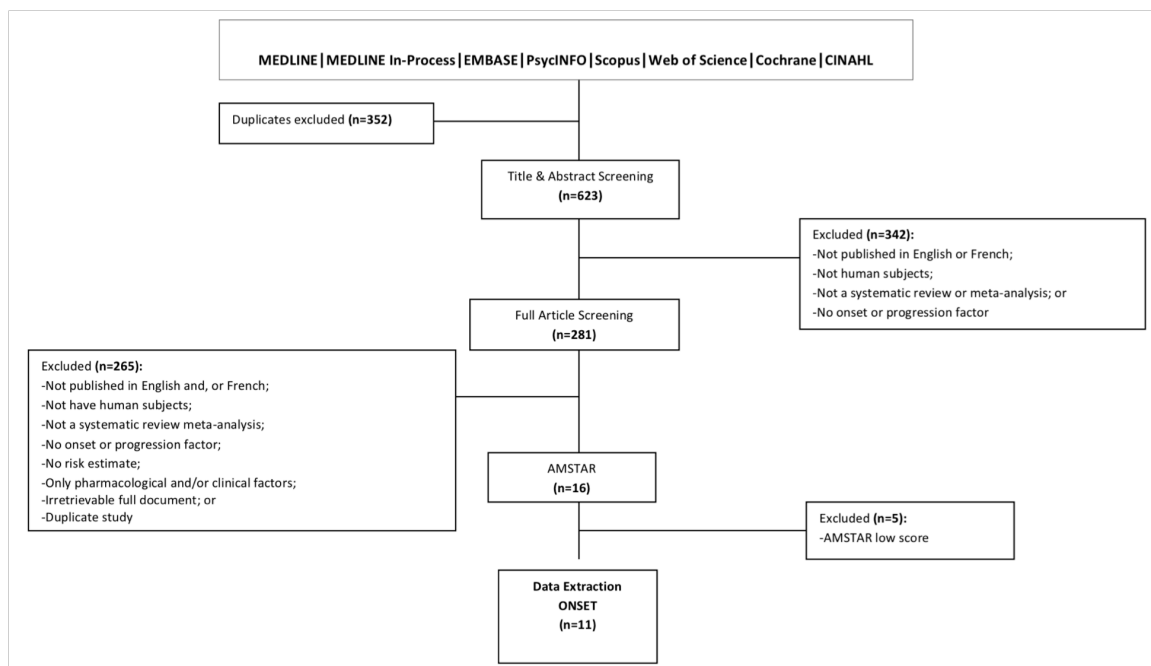


Figure 1. Locating systematic reviews and meta-analyses.

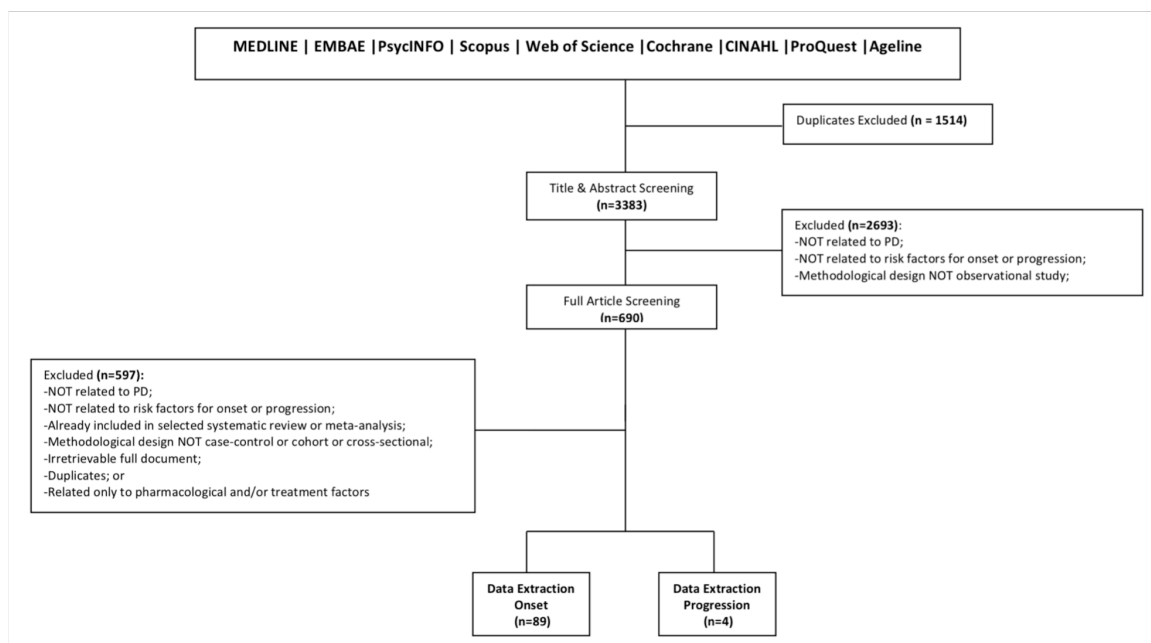


Figure 2. Locating observational studies.

Systematic reviews and meta-analyses

Factors related to the onset of Parkinson's disease

The selected meta-analyses reported several factors associated with the onset of PD (Table 1). Across all 11 meta-analyses, the same factor was commonly reported more than once with either similar or contradictory findings. For example, cigarette smoking was reported in three meta-analyses (Hernán et al., 2002; Noyce et al., 2012; Sugita et al., 2001) to be negatively associated with PD onset, while one meta-analysis (Allam et al., 2003) found a non-significant association. Likewise, caffeine intake through coffee drinking was also reported in three meta-analyses (Costa et al., 2010; Hernán et al., 2002; Noyce et al., 2012) to have a

negative association with PD onset. In addition, Li et al. (2012) reported caffeine intake through tea drinking to also have a negative association. In contrast, one meta-analysis (Noyce et al., 2012) found a non-significant association with tea drinking and PD onset. Pesticide exposure was another factor reported in three meta-analyses (Van Maele-Fabry et al., 2012; van der Mark et al., 2012; Noyce et al., 2012) suggesting a positive association with the onset of PD. The association between diabetes mellitus and the onset of PD was addressed in two meta-analyses with Cereda et al. (2011) reporting a positive association, while Noyce et al. (2012) reported a non-significant association.

Several additional factors were reported by only one meta-analysis. For instance, dietary vitamin E intake (Etminan et al., 2005), welding exposure (Mortimer et al., 2012), and alcohol intake (Noyce et al., 2012) were each reported to have a negative association with PD onset. In contrast, other factors were positively associated with the onset of PD, including: constipation, farming occupation, family history of PD, head injury, mood disorder, rural living, and well-water drinking (Noyce et al., 2012). Factors with non-significant findings included dietary intake of beta-carotene (Etminan et al., 2005), vitamin C (Etminan et al., 2005), manganese exposure (Mortimer et al., 2012), and diagnoses of cancer (Noyce et al., 2012) or gastric ulcers (Noyce et al., 2012).

First Author Last Name, Year	Methodological Designs Included	AMSTAR Quality Score	Years Included	Databases Searched	Factor Reported	Relative Risk (RR) 95% CI Odds Ratio (OR) 95% CI	Publication Bias Addressed
Onset							
Allam, 2003	Case-control	Moderate	1887 – 2000	Medline, Embase, PsycLIT, Current Contents, Best Evidence, Nisc Mexico Biblioline	Cigarette Smoking	RR 0.77 (0.59-1.01)	No
Cercda, 2011	Case-control, cohort	High	Until 2011	PubMed, Embase, Scopus	Diabetes	RR 1.37 (1.21-1.55)	No
Costa, 2010	Case-control, cohort	Moderate	Until 2009	Medline, Scopus, Web of Science, LILACS	Caffeine Intake	RR 0.75 (0.68-0.82)	Yes
Elmman, 2005	Case-control studies, Cohort studies, cross-sectional	High	1966 – 2005	Medline, Embase, Cochrane Library	Beta Carotene Vitamin C Vitamin E	RR 0.91 (0.71-1.15) RR 1.02 (0.87-1.18) RR 0.81 (0.67-0.98)	Yes
van Maele- Fabry, 2012	Cohort	Moderate	1966 – 2011	Medline	Occupational Pesticide Exposure	RR 1.28 (1.03–1.59)	Yes
Herran, 2002	Case-control, cohort	Moderate	1966 – 2002	Medline, Embase, LILACS	Cigarette Smoking Coffee Drinking	RR 0.59 (0.54-0.63) RR 0.69 (0.59-0.80)	Yes
Li, 2012	Case-control studies	Moderate	1966 – 2010	PubMed	Tea Drinking	OR 0.85 (0.74-0.98)	Yes
van der Mark, 2012	Case-control, cohort	High	1950 – 2010	Medline, Embase	Pesticide Exposure	RR 1.62 (1.40-1.88)	Yes
Mortimer, 2012	Case-control, cohort, mortality	Moderate	1974 – 2011	PubMed	Manganese Exposure Welding Exposure	OR 0.76 (0.41–1.42) RR 0.86 (0.80-0.92)	No
Noyce, 2012	Case-control, cohort	High	1966 – 2011	Medline	Alcohol Cancer Cigarette Smoking Coffee Drinking Constipation Diabetes Mellitus Farming Occupation Family History of PD Head Injury Mood Disorder Pesticides Rural living Tea Drinking Gastric Ulcers Well-water Drinking	RR 0.90 (0.84-0.96) RR 1.01 (0.94-1.09) RR 0.44 (0.39-0.50) RR 0.67 (0.58-0.78) RR 2.34 (1.55-3.53) RR 0.91 (0.72-1.21) RR 1.26 (1.10-1.44) RR 4.45 (3.39-5.83) RR 1.58 (1.30-1.91) RR 1.86 (1.64-2.11) RR 1.78 (1.50-2.10) RR 1.43 (1.13-1.80) RR 1.00 (0.72-1.38) RR 1.37 (0.36-5.31) RR 1.21 (1.04-1.40)	No
Sugita, 2001	Case-control, cohort	Moderate		Medline	Cigarette Smoking	RR 0.57 (0.52-0.63)	Yes

Table I. Description of selected meta-analyses for Parkinson's disease onset.

Primary studies

Factors for onset of Parkinson's disease

The selected primary articles reported several factors associated with the onset of PD (*Supplementary Material III*). Among these, medical diagnosis was the most common factor, as it was reported on numerous occasions. Two articles, Alonso et al. (2007) and de Vera et al. (2008), reported gout to be negatively associated with the onset of PD. Goldman et al. (2006) and Stern et al. (1991) reported head injury to be positively associated with PD onset. Fifteen other medical diagnoses were positively related to PD onset, including: dementia (Aarsland et al., 2003), bowel movement (Abbott et al., 2001; Gao et al., 2011), methamphetamine-use (MU) disorders (Callaghan et al., 2010), depression (Fang et al., 2010), depression and anxiety (Jacob et al., 2010), erectile dysfunction (Gao et al., 2007), Type 2 diabetes (Hu et al., 2007b), bone breaks (Leibson et al., 2006), hip fracture (Leibson et al., 2006), cerebrovascular disease (Patel et al., 2011), hypertension (Qiu et al., 2011), anemia (Savica et al., 2009), essential tremor (Tan et al., 2008), phobic anxiety (Weisskopf et al., 2003), and excessive daytime sleepiness (Abbott et al., 2005). In another eight observational studies, authors reported that the following medical diagnoses were not significantly associated with PD onset: early menopause (Benedetti et al., 2001), lifetime major depressive disorder (MDD) (Ishihara-Paul et al., 2008), lifetime generalized anxiety disorder (GAD) (Ishihara-Paul et al., 2008), psychological distress (defined by the five item metal health inventory (MHI-5)) (Ishihara-Paul et al., 2008), cancer (Leibson et al., 2006), dementia (Leibson et al., 2006), diabetes (Leibson et al., 2006), ischemic heart disease (Leibson et al., 2006), myocardial infarction (Leibson et al., 2006), stroke (Leibson et al., 2006), and autoimmune disease (Rugbjerg et al., 2009). Of those factors listed in the above-

mentioned observational studies, five medical diagnoses were reported with inconsistent associations across different studies, namely dementia, depression, diabetes, cerebrovascular disease, and anxiety.

The next commonly reported factor associated with the onset of PD was occupation. Two articles (Park et al., 2005 and Tanaka et al., 2011b) reported technical occupations to be negatively associated with PD onset in men. Four other occupations were also found to be negatively associated with PD onset, and these included: processing occupations (Dick et al., 2007), transport and communication (Dick et al., 2007), maximal outdoor work (Kenborg et al., 2011), and service (Park et al., 2005). Gorell et al. (2004) and Skeie et al. (2010) reported farming and agricultural occupation to be positively associated with PD onset, respectively. The following occupations were also shown to be positively associated with PD onset: past work in an electronics plant (Dhillon et al., 2008), metallurgic activity (Pals et al., 2003), healthcare services (Tsui et al., 1999), and teaching (Tsui et al., 1999). In contrast, Firestone et al. (2010) and Tanaka et al. (2011b) reported a non-significant association with either medical or dental technical occupations (both for female participants only). Furthermore, four articles reported non-significant association with exposure to agricultural processes (Dhillon et al., 2008), agricultural occupation (Dick et al., 2007; Kirkey et al., 2001), and occupations related to agriculture, fishery, and forestry (Park et al., 2005). Additional occupations with a non-significant association were past work in paper/lumber mill (Dhillon et al., 2008), men physicians (Firestone et al., 2010), service (Kirkey et al., 2001); fishery, forestry, and labor in mining, construction, manufacturing, and sales (Park et al., 2005); and protective service and transport (Tanaka et al., 2011b).

Cigarette smoking was another commonly reported factor associated with the onset of PD. Nine articles reported a negative association with PD onset (Chen et al., 2010; Dong et al., 2003; Gorell et al., 2004; Nicoletti et al., 2010; Scott et al., 2005; Sipetic et al., 2012; Skeie et al., 2010; Stern et al., 1991; Thacker et al., 2007). More specifically, a smoking history of less or greater than 20 years (Dong et al., 2003) and a smoking history of greater than 30 pack years (Gorell et al., 2004) were each negatively associated with PD onset. Further, being either a current (Chen et al., 2010; Dong et al., 2003; Sipetic et al., 2012; Thacker et al., 2007), past (Chen et al., 2010; Scott et al., 2005), ever (Scott et al., 2005), or regular smoker (Scott et al., 2005) was negatively associated with PD onset. Interestingly, four other articles examining smoking or exposure to smokers (Gorell et al., 2004; O'Reilly et al., 2009; Ragonese et al., 2003; Scott et al., 2005) report a non-significant association with the onset of PD.

Dietary intake was reported in four primary studies to be a factor associated with the onset of PD. Specifically, a Mediterranean-type diet (Alcalay et al., 2012) and dietary intake of vitamin B₆ (de Lau et al., 2006), iron, magnesium, zinc (Miyake et al., 2011a), beta carotene, and vitamin E (Miyake et al., 2011b) were each found to have a negative association with PD onset. In contrast, dietary intakes high in cholesterol and fats were positively associated with PD onset (Miyake et al., 2010). Interestingly, dietary factors reported as having no significant association with the onset of PD were intake of western versus Japanese diet (Grandinetti, 1994), calcium (Miyake et al., 2011c), non-heme iron (Logroscino et al., 2008), dairy products (Miyake et al., 2011c), and vitamin D (Miyake et al., 2011c).

Biological markers were also reported as factors associated with the onset of PD. Of these, only serum uric acid (Grandinetti, 1994) was found to have a negative association with PD onset. Articles reported that several markers were positively associated with the onset of PD, including: fibrinogen (Chen et al., 2008; Wong et al., 2010), substantia nigra hyperchogenecity (Berg et al., 2011), serum pesticide (Richardson et al., 2009), serum Beta-Hexachlorocyclohexane (B-HCH) (Richardson et al., 2011), a high white blood cell (WBC) count in men (Ton et al., 2012), bone lead (Weisskopf et al., 2010a,b), and serum dieldrin (Weisskopf et al., 2010a,b). Marker association with PD onset was inconclusive for tumor necrosis factor (TNF) R1 (Chen et al., 2008) and TNF-R2 (Chen et al., 2008). Two biological markers were reported with inconsistent associations across different studies, namely high sensitivity-C Reactive Protein (hs-CRP) (Chen et al., 2008; Song et al., 2011) and interleukin-6 (IL-6) (Chen et al., 2008; Ton et al., 2012).

Exposure to pesticides was identified as a risk factor for PD onset; however, results are contradictory. Two articles (Baldi et al., 2003; Kamel et al., 2007) reported a positive association between pesticide exposure and PD onset. More specifically, positive associations were reported following exposure to pesticide products such as maneb or paraquat (Costello et al., 2009), chlorpyrifos (Dhillon et al., 2008), and rotenone (Dhillon et al., 2008). In contrast, three other articles found non-significant associations between exposure to various pesticides and PD onset (Costello et al., 2009; Dhillon et al., 2008, Firestone et al., 2010).

Exposure to chemicals or metals was another reported factor associated with PD onset. Specifically, exposures to fluorides (Dhillon et al., 2008), lead (Coon et al., 2006), copper, iron-copper, lead-copper, lead-iron, and manganese (Gorell et al., 1997; Willis et al., 2010) were positively associated with the onset of PD. Contrary to this, some studies found that exposure to certain chemicals and metals was not significantly associated with the onset of PD, including exposure to industrial solvents (Firestone et al., 2010), manganese (Park et al., 2006) and copper (Willis et al., 2010).

Life events were reported to be either negatively or positively associated with PD onset. Specifically, one paper reported that divorce, the death of a spouse or a child, and long-term unemployment was negatively associated with PD onset (Rod et al., 2010). In contrast, fathering at least one child (Frigerio et al., 2007), being never employed (Rod et al., 2010), being a woman who was never married (Rod et al., 2010), having a history of cumulative length of pregnancies longer than 30 months (Ragonese et al., 2004), and having a fertile life length shorter than 36 years (Ragonese et al., 2004) were positively associated with PD onset.

Associations between well water consumption and PD onset were inconsistent. One paper (Wright and Keller-Byrne, 2005) reported that well-water consumption in the first 20 years of life was not significantly associated with PD onset, while three papers (Gatto et al., 2009, Sanyal et al., 2010; Wright and Keller-Byrne, 2005) found that well water consumption was positively associated with PD onset. Interestingly, Gatto et al. (2009) attribute their findings to pesticide and insecticides in the well water being consumed. These findings further

support the observational studies that have identified pesticide exposure as being positively correlated with the onset of PD.

Various personality traits were also identified as being associated with PD onset.

Introversion (Arabia et al., 2010), neuroticism (Sullivan, 2011), and harm avoidance (Sullivan, 2011) were found to be positively associated with PD onset. However, two papers found non-significant associations with specific personality characteristics and motor skills in relation to occupations (Gatto et al., 2011) and extroversion (Ishihara-Paul et al., 2008).

Family history of melanoma, having first- or second-degree relatives with PD, and having at least one affected relative with PD were respectively reported by three articles as being positively associated with PD onset (Gao et al., 2009; Gorell et al., 2004; De Michele et al., 1996).

Tea and coffee drinking were reported to be negatively associated with PD onset (Hu et al., 2007a; Nicoletti et al., 2010; Ragonese et al., 2003; Tanaka et al., 2011a). Likewise, general alcohol consumption (Ragonese et al., 2003) and wine consumption (Nicoletti et al., 2010) were also reported to be negatively associated with PD onset. Furthermore, skin fold thickness of triceps (Abbott et al., 2002) and body mass index (BMI) (Ragonese et al., 2008) were reported as not being significantly associated with PD onset.

Lastly, we identified factors associated with PD onset that were only reported once. For example, age (Park et al., 2006) and physical activity (Xu et al., 2010) were reported to be

negatively associated with PD onset, while nine or more years of education (Frigerio et al., 2005) was positively associated with PD onset.

Factors for disease progression

Among included observational studies, urate was the only reported factor associated with the progression of PD. Some studies reported urate as being negatively associated with PD progression (Ascherio et al., 2009; Chen et al., 2008; Scwarzschild et al., 2008), while one study (Weisskopf et al., 2007) reported that the association was not significant (*Supplementary Material III*).

Review of PDGene “Top Results”

The PDGene (2013) database summarized evidence from 881 original studies on 915 genes, 3,446 polymorphisms, and 889 meta-analyses. The most strongly associated genes (based on known polymorphisms), listed in order of decreasing strength of association with PD according to P-value were: MAPT/STH, SNCA, GBA, LRRK2, PM20D1, GAK, MCC1, STK39, BST1, GPNMB, SETD1A, GWA 8p22, SYT11/RAB25, FAM47E, HLA-DRB5, CCDC62/HIP1R, ACMSD/TMEM163, and MED13.

According to P-value and listed in order of decreasing strength of association, the following genes were reported to be positively associated with PD: SNCA (OR 1.30, 95% CI 1.25-1.34, P-value 3.06E-49), GBA (OR 3.37, 95% CI 2.67-4.29, P-value 1.11E-24), LRRK2 (OR 2.23, 95% CI 1.89-2.63, P-value 2.97E-21), GAK (OR 1.29, 95% CI 1.20-1.38, P-value 6.54E-13), STK39 (OR 1.28, 95% CI 1.19-1.38, P-value 1.54E-11), SETD1A (OR 1.14, 95%

CI 1.09-1.19, P-value 4.68E-10), SYT11/RAB25 (OR 1.67, 95% CI 1.41-1.98, P-value 5.70E-09), CCDC62/HIP1R (OR 1.17, 95% CI 1.09-1.25, P-value 2.99E-06), ACMSD/TMEM163 (OR 1.40, 95% CI 1.2-1.63, P-value 1.61E-05), and MED13 (OR 1.13, 95% CI 1.07-1.2, P-value 6.09E-05).

In contrast, according to P-value and listed in order of decreasing strength of association, the following genes were reported to be negatively associated with PD: MAPT/STH (OR 0.78, 95% CI 0.75-0.80, P-value 3.54E-52), PM20D1 (OR 0.74, 95% CI 0.69-0.80, P-value 1.01E-14), MCC1 (OR 0.84, 95% CI 0.80-0.89, P-value 8.72E-12), BST1 (OR 0.87, 95% CI 0.83-0.91, P-value 2.28E-10), GPNMB (OR 0.89, 95% CI 0.86-0.93, P-value 2.69E-10), GWA 8p22 (OR 0.89, 95% CI 0.86-0.93, P-value 2.59E-9), FAM47E (OR 0.89, 95% CI 0.85-0.93, P-value 1.07E-07), and HLA-DRB5 (OR 0.75, 95% CI 0.68-0.84, P-value 2.90E-07).

Polymorphism MAPT_H1H2 of the MAPT/STH gene is reported to significantly decrease the risk of PD among Caucasians, while polymorphism rs34778348 of the LRRK2 gene is reported to significantly increase the risk of PD in Asians.

Levels of evidence

Sufficient

This review identified sufficient evidence from meta-analyses that pesticide exposure, preceding constipation, farming occupation, family history of PD, previous head injury, mood disorder, rural living, and well-water drinking were positively associated with PD onset. Likewise, sufficient evidence from meta-analyses identified that cigarette smoking,

general caffeine intake, tea drinking, coffee drinking, vitamin E intake, and welding exposure were negatively associated with PD onset.

Limited

This systematic review identified limited, and by definition inconsistent, evidence for the association between PD onset and several factors. Specifically, association with the medical diagnosis of diabetes was inconsistent among both the included meta-analyses and observational studies. This was also true for other factors such as tea drinking, exposure to pesticides products (such as rotenone, chlorpyrifos, ziram, paraquat, and maneb), manganese, copper, urate, dementia, depression, cerebrovascular disease, anxiety, technical occupation, hs-CRP, and IL-6.

Inadequate

This review identified several factors associated with PD onset where supporting evidence of the association was inadequate, meaning that non-significant findings were identified among these included meta-analyses and/or primary articles. Factors with inadequate evidence of association included: skin-fold thickness of triceps, early menopause, TNF – R1 and R2, exposure to maneb or paraquat, past work in paper/lumber mill, exposure to cadmium, medical or dental technicians, women physicians, exposure to industrial toxicants such as solvents, personality characteristics and motor skills attributed to jobs held, western versus Japanese diet, extroversion, lifetime MDD, lifetime GAD, MHI-5, neuroticism, cancer, ischemic heart disease, myocardial infarction, stroke, dietary non-heme iron, calcium intake,

dairy products, vitamin D intake, fishery, forestry, mining, construction, manufacturing, transport, sales occupation, BMI, autoimmune disease, and protective service occupation.

DISCUSSION

We systematically reviewed and assessed the scientific literature for factors related to the onset and progression of PD. A number of environmental, occupational, comorbid, genetic, lifestyle, and biological factors were identified to be associated with either the onset and/or progression of the PD. For the purposes of this discussion, these factors are summarized according to how they influence PD onset or progression; that is, by being inducing (a positive association) or protective (a negative association).

PD inducing factors

Related factors in the natural or physical environment such as pesticide exposure, rural living, well water drinking, and farming occupation were consistently found to increase the risk of PD, which suggests an environmental link to the etiology of the disease. Family history and polymorphisms to key genes were also found to consistently increase the risk of PD. Among included meta-analyses and observational studies, family history of PD was reported as being positively associated with PD onset.

PD protective factors

Certain lifestyle choices such as coffee drinking and cigarette smoking were consistently found to decrease the risk of PD. Cigarette smoking was found to be protective in multiple meta-analyses, which was supported by several observational studies. Likewise, coffee

drinking was consistently found to be protective for the onset of PD among the meta-analyses and observational studies.

Limitations

Due to time and resource limitations, our grey literature search was restricted to searching an electronic database of dissertations and indexes. Thus, similar to other systematic reviews, our review may be impacted by reporting and publication biases. Additionally, we only included studies published in English or French (language bias), which may have limited our ability to identify all reported factors related to the onset and progression of PD. Moreover, our included studies may be biased as a result of us employing the liberal accelerated method (due to time constraints and number of articles) to screen citations and extract data, and based on limitations of our search strategies. Finally, it is likely that new PD risk factors have been proposed and that knowledge of identified risk factors has increased since our last systematic search of the literature (October 2012), including knowledge of prodromal PD markers.

CONCLUSIONS

Through a systematic search of the literature we identified and summarized systematic reviews and primary studies pertaining to factors associated with the onset and progression of PD. Factors that were positively correlated with PD onset were typically related to the environment and genetics, while factors that consistently demonstrated negative associations with PD onset related to lifestyle choices. Urate was the only factor found to be associated with the progression of PD; however, no definitive statement can currently be made about

whether urate is positively or negatively associated with PD progression. While limited conclusions can be drawn about factors associated with PD progression, our review summarizes the evidence of association, both positive and negative, between modifiable risk factors (such as lifestyle and environmental exposures) and PD onset. Thus, from a population health perspective, and in consideration of ethical practices, recommendations pertaining to modifiable risk factors (such as promoting the use of helmets in sports, limiting or eliminating exposures to pesticides, and supporting a reasonable intake of caffeine) offer the greatest promise in preventing the onset of PD. Future observational studies examining relationships between factors associated with PD onset and progression will shed light on PD disease etiology and will give rise to interventions that may prove effective in reducing the many burdens of PD. Lastly, our summary of factors associated with the onset and progression of PD may be used by stakeholders, including policy makers and non-governmental organizations, to inform policies and other interventions that target modifiable PD risk factors.

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CONFLICTS OF INTERESTS STATEMENT

There are no conflicts of interest.

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UPDATE

A supplementary search of the MEDLINE database was performed to identify recently published studies of factors associated with the onset or progression of PD that may be of interest to readers. The supplementary search returned 253 citations between 2012 and 2015, 118 of which remained after title and abstract screening according to our previously defined inclusion criteria. Subsequent full-text screening identified 97 studies that reported on factors associated with the onset of PD. No systematic review or meta-analysis reporting on factors associated with PD progression was identified by our supplementary search. The majority of identified studies published since our initial search report on genes possibly associated with the onset of PD. A list of the 97 articles identified is included in *Supplementary Material IV*.

SUPPLEMENTARY MATERIAL

Supplementary material I

1. exp Meta-Analysis/
2. (meta-anal* OR metaanal*).ab,sh,ti
3. 1 OR 2

4. ((methodol* OR systematic* OR quantitativ*) adj (review* OR overview* OR survey*)).ab,sh,ti.
5. review.ab,sh,ti.
6. 4 AND 5

7. 3 OR 6

8. exp Parkinson Disease/
9. parkinson*.mp
10. 8 OR 9

11. exp Risk Factors/
12. Risk* .mp
13. 11 OR 12

14. 7 AND 10 AND 13

Supplementary material II

1. exp Parkinson Disease/
2. parkinson*.mp.
3. 1 OR 2

4. exp Risk Factors/
5. risk*.mp.
6. 4 OR 5

7. exp Psychology, Social/
8. psychosoc*.mp.
9. 7 OR 8

10. exp Life Style/
11. lifestyl*.mp.
12. 10 OR 11

13. exp Genetic Predisposition to Disease/
14. exp Genetics, Medical/
15. genetic*.mp.
16. 13 OR 14 OR 15

17. exp Biological Factors/
18. biologic*.mp. OR biol*.mp.
19. 17 OR 18

20. exp Socioeconomic Factors/
21. socioeconomic*
22. 20 OR 21

23. exp Comorbidity/
24. comorbid*.mp.
25. 23 OR 24

26. exp Environmental Exposure/
27. environment*.mp.
28. 26 OR 27

29. etiolog*.mp. OR onset*.mp. OR progress*.mp.
30. epidemiologic studies/
31. exp Case-Control Studies/
32. exp Cohort Studies/
33. case control.tw
34. (cohort adj (study or studies)).tw.
35. Cohort analy\$.tw.

36. (Follow up adj (study or studies)).tw.
 37. (observational adj (study or studies)).tw.
 38. Longitudinal.tw.
 39. Retrospective.tw.
 40. Cross sectional.tw.
 41. Cross-sectional studies/
 42. 30 OR 31 OR 32 OR 33 OR 34 OR 35 OR 36 OR 37 OR 38 OR 39 OR 40 OR 41
 43. 3 AND 6 AND 9 AND 42 (limit to humans, English or French)
 44. 3 AND 6 AND 12 AND 42 (limit to humans, English or French)
 45. 3 AND 6 AND 16 AND 29 AND 42 (limit to humans, English or French)
 46. 3 AND 6 AND 19 AND 29 AND 42 (limit to humans, English or French)
 47. 3 AND 6 AND 22 AND 29 AND 42 (limit to humans, English or French)
 48. 3 AND 6 AND 25 AND 29 AND 42 (limit to humans, English or French)
 49. 3 AND 6 AND 28 AND 29 AND 42 (limit to humans, English or French)
 50. 3 AND 6 AND 45 AND 29 AND 42 (limit to humans, English or French)

Supplementary material III

First Author Last Name, Year	Study Design	Sample Sizes Case-Control: cases/Controls Cohort: final/original cases	Factor Reported	Hazard Ratio (HR); Relative Risk (RR); Odds Ratio (OR) 95% CI
Onset				
Aarsland, 2003	Case-control	224/3,295	Dementia	OR 3.3 (1.2-8.5)
Abbott, 2001	Cohort	96/6,750	<1 bowel movement per day	RR 2.7 (1.3- 5.5)
Abbott, 2002	Cohort	137/7,990	Triceps Skin-fold Thickness (TSF)	RR 1.5 (0.9-2.8)
Abbott, 2005	Cohort	43/3,078	Excessive daytime sleepiness	OR 3.3 (1.4 to 7.0)
Alcalay, 2012	Case-control	257/198	Mediterranean-type diet	OR 0.86 (0.77–0.97)
Alonso, 2007	Case-control	1052/6634	Gout	OR 0.69 (0.48-0.99)
Arabia, 2010	Cohort	156/6,822	Introversion	HR 1.39 (1.06–1.84)

First Author Last Name, Year	Study Design	Sample Sizes Case-Control: cases/Controls Cohort: final/original cases	Factor Reported	Hazard Ratio (HR); Relative Risk (RR); Odds Ratio (OR) 95% CI
Baldi, 2003	Cohort	84/252	Occupational pesticide exposure	OR 2.2 (1.1-4.3)
Benedetti, 2001	Case-control	72/72	Early menopause	OR 2.18 (0.88-5.39)
Berg, 2011	Cohort	11/1,535	Substantia Nigra Hyperechogenicity	RR 17.37 (3.71-81.34)
Callaghan, 2010	Cohort	/1,863+9,315	Methamphetamine-Use (MU) Disorders	HR 2.65 (1.17-5.98)
Chen, 2008	Case-control	84/165	Plasma concentration: Fibrinogen Hs-CRP IL - 6 TNF - R1 TNF - R2	OR 3.4 (1.1-10) OR 1.2 (0.4-3.7) OR 1.5 (0.5-4.1) OR 1.3 (0.4-3.7) OR 2.7 (0.8-8.8)
Chen, 2010	Cohort	1,662/305,468	Cigarette smoking: Current smokers Past smokers	OR 0.56 (0.45-0.70) for current smokers OR 0.78 (0.70-0.86) for past smokers
Coon, 2006	Case-control	121/414	Lead	OR 2.27 (1.13-4.55)
Costello, 2009	Case-control	368/341	Maneb or Paraquat Both	OR 2.27 (0.91-5.70) OR 4.17 (1.15-15.16)

First Author Last Name, Year	Study Design	Sample Sizes Case-Control: cases/Controls Cohort: final/original cases	Factor Reported	Hazard Ratio (HR); Relative Risk (RR); Odds Ratio (OR) 95% CI
Dhillon, 2008	Case-control	100/84	Past work in an electronics plant Past work in paper/lumber mill Occupational and Environmental Exposures: Agricultural processes (Pesticide applications done in the past year) Cadmium Chlorpyrifos Fluorides Paraquat Rotenone	OR 5.1 (1.1-23.6) OR 6.35 (0.7-51.8) OR 4.4 (0.5-38.1) OR 5.3 (0.6-44.9) OR 2.0 (1.02-3.8) OR 3.3 (1.03-10.3) OR 3.5 (0.4-31.6) OR 10.0 (9.9-34.3)
Dick, 2007	Case-control	649/1,587	Agriculture Processing occupations Transport and communication	OR 1.32 (0.81-2.16), OR 1.30 (0.84- 2.02) OR 0.69 (0.5-0.95) OR 0.60 (0.37-0.97)
Dong, 2003	Case-control	114/205	Cigarette smoking: Current smokers Ever smokers Former smokers Smoked less than 20 years Smoking history longer than 20 years	OR 0.44 (0.23-0.86) OR 0.49 (0.30- 0.79) OR 0.54 (0.30-0.96) OR 0.57 (0.33-0.99) OR 0.40 (0.21-0.81)
Fang, 2010	Case-control	992/279,958	Depression	OR 4.7 (3.9-5.7)

First Author Last Name, Year	Study Design	Sample Sizes Case-Control: cases/Controls Cohort: final/original cases	Factor Reported	Hazard Ratio (HR); Relative Risk (RR); Odds Ratio (OR) 95% CI
Firestone, 2010	Case-control	404/526	Occupation: Medical or dental technicians Pesticides Physicians Industrial toxicant: Solvents	OR 2.8 (0.82-9.29) OR 3.9 (0.39-39.4) OR 6.1 (0.65-56.3) OR 1.7 (0.98-3.04)
Frigerio, 2005	Case-control	196/196	Nine or more years of education	OR 2.0 (1.1-3.6)
Frigerio, 2007	Case-control Cohort	193/193 /6,341	Fathering at least one child	OR 2.7 (1.2– 6.1)
Fukushima, 2010	Case-control	214/327	Alcohol drinking	OR 3.39 (1.10-11.0)
Gao, 2007	Cohort	200/32,616	Erectile dysfunction	RR 3.8 (2.4-6.0)
Gao, 2009	Cohort	616/157,036	Family history of melanoma	RR 1.85 (1.2-2.8)
Gao, 2011	Cohort	156/33,901 (men) 402/93,767 (women)	Bowel movement frequency < every 3 days	RR 3.93 (2.26-6.84), pooled analysis of 2 cohorts
Gatto, 2009	Case-control	368/341	Well-water consumption: Chlorpyrifos Methomyl Propargite	OR 1.87 (1.05–3.31) OR 1.67 (1.00–2.78) OR 1.92 (1.15–3.20)

First Author Last Name, Year	Study Design	Sample Sizes Case-Control: cases/Controls Cohort: final/original cases	Factor Reported	Hazard Ratio (HR); Relative Risk (RR); Odds Ratio (OR) 95% CI
Gatto, 2011	Case-control	355/355	<p>Personality characteristics and motor skills attributed to occupations:</p> <p>Involving feelings, ideas, or facts</p> <p>Involving greater abstract and creative abilities</p> <p>Ability to make generalizations, judgments, or decisions</p>	<p>OR 0.71 (0.45-1.11)</p> <p>OR 0.61 (0.38-0.95)</p> <p>OR 0.57 (0.36-0.91)</p>
Goldman, 2006	Case-control	93/93	Head injury	OR 3.8 (1.3–11.0)
Gorell, 1997	Case-control	144/464	Occupational exposure:	
			Copper	OR 2.49 (1.06-5.89)
			Iron-copper	OR 3.69 (1.40-9.71)
			Lead-copper	OR 5.24 (1.59-17.21)
			Lead-iron	OR 2.83 (1.07-7.50)
			Manganese	OR 10.61 (1.06-105.83)
Gorell, 2004	Case-control	144/464	Family history of PD in first- or second-degree relatives	OR 4.22 (2.24-7.94)
			Farming as an occupation	OR 2.79 (1.03-7.54)
			Smoking:	OR 0.73 (0.47-1.13)
			30 pack years	OR 0.42 (0.25-0.71)
			>30 pack years	
Grandinetti, 1994	Case-control	84/336	Serum uric acid	OR 0.60 (0.37-0.97)
			Western diet compared to Japanese	OR 0.60 (0.35-1.01)

First Author Last Name, Year	Study Design	Sample Sizes Case-Control: cases/Controls Cohort: final/original cases	Factor Reported	Hazard Ratio (HR); Relative Risk (RR); Odds Ratio (OR) 95% CI
Hu, 2007	Cohort	200/29,335	Tea drinking (3 cups daily)	HR 0.41 (0.20-0.83)
Hu, 2007	Cohort	633/51,552	Type 2 diabetes	HR 1.85 (1.23-2.80)
Ishihara-Paul, 2008	Cohort	175/20,855	Extroversion (per SD increase) Lifetime MDD Lifetime GAD MHI-5 (per SD decrease) Neuroticism (per SD increase)	HR 1.09 (0.80-1.48) HR 2.01 (0.95-4.22) HR 2.52 (0.78-8.20) HR 1.28 (0.97-1.68) HR 1.33 (0.98-1.79)
Jacob, 2010	Case-control	371/517	Depression and anxiety	OR 1.42 (1.01-2.00)
Kamel, 2006	Cohort	78/55,931	Pesticides	OR 2.3 (1.2-4.5)
Kenborg, 2011	Case-control	3,819/19,282	Maximal outdoor work	OR 0.72 (0.63-0.82)
Kirkey, 2001	Case-control	144/464	Agricultural occupation Service occupation	OR 1.74 (0.85-3.60) OR 0.69 (0.47-1.00)
de Lau, 2006	Cohort	72/5,289	Dietary Vitamin B ₆	HR 0.69 (0.50-0.96)
Leibson, 2006	Case-control	197/197	Bone breaks Cancer Dementia Diabetes Hip fracture Ischemic heart disease Myocardial infarction Stroke	RR 1.9 (1.2-3.0) RR 1.4 (0.9-2.0) RR 1.8 (0.9-3.6) RR 0.7 (0.4-1.4) RR 5.6 (2.2-15.0) RR 0.9 (0.6-1.4) RR 0.9 (0.5-1.6) RR 1.6 (0.8-3.2)

First Author Last Name, Year	Study Design	Sample Sizes Case-Control: cases/Controls Cohort: final/original cases	Factor Reported	Hazard Ratio (HR); Relative Risk (RR); Odds Ratio (OR) 95% CI
Logroscino, 2008	Cohort	422/124,353	Dietary non-heme iron intake	RR 1.27 (0.92-1.76)
Michele, 1996	Case-control	116/232	Family history of PD with at least one affected relative	OR 14.6 (7.2 - 29.6)
Miyake, 2010	Case-control	249/368	Cholesterol intake Dietary fat intake	OR 1.78 (1.04-3.05) OR 2.09 (1.21-3.64)
Miyake, 2011	Case-control	249/368	Dietary intake of metals: Iron Magnesium Zinc	OR 0.24 (0.10-0.57) OR 0.33 (0.13-0.81) OR 0.50 (0.26-0.95)
Miyake, 2011	Case-control	249/368	Beta carotene Vitamin E	OR 0.56 (0.33-0.97) OR 0.45 (0.25-0.79)
Miyake, 2011	Case-control	249/368	Calcium intake Dairy products Vitamin D intake	RR 0.69 (0.37-1.30), highest quintile RR 0.85 (0.50-1.45), highest quintile RR 0.82 (0.46-1.47), highest quintile
Nicoletti, 2010	Case-control	492/459	Cigarette smoking Coffee drinking Wine consumption	OR 0.51 (0.36-0.72) OR 0.61 (0.43-0.87) OR 0.62 (0.44-0.86)
O'Reilly, 2009	Cohort	455/ 121,701 + 51,529	Parent cigarette smoking	RR 0.73 (0.53-1.00)
Pals, 2003	Case-control	423/205	Metallurgic activity	OR 3.1 (1.04-9.20)

First Author Last Name, Year	Study Design	Sample Sizes Case-Control: cases/Controls Cohort: final/original cases	Factor Reported	Hazard Ratio (HR); Relative Risk (RR); Odds Ratio (OR) 95% CI
Park, 2005	Case-control	367/309	Occupation: Agriculture, fishery, and forestry Laborers in mining, construction, manufacturing, and transport Technicians Sales Service	OR 1.54 (0.92-2.59) OR 1.06 (0.69-1.61) OR 0.46 (0.24-0.87) OR 0.77 (0.47-1.29) OR 0.42 (0.21-0.86)
Park, 2006	Cohort	/38,560	Age Manganese exposure	RR 1.136 (1.057–1.221) RR (0.959-18.283)
Patel, 2011	Case-control	85/85	Cerebrovascular disease (CVD)	OR 2.2 (1.1–4.6)
Qiu, 2011	Cohort	794/59,540	High-normal blood pressure Hypertension	HR 1.63 (1.07-2.47), in women HR 1.62 (1.09 -2.42), in women
Ragonese, 2003	Case-control	150/150	Alcohol drinking Cigarette smoking Coffee consumption	OR 0.61 (0.39–0.97) OR 0.66 (0.41–1.05) OR 0.16 (0.05–0.46)
Ragonese, 2004	Case-control	131/131	Cumulative length of pregnancies longer than 30 months Fertile life length shorter than 36 years	OR 2.19 (1.22-3.91) OR 2.07 (1.00-4.30)
Ragonese, 2008	Case-control	318/318	Body Mass Index (BMI)	OR 0.99 (0.94–1.03)
Richardson, 2009	Case-control	50/43	Serum pesticide	OR 4.39 (1.67-11.6)

First Author Last Name, Year	Study Design	Sample Sizes Case-Control: cases/Controls Cohort: final/original cases	Factor Reported	Hazard Ratio (HR); Relative Risk (RR); Odds Ratio (OR) 95% CI
Richardson, 2011	Case-control	149/134	Serum b-HCH	OR 2.85 (1.8-4.48)
Rocca, 1996	Case-control	62/124	Farmers	OR 0.6 (0.3-1.3)
Rod, 2010	Case-control	13,695/68,445	Divorce, death of a spouse or a child, or long-term unemployment Never employed (men) Never employed (women) Never married (women)	OR 0.58 (0.34-0.99) OR 1.47 (1.18-1.82) OR 1.30 (1.05-1.61) OR 1.16 (1.04- 1.29)
Rugbjerg, 2009	Case-control	13,695/68,445	Autoimmune disease	OR 0.96 (0.85-1.08)
Saaksjarvi, 2008	Cohort	101/6,609	Coffee drinking	RR 0.26 (0.07-0.99)
Sanyal, 2010	Case-control	175/350	Well-water drinking	OR 4.5 (2.1-9.9)
Savica, 2009	Case-control	196/196	Anemia or low hemoglobin levels	OR 2.00 (1.31-3.06)
Schuurman, 2002	Cohort	Depressed: 19/1,358 Nondepressed: 259/67,570	Depression	HR 3.13 (1.95-5.01)
Scott, 2005	Case-control	143/168	Cigarette smoking: Ever smoked Current regular smoking Past regular smoking	OR 0.41 (0.21-0.80) OR 0.23 (0.09-0.61) OR 0.55 (0.27-1.14)

First Author Last Name, Year	Study Design	Sample Sizes Case-Control: cases/Controls Cohort: final/original cases	Factor Reported	Hazard Ratio (HR); Relative Risk (RR); Odds Ratio (OR) 95% CI
Sipetic, 2012	Case-control	110/220	Current cigarette smoking Current alcohol consumption Current coffee consumption	OR 0.44 (0.23–0.82) OR 4.78 (2.67-8.55) OR 2.54 (1.36-4.75)
Skeie, 2010	Case-control	212/175	Agricultural occupation Cigarette smoking	OR 1.75 (1.03–3.0) OR 0.63 (0.42–0.95)
Song, 2011	Case-control	63/117	hs-CRP	2.094 (1.017–4.311)
Stern, 1991	Case-control	149/149	Cigarette smoking Head injury Rural living	OR 0.5 (0.3-0.9) OR 2.9 (1.5-5.8) OR 1.7 (0.9-3.1)
Sullivan, 2011	Case-control	89/99	Neuroticism Harm avoidance	OR 1.05 (1.00-1.11) OR 1.07 (1.00-1.15)
Tan, 2008	Case-control	204/396	Essential tremor	OR 10.87 (1.39-85.15)
Tan, 2010	Case-control	157/157	Alcohol Depression Family history Insecticide exposure Mental work	OR 2.03 OR 5.20 OR 6.75 OR 2.42 OR 2.37
Tanaka, 2011	Case-control	249/368	Black tea Coffee drinking Japanese and Chinese teas	OR 0.58 (0.35-0.97) OR 0.52 (0.30-0.90) OR 0.59 (0.35-0.99)

First Author Last Name, Year	Study Design	Sample Sizes Case-Control: cases/Controls Cohort: final/original cases	Factor Reported	Hazard Ratio (HR); Relative Risk (RR); Odds Ratio (OR) 95% CI
Tanaka, 2011	Case-control	249/369	Protective service occupation Technical occupation (both sexes) Technical occupation (men) Technical occupation (women) Transport occupation	OR 2.73 (0.56-14.86) OR 0.59 (0.32-1.06) OR 0.22 (0.06-0.67) OR 0.99 (0.47- 2.07) OR 1.74 (0.65-4.74)
Thacker, 2007	Cohort	413/143,325	Cigarette smoking: Current smokers Former smokers	RR 0.27 (0.13 -0.56) RR 0.78 (0.64-0.95)
Ton, 2012	Cohort	154/5,888	Per doubling of Interleukin-6 (women) Per doubling of White blood cells (men)	OR 1.5 (1.0-2.4) OR 2.4 (1.2-4.9)
Tsui, 1999	Case-control	414/6,659	Healthcare services occupation Teaching occupation	OR 2.07 (1.34-3.20) OR 2.50 (1.67-3.74)
De Vera, 2008	Cohort	1,182/11,258+56,199	Gout	RR 0.70 (0.59–0.83)
Wang, 2011	Case-control	362/341	Combined ambient exposure to ziram, maneb, and paraquat	OR 3.09 (1.69-5.64)
Weisskopf, 2003	Cohort	189/35,815	Phobic Anxiety	RR 1.5 (1.0 –2.1)
Weisskopf, 2010	Case-control	101/349	Serum dieldrin concentration	OR 1.95 (1.26–3.02)
Weisskopf, 2010	Case-control	330/308	Bone Lead	OR 3.21 (1.17–8.83)

First Author Last Name, Year	Study Design	Sample Sizes Case-Control: cases/Controls Cohort: final/original cases	Factor Reported	Hazard Ratio (HR); Relative Risk (RR); Odds Ratio (OR) 95% CI
Willis, 2010	Cohort	34,584/5,138,648	Copper Manganese	RR 1.1 (0.94-1.31) RR 1.78 (1.54-2.07)
Wong, 2010	Cohort	122/3,741	Fibrinogen	OR 2.07 (1.10-3.88)
Wright, 2005	Case-control	102/133	Well-water drinking: 40 years of exposure First 20 years of life	OR 7.1 (2.3-22.1) OR 2.1 (0.7-6.4)
Xu, 2010	Cohort	767/213,701	Physical activity in the past 10 years	OR 0.65 (0.51-0.83)
Progression				
Ascherio, 2009	Prospective	774 subjects for serum 713 subjects for CSF	Serum and CSF urate	HR 0.64 (0.44-0.94)
Chen, 2008	Cohort	95/15,792	Plasma urate	OR 0.4 (0.2-0.8)
Schwarzschild, 2008	Prospective	804/	Serum urate	HR 0.51 (0.37-0.72)
Weisskopf, 2007	Cohort	84/18,018	Plasma urate	RR 0.43 (0.18-1.02)

Abbreviations: MDD, Major Depressive Disorder; GAD, Generalized Anxiety Disorder; MHI-5, Five Item Mental Health Inventory.

Supplementary material IV

A supplementary search of the MEDLINE database to identify recently published studies yielded the following 97 citations published between 2012 and 2015, after title and abstract and full text screening according to the original inclusion criteria.

1. Agundez, J.A., Lorenzo-Betancor, O., Pastor, P., Garcia-Martin, E., Luengo, A., Alonso-Navarro, H., et al. 2012. LINGO1 rs9652490 and rs11856808 are not associated with the risk of Parkinson's disease: results of a meta-analysis. *Parkinsonism Relat Disord.* 18:657-9.
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APPENDIX III: Supplementary information

Due to page constraints in the (published) manuscripts that comprise this thesis, additional information on the studies presented in Chapters II, III, and V is provided in the following sections.

HEALTH FACTS® DATAWAREHOUSE

Health Facts® is a database of electronic medical records that is owned and managed by the Cerner Corporation (Kansas City, Missouri), a leading supplier of health information technology in the United States of America (USA). Beginning in January 2000, Health Facts® has stored demographic, clinical, laboratory, pharmacy, hospital, and billing data for more than 300 subscribing medical facilities across the USA. As of 2015, Health Facts® contains data from more than 230 million unique patient encounters, representing over 41 million distinct individuals. The majority of subscribers are academic medical centers, which contribute approximately 65% of all encounters.

The use of Health Facts® to conduct research on the use and safety of medications has a number of advantages, including 1) large sample sizes supports risk characterization (stratification), the study of rare outcomes, and the study of populations that may be underrepresented in clinical trials (such as children and the elderly), 2) longitudinal tracking of individuals, often across many years and/or episodes of care (50% of individuals have more than a single encounter, while 10% of individuals have more than 10 encounters), 3) in-depth diagnostic (up to 18 diagnostic codes per encounter, one designated as primary), laboratory (all tests processed within the hospital), and inpatient pharmacy information (all

medications dispensed from hospital pharmacy), and 4) date-time stamping to minute-wise resolution for select events (such as admissions, discharges, procedures, and medication orders).

As with any database comprised of electronic health records, the use of Health Facts® for Parkinson disease (PD) research is subject to certain limitations, the most important of which is that these data may not capture all of the information that is reflective of an individual's overall health status and their experience at a given medical facility. More specifically, comorbidities and certain test results (such as those sent to outside laboratories) may not be documented for every encounter, medications given from specialty units (such as surgery and radiology) and floor or crash carts may not appear as dispensed pharmacy orders, and measures of PD severity (such as Unified Parkinson's Disease Rating Scale or Hoehn and Yahr staging values) are not recorded. Additionally, information on health behaviours (such as smoking, alcohol consumption, and level of physical activity) and outpatient use of medications within Health Facts® is limited. As a result, the possibility of residual bias attributed to the effects of unmeasured and undocumented health data remains for estimates of association reported within this thesis. Although our findings regarding associations between non-ergot dopamine agonist (DA) exposure and heart failure and associations between anticholinergic burden and adverse clinical outcomes (fracture and delirium) are supported by known and plausible mechanisms of action and the findings of other studies, we are unable to make definitive conclusions regarding the temporality of these associations within our version of Health Facts®. Nonetheless, the database remains well suited for examining inpatient medication use and its association with hospital revisits. Moreover, well-

designed cross-sectional studies that examine medication-outcome associations using data from a single encounter/individual may provide preliminary findings to support pharmacoepidemiology research using other data sources, including data from the Centers for Medicare and Medicaid Services (USA) and the Institute for Clinical Evaluative Sciences (Ontario, Canada).

MEASUREMENT OF MEDICATION USE

Since Health Facts® currently lacks detailed outpatient pharmacy data (<10% of all encounters have documented use of one or more medications in outpatient settings), each of the previously described studies involving Health Facts® data were restricted to inpatients. Individuals were classified as users of a given medication during their inpatient encounter if a dispensed pharmacy order for the drug in question was recorded at any point during their hospitalization. Medication dose was not taken into account due to inconsistencies in the way dose values were recorded. Medications dispensed in inpatient settings were presumed continuations of outpatient treatment regimens; however, it remains possible that some medications, especially anticholinergics (such as haloperidol, quetiapine, or amitriptyline), were prescribed for acute changes to mental status or the treatment of pain subsequent to an individual's admission to hospital. Although delays to medication receipt occur, prior studies suggest that dramatic changes to antiparkinson treatment regimens do not dramatically differ between inpatient and outpatient settings, findings that support the need to actively treat PD motor and non-motor symptoms [1, 2]. We intend to examine whether the inpatient use of antiparkinson and anticholinergic medications by individuals with PD is comparable to the use of these medications by the same population in outpatient settings using a version of

Health Facts® with updated pharmacy information, which may be available in future updates of the database.

EXAMINING CHANGES IN DRUG UTILIZATION

In Chapter II, we examined temporal changes in the inpatient utilization of antiparkinson medications in relations to events hypothesized to influence prescribing. Specifically, we examined the change in levodopa and DA use between the event year and 1, 2, and 3 years after (1) publication of the April 2006 American Academy of Neurology practice parameter reporting that levodopa does not accelerate PD progression and that no pharmacological intervention is neuroprotective, (2) the voluntary withdrawal of pergolide (an ergot-derived DA) from the market in 2007 due to concerns about cardiotoxicity, and (3) the December 2008 pramipexole label revisions which added precautions about uncontrollable urges to the label.

In the published manuscript corresponding to this study, we provided an abbreviated description of our analytical strategy as:

“... Using data from the 2005 American Community Survey (USA Census Bureau), we calculated annual standardized (age, sex, race, and census region) antiparkinson drug use to examine prescribing trends over time.... We used a Wilcoxon-Mann-Whitney test to examine whether standardized annual prevalence of levodopa and DA use significantly changed after events of interest. In order to ensure independence of the data between the two years being compared, individuals appearing in both years (6-25% of sample depending on the particular comparison) were excluded from the

analyses. Two-tailed p values less than 0.0015 were considered statistically significant.” [3] (Page 1,013).

Additional details on our statistical analyses are provided below.

The Wilcoxon Mann Whitney is a nonparametric test based on the order of observations from two arrays [4]. For our analyses, we ranked the standardized (age, sex, race, and census region) drug use for each individual (i.e., user status (1 or 0) multiplied by calculated weights for each standardization variable) for examined years, which is a crude indicator of standardized annual antiparkinson drug use. Non-normality of these data was confirmed using the Kolmogorov-Smirnov test (significance level set at 0.05). The sum of ranked scores was then compared between years (significance level set at 0.05).

Analyses conducted crudely enabled us to examine changes in the standardized annual antiparkinson use between years of interest. Although more sophisticated statistical approaches based on interrupted time series analyses could be contemplated, the Wilcoxon Mann Whitney provides a simpler approach to addressing the same question in a practical manner.

MULTIPLE COMPARISONS

In pharmacoepidemiology, when conducting a single significance test at level α , the probability of incorrectly rejecting the null hypothesis (type I error) is referred to as the comparison-wise error rate α , commonly referred to as the individual level error rate [5]. The

probability of not rejecting the null hypothesis is therefore $1 - \alpha$ [5]. There is a greater probability of making a type I error as the number of statistical tests performed within a study increases, a concept known as the problem of multiple testing or multiple comparisons [6]. To reduce the risk of type I errors, investigators often adjust the target significance level within their study to account for the number of statistical tests being performed. Although there are many methods to adjust the target significance level, the easiest and most frequently applied is the Bonferroni procedure, which determines target significance level by dividing α by the number of individual tests performed [5]. It is widely accepted that adjustments for multiple comparisons are unnecessary for exploratory studies and those with explicit objectives but unspecified hypotheses [5-8]. Moreover, the need to ever adjust the target significance level due to multiple comparisons is heavily debated, with leading epidemiologists such as Kenneth Rothman arguing against such procedures due to the fact that they increase the chances of type II errors (failing to reject the null hypothesis) and that such procedures rely on the premise that chance is the first-order explanation for observed effects [6-8].

In our assessment of changes in antiparkinson utilization trends in the USA, we applied a Bonferroni correction to determine our target significance level ($p=0.0015 \approx 0.05/36$, to control for the 36 individual tests conducted); however, recognize that this is most likely an overcorrection and risks type II errors, since it is not unreasonable to believe that some events influenced the prescribing and use of multiple drugs. While calculated p-values are important for the interpretation of our findings, it is equally important to disengage from statistical significance and qualitatively examine trends in observed medication use [9]. As

such, and in consideration that our primary unit of measurement (standardize annual prevalence of antiparkinson medication use) is an imprecise instrument for measuring temporal changes in medication use in relation to specific events, we refrained from overstating the statistical significance of our findings in our discussion of results.

Adjustments for multiple comparisons were not made in our study of adverse cardiovascular reactions, nor in our study of anticholinergic effects in PD, as these studies were exploratory and provide the initial groundwork from which hypothesis driven research may be proposed and carried out with other population-based datasets.

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