THE JOURNAL OF
SEXUAL MEDICINE

ORIGINAL RESEARCH

PHARMACOTHERAPY

Erectile Dysfunction Medications and Treatment for Cardiometabolic Risk Factors: A Pharmacoepidemiologic Study

Sean C. Skeldon, MD, MSc,[1,2] Lucy Cheng, MSc,[1] Steven G. Morgan, PhD,[1] Allan S. Detsky, MD, PhD,[3] S. Larry Goldenberg, MD,[4] and Michael R. Law, PhD[1]

ABSTRACT

Background: Erectile dysfunction (ED) can be a sentinel marker for future cardiovascular disease and has been described as providing a "window of curability" for men to receive targeted cardiovascular risk assessment.

Aim: To determine whether the prescription of phosphodiesterase type 5 inhibitors (PDE5is) for ED leads to the detection and treatment of previously undiagnosed cardiometabolic risk factors.

Methods: We performed a retrospective population-based cohort study of residents of British Columbia, Canada using linked health care databases from 2004 to 2011. An individual-level time series analysis with switching replications was used to determine changes in drug use for hypertension, hypercholesterolemia, and diabetes in men 40 to 59 years old. The observation window for each patient was 720 days before and 360 days after the index date.

Outcomes: The primary outcome was changes in prescriptions for antihypertensive, statin, and oral antidiabetic drugs, with secondary outcomes being laboratory tests for plasma cholesterol and glucose.

Results: 5,858 men 40 to 59 years old newly prescribed a PDE5i were included in the analysis. We found a sudden increase in prescriptions for antihypertensive drugs (40 per 1,000; $P < .001$), statins (10 per 1,000; $P = .001$), and antidiabetic drugs (17 per 1,000; $P = .002$) in the 90 days after a new prescription for a PDE5i. For hypercholesterolemia and diabetes, most of this change was observed in men with relevant screening tests performed in the 30 days after their PDE5i prescription. Only 15% and 17% of men who did not have a screening test for cholesterol and glucose, respectively, in the year before their PDE5i prescription went on to have one in the subsequent 30 days.

Clinical Implications: The paucity of screening tests observed in our study after PDE5i prescriptions suggests that physicians should be educated on the recommended screening guidelines for men newly diagnosed with ED.

Strengths and Limitations: The number of men who were ordered a laboratory test or written a prescription but chose not to complete or fill it, respectively, is unknown.

Conclusion: Treatment for ED with PDE5is can be a trigger or "gateway drug" for the early detection and treatment of cardiometabolic risk factors provided physicians perform the requisite screening investigations. **Skeldon SC, Cheng L, Morgan SG, et al. Erectile Dysfunction Medications and Treatment for Cardiometabolic Risk Factors: A Pharmacoepidemiologic Study. J Sex Med 2017;14:1597−1605.**

Key Words: Cardiovascular Disease; Men's Health; Pharmacoepidemiology; Preventive Care; Screening

INTRODUCTION

Heart disease is the second leading cause of death in men in Canada[1] and the leading cause in the United States and United Kingdom.[2,3] The detection and treatment of cardiometabolic risk factors (CMRFs) such as hypertension, hypercholesterolemia, and diabetes have been shown to be effective in preventing

Received July 13, 2017. Accepted October 14, 2017.

[1]The Centre for Health Services and Policy Research, School of Population and Public Health, The University of British Columbia, Vancouver, BC, Canada;

[2]Department of Family and Community Medicine, University of Toronto, Toronto, ON, Canada;

[3]The Institute of Health Policy, Management and Evaluation and Department of Medicine, University of Toronto, and the Department of Medicine, Mount Sinai Hospital and University Health Network, Toronto, ON, Canada;

[4]Department of Urological Sciences, The University of British Columbia, Vancouver, BC, Canada

https://doi.org/10.1016/j.jsxm.2017.10.063

future heart disease.[4,5] Unfortunately, because these CMRFs are typically asymptomatic, many affected individuals are undiagnosed.[6] This is particularly true for men[7] who use the health care system less than women and subsequently miss opportunities for screening and preventive care.[8–10]

Although men are generally reluctant to seek out medical care, they are more inclined to do so when it concerns their sexual function.[11] Erectile dysfunction (ED) is a common condition affecting men, with almost half the men older than 40 years reporting some degree of it.[12] ED has been shown to be an independent risk marker for cardiovascular disease,[13,14] particularly in men younger than 60 years.[15,16] This is perceived to be due to a shared pathophysiology including endothelial and smooth muscle dysfunction.[17,18] Similarly, ED is associated with modifiable CMRFs such as hypertension, hypercholesterolemia, and diabetes.[19,20] Because a readily available, effective treatment for ED exists in the form of phosphodiesterase type 5 inhibitors (PDE5is),[21] it has been suggested that ED can provide a "window of curability" for men to receive targeted cardiometabolic risk assessment.[22,23] Therefore, we investigated whether men who received a new PDE5i prescription for ED were more likely to undergo testing and treatment for previously undiagnosed CMRFs.

METHODS

Setting

We conducted a retrospective population-based cohort study of residents of British Columbia (BC), Canada using linked health care databases inclusive from January 1, 2004 through December 31, 2011. BC is the most ethnically diverse province in Canada,[24] with a population of more than 4.4 million persons. All residents of BC have universal coverage to hospital and physician services through the BC Medical Services Plan. The University of British Columbia Behavioural Research Ethics Board approved this study.

Data Sources

This study was conducted using individual-level, de-identified, longitudinal data from 3 population-based linked health care databases: Population Data BC, PharmaNet, and the College of Physicians and Surgeons of BC. Population Data BC includes information on demographics, hospitalizations, and physician services (inpatient and outpatient) for all residents of BC excluding those with federal coverage of health care services such as Status Indians, veterans, federal inmates, and members of the Royal Canadian Mounted Police. PharmaNet records all prescriptions, regardless of payer, dispensed from community pharmacies or hospital outpatient pharmacies in the province of BC. Demographic and specialty data for all physicians licensed to practice in BC were obtained from the College of Physicians and Surgeons of BC. These databases have been shown to be of high quality and valid at the population level and have been used extensively in pharmacoepidemiology research.[25–27]

Cohort Design

We first identified a cohort of patients 40 to 59 years old newly prescribed a PDE5i (sildenafil, tadalafil, or vardenafil) from January 1, 2007 through December 31, 2010 with a 3-year lookback period (Figure 1). We analyzed men 40 to 59 years old because studies have suggested that the prognostic value of ED for future cardiovascular disease is strongest in middle-age men younger than 60 years.[15,16,20,28] To identify the date on which the PDE5i was actually prescribed, the unique practitioner (physician) number was used to link the prescription to the closest outpatient visit within 60 days before or including the date the prescription was dispensed. This date was considered the index date, or time 0, for each patient. To ensure that each patient was newly prescribed a PDE5i, we excluded all patients not registered with the Medical Services Plan of BC (required of all BC residents) in the full 3 years before their index date. Patients with a history of prostate cancer or primary pulmonary hypertension also were excluded because of their having a predisposing iatrogenic risk for ED or a different indication for receiving a PDE5i, respectively.[29]

Control Group

With ED sharing similar pathophysiology[17] and risk factors as cardiovascular disease,[12,19] using an age-matched control group, as done in previous studies,[30] would lead to an obvious selection bias. To avoid this, an innovative approach was implemented by using switching replications for the time series analysis (Figure 1).[31,32] A control cohort was derived from the initial ED cohort. For each patient in the ED cohort, a control patient was created with an index date or pseudo-intervention date exactly 1 year before his actual index date (Figure 1). This interval was chosen to control for seasonality between groups. Therefore, before matching, each patient would be in the ED and control cohorts, with follow-up time 24 months before and 12 months after the index date. This was done to decrease potential age and selection bias based on cardiovascular risk.

Men were excluded from each cohort if they had a history of cardiovascular disease (ischemic heart disease, cerebrovascular disease, or congestive heart failure) or had received cardiac procedures (coronary artery bypass grafting or percutaneous coronary intervention) in the 2 years before their index date (Figure 2). Because these men would already have established cardiovascular disease, they would be managed with secondary prevention therapies.

Matching

A matching algorithm was applied to select matched pairs from the ED and control cohorts. (i) A patient in the ED cohort was randomly selected. (ii) All potential matches from the control cohort were identified based on having the same age and calendar month and year of index date (Figure 1). This was done to control for history and maturation biases, important threats to internal validity. (iii) 1 patient was randomly selected from the