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PHARMACOTHERAPY

Risk of Melanoma With Phosphodiesterase Type 5 Inhibitor Use Among Patients With Erectile Dysfunction, Pulmonary Hypertension, and Lower Urinary Tract Symptoms

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ABSTRACT

Background: Phosphodiesterase type 5 inhibitors (PDE5is), a treatment for erectile dysfunction, pulmonary hypertension (pHTN), and lower urinary tract symptoms (LUTS), have been implicated in melanoma development.

Aim: We sought to determine the association between PDE5i use and melanoma development among patients with erectile dysfunction, pHTN, and LUTS.

Methods: This was a retrospective cohort study of subjects contained within the Truven Health MarketScan claims database, which provides information on insurance claims in the United States for privately insured individuals, from 2007−2015. Individuals taking PDE5i were identified through pharmacy claims. A comparison group of men diagnosed with conditions for which PDE5i are prescribed was assembled.

Outcomes: Cox proportional hazard models were used to estimate the hazard ratio (HR) (95% CI) of incident melanoma, basal cell carcinoma, and squamous cell carcinoma.

Results: Of 610,881 subjects prescribed PDE5i, 636 developed melanoma (0.10%). The control group had 8,711 diagnoses of melanoma. There was an association between increased PDE5i tablet use and melanoma (HR 1.05, 95% CI 1.05−1.09). This association was also present between PDE5i use and basal cell carcinoma (HR 1.04, 95% CI 1.02−1.07) and squamous cell carcinoma (HR 1.04, 95% CI 1.01−1.07). In patients with pHTN and LUTS prescribed PDE5is, there was no relationship between exposure and melanoma incidence (HR 0.74, 95% CI 0.48−1.13; and HR 1.03, 95% CI 0.97−1.10, respectively).

Clinical Implications: There is little evidence for a clinically relevant association between PDE5i use and melanoma incidence.

Strengths & Limitations: Our current work represents the largest study to date evaluating the relationship between PDE5i use and melanoma risk, and the first to examine all current indications of PDE5i use among men and women. Limitations include a patient population limited to commercially insured individuals, unknown patient medication compliance, and lack of information on patient skin type, lifestyle, and sun-exposure habits.

Conclusion: There is a slight association between higher-volume PDE5i use and development of melanoma, basal cell carcinoma, and squamous cell carcinoma. This association among all skin cancers implies that confounding may account for the observed association. **Shkolyar E, Li S, Tang J, et al. Risk of Melanoma With Phosphodiesterase Type 5 Inhibitor Use Among Patients With Erectile Dysfunction, Pulmonary Hypertension, and Lower Urinary Tract Symptoms. J Sex Med 2018;XX:XXX−XXX.**

Key Words: Melanoma; Basal Cell Carcinoma; Squamous Cell Carcinoma; Phosphodiesterase Type 5; Erectile Dysfunction; Lower Urinary Tract Symptoms; Pulmonary Hypertension

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INTRODUCTION

Nearly 87,000 people will receive a new diagnosis of melanoma in 2017 with men accounting for nearly 60% of these new diagnoses.[1] Mutations in the RAS-RAF-MEK-ERK signaling pathway appear to play an important role in melanoma tumorigenesis. Decreased levels of phosphodiesterase type 5 (PDE5) may facilitate melanoma invasion.[2−4] Pharmaceutical PDE5

inhibition is approved for treatment of erectile dysfunction (ED), pulmonary hypertension (pHTN), and lower urinary tract symptoms (LUTS) via PDE5 inhibitors (PDE5is).[5–8] Given the role of PDE5 in the RAS-RAF-MEK-ERK pathway and potential effect on melanoma invasiveness, the role of PDE5is in melanoma incidence has become a topic of recent investigation.

In 2014, Li et al[9] reported an association between sildenafil use for the treatment of ED and incident melanoma (hazard ratio [HR] 1.84, 95% CI 1.04–3.22) using the Health-Professional's Follow-Up Study. Since then, other investigators have reported on the association between PDE5i use and melanoma risk. Loeb et al[10] explored Swedish national registries and identified a risk among all PDE5i users. However, a lack of dose-response effect and similar elevated risk of basal cell carcinoma among PDE5i users caused the group to question the causality of the identified association. Pottegard et al[11] conducted a similar study using data from the Danish Nationwide Health Registries and the Kaiser Permanente Northern California database. Among roughly 10,000 total men who used PDE5is, they found a trend toward a higher odds ratio in very high-volume users, but this was not statistically significant and the trend was attributed to higher health care utilization leading to increased diagnosis of melanoma through screening bias. While limited other studies have been conducted demonstrating an association between melanoma and PDE5i use, causality has been highly suspect.[12,13] This is especially true given the recent meta-analysis of the 5 existing studies demonstrating an association between PDE5i use for ED and melanoma (relative risk 1.11, 95% CI 1.02–1.22), with significance limited to men with low PDE5i exposure and low-stage melanoma.[14]

Despite the uncertainly, the use of PDE5is is on the rise globally.[15–18] Given the safety concerns, our objective was to examine the relationship between PDE5i and melanoma using a large, national insurance claims database and also assess if the effect was modified based on dose, specific type of PDE5i used, sex, and the indication for PDE5i use.

METHODS

Patients

We analyzed subjects contained within the Truven Health MarketScan Commercial Claims and Encounters database. This database provides information from adjudicated and paid insurance claims filed for the care of privately insured individuals with employment-based insurance through a participating employer. MarketScan provides claims data on over 200 million covered lives since 1996. This study used data from 2007–2015. The number of individuals represented in the database varies over time; the more recent years of the data contain more than 30 million covered lives.

We identified individuals who were prescribed PDE5is and recorded the date of prescription, number of pills prescribed, and number of refills obtained. We also identified individuals diagnosed with ED (*International Classification of Diseases, Ninth Revision* [*ICD-9*] 302.72, 607.84), pHTN (*ICD-9* 416.0. 416.8), and LUTS (*ICD-9* 600.x) (Food and Drug Administration–approved indications for PDE5i use) from inpatient and outpatient records and recorded the date of diagnosis as the index date. We also identified individuals with these diagnoses who were not prescribed PDE5is to serve as a reference cohort to ascertain the risk of exposure. The index date for this group was determined using the date of diagnosis.

As a cancer diagnosis and treatment can lead to sexual dysfunction, individuals with any claim with a diagnosis code for cancer prior to the index date or within 1 year after the index date were excluded (*ICD-9* 140–239, excluding cutaneous squamous cell carcinoma [173.x2], basal cell carcinoma [173.x1], and other non-melanoma skin cancer [173.14]).

For each individual in the cohort, the number of outpatient visits after the index date was ascertained based on the presence of claims with *Current Procedural Terminology* (*CPT*) codes indicating new and follow-up office visits, consultations, or preventative medicine encounters. Medical comorbidities were determined based on *ICD-9* codes on any claim and included obesity (278.0) and smoking (305.1, V1582).

Outcome Ascertainment

Skin cancers were identified using diagnosis codes on inpatient and outpatient claims. We identified men with *ICD-9* codes indicating the presence of cancers: melanoma (172), non-melanoma skin cancer (173), basal cell carcinoma (173.x1), and squamous cell carcinoma (173.x2).

Treatment for melanoma was based on *CPT* codes linked to the diagnosis of melanoma: chemotherapy: 96400–96450, 96542–96549; radiotherapy: 77413, 77427, 77334, 77200–77599, 77789–77799; and lymph node dissection: 38500–38564, 38740, 38745. Metastatic disease was based on diagnosis and treatment codes: liver—*ICD-9* codes 50.22, 50.3, and *CPT* codes 47120, 47122, 47125, 47130; lung—*ICD-9* codes 32.3, 32.4, 32.5, 132.9, and *CPT* codes 32440, 32442, 32445, 32480, 32482, 32484, 32500, 32520; bone—*ICD-9* code 198.5, and

CPT codes 23200, 23210, 23220, 27075, 27076, 27077, 27078, 27365, 27645, 27646; and brain—*ICD-9* codes 191, 225.0, and *CPT* codes 61518–61521, 62164.

Statistical Analysis

Men accrued at-risk time beginning from their prescription or diagnosis date. Men with less than 1 year of follow-up were excluded. We compared the risk of skin cancer incidence of individuals based on PDE5i use. For individuals with a diagnosis of ED, pHTN, or LUTS, we compared PDE5i users to non-users using a Cox proportional hazard regression model that adjusted for age, gender, obesity, diabetes, smoking, number of outpatient visits, and geographic location (as a proxy for ultraviolet