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Risk of sudden sensorineural hearing loss in adults using phosphodiesterase type 5 inhibitors: Population-based cohort study

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Abstract

Purpose: The objective of the study was to determine the risk of sudden sensorineural hearing loss (SNHL) associated with use of phosphodiesterase type 5 (PDE5) inhibitors.

Methods: We conducted a retrospective cohort study in the MarketScan Commercial Claims and Encounters Database including adult men who initiated a PDE5 inhibitor (n = 377,722) and 1,957,233 nonusers between 1998 and 2007. Periods of drug exposure were assessed on a weekly basis based on pharmacy billing records, assuming use of 1 dose per week (current use). Incident sudden SNHL was defined based on inpatient or outpatient visits with International Classification of Diseases, Ninth Revision, Clinical Modification codes 389.1x, 389.2x, or 388.2 plus ≥2 procedure codes for audiometric hearing testing within ±30 days of sudden SNHL diagnosis. We used age- and propensity score-adjusted Cox proportional hazards model to evaluate the risk of sudden SNHL during periods of current or recent use compared with that of nonuse. We conducted sensitivity analyses by varying the assumed drug utilization frequency and sudden SNHL case definition.

Results: We evaluated 1233 sudden SNHL cases, resulting in an incidence of 4.35, 5.58, and 2.38 per 10,000 person-years for current, recent, and nonuse of PDE5 inhibitors, respectively. Compared with nonuse, the adjusted hazard ratio was 1.25 (1.01-1.55) for current use with a risk difference of 1.97 (1.12-2.82) per 10,000 person-years. For recent use, the adjusted hazard ratio was 1.60 (1.33-1.94) and risk difference was 3.19 (2.24-4.14). Estimates were consistent across the sensitivity analyses.

Conclusions: Use of PDE5 inhibitors is associated with a small but significantly increased risk of sudden SNHL.

KEYWORDS

erectile dysfunction, ototoxicity, pharmacoepidemiology, phosphodiesterase 5 inhibitor, sudden sensorineural hearing loss

1 | INTRODUCTION

Approximately 18 to 30 million men in the United States are affected by erectile dysfunction (ED).[1,2] Phosphodiesterase type 5 (PDE5) inhibitors are the recommended first-line treatment for ED.[3] These drugs are generally considered to be safe and efficacious in most ED patients regardless of the underlying cause of ED.[4,5]

Sudden sensorineural hearing loss (SNHL) associated with sildenafil was first reported in April 2007.[6] The Food and Drug Administration (FDA) subsequently reviewed 29 cases in the Adverse Event Reporting System whose hearing loss had a strong temporal relationship with PDE5 inhibitor use.[7] Of these, 27 patients reported onset of hearing loss within 24 hours of drug ingestion. Occasional sudden SNHL cases were also reported in clinical trials.[8,9] Acting on the

safety signal, the FDA approved more stringent labeling alerting to the potential risk of sudden hearing loss in men by using PDE5 inhibitors.[7] Since then, additional data from mouse model,[10-12] case reports,[13-15] small clinical studies,[16,17] and pharmacovigilance[18] have been published, raising further concern. While the association is perhaps initially surprising, a plausible mechanism for PDE5 inhibitor ototoxicity involves the nitric oxide-cyclic guanosine monophosphate signaling pathway[13] that has also been implicated with ototoxicity of gentamicin and cisplatin[19,20]

To date, no large postmarketing safety studies of PDE5 inhibitor ototoxicity have been reported. We conducted a retrospective cohort study to evaluate this emerging safety concern.

KEY POINTS

- Sudden sensorineural hearing loss (SNHL) associated with sildenafil use was first published in literature in April 2007. After reviewing 29 cases in the Adverse Event Reporting System (AERS) whose hearing loss had a strong temporal relationship with PDE5 inhibitor use, the FDA required labeling update for all PDE5 inhibitor products.
- Since then, additional data from mouse model, case reports, small clinical studies, and pharmacovigilance have been published, raising further concern. But no large postmarketing safety studies of PDE5 inhibitor ototoxicity have been reported to quantify the risk till now.
- In a large cohort study of adult males enrolled in a health insurance and encounter database in the United States, initiation of phosphodiesterase type 5 (PDE5) inhibitor medications was associated with a small but significantly increased risk of sudden sensorineural hearing loss (SNHL) compared with nonusers of PDE5 inhibitors.
- The increased risk remained numerically stable across all sensitivity analyses that account for different drug utilization frequency, residual confounding, and sudden SNHL case definition. This study thus strengthens the evidence for a link between PDE5 inhibitor use and risk of sudden SNHL.

2 | METHODS

2.1 | Data source

The MarketScan Commercial Claims and Encounters (CCAE) database contains longitudinal, person-specific deidentified data on health services provided to insured employees, their spouses, and dependents up to 64 years. The encrypted data contain information on beneficiary demographics, enrollment history, inpatient and outpatient services, and dispensing of prescription drugs.[21,22] The institutional review and privacy boards approved this study.

2.2 | Study design and population

We employed a retrospective "new user" cohort design including billing records of men aged 18 to 64 years, 1998 to 2007. New users entered the cohort at their first pharmacy dispensing record for a PDE5 inhibitor (index date) following a look-back period of at least 183 days of continuous insurance eligibility. A randomly selected index date, which was preceded by at least 183 days of continuous eligibility, was chosen for nonusers. We followed subjects from the index date until first sudden SNHL, loss of insurance eligibility, their 65th birthday, or December 31, 2007, whichever came first.

Patients were excluded if inpatient or outpatient records during the look-back period suggested presence of hearing loss of any form, cancer (except prostate and bladder cancer), organ transplantation, HIV/AIDS, cytomegalovirus infection, rubella, syphilis, bacterial meningitis, viral encephalitis, severe head injury, and head or neck radiation. We excluded 1016 patients with pulmonary hypertension where daily chronic dosing of a PDE5 inhibitor was indicated.[23] Finally, we excluded patients who filled prescriptions for drugs with known ototoxicity including aminoglycosides, interferon, cisplatin, cyclosporine, vinblastine, or vincristine (eTable 1).

2.3 | Definition of outcome

The study outcome was the first sudden SNHL event diagnosed during follow-up. Sudden SNHL was determined based on at least 1 medical service claim indicating SNHL (International Classification of Diseases, Ninth Revision, Clinical Modification codes: 389.1x, 389.2x, or 388.2) and presence of 2 procedure codes for an audiometric test. The first test had to occur at or up to 30 days before the day of the SNHL diagnosis, while the second test had to occur between 4 to 30 days after diagnosis (eTable 2). Short interval, serial audiometric testing associated with SNHL is typically only performed when sudden, clinically significant changes are observed, thus allowing distinction between sudden and gradual SNHL.[24] Cases involving follow-up audiometry performed within 3 days of SNHL diagnosis were excluded to avoid spurious findings due to billing data errors. In a sensitivity analysis, we refined the cases' definition by further requiring treatment with oral or intratympanic steroids therapy within 30 days after SNHL diagnosis.[25]

2.4 | Definition of exposure

We made assumptions about frequency of PDE5 inhibitor use based on results from recent surveys, which suggested that about 40 to 50% of the men interviewed took the medication once or twice per week, and about 75% use it once or twice per month.[26-31] Duration of exposure was calculated accordingly as the number of prescribed tablets multiplied by 7 days. If a patient received 4 tablets, we computed the duration of exposure to be 28 days. We then added an additional 30-day grace period, because patients may not use the full monthly supply,[32] may split their pills to achieve cost savings,[33] or may not refill their prescriptions on time.[34] They may also delay seeking care or experience delay in receiving referrals to a specialist for definitive hearing testing.[35]

For each week of follow-up time, we categorized PDE5 inhibitor exposure based on most days attributed to current, recent, or nonuse. Current use included the time from a PDE5 inhibitor dispensing to the estimated end of supply plus the 30-day grace period. Recent use included person-time up to 365 days after current use, and nonuse periods were defined as time with no PDE5 inhibitor use in the past 365 days. If a patient received a new dispensing before the estimated days' supply was exhausted, the excess supply was not carried over. Switching between different PDE5 inhibitors or change in dosage did not affect current use designation.

2.5 | Definition of confounders

We ascertained demographic variables from enrollment data. Other baseline covariates including presence of comorbid conditions, concurrent use of medications, and health service utilization were defined by using medical and pharmacy claims during the 183-day look-back period (eTable 3). The CCAE database does not have information on smoking, body mass index, or family history of hearing loss.

2.6 | Statistical analysis

We compared baseline characteristics of users against nonusers of PDE5 inhibitors and calculated crude incidence rates and incidence rate differences with 95% confidence intervals (CIs). We used logistic regression to calculate a propensity score (PS)[36,37] for the estimated probability of PDE5 inhibitor use versus nonuse, based on observed patients' characteristics at baseline. To check whether the PS adequately balanced the covariates, we calculated the standardized mean difference between the 2 groups and found that the standardized differences were less than 0.1 for all covariates.

Cox proportional hazard models were used to estimate the hazard ratio (HR) comparing current or recent use to nonuse of PDE5 inhibitors. The final models contained PDE5 inhibitor exposure, the logit transformed PS, and age (continuous) as a time-dependent variable. The proportional hazard assumption was assessed by including interaction terms of each regressor and survival time, which showed that there was no violation of this assumption.[38]

We conducted several sensitivity analyses to explore the robustness of primary findings. First, we changed the assumed frequencies of PDE5 inhibitor use to 1 dose every 14, 21, or 30 days. Second, we used PS matching to form study cohorts because some theoretical work has suggested that PS matching has advantages over other confounding adjustment approaches.[36,39] Third, in addition to diagnostic and procedure codes, we restricted sudden SNHL cases to those receiving oral or intratympanic steroids therapy within 30 days after SNHL diagnosis.[25] Fourth, we required each individual to have an ED diagnosis during study period to reduce residual confounding due to misclassifying subjects with off-label use of PDE5 inhibitor for nonurologic indications.[23] SAS 9.2 version was used (SAS Institute, Inc., Cary, NC), and all *P* values were 2-sided with a predefined alpha of .05.

3 | RESULTS

We identified 610,238 men who filled at least 1 prescription for a PDE5 inhibitor and 18,293,501 nonusers, 1998 to 2007. After removal of patients who met exclusion criteria or lacked the required look-back period, 377,722 new users and 1,957,233 nonusers formed the final study cohorts (Figure 1).

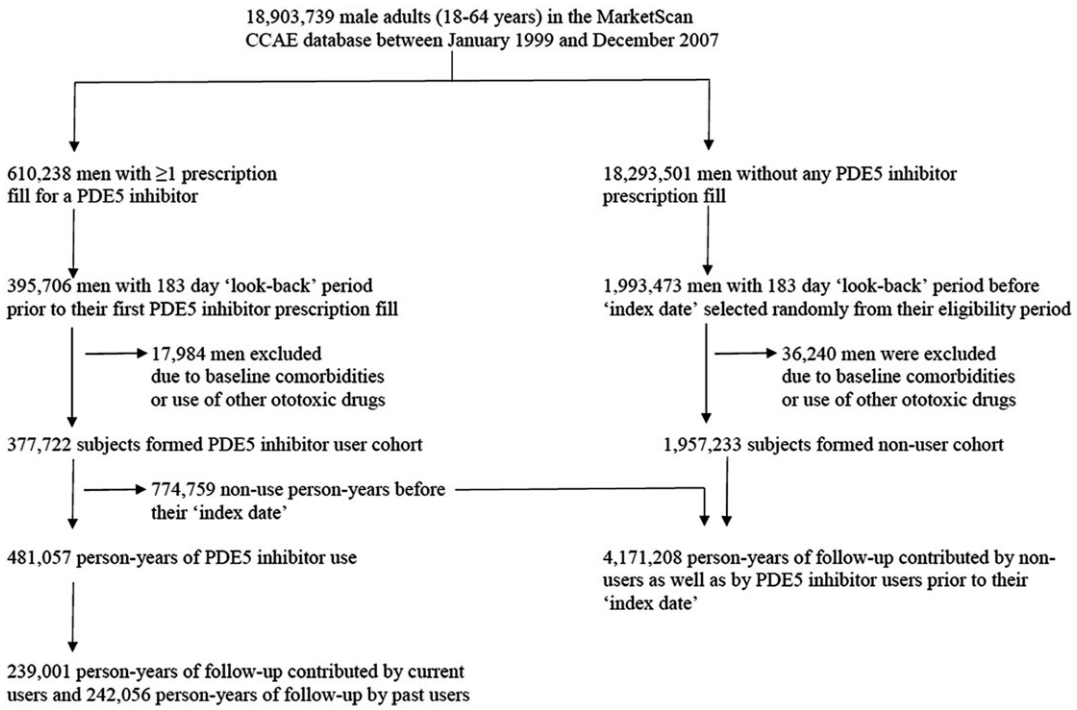

FIGURE 1 Composition of the study cohort. Legend: Figure 1 shows the study cohort selection process. After applying the inclusion and exclusion criteria, the cohort included 377,722 phosphodiesterase type 5 inhibitor new users and 1,957,233 nonusers

TABLE 1 Baseline characteristics of cohort members

Characteristic	Original Cohort		Cohort Matched by Exposure Propensity Score	
	PDE5 Inhibitor Nonusers	PDE5 Inhibitor New Users	PDE5 Inhibitor Nonusers	PDE5 Inhibitor New Users
N	1,957,233	377,722	302,067	302,067
Age, years, mean ± SD	41.7 ± 12.7	52.9 ± 7.8	52.9 ± 7.9	52.4 ± 7.9
Age (%)				
18-39	43.6	7.4	7.3	7.5
40-54	37.7	45.9	46.1	46.3
55-64	18.7	46.7	46.6	46.2
Health plan type (%)				
Employer-based	76.8	88.4	86.9	87.7
Large health plan	23.2	11.8	13.1	12.3
Region (%)				
Northeast	11.4	10.2	10.8	10.5
North central	26.2	34.9	31.8	33.6
South	39.0	36.6	38.1	37.1
West	22.3	17.3	18.4	17.9
Unknown	1.1	1.0	0.9	0.9
Year of index date (%)				
1998	0.9	0.8	0.6	0.8
1999	3.3	2.1	2.4	2.0
2000	3.7	2.7	3.0	2.7
2001	5.0	5.0	4.8	5.0
2002	8.9	10.3	9.0	10.4
2003	13.9	13.1	12.9	13.3
2004	17.1	15.1	16.5	15.0
2005	17.0	15.0	16.3	15.7
2006	14.3	16.9	16.2	16.8
2007	15.7	19.1	18.8	18.8
Comorbid conditions (%)				
Myocardial infarction	0.5	1.1	1.2	1.1
Atrial fibrillation	0.4	1.1	1.1	1.0
Ventricular arrhythmias	0.2	0.4	0.4	0.4
Congestive heart failure	0.3	0.7	0.8	0.7
Hypertension	9.3	26.9	25.6	24.7
Cerebrovascular disease	2.2	6.0	6.1	5.7
Peripheral vascular disease	0.2	0.6	0.5	0.5
Hyperlipidemia	10.0	26.3	26.0	24.4
Alcoholism	0.2	0.6	0.5	0.5
Smoking	0.4	0.9	0.8	0.8
Diabetes mellitus	4.5	15.4	13.6	13.8
Recorded obesity	0.4	0.8	0.8	0.7
Depression	2.2	4.9	4.4	4.3
Anxiety	1.0	1.8	1.8	1.6
Chronic kidney disease	0.3	0.7	0.7	0.7
Prostate cancer	0.4	3.6	1.5	2.2
Bladder cancer	0.1	0.2	0.2	0.2
Lower urinary tract syndrome	1.8	7.9	5.7	6.2
Erectile dysfunction	0.4	9.1	1.4	2.6
Comedications (%)				
Angiotensin-converting enzyme inhibitors	6.4	18.6	17.9	17.4
Angiotensin receptor blockers	1.8	5.6	5.1	5.0
Beta blockers	5.6	13.9	13.4	14.3

TABLE 1 (Continued)

Characteristic	Original Cohort		Cohort Matched by Exposure Propensity Score	
	PDE5 Inhibitor Nonusers	PDE5 Inhibitor New Users	PDE5 Inhibitor Nonusers	PDE5 Inhibitor New Users
Calcium channel blockers	4.4	13.5	12.6	12.4
Diuretics	5.9	18.2	17.1	16.7
Statins	9.9	29.0	28.3	27.1
Other lipid-lowering drugs	2.9	8.6	8.2	8.0
Benzodiazepines	3.5	9.9	8.8	8.8
SSRI	4.0	8.7	8.6	8.1
Antipsychotics	0.6	1.2	1.1	1.1
Nonsteroidal antiinflammatory drugs	9.0	19.9	18.9	18.3
Flu vaccination	2.1	5.1	4.9	4.7
Pneumococcal vaccination	0.3	0.9	0.8	0.8
Health service utilization (%)				
Number of outpatient visits	1.2 ± 1.9	2.6 ± 2.6	2.4 ± 2.6	2.3 ± 2.3
Number of emergency department visits	0.1 ± 0.3	0.1 ± 0.4	0.1 ± 0.3	0.1 ± 0.4
Number of hospitalization	0.02 ± 0.13	0.04 ± 0.20	0.04 ± 0.2	0.04 ± 0.2

PDE5, phosphodiesterase type 5.

About 60%, 20%, and 20% of new users initiated therapy with sildenafil, vardenafil, and tadalafil, respectively. The mean age at study entry was 52.9 years (SD, 7.8) for new users and 41.7 years (SD, 12.7) for nonusers. Reflecting the age difference, new users of PDE5 inhibitors were more likely than nonusers to have a diagnosis of cardiovascular disease, diabetes mellitus, and hyperlipidemia, and to use cardiovascular drugs, lipid-lowering drugs, nonsteroidal antiinflammatory drugs, antidepressants, and antipsychotic medications. New users were also more likely to have prostate cancer, low urinary tract syndrome, and ED (Table 1). Matching patients by exposure PS, as used in the sensitivity analysis, produced groups that were balanced with respect to all examined characteristics.

There were 104 incident cases of sudden SNHL for 239,001 person-years of follow-up or 4.35 cases per 10,000 person-years. The crude incidence rates in the recent use and nonuse groups were 5.58 (n = 135) and 2.38 (n = 994) per 10,000 person-years, respectively (Table 2). After controlling for logit transformed PS and age, current use of a PDE5 inhibitor was associated with an elevated risk of sudden SNHL compared with nonuse (HR = 1.25, 95% CI, 1.01-1.55) with an excess risk of 1.97 (95% CI, 1.12-2.82) per 10,000 person-years. The adjusted relative risk of sudden SNHL associated with recent use compared with nonuse was 1.60 (95% CI, 1.33-1.94).

TABLE 2 Hazard ratios and 95% confidence intervals of association between PDE5 inhibitor use and risk of sudden SNHL according to use or nonuse of PDE5 inhibitors (primary outcome[b])

	No Use	Current Use	Recent Use
No. of events	994	104	135
Person years	4,171,208	239,001	242,056
Incidence rate[a]	2.38	4.35	5.58
HR* (95% CI)	Reference	1.25 (1.01, 1.55)	1.60 (1.33, 1.94)
IRD[a] (95% CI)	Reference	1.97 (1.12, 2.82)	3.19 (2.24, 4.14)

CI, confidence interval; HR, hazard ratio; IRD, incidence rate difference; PDE5, phosphodiesterase type 5; SNHL, sensorineural hearing loss.

[a]Per 10,000 person-years.

*Adjusted for age (continuous) as time-dependent variable and logit of propensity score.

[b]In primary analysis, we assumed frequencies of use to be 1 PDE5 inhibitor dose each week.

In sensitivity analyses, assuming patients consumed 1 PDE5 inhibitor pill every 14, 21, or 30 days, we consistently found a 20 to 30% increased risk of sudden SNHL comparing current use to nonuse (Table 3).

Propensity score matching to adjust for confounding, using the base assumption of 1 dose per week, resulted in an adjusted HR of 1.38 (95% CI, 1.07-1.74) and 1.58 (95% CI, 1.18-1.95), respectively, comparing current and recent use to nonuse.

Requiring treatment with steroids in the case definition, we found 510 sudden SNHL cases (52 cases in the current use group or 1.75 per 10,000 person-years; 417 cases in the nonuse group or 1.0 per 10,000 person-years) and an adjusted HR of 1.34 (95% CI, 0.99-1.83) and 1.61 (95% CI, 1.15-2.25), respectively, comparing current and recent use to nonuse. Thus, the HRs from these secondary analyses were similar to those from the primary analysis (Table 3).

Finally, the requirement of at least 1 diagnosis of ED resulted in an adjusted HR of 1.37 (95% CI, 0.93, 2.02) and 1.73 (95% CI, 1.14, 2.63) comparing current and recent use to nonuse. Although these point estimates were similar to the primary analysis, confidence bounds were wider because of smaller sample size and less statistical power (Figure 2).

4 | DISCUSSION

We followed almost 2.5 million privately insured male adults and found a small but significantly increased risk of sudden SNHL (HR = 1.25, 95% CI 1.01-1.55) comparing new users of PDE5 inhibitors to nonusers, resulting in an excess risk difference of roughly 2 cases per 10,000 person-years. The adjusted estimate for recent versus nonuse was 1.60 (95% CI, 1.33-1.94), suggesting the possibility that this may

TABLE 3 Hazard ratios and 95% confidence intervals of association between PDE5 inhibitor use and risk of sudden SNHL according to use or nonuse of PDE5 inhibitors (sensitivity analyses)

	No Use	Current Use	Recent Use
Supplemental Analysis 1: Take 1 PDE5 Inhibitor Every 14 days			
No. of events	991	141	101
Person years	4,154,314	324,568	173,129
Incidence rate[a]	2.38	4.34	5.83
HR[b] (95% CI)	Reference	1.24 (1.02, 1.50)	1.66 (1.34, 2.06)
IRD[a] (95% CI)	Reference	1.96 (1.23, 2.69)	3.45 (2.30, 4.60)
Supplemental analysis 2: Take 1 PDE5 inhibitor every 21 days			
No. of events	988	179	66
Person years	4,139,987	372,119	139, 069
Incidence rate[a]	2.39	4.81	4.75
HR[b] (95% CI)	Reference	1.37 (1.15, 1.63)	1.33 (1.03, 1.73)
IRD[a] (95% CI)	Reference	2.42 (1.70, 3.14)	2.36 (2.20, 3.51)
Supplemental analysis 3: Take 1 PDE5 inhibitor every 30 days			
No. of events	985	198	50
Person years	4,124,917	413,627	113,467
Incidence rate[a]	2.39	4.79	4.41
HR[b] (95% CI)	Reference	1.35 (1.14, 1.60)	1.24 (0.92, 1.66)
IRD[a] (95% CI)	Reference	2.40 (1.72, 3.08)	2.02 (0.79, 3.25)
Supplemental analysis 4: Propensity score-matched analysis			
No. of events	249	88	112
Person years	1,042,802	203,151	209,748
Incidence rate[a]	2.39	4.33	5.34
HR[b] (95% CI)	Reference	1.38 (1.07, 1.74)	1.58 (1.18, 1.95)
IRD[a] (95% CI)	Reference	1.94 (1.36, 2.92)	2.95 (2.04, 3.87)
Supplemental analysis 5: Require sudden SNHL cases to have evidence of treatment with steroids			
No. of events	417	52	41
Person years	4,164,192	297,278	191,946
Incidence rate[a]	1.0	1.75	2.14
HR[b] (95% CI)	Reference	1.34 (0.99, 1.83)	1.61 (1.15, 2.25)
IRD[a] (95% CI)	Reference	0.75 (0.26, 1.23)	1.14 (0.47, 1.80)
Supplemental analysis 6: Require an ED diagnosis for both users and nonusers			
No. of events	78	42	33
Person years	210,954	84,452	50,907
Incidence rate[a]	3.70	4.97	6.48
HR[b] (95% CI)	Reference	1.37 (0.93, 2.02)	1.73 (1.14, 2.63)
IRD[a] (95% CI)	Reference	1.27 (−0.44, 2.99)	2.78 (0.43, 5.14)

CI, confidence interval; HR, hazard ratio; IRD, incidence rate difference; PDE5, phosphodiesterase type 5; SNHL, sensorineural hearing loss.

[a]Per 10,000 person-years.

[b]Adjusted for age (continuous) as time-dependent variable and logit of propensity score.

reflect the time that is likely required to get a referral to a specialist and receive testing and a formal diagnosis of SNHL. The increased risk remained numerically stable across all sensitivity analyses. This study thus strengthens the evidence for a link between PDE5 inhibitor use and risk of sudden SNHL.

Prior evidence related to this topic has been limited to infrequent cases in clinical trials,[8,9] case reports,[6,13-15,40] small clinical studies,[16,17] and pharmacovigilance data from regulatory agencies.[7,18] Common to all previous reports is the small sample size, limiting their abilities to quantify the risk. For example, 5 cases were reported from approximately 25,000 sildenafil-treated patients in prelicensing trials. Similarly, 3 and 4 patients experienced sudden SNHL from about 16,000 and 18,000 enrollees in vardenafil and tadalafil trials, respectively.[8] The reporting rate from Pfizer's postmarketing safety database was about 0.01% (3/39,277).[9] Although objective audiometric testing was used to determine the hearing threshold change in 2 hospital-based studies, the small number of subjects included (n < 25) made the findings inconclusive.[16,17]

There has been only 1 population-based epidemiological study that evaluated the ototoxicity of PDE5 inhibitors. Using the 2003 to 2006 Medical Expenditure Panel Survey, McGwin et al assessed 11,525 men over the age of 40 and found that subjects with self-

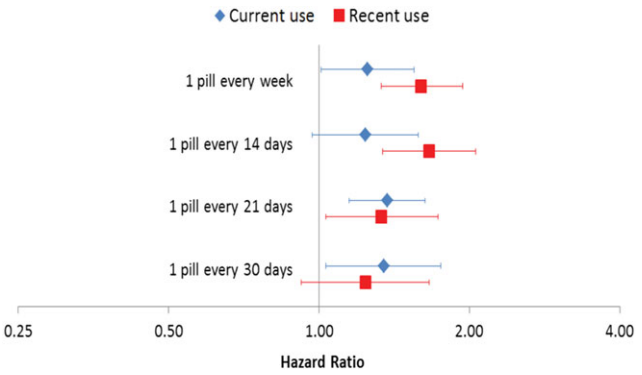

FIGURE 2 Primary and secondary analyses of the association between phosphodiesterase type 5 (PDE5) inhibitor medication use and risk of sudden sensorineural hearing loss. Legend: Figure 2 shows the hazard ratio comparing current or recent to nonuse of PDE5 inhibitors adjusting for age (continuous) as time-dependent variable and logit of propensity score, in primary and secondary analyses [Colour figure can be viewed at wileyonlinelibrary.com]

reported hearing impairment were twice more likely to have also reported use of a PDE5 inhibitor. However, because of its cross-sectional design, the study was unable to determine the temporal relationship between PDE5 inhibitor use and occurrence of hearing loss and it did not comprehensively adjust for confounding.[41]

Several experimental studies have provided direct testing on the ototoxic effect of PDE5 inhibitor, but their results are conflicting. Using a mouse model, Hong et al showed that high dose sildenafil treatment (up to 10 mg/kg) can cause threshold shift of auditory brainstem responses and changes in transient evoked otoacoustic emissions after long-term treatment (up to 105 days) which suggested that cochlear outer hair cells were damaged by sildenafil.[10] In a study that examined inner ear specimens from mice given sildenafil, increased caspase 3 immunoreactivity was observed, suggesting that apoptosis was responsible for the induced hearing impairment.[11] In contrast, another study found that daily administration of sildenafil 10 mg/kg for 30 days did not affect hearing in mice.[12]

Despite these scattered reports, exact biological mechanisms responsible for PDE5 inhibitor-induced sudden SNHL are still unclear. The nitric oxide-cyclic guanosine monophosphate signaling pathway regulates cochlear physiology,[42,43] and cGMP was found to induce gene expression that regulates oxidative stress and endothelial dysfunction.[44] The "cellular stress" caused by localized inflammation and cochlear infarction secondary to the endothelial dysfunction or thrombosis is postulated as a potential mechanism.[13] The unilaterality of most sudden SNHL cases seems to support the "cellular stress" theory.

Our study has several strengths that support the validity of the detected association between PDE5 inhibitor use and hearing loss. First, because a history of filling PDE5 inhibitor prescriptions and experience of side effects may affect a subject's subsequent likelihood of drug use and hence his risk of sudden SNHL, we examined patients who initiated PDE5 inhibitors by using a "new user design."[45,46] We used a time-varying definition of drug exposure that allowed close examination of periods of current and former use of PDE5 inhibitors. Because PDE5 inhibitors are used as needed, we varied our assumptions about the frequency of use in sensitivity analyses. We defined the duration of drug exposure based on the dispensed supply recorded in pharmacy claims and the frequency of PDE5 inhibitor use reported in previous surveys. If frequency of use or dosage was misclassified, then this could result in an overestimation or underestimation of the time or intensity of drug exposure. For example, patients may use dispensed pills less frequently than assumed or they may split pills, both resulting in a larger than calculated exposure time. In this case, exposed time would have been attributed to "recent use" periods, resulting in an underestimation of current use risk and overestimation of former use risk. We noted changes in the HRs of current and former use due to variation of the assumed duration of a dispensed supply with a larger risk attributed to former use than current use with shorter assumed use periods. With longer assumed use periods (eg, 1 dose per month), sudden SNHL risk of former use was similar to that of nonusers, suggesting limited residual confounding (ie, baseline risks of users and nonusers were well balanced). Another source of exposure misclassification would be patients paying cash for the medication. Such misclassification would mask differences between users and nonusers and limit our ability to find a difference in risk. The diagnosis of ED was based on the International Classification of Diseases, Ninth Revision, Clinical Modification codes which can introduce misclassification bias. Furthermore, restriction of our cohort to patients with an ED diagnosis might have resulted in a higher likelihood of misclassifying PDE5 users as nonusers because they obtained medication outside of their insurance coverage, revealing similar results.

We used PS adjustment to balance baseline risk factors and introduced a sensitivity analysis that required all men to have a diagnosis of ED, further equalizing clinical characteristics among comparison groups. We cannot rule out the possibility of residual confounding by indication or by other factors that are not measured in claims data, because ED and sudden SNHL share several common risk factors such as diabetes and cardiovascular disease. It is noteworthy that among the cohort required to have an ED diagnosis, the decision to initiate PDE5 inhibitors might suggest an overall superior health status compared with ED patients who did not initiate therapy and thus a smaller baseline risk for SNHL.

We based our identification of sudden SNHL on our previous research on aminoglycoside ototoxicity[47] and performed sensitivity analyses to minimize potential ascertainment bias. Our crude incidence of 2.39 per 10,000 person-years in this privately insured population was slightly higher than previously reported estimates (5-20 per 100,000 persons), but the exact incidence of sudden SNHL is uncertain and as many as 65% of sudden SNHL cases may resolve spontaneously.[48] The diagnosis and procedure codes we used were specific for SNHL. In adults, multiple audiograms within a narrow period of time for SNHL are generally only performed when there is a marked change in sensorineural function. The validity of this approach was supported by the robustness of findings upon adding the requirement for treatment with either systemic or intratympanic steroids, the first-line therapy for sudden SNHL. Requiring such a stringent timeline of procedure and diagnosis codes would be expected to underestimate the incidence of sudden SNHL and thus result in smaller absolute differences in SNHL incidence among PDE5 inhibitor users and nonusers. It is also noteworthy that we restricted our study to a time period when the potential for an association between SNHL and PDE5 inhibitors was unknown, further reducing ascertainment bias.

Finally, the MarketScan CCAE database reflects a commercially insured, relatively affluent population. Therefore, our study might not be generalizable to uninsured or low-income populations who might have a larger number of risk factors for SNHL.

5 | CONCLUSIONS

In a large cohort of privately insured male adults, initiation of PDE5 inhibitor medications was associated with a small but significantly increased risk of sudden SNHL compared with nonusers of PDE5 inhibitors. Although the absolute excess risk of sudden SNHL due to PDE5 inhibitor exposure was low, our results support the regulatory decision to update product labels. Given the increasing number of patients who are exposed to PDE5 inhibitors, the nature of this adverse event, and its impact on the quality of life of affected individuals, the potential ototoxicity remains an important concern. Continued monitoring for ototoxicity and evaluation of the comparative safety of PDE5 inhibitors is warranted.

ETHICS STATEMENT

This study was exempted from review by the Institutional Review Board of the University of Florida.

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CONFLICT OF INTEREST

Dr Antonelli has received financial support from the industry, but none represents any conflict with the present study: consulting fees from Otonomy and research support from Alcon Laboratories, Sound Pharmaceuticals, Auris Medical, Edison Pharmaceuticals, and Otonomy. No other disclosures were reported.

Dr Wei Liu is currently an employee of the U.S. Food and Drug Administration (FDA). The work presented in this paper was conducted when he was a graduate student at the University of Florida. The views expressed in this article represent those of the authors and not necessarily those of the FDA.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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