

# Phosphodiesterase Type 5 Inhibitor Use and Hearing Impairment

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**Objective:** To compare use of phosphodiesterase type 5 inhibitors (PDE-5i) between participants with and without self-reported hearing impairment using logistic regression, with and without adjustment for potentially confounding sociodemographic, behavioral, and health-related characteristics.

**Design:** Cross-sectional.

**Setting:** United States.

**Patients:** A population-based sample of 11 525 men 40 years or older (248 217 013 weighted men) in the United States, selected from the Medical Expenditure Panel Survey (2003-2006).

**Main Outcome Measure:** Self-reported hearing impairment.

**Results:** The overall prevalence of self-reported hearing impairment and PDE-5i use in each group was 17.9% and 2%, respectively. Men who reported hearing impairment were more likely to have also reported the use of any PDE-5i (odds ratio [OR], 2.23; 95% confidence interval [CI], 1.36-3.66). However, this association was limited to sildenafil (Viagra) (OR, 2.05; 95% CI, 1.23-3.43); no significant associations were observed for tadalafil (Cialis) or vardenafil (Levitra) (ORs, 1.40 [95% CI, 0.49-4.04] and 0.88 [95% CI, 0.35-2.22], respectively).

**Conclusions:** Current warnings regarding the risk of hearing loss related to PDE-5i use seems to be justified. However, the cross-sectional nature of the current study provides only limited insight regarding this relationship, and thus additional research is warranted.

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**H**EARING LOSS (HL) IS THE most common sensory impairment among older adults, with both genetic and environmental factors contributing to its etiology. It is estimated that 28 million Americans experience some type of hearing impairment.<sup>1</sup> Risk factors include age, sex, occupation, education, smoking, diabetes mellitus, and cardiovascular disease.<sup>1-3</sup> Genetic risk factors are less well understood, although multiple possible susceptibility genes have been identified.<sup>4</sup>

Recent reports suggest that sudden sensorineural HL (SSHL) may be associated with the use of phosphodiesterase type 5 inhibitors (PDE-5i), including sildenafil citrate (Viagra and Revatio; Pfizer Inc, New York, New York), vardenafil (Levitra; Bayer Healthcare Pharmaceuticals, Montville, New Jersey, Schering-Plough, Kenilworth, New Jersey, and GlaxoSmithKline, London, England), and tadalafil (Cialis; Eli Lilly, Indianapolis, Indiana).<sup>5</sup> Following the published report of a single patient who experienced SSHL after taking sildenafil for 15 days,<sup>6</sup> the US Food and Drug Administration (FDA) identified a total of 29 reports of sudden HL potentially related to

PDE-5i use.<sup>5</sup> This prompted the FDA to require that material associated with these products mention the possibility of HL. Details regarding most of the cases reported to the FDA as well as 2 additional cases were subsequently described in the literature.<sup>7</sup> A number of mechanisms have been proposed and evaluated that lend support to the notion that PDE-5i use may indeed play a causal role in HL.<sup>8</sup>

To my knowledge, no epidemiologic studies to date have evaluated the association between PDE-5i use and HL. To help fill this void in the current literature, this study evaluates this relationship in a population-based sample of men in the United States.

## METHODS

### DATA SOURCE AND STUDY DESIGN

The Medical Expenditure Panel Survey (MEPS) is a longitudinal, overlapping panel cohort, with each cohort consisting of approximately 15 000 households, including a subsample of approximately 39 000 individuals chosen from the National Health Interview Survey using a stratified and clustered sample with weights that produce nationally representative estimates.<sup>9</sup>

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Participants are interviewed 5 times over a 2-year period with respect to demographic, health status, and health care utilization, including prescription medication use. For the purposes of this cross-sectional study, data for men 40 years or older from the 2003-2006 MEPS Household Component (HC) were combined. These years have a common variance structure necessary to ensure compatibility and comparability among the specific variables and represent the most recent data available. The institutional review board at the University of Alabama at Birmingham approved this study.

## VARIABLE DEFINITIONS

### Hearing Impairment

The MEPS-HC respondents are asked a series of questions regarding HL; these questions are asked of all household members. Specifically, respondents are asked about the use of a hearing aid, any difficulty hearing (with or without the use of a hearing aid), deafness, and the ability to hear most or some of things people say. Responses to these questions are summarized into a single variable that classifies individuals with respect to the extent of their hearing impairment. For the purposes of this study, individuals classified as having no hearing difficulty are compared with those with slight, moderate, or major HL or deafness. This same classification has been used previously to describe the prevalence of HL in the United States.<sup>10</sup>

### PDE-5i Use

During each round of the MEPS-HC, all respondents are asked to supply the name of any prescribed medications they or their family members purchased or otherwise obtained. For each medication, a variety of information is obtained, including the name(s) of any health problems for which the medicine was prescribed, frequency of purchase, and the date of first use. For the purposes of this study, respondents with reported use of sildenafil, vardenafil, and tadalafil were classified as PDE-5i users; nonusers were those with no record of having reported use of these medications. Revatio is another PDE-5i used in the treatment of pulmonary arterial hypertension; however, no respondent reported using it during the study period.

### Potential Confounders

A number of demographic, environmental, and medical characteristics have been linked to HL<sup>4</sup> and therefore serve as potential confounders for the relationship between PDE-5i use and hearing impairment. Thus, in addition to sociodemographic characteristics (ie, age, race, household income), information pertaining to current smoking, the use of ototoxic medications, diabetes mellitus, cardiovascular disease, and job characteristics was selected from the MEPS-HC. Information regarding other potential confounders (eg, alcohol consumption) is not available in the MEPS, and therefore the confounding influence of such characteristics cannot be evaluated. Ototoxic medication use, including antibiotics, diuretics, salicylates, and quinine derivatives, was defined using the same information source used to define PDE-5i use. Information on acute and chronic medical conditions in the MEPS-HC is obtained via a number of mechanisms, including the report of a medical event (eg, hospital stay, medication purchase), whether the condition was responsible for 1 or more disability days, or if the condition was reported as "bothering" the person. For certain conditions (eg, diabetes mellitus, coronary heart disease) respondents are asked explicitly whether they were told by a physician or other health care provider that they have a spe-

cific condition. Medical conditions reported by respondents are coded by professional coders to *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* codes, although, to protect respondent confidentiality, nearly all codes are available only at the 3-digit level. This information was used to identify the presence of diabetes mellitus and cardiovascular disease, the latter including coronary heart disease, angina, myocardial infarction, or other heart conditions. Finally, the MEPS collects information related to current and former jobs, including industry and occupation. Industry and occupation codes are assigned by professional coders at the US Census Bureau based on verbatim descriptions provided by respondents during the survey interview. The detailed codes are collapsed into broader groups to ensure confidentiality. For the purposes of this analysis, individuals were classified as having ever worked in any of the following occupational categories: management/business/financial, professional, service, sales, office/administrative, farming/fishing/forestry, construction, production/transportation, or military.

## STATISTICAL ANALYSIS

Given the complexity of the MEPS study design, it is necessary to account for the sampling strategy as well as the longitudinal nature of the data collection. To aid in the analysis of data across several years, the MEPS provides weight and variance estimation variables that must be applied when producing national estimates and appropriate estimates of variability for longitudinal analyses. Thus, all analyses conducted as part of this study use these statistical weights.

Demographic, environmental, and medical characteristics were compared between those with and without hearing impairment using *t* test and  $\chi^2$  test for continuous and categorical variables, respectively. The association between HL and PDE-5i use was estimated using logistic regression with and without adjustment for the characteristics given in the "Potential Confounders" subsection of the "Methods" section. *P* values of  $\leq .05$  (2-sided) were considered statistically significant.

## RESULTS

This analysis represents data on a total of 248 217 013 (11 525 unweighted) men 40 years or older in the United States from 2003 through 2006, approximately 62 million participants per year. These figures are comparable with US Census Bureau estimates for the male population 40 years or older during this same time period. The overall prevalence of HL was 17.9% and increased with age. The prevalence among those in their forties was 7.5%, and this increased to 15.0%, 24.4%, 32.9%, and 47.2% in subsequent decades. Approximately 2% of men reported having obtained a PDE-5i; use was lowest among those in their forties (0.8%), steadily increased until men were in their 60s (3.3%), and then subsequently declined to 0.5% for men 80 years or older. Among those reporting PDE-5i use, sildenafil was the most frequently used (80.3%), followed by vardenafil (20.2%) and tadalafil (12.8%).

**Table 1** presents demographic and health-related characteristics according to HL status. Those classified as hearing impaired were approximately 10 years older, more likely to be white, and had lower household incomes compared with those not classified as such. Those with hearing impairment were less likely to have worked

**Table 1. Sociodemographic, Health, and Behavioral Characteristics According to Self-Reported Hearing Impairment<sup>a</sup>**

Characteristic	Hearing Impairment		P Value
	Yes (n=9 125 761)	No (n=239 091 252)	
Age, mean, y	64.1	54.8	<.001
Race			
White	91.1	83.0	<.001
Black	4.9	10.8	
Other	4.1	6.2	
Household income <sup>b</sup>			
Low (<200%)	25.5	21.5	<.001
Middle (200% to <400%)	30.9	29.0	
High (≥400%)	43.6	49.5	
Occupation, ever			
Management	18.5	21.3	.01
Professional	16.7	17.3	.64
Service	10.2	11.1	.27
Sales	9.6	10.2	.51
Office/administrative	6.6	7.4	.21
Farming/forestry	1.3	1.1	.38
Construction	22.2	17.4	<.001
Transportation	24.0	22.1	.08
Military	3.4	1.7	.001
Current smoker, yes	23.4	23.6	.91
Diabetes mellitus, yes	16.8	10.5	<.001
Cardiovascular disease, yes	30.4	15.6	<.001
Ototoxic medication use	22.4	14.5	<.001

<sup>a</sup>Data are given as percentages except where noted.

<sup>b</sup>Income based on family income relative to the poverty line (based on family size and composition).

**Table 2. Prevalence of Hearing Impairment According to Phosphodiesterase Type 5 Inhibitor (PDE-5i) Use and Associated Odds Ratios (ORs) and 95% Confidence Intervals (CIs)**

PDE-5i Use <sup>a</sup>	Hearing Impairment, %		Unadjusted OR (95% CI)	Adjusted OR (95% CI) <sup>b</sup>
	Yes (n=9 125 761)	No (n=239 091 252)		
Use of any PDE-5i	3.0	1.4	2.16 (1.56-3.00)	2.23 (1.36-3.66)
Sildenafil (Viagra)	2.3	1.1	2.05 (1.42-2.98)	2.05 (1.23-3.43)
Tadalafil (Cialis)	0.4	0.2	2.62 (0.98-6.98)	1.40 (0.49-4.04)
Vardenafil (Levitra)	0.4	0.3	1.21 (0.55-2.69)	0.88 (0.35-2.22)

<sup>a</sup>Manufacturers' information: Viagra, Pfizer Inc, New York, New York; Cialis, Eli Lilly, Indianapolis, Indiana; and Levitra, Bayer Healthcare Pharmaceuticals, Montville, New Jersey, Schering-Plough, Kenilworth, New Jersey, and GlaxoSmithKline, London, England.

<sup>b</sup>Adjusted for age, race, household income, smoking, diabetes mellitus, cardiovascular disease, use of ototoxic medications, and occupation.

in the management or business field but more likely to have worked in the construction industry or have been in the military. There was no difference with respect to current smoking; however, individuals with hearing impairment were more likely to have diabetes mellitus, cardiovascular disease, or used ototoxic medications compared with those without such impairment.

**Table 2** presents the overall and medication-specific prevalence of PDE-5i use among those with and without HL. The use of any PDE-5i was more common among those with hearing impairment compared with those without (3.0% vs 1.4%); a similar pattern was observed for those taking specific PDE-5i medications, although the differences were most apparent for those taking sildenafil and tadalafil. The adjusted results indicate that those with HL had more than 2-fold increased odds

of PDE-5i use compared with those without HL. This association seemed to be limited to sildenafil use (odds ratio [OR], 2.05; 95% confidence interval [CI], 1.23-3.43); there was no significant association for tadalafil (OR, 1.40; 95% CI, 0.49-4.04) or vardenafil (OR, 0.88; 95% CI, 0.35-2.22).

#### COMMENT

In 2007, the FDA announced labeling changes for PDE-5i medications, including sildenafil, vardenafil, and tadalafil,<sup>5</sup> such that the risk of sudden hearing problems is more prominently displayed.<sup>5</sup> To my knowledge, prior to the current study, no epidemiologic studies had evaluated this relationship. The current findings suggest that men

40 years or older with self-reported hearing impairment were more than twice as likely to report PDE-5i use compared with those not reporting HL. This association persisted following adjustment for a number of potential demographic- and health-related confounding characteristics. Moreover, this relationship seems to be limited to sildenafil use, although an elevated, yet not statistically significant, association was also observed for tadalafil. The lower frequency of tadalafil and vardenafil use may have precluded the identification of similarly increased risks owing to limited statistical power. The association between PDE-5i use, specifically sildenafil, and sensory impairment is not novel. In 2005, following a small case series, the FDA required that PDE-5i users be warned about the risk of sudden-onset blindness or non-arteritic ischemic optic neuropathy (NAION).<sup>11</sup> A subsequent case-control study<sup>12</sup> reported no significant association between NAION and sildenafil and/or tadalafil use, although an increased risk was observed for those with a family history of myocardial infarction. A reanalysis of the data from this study revealed that any increased risk was limited to sildenafil use (G.M., unpublished data, 2009).

Given the dearth of published literature regarding PDE-5i medications and HL, it is difficult to place the results of the current study into context. One important consideration in evaluating the nature of this relationship is the existence of a plausible biological mechanism. It has been hypothesized that PDE-5i might cause HL owing to their ability to affect nasal physiologic characteristics and thus eustachian tube function. Specifically, PDE-5i use causes congestion of nasal erectile tissue that results in elevated middle ear pressure.<sup>13,14</sup> It has also been suggested that PDE-5i may intensify the effects of nitric oxide, which has been implicated in a number of otologic diseases, or simulate the effects via activated intracellular cyclic guanosine monophosphate (cGMP).<sup>7,8</sup> The PDE-5i function by blocking the degradation of cGMP, the accumulation of which induces gene expression via transcription factors by protein phosphorylation by specific kinases, which themselves have been associated with damage to cochlear hair cells.<sup>7</sup> To my knowledge, no study has provided evidence for or against these mechanisms. However, nitric oxide is increased following auditory organ injury, and high nitric oxide levels are associated with inner ear dysfunction<sup>15</sup>; increased nitric oxide production has also been observed in animals with HL.<sup>16-18</sup> In addition, high doses of sildenafil have been observed to induce hearing impairment in mice.<sup>8</sup> In a study<sup>13</sup> of 18 men using PDE-5i for erectile dysfunction, 4 showed a temporary decrease in hearing threshold, although no permanent deleterious effect was observed. Interestingly, it has been suggested that vardenafil might be useful in the treatment of tinnitus, although research has failed to support this proposal.<sup>19</sup>

Maddox et al<sup>7</sup> expressed several concerns that argue against a causal relationship between PDE-5i use and HL. These authors suggest that the published case reports of SSHL attributed to PDE-5i may simply reflect the natural incidence of this condition rather than excess risk posed by the use of these medications. In the context of

a case report or series that lacks a suitable comparison group, this is a reasonable concern. Another concern is the fact most cases reported in the literature have been of patients found to have unilateral HL. Yet HL attributable to the toxic effects of PDE-5i use would be expected to be bilateral. Finally, for several of the reported cases there is not a clear temporal relationship between the SSHL and PDE-5i use. Yet, for most (approximately 90%) of the cases reported by Maddox et al,<sup>7</sup> HL occurred within 24 hours of taking a PDE-5i, and of those, most cases occurred within 12 hours. Finally, the lack of information on potentially confounding characteristics has precluded definitive conclusions regarding causality.

The present study compared individuals with self-reported hearing impairment with those without such impairment and adjusted for the potentially confounding influence of demographic- and health-related characteristics. Thus, the concern that previously reported cases may simply reflect the background incidence of hearing impairment or confounding is diminished, although information on certain potential confounders was not available. My results suggest that the previously reported cases may be over and above the natural incidence and possibly attributed to PDE-5i use. However, a number of the concerns mentioned herein could not be resolved in the current study. First, the study design was cross-sectional, and thus I cannot evaluate the temporal relationship between the onset of HL in relation to timing, frequency, or duration of PDE-5i use; this is despite the longitudinal nature of MEPS. The structure of the questions regarding HL does not easily lend itself to the identification of incident hearing problems. Second, I did not have information on SSHL but instead focused on self-reported hearing impairment. Although those with SSHL are likely to be captured with questions about hearing impairment in general, it is more than likely that they represent the minority of those with self-reported HL. Given the observed results, if the association between PDE-5i use and SSHL is real, then it is either strong enough to overcome any misclassification or, and perhaps more plausibly, PDE-5i use is associated with hearing impairment in general as well as SSHL specifically. That said, there has been great debate regarding the usefulness of information regarding self-reported hearing impairment. It has been suggested that the sensitivity of self-reported HL is low (ie, 41%-65%) compared with audiometric measurement,<sup>1</sup> and that self-reported prevalence estimates may vary owing to the nature of the question being asked.<sup>10</sup> However, others have been more optimistic regarding the usefulness of self-reported hearing impairment for documenting prevalence and trends<sup>20,21</sup> although greater caution is warranted when using self-report for etiologic associations.<sup>21</sup> Ultimately, in the context of the present study the main concern is bias, and there is no reason to expect PDE-5i users to differentially report HL; particularly because at the time the data used in this study were collected, information regarding the potential relationship between PDE-5i use and HL was not widespread. Moreover, risk factors for HL demonstrate a high degree of consistency whether impairment is defined via self-report or audiometry<sup>22,23</sup> and have



been shown to have equivalent reductions in quality of life.<sup>24</sup> Thus, whether defined based on audiometry or self-report, the etiology of HL is likely to be similar.

Based on several case reports, the FDA required the manufacturers of PDE-5i medications to warn users regarding the potential for sudden-onset HL. While case reports and the hypotheses they generate are often useful in laying the foundation for future epidemiologic studies, they provide limited evidence for causality. The results of the current study in conjunction with a plausible biologic mechanism lend support to the FDA's decision to warn patients about the potential risk posed by PDE-5i use. However, this support must be tempered in light of the limitations mentioned herein. The largely irreversible nature of HL and its impact on quality of life underscore the need for additional research regarding the etiologic role of PDE-5i use. In the interim, it is prudent that patients using these medications, specifically sildenafil, be warned about the signs and symptoms of hearing impairment and be encouraged to seek immediate medical attention to potentially forestall permanent damage.

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