ISMP INSTITUTE FOR SAFE MEDICATION PRACTICES
QuarterWatch
Monitoring FDA MedWatch Reports

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SAFETY PERSPECTIVES IN THIS ISSUE

Executive Summary

In this issue we identify major differences in reports of cancer associated with drugs for psoriasis, a common skin disorder affecting an estimated 7.5 million people. While corticosteroid and other topical drugs are sufficient for many cases, potent immunosuppressant drugs are used in increasing numbers. In this report we also provide new evidence that drugs for erectile dysfunction and pulmonary arterial hypertension can cause deafness or sudden hearing loss.

QuarterWatch™ is an independent publication of the Institute for Safe Medication Practices (ISMP) that monitors all adverse drug event reports submitted to the U.S. Food and Drug Administration. We analyze computer excerpts from the FDA Adverse Event Reporting System (FAERS). These reports (best known as MedWatch reports) are a cornerstone of the nation's system for monitoring the safety of prescription drugs after FDA marketing approval.

In the third quarter of 2015, the FDA received 332,226 new adverse drug event reports, a 31.2% increase over the previous calendar quarter, and a 59.7% increase from the same quarter one year earlier. The large increase in reports consisted almost entirely of non-serious events from drug manufacturers. The key subset of serious events occurring in the U.S. in fact declined 2.2% from 78,854 reports in Q2 to 77,117 in Q3.

The 190,911 reports about non-serious adverse drug events were of generally poor quality, with 72% lacking information about one or more of the following: age, gender, or an event date. Consumers were the original source for 80% of these cases, and the leading complaint was that the drug was ineffective.

Ustekinumab (STELARA) Leads Psoriasis Drugs in Cancer Reports

Reddened patches of skin capped with a silvery scale of dead cells are one typical manifestation of psoriasis. Because the disorder has an autoimmune component, the more serious cases are often treated with drugs targeting different elements of the human immune system. But typically with immunosuppression, the risk of cancer also increases. We evaluated reports of cancer and benign tumors in 38,952 newly reported cases of all types of adverse events in the psoriasis patient population. Apremilast (OTEZLA), a new psoriasis drug without known immunosuppressant properties, was used as the reference drug.

The strongest association was for ustekinumab (STELARA) a biological product that inhibits Interleukin 12 and 23. The odds of a cancer case being reported for ustekinumab were 15 times higher ($p < 0.001$) than

for the reference drug. A strong signal was also observed for immunosuppressant biological products that block tumor necrosis factor (anti-TNF). The odds of a cancer case were 5.3 times higher ($p < 0.001$) than the reference drug. We saw no signal for secukinumab (COSENTYX), the drug that binds to Interleukin 17a, but our sample of cases for this biological product was too small for a conclusive evaluation.

Assessing the cancer risks of drugs is scientifically challenging using any of the accepted methods. But by analyzing a large group of cases (n = 38,952) in the same patient population using standard event definitions, this report provides the first comparative assessment of cancer risks of these drugs. Our methods and results are described in detail later in this report.

Erectile Dysfunction Drugs and Sudden Hearing Loss

We found new evidence that tadalafil (CIALIS) and sildenafil (VIAGRA) can cause sudden loss of hearing in one or both ears. Drugs that inhibit phosphodiesterase 5 (PDE5) are established treatments for both erectile dysfunction and pulmonary hypertension. Tadalafil is also approved for benign prostatic hyperplasia (BPH). Early reports of isolated cases of hearing loss began to appear in 2007, and the FDA required a cautiously worded warning with the key qualification that a causal relationship had not been proven.

To assess this risk, we selected all cases for any of the PDE5 drugs in the most recent 12 months and used propensity score matching to select a group of otherwise similar cases for comparison. The endpoint was any report term containing sudden hearing loss or any preferred term including the word *deafness*. Reports of this adverse event were rare—we found 214 reports among our 50,879 study cases—but the odds of hearing loss report among the PDE5 drugs were 21.5 times higher than otherwise-similar comparators. Tadalafil had a disproportionately large effect on the results, both in the number of cases and size of the effect (OR 29.9, $p < 0.001$). Also, there were not enough cases to evaluate vardenafil (LEVITRA) separately.

Adverse Event Reporting System

Large Report Increase Not a Safety Signal

Changes in the number of adverse event reports often provide important signals of emerging drug risks, and over time provide a rough gauge of overall trends in drug safety. In this quarter, however, one of the largest increases in recent years reflected only a surge in reports that were not serious and mostly involved events such as drug ineffective, fatigue, nausea, and headache.

Separately, in February the QuarterWatch team published in the journal *Pharmacoepidemiology and Drug Safety* a more comprehensive assessment of the completeness of reports in 2014, focusing on events that were serious. Among manufacturer reports, 37.9% lacked age, 14.2% lacked gender, and 46.9% omitted an event date. By comparison, 86.2% of direct reports to the FDA contained all three basic elements of report information.

These results further underline the need for the FDA to modernize its adverse event reporting regulations and guidances to focus industry resources on gathering more complete, higher quality information in a more systematic way.

About QuarterWatch Data

Our findings should be interpreted in light of the known limitations of a reporting system that does not collect data systematically. The submission of an individual report does not in itself establish that the suspect drug caused the event described—only that an observer suspected a relationship. While the sheer numbers

of case reports have scientific weight, because of variation in reporting rates, they reveal little about how frequently the events occur in the broader patient population. More complete disclaimers and descriptions of our criteria are included in the Methods Summary section of this report. A disclosure statement expands our description of this project and its staff.

Conclusions

Biological products that target different elements of the immune system are being used for a growing spectrum of medical disorders, including psoriasis, rheumatoid arthritis, multiple sclerosis, Crohn's disease, ankylosing spondylitis, and lupus. While clinical trial tools for assessing drug benefits are sophisticated and well developed (when used), the evaluation of cancer risk is more primitive. Animal carcinogenicity findings—when risk is found—typically trigger a debate about whether the findings apply to humans. Registries and long-term extensions of clinical trials usually lack a meaningful comparison group and have high dropout rates. The relative scarcity of definitive findings about the cancer risks of drugs should not be construed as evidence that the risks are minor or unimportant. In the case of ustekinumab, our main report shows that evidence from the mechanism of action, animal studies, and clinical trials also provide evidence of increased cancer risk.

Our analysis of sudden hearing loss and the PDE5 inhibitor drugs confirms and extends the evidence that these drugs are a causal agent. It is noteworthy that a medically significant side effect of a drug taken each year by millions of people remained uncertain more than 25 years after the approval of the first drug in this class. Earlier efforts to pinpoint this side effect were complicated by the problem that hearing loss in older men is very common, absent drug treatment. Our analysis avoided this pitfall by a focus on cases that had sudden onset, or were extensive enough to justify the term *deafness*.

The FDA's adverse event reporting system remains the primary tool for identifying adverse effects of drugs after marketing. This report identifies two specific and clinically significant adverse effects that were not clearly understood before marketing approval. These findings further illustrate the need for the FDA to modernize FAERS.

QUARTERWATCH PROJECT TEAM

Thomas J. Moore
Senior Scientist, Drug Safety and Policy, ISMP

Michael R. Cohen, RPh, MS, ScD (hon)
President, ISMP

Curt D. Furberg, MD, PhD
Professor Emeritus of Public Health Sciences,
Wake Forest University School of Medicine

Donald R. Mattison, MD, MS
Chief Medical Officer
Risk Sciences International

MEDIA INQUIRIES

Renee Brehio
ISMP Public Affairs
rbrehio@ismp.org 704-831-8822

CORRESPONDENCE

Thomas J. Moore
QuarterWatch Project Director
Institute for Safe Medication Practices
101 N. Columbus Street, Suite 410, Alexandria, VA 22314
tmoore@ismp.org

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This revised edition reflects a correction listed at http://www.ismp.org/quarterwatch/clarifications.aspx

Methods Summary

QuarterWatch monitors the safety of prescription drugs through analysis of adverse drug events reported to the FDA by consumers and health professionals, either directly to the agency or through drug manufacturers. The agency releases computer excerpts for research use on a quarterly basis, and these case reports are our primary data source.[1] A full description of our methodology is available on the QuarterWatch pages of the ISMP web site (http://www.ismp.org/QuarterWatch/detailedMethods.aspx).

The severity of the adverse event was classified as serious if the case report specified an outcome of death, disability, hospitalization, required intervention to prevent harm, was life threatening, or had other medically serious consequences. Cases without these outcomes were classified as not serious, and all new cases were included in this analysis unless indicated otherwise. Earlier QuarterWatch issues have focused primarily on a subset of adverse events, those that are domestic and coded with serious outcomes. We continue to monitor domestic, serious reports as an important category of the newly released case reports.

In these data, the adverse events reported are described by medical terms selected from the Medical Dictionary for Regulatory Activities (MedDRA), a terminology developed by the pharmaceutical industry to describe adverse events in clinical studies and postmarketing reports.[2] The MedDRA terminology also defines broader categories of adverse events that can include any of a list of more specific and related medical terms. We use these categories, called Standardized MedDRA Queries (SMQs), to identify possible cases of some adverse events.[3] We also group adverse event terms using a MedDRA category called High Level Terms (HLTs) that also combine several related but more specific medical terms. High Level Group Terms (HLGTs) combine several related HLTs, and System Organ Classes combine the terms into 26 categories. The QuarterWatch database was updated in November 2015 to MedDRA version 18.1.

Measuring the strength of the association between a therapeutic drug and an adverse event requires a comparison group. Several established statistical methods simply select all other reports in the period as the comparator.[4–6] However, “all other” reports embrace many different kinds of drugs, medical disorders, and patient populations. In this issue, we used propensity score matching (nearest neighbor method) [7] to select a comparison group of reports (on a 4:1 ratio) that more closely resembles the cases under study. The reports were matched for similar report source (e.g., foreign, health professional, consumer), report outcome (e.g., death, hospitalization), and completeness (not missing age or gender). This approach was used as the primary analysis for the hearing loss cases and as a sensitivity analysis for the psoriasis products and reports of cancer. We used logistic regression to assess the resulting association, which produces an odds ratio (endpoint cases/non-endpoint cases) to produce an estimate of risk, 95% confidence intervals, and a probability the result occurred by chance. To compare relative risk to odds ratio, consider six-sided dice. The “risk” of rolling a six is 1 in 6 (success/all outcomes) the odds are 1 in 5 (success/fail).

To provide a broader perspective on the adverse events reported, we assess the patient exposure to drugs on the basis of dispensed outpatient prescription data provided by IMS Health Inc. The data we rely on are an estimate of total non-governmental prescriptions dispensed through retail and mail channels. Our agreement with IMS includes the following disclaimer:

“The statements, findings, conclusions, views, and opinions contained and expressed in QuarterWatch are based in part on data obtained under license from an IMS Health Inc. information service called the National Prescription Audit™ for 2015 (All Rights Reserved). Such statements, findings, conclusions, views, and opinions are not necessarily those of IMS Health Incorporated or any of its affiliated or subsidiary entities.”

Events in QuarterWatch are attributed to the product identified as the primary suspect drug in the case report. The drug names are standardized to drug ingredient names based on the National Library of Medicine’s RxNorm terminology.[8] When cited in the text, tables, or charts, the brand name of drugs used is the one most frequently indicated on the case reports but may account for a small or large share of the prescriptions dispensed. Unless specified, QuarterWatch does not distinguish dose, route of administration, or extended release and other preparations.

Results

Report Trends

The overall numbers of adverse drug event reports submitted to the FDA continued to expand rapidly. In the third quarter of 2015, the agency received 332,226 new reports of adverse drug events, an increase of 31.2% from the previous quarter and 59.7% from the third quarter of 2014. In five years the total volume of reports has increased more than 2-fold, from 131,453 in 2010 Q3.

However, in the latest quarter of data the increase was explained by a surge in reports from drug manufacturers about domestic events that were not serious. Non-serious domestic reports totaled 190,911 new cases, an increase of 83,632 (78%) cases from the previous quarter and a 1.5-fold increase from the same quarter in the preceding year. The reports were mostly of low quality, with 72% lacking information about one of the following basic elements: age, gender, or event date. The quarterly total was also increased because after three years, companies may report non-serious events on an annual rather than quarterly basis.

We examined the non-serious cases to investigate the content and cause of so many reports. The companies are shown in Table 1. All those listed are large pharmaceutical companies except Jazz Pharmaceuticals, a specialty manufacturer that markets sodium oxybate (XYREM). Because of its abuse potential, the FDA requires the company to contact every patient every month.[9]

The large totals for Eli Lilly were primarily explained by reports submitted on an annual basis for two products: insulin with 23,737 non serious reports, and duloxetine (CYMBALTA), with 12,205.

Table 1. Leading manufacturers submitting non-serious reports, 2015 Q3

Company	Reports	pct
Eli Lilly and Co	71,360	(38.1)
Janssen	13,122	(7.0)
Roche	12,841	(6.9)
Amgen	9,686	(5.2)
Jazz	8,442	(4.5)
Pfizer	6,960	(3.7)
Total non-serious	190,911	

The largest single complaint in the non-serious reports was that the drug was ineffective (n = 15,636). Other prominent complaints included nausea (n = 11,089), fatigue (n = 9,331), and headache (8,976). In a previous issue of QuarterWatch[10] we have described the disconnect between outdated adverse event reporting regulations and increasing direct contact by manufacturers with individual patients for educational and marketing purposes.

In a separate study published in February [11], we focused on the completeness of serious reports received by the FDA during 2014. Even for serious cases, manufacturer report quality was poor: Only 41.4% of manufacturer reports contained basic information (such as age, gender, event date), compared to 86.2% of reports volunteered directly to the FDA by consumers and health professionals.

Ustekinumab (STELARA) Leads Psoriasis Drugs in Cancer Reports

We identified large differences among drugs when we compared the incidence of reported cancers and benign tumors for five treatments for psoriasis. This chronic skin disorder affects an estimated 7.5 million persons in the U.S., and approximately 2% of the worldwide population.[12] [13] The most common forms of psoriasis involve thickened patches of reddened skin covered with a white scale of dead cells. Other forms of psoriasis appear as pustules, or as widespread areas of inflamed skin. Approximately 30% of cases progress to psoriatic arthritis. Psoriasis can appear as lesions on the elbows, knees, and scalp; however, it can extend to much larger areas of the body surface. It has both genetic features and an autoimmune component.

The cancer risks were investigated because of the growing and widespread use of drugs and biologic products that suppress some component of the immune system. To assess this risk, we selected every case

reported in the 12 months ending September 30, 2015, in which any drug taken was reported as being administered for psoriasis. We excluded cases for drugs sometimes used to treat psoriasis where the diagnosis or indication was for some other medical condition, or was not specifically stated. This resulted in 38,952 cases making up the psoriasis patient population for study. As an additional comparison we used propensity score matching to select four similar comparators without the disorder for each psoriasis patient case. (See Methods Summary for explanation.)

Drugs Identified

The psoriasis drugs were grouped primarily by mechanism of action into these categories:

- **Interleukin 12/23 inhibitor**. Ustekinumab (STELARA) is the only approved drug with this immunosuppressant mechanism of action.
- **Anti-Tumor Necrosis Factor (anti-TNF).** The five agents that inhibit TNF were etanercept (ENBREL), infliximab (REMICADE), adalimumab (HUMIRA), certolizumab (CIMZIA), and golimumab (SIMPONI).
- **Interleukin 17a inhibitor.** Secukinumab (COSENTYX) is the only approved immunosuppressant that binds to this signaling protein.
- **Phosphodiesterase inhibitor 4 (PDE4).** Apremilast (OTEZLA) differed from the other agents in that it had no identified immunosuppressant properties.
- **All Other.** This miscellaneous category was primarily composed of generic immunosuppressant drugs, cyclosporine and methotrexate.

Neoplasm Endpoints

We identified 1,315 cases (3.4%) among psoriasis patients indicating a malignant or benign tumor, defined as any MedDRA term in the Neoplasms System Organ Class (SOC). The most frequent terms are shown in Table 2.

Table 2. Frequently reported neoplasms in psoriasis cases*

Preferred Term	Count,pct	
Basal Cell Carcinoma	85	(5.7)
Breast Cancer	68	(4.6)
Neoplasm Malignant	57	(3.8)
Skin Cancer	56	(3.8)
Squamous Cell Carcinoma	55	(3.7)
Prostate Cancer	51	(3.4)
Malignant Melanoma	47	(3.2)
Lung Neoplasm Malignant	41	(2.8)
Skin Papilloma	35	(2.4)
Lymphoma	34	(2.3)
Squamous Cell Carcinoma of Skin	31	(2.1)
Renal Cancer	23	(1.5)
Colon Cancer	22	(1.5)
Bladder Cancer	21	(1.4)
Uterine Leiomyoma	20	(1.3)

* Only terms with ≥ 20 mentions shown. Report can include > 1 term.

Almost all the cases were identified as active cancers, with the notable exception of skin papilloma (n = 35). Non-melanoma skin cancers formed the largest group (n = 254), followed by breast and prostate cancers.

Basis of Comparison

To compare reported cancer cases among the five groups of psoriasis drugs, we selected apremilast as the reference drug because as a PDE4 inhibitor it was the only one of the group without any identified immunosuppressant properties. We then used logistic regression to calculate the odds ratio for the other drugs. The results are shown in Table 3.

Table 3. Neoplasm reports for psoriasis drugs

Drug group	Neoplasm* cases,pct		Total cases
Interleukin 12/23	296	(9.1)	3,250
Anti-tumor necrosis factor (TNF)	882	(3.4)	25,920
Other psoriasis	85	(7.7)	1,105
Interleukin 17a	2	(0.3)	768
Phosphosdiesterase 4 (PDE4)	50	(0.7)	7,547

*Neoplasm, benign and malignant MedDRA System Organ Class

Odds ratio for neoplasm cases

	Unadjusted OR (95% CI)**	Adjusted* OR (95% CI)
Interleukin 12/23	15.0 (11.1-20.3)	18.2 (12.4-26.7)
Anti-TNF	5.28 (4.0-7.0)	4.9 (3.4-7.0)
Other psoriasis	12.5 (8.8-17.8)	11.9 (7.7-18.4)
Interleukin 17a	.39 (NS)	.29 (NS)
PDE4 (reference)	1	1

* adjusted for age and gender

** p < 0.001 unless NS = not statistically significant

Ustekinumab Signal

In this primary analysis, ustekinumab, the Interleukin 12/23 inhibitor, had the strongest association with reported cancers (OR 15.0 95% CI 11.1-20.3), and almost a three-fold higher risk than the anti-TNF agents. However, the anti-TNF biological products still showed a 5-fold risk compared to apremilast, the phosphodiesterase 4 inhibitor without known immunosuppressant properties. The cancer signal for ustekinumab was stronger when the psoriasis cases were adjusted for differences in age and gender with an odds ratio of 18.2. However, the adjusted estimate excluded numerous cases where age or gender was not reported and therefore assesses smaller amounts of data.

Sensitivity Analysis

In additional comparisons we used propensity score matching to compare the psoriasis cases to reports for other drugs and indications, but with similar report characteristics and completeness. The psoriasis cases

were matched on a 4:1 ratio using the nearest neighbor method. This comparison group, however, included chemotherapy agents and other kinds of immunosuppressant drugs. In this analysis, ustekinumab association remained strong (OR 5.2 95% CI 4.6 - 5.9), as did the anti-TNF agents (OR 1.8 95% CI 1.7-2.0). The odds ratios for both groups of agents were higher when adjusted for age and gender. The ustekinumab findings were not sensitive to statistical method.

Limitations

Although the number of study cases was substantial (n = 38,952), they were limited to those reported for the first time in the 12 months ending in 2015 Q3. In addition, there were too few cases for secukinumab, the Interleukin 17a agent, for a meaningful evaluation; its differences with comparators were not statistically significant. Also, this analysis did not measure duration of treatment or medical history that might include prior exposure to other immunosuppressant agents. Finally, because a large majority of adverse events are never reported, these data do not provide a reliable estimate of the incidence of cancer. For ustekinumab, the drug with the strongest association with cancer, we also evaluated other sources of information about its potential cancer risk.

Focus on Ustekinumab

Ustekinumab was the first agent approved to block the effect of two elements of the immune system, Interleukin 12 and 23, by binding to a common site.[14] Despite a drug with a novel immunosuppressant effect, the FDA did not require standard animal carcinogenicity assays.[15] However, the animal model information, primarily from mice, suggested a cancer risk. Interleukin 12 itself has an anti-tumor effect; therefore, blocking it might permit cancer growth. Mice engineered to have no Interleukin 12 or 23 developed bigger skin cancers more rapidly when exposed to UV radiation than did mice with normal Interleukin 12/23.

The largest, longest clinical trial of ustekinumab excluded patients with any history of most cancers, and those with a history of non-melanoma skin cancer within the last 5 years.[16] Nevertheless, at 100 weeks of followup 30 malignancies had been reported in 26 patients among approximately 1,230 patients originally enrolled. These included three cases of prostate cancer, two melanomas, and single cases of breast, colon, endometrial, and pancreatic cancer. In a broader assessment of all treated patients, the company reported that 3.2% of patients developed cancer. Interpreting these results is difficult because of lack of comparators. In the largest trial the placebo patients were crossed over to active treatment at 12 weeks.[14]

An FDA-mandated registry provided follow-up information on 12,093 patients taking ustekinumab or other immunosuppressant drugs.[17] Although 1.4% of the ustekinumab patients developed cancer, the results could not be interpreted. The cancer total excluded the most common cancers (and those expected from animal studies), basal cell and squamous cell. It excluded patients with psoriasis but not treated with a potent immunosuppressant. Cancers were counted as occurring for ustekinumab even though 18% dropped out, 46.0% took an anti-TNF drug for a median of 1 year, and 23% took either methotrexate or cyclosporine, themselves immunosuppressant drugs with cancer risks.

Company View

Janssen, the manufacturer of ustekinumab, disagreed with our assessment of the drug's cancer risks. We shared preliminary event counts for ustekinumab with Janssen and sought a response. The company said the product had a warning about a theoretical risk of malignancy, but noted it does not believe "any events have been causally associated with the use of [ustekinumab]." The company cited its large registry study[17] (reviewed in the preceding paragraph), in which rates of malignancy for ustekinumab were comparable to other immunosuppressant treatments in the study.

Conclusions

In this study three immunosuppressant treatments for psoriasis were associated with unexpectedly large numbers of reported cancers. The signal was strongest and most robust for ustekinumab. Apremilast, the

treatment without identifiable immunosuppressant effects, was not associated with reports of cancer, and there were insufficient data to evaluate secukinumab, the IL-17a inhibitor.

Erectile Dysfunction Drugs and Sudden Hearing Loss

Phosphodiesterase 5 inhibitor (PDE5) drugs revolutionized the treatment of male erectile dysfunction with the approval of sildenafil (VIAGRA) in 1998, followed by tadalafil (CIALIS) and vardenafil (LEVITRA) in 2003. Medical use has been expanded to other indications. Tadalafil is approved for benign prostatic hyperplasia, and both sildenafil and tadalafil are approved for pulmonary arterial hypertension. In the years following approval, reports of sudden hearing loss and other forms of impaired hearing began to appear.[18] Nevertheless, the current prescribing information warnings communicated substantial uncertainty, specifically noting that impaired hearing was common in older men, and expressing the view that a causal relationship had not been established. In some studies, the prevalence of impaired hearing in older persons was around 17%. After observing a substantial group of new adverse event reports about hearing loss in the most recent 12 months of data, we investigated whether the PDE5 drugs were associated with those reports.

For this assessment we selected every new adverse event report for any of the PDE5 drugs submitted to the FDA in the four calendar quarters ending 2015 Q3. The endpoint was any MedDRA term indicating deafness or sudden hearing loss. For comparison with other drugs we used propensity score matching to select, with a 4:1 ratio, reports for other drugs that were otherwise similar in types of reports, health outcomes, completeness, and report source. The drugs and comparators are shown in Table 4. The matched reports were similar to the PDE5 drugs, except for gender, where as expected far more males were identified (86% v, 35%). In Table 6 below the results are adjusted for gender differences.

Table 4. Report characteristics for PDE5 drugs and matched cases

	PDE5 drugs		Matched (4:1)	
Total cases	10,174		40,696	
Age (median, IQR)*	59	(51-68)	57	(42-68)
Male gender, No.,pct**	8,455	(86)	13,155	(35)
Missing age or gender	4,705	(46.2)	18,820	(46.2)
Report code, No.,pct				
Direct	98	(1.0)	392	(1.0)
Expedited	1,995	(19.6)	7,980	(19.6)
Periodic	8,081	(79.4)	32,324	(79.4)
Report source, No.,pct				
Consumer	8,564	(84.2)	34,256	(84.2)
Foreign	695	(6.8)	2,780	(6.8)
Health professional	858	(8.4)	3,432	(8.4)
Lawyer	57	(0.6)	228	(0.6)

PDE5 = sildenafil,tadalafil, vardenafil.

* Interquartile range. ** Pct excluded missing values.

Terms Identified

In this data set reports of deafness or sudden hearing loss were rare, totaling just 214 (0.4%) identifiable cases among a total of 50,870 event reports. The Preferred Term "Deafness" accounted for the majority of reports (n = 121). The frequency of the MedDRA preferred terms are shown in Table 5. Although hearing loss is common among older persons, these data show that these deafness terms are rarely reported as an adverse event with an identifiable suspect drug.

Table 5. Frequency of deafness terms

Preferred term	Count,pct*	
Deafness	121	(56.5)
Deafness unilateral	50	(23.4)
Sudden hearing loss	22	(10.3)
Deafness bilateral	10	(4.7)
Deafness transitory	8	(3.7)
Deafness neurosensory	6	(2.8)

*Of all endpoint cases (n = 214). More than one term can appear in one case.

Results

We used logistic regression to calculate the odds ratio for a deafness report for the PDE5 drugs compared to the matched comparators, and then examined each drug separately. The results are shown in Table 6. This assessment reveals a strong association between the drugs and reports of deafness and sudden hearing loss (OR 21.5, 95% CI 14.9-31.1). However, differences among drugs were observed as shown in the table. Notably there were no deafness reports for vardenafil, which we attributed to the small number of reports for the drug overall (n = 116). The results for the drug group were primarily driven by the cases for tadalafil (OR 29.5 95%CI 20.3-42.9).

Table 2. Association of PDE5 drugs with deafness reports

	Deafness cases	All cases	Unadjusted OR (95% CI)	Adjusted* OR (95% CI)
All PDE5	180	10,174	21.5 (14.9-31.1)	16.6 (10.9-25.2)
Specific drug				
Tadalafil	152	6,308	29.5 (20.3-42.9)	23.3 (15.2-35.8)
Sildenafil	28	3,750	9 (5.5-14.9)	6.9 (3.9-11.9)
Vardenafil	0	116	0, (NS)	0 (NS)

Reference= 1: Propensity score matched cases (4:1)

*Adjusted for gender. NS = not statistically significant.

Sensitivity Analysis

To assess whether these findings were robust, we adjusted the odds ratio to account for the differences in gender between the PDE5 drugs and the selected comparators. (But this analysis excluded cases where gender was not reported.) As shown above, the adjusted odds ratios were reduced modestly. In addition, we also compared the PDE5 drugs and comparators using the broadest possible definition of hearing impairment, the MedDRA System Organ Class for any ear or labyrinth disorder. With this broad definition (which included terms such as tinnitus, vertigo, and ear pain), the relationship remained but the odds ratio for the group was reduced (OR 2.8 95% CI (2.4-3.2)).

Limitations

While these results establish a strong association between the PDE5 drugs and reports of hearing loss (especially for tadalafil), adverse drug events do not provide an estimate of how frequently they might be occurring in a broad patient population. These data also lacked information about the time of onset of hearing loss, and follow up to assess whether the hearing loss resolved when treatment was discontinued. Nevertheless, the results confirm and extend the findings of previous studies. While previously published analysis noted below reported a class effect of the drugs, there were not enough cases for vardenafil to support a separate analysis.

Other Evidence

Two previous investigations of adverse drug event reports have found a relationship between PDE5 drugs and sudden hearing loss. In 2007 the FDA reported assessing 29 cases of sudden hearing loss including 10 cases where the event occurred after the first dose.[19] In 2011, a British research term evaluated 47 cases obtained from the literature and from regulatory agencies in North America, Europe, and Australia.[20] They reported cases for all three PDE5 drugs and found 88% of the cases occurred in only one ear, with most occurring within 24 hours of ingesting the drug in new or continued intermittent use. In addition, the FDA identified 5 cases among 660 patients in a clinical trial of sildenafil for pulmonary arterial hypertension.[19] Most events, however, occurred in an extension of a clinical trial without a comparison group. The results were notable because tadalafil was taken continuously rather than intermittently. A mechanism of action is less clear, and a 2009 summary of new and previous case reports assessed the literature on mechanism and found several possible but no clearly established molecular pathways.[21]

Conclusions

These new data extend and confirm the association between sudden hearing loss and PDE5 agents. Evidence to support a causal relationship includes evidence from clinical trials, case reports of immediate onset, and adverse drug events from multiple countries over many years' time, and includes analysis of individual cases and the quantitative assessment reported here. However, the evidence in this study was insufficient to evaluate vardenafil independent of drugs with a similar mechanism of action.

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QuarterWatch Team and Funding Sources

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Thomas J. Moore serves as a part-time project director for QuarterWatch. He has developed and maintains the master adverse event database that serves as the primary data source for the publication and conducts the primary analysis for each issue. Mr. Moore receives an honorarium from ISMP for each issue, with the remaining work being on a volunteer basis. He is also a lecturer in the Department of Epidemiology and Biostatistics in the Milken Institute School of Public Health at The George Washington University. Mr. Moore also conducts and publishes other independent studies in the peer-reviewed scientific literature and works as a consultant on drug safety issues, doing business under the name Drug Safety Research. He was a consulting expert to the Attorney General of the State of Texas in a Medicaid fraud lawsuit against Johnson & Johnson regarding the antipsychotic drug Risperdal (risperidone), and was an expert witness for the United States Army in connection with a criminal case involving Chantix (varenicline). He was a consulting expert for plaintiffs in the civil litigation regarding varenicline. In 2012 he was a consulting expert for the plaintiffs in the Celexa and Lexapro Marketing and Sales Practices Litigation. He also conducts confidential assessments for attorneys inquiring about the safety profiles of drugs.

Curt D. Furberg, MD, PhD is a Professor Emeritus of Public Health Sciences at Wake Forest University School of Medicine and serves as senior medical adviser to QuarterWatch. He receives no compensation for his work in assessing scientific evidence, defining safety issues, shaping the written report, and communicating with the FDA and others about QuarterWatch findings. He continues to have a research role at Wake Forest and has published more than 450 peer-reviewed scientific articles. An expert on clinical trials of drug treatments, Dr. Furberg is author of a major textbook on that subject, and has worked for the National Institutes of Health and the pharmaceutical industry as an investigator in clinical drug research. In the past 4 years he has given expert testimony or depositions in cases involving COX-2 inhibitors, Vytorin (ezetimibe-simvastatin), Pradaxa (dabigatran), and incretin-based medications. Dr. Furberg is a member of the British Medical Journal Advisory Board.

Donald R. Mattison, **MD, MS** is a retired captain in the United States Public Health Service who has held senior positions at the National Institutes of Health and in graduate public health education. He is currently chief medical officer and senior vice president of Risk Sciences International in Ottawa, Canada, and associate director of the McLaughlin Centre for Population Health Risk Assessment at the University of Ottawa. He is author of more than 200 peer-reviewed scientific studies and is an elected member of the National Academy of Medicine (formerly the Institute of Medicine), the Royal Society of Medicine, the New York Academy of Medicine, and the American Association for the Advancement of Science. Risk Sciences International is a consulting company, established in partnership with the University of Ottawa, specializing in the assessment, management, and communication of health and environmental risks. The company has clients in government, industry, and academia, including Health Canada and the FDA.

Michael R. Cohen, RPh, MS, ScD (hon) is founder and President of ISMP and guides the overall policies and content of QuarterWatch. He also edits the other ISMP newsletters and is author of the textbook *Medication Errors*. He has served as an advisor and consultant to the FDA, and for his work in medication safety was recognized as a MacArthur Fellow by the John D. and Catherine T. MacArthur Foundation. Dr. Cohen receives a regular salary as president of ISMP and does not engage in outside consulting or legal testimony.