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Phosphodiesterase-5 (PDE-5) Inhibitors and Ototoxicity: A Systematic Review

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Objective: This study explores the current literature regarding associations between phosphodiesterase-5 (PDE-5) inhibitors and ototoxicity and provides a detailed summary and discussion of the findings.
Data Sources: A comprehensive electronic search of PubMed/MEDLINE, Scopus, and Cochrane Library for studies published from database inception through March 21, 2018.
Study Selection: Basic science articles, epidemiological studies, randomized controlled trials, cohort studies, case reports, reviews, meta-analyses, press releases, and newsletters were included. The PRISMA search strategy was used to select papers. Search terms are included in the appendix (http://links.lww.com/MAO/A733).
Results: Twenty-two articles met the inclusion criteria. Among case reports, there were a total of nine patients, all male, with an average age of 57.4 years (37–79 years, SD = 13.87 years). Of the cases of hearing loss, 25% (2/8 cases) were bilateral and 75% (6/8) were unilateral; 22% (2/9) were associated with tinnitus; and 33% (3/9) had accompanying vestibular symptoms (including vertigo and dizziness). Among multipatient studies, all prospective studies failed to find a significant association between ototoxicity and PDE-5 inhibitor use. Results of the retrospective studies were also heterogeneous. Many key molecules in the PDE-5 inhibition pathway have been demonstrated to exist in the cochlea. However, mirroring the clinical studies, the basic science mechanisms have suggested both ototoxic and otoprotective effects.
Conclusions: Currently, the literature is inconclusive regarding the interaction between PDE-5 inhibitor use and ototoxicity. Future study such as a double-blinded placebo controlled randomized trial with audiometric assessment would provide more sound evidence. Similarly, a unified molecular model is necessary. **Key Words:** Cialis—Vardenafil—Erectile dysfunction (ED)—Levitra—Ototoxicity—Phosphodiesterase-5 (PDE-5) inhibitor—Pulmonary hypertension—Sildenafil citrate—Sudden Sensorineural hearing loss—Tadalafil—Tinnitus—Viagra.

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INTRODUCTION

Sildenafil citrate (Viagra and Revatio, Pfizer) is a phosphodiesterase type 5 (PDE-5) inhibitor and is frequently prescribed for erectile dysfunction (ED) and pulmonary hypertension (PH). Since its commercial introduction two decades ago, there have been many reported ototoxic events associated with the drug, including sudden sensorineural hearing loss (SSNHL) (1). Hearing loss of >30 decibels (dB) at three sequential frequencies occurring over a period of three days defines SSNHL (2). Since its commercial introduction, hypoacusis, tinnitus, and vestibular disorders have been reported to a significant degree (1). Other PDE-5 inhibitors including tadalafil (Cialis, Eli Lilly) and vardenafil (Levitra, GlaxoSmithKline) have been linked with similar adverse events. Since 2007, the Food and Drug Administration (FDA) has mandated that all PDE-5 inhibitors display a prominent warning on labels stating the potential risk of developing sudden hearing loss as a side effect (1).

The FDA Adverse Events Reporting System (AERS) Public Dashboard reports 645, 112, and 441 cases of ''ear and labyrinth disorders'' reported after ingestion of Viagra, Levitra, and Cialis, respectively. Reported ototoxic events increased between 2007 and 2010 when compared to the years prior and after this period (Fig. 1). Since 2007, there has been a burgeoning in the literature regarding the association between PDE-5 inhibitors and hearing disorders.

Patents for all three major PDE-5 inhibitors will expire between 2018 and 2020. Teva Pharmaceuticals released a generic version of sildenafil in December 2017, thereby increasing the availability and usage of these drugs in the next few years.

The current literature comprises studies varying widely in scope. The objective of this review is to collate

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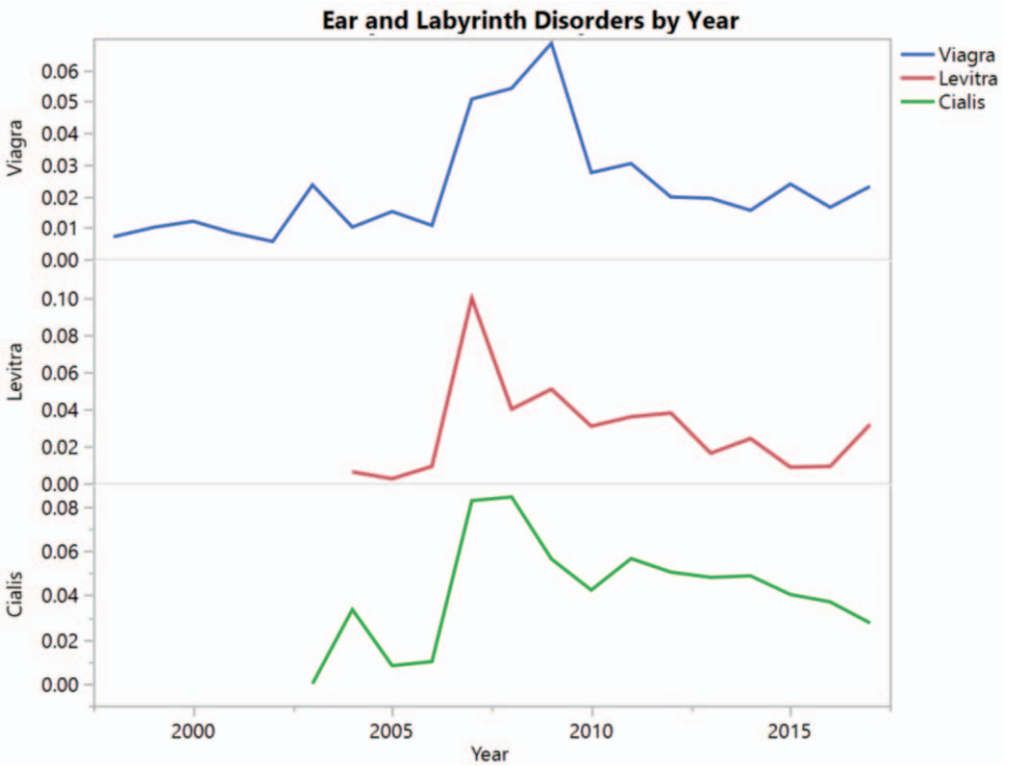

FIG. 1. Reported ear and labyrinth disorders as a proportion of total adverse events yearly. To relativize the values, the number of reported cases were divided by the total number of adverse effects for each year. Values taken from AERS Public Dashboard located at: https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm070093.htm.

the current medical literature on the association of PDE-5 inhibitors and its effects on the ear. The aim is to present a cohesive narrative to inform participants and influence future practice interventions and inquiry. All formally published case studies to date will first be presented. Next, all relevant multipatient studies will be organized by study type and subsequently summarized. Additionally, data from basic science articles will be explored to shed light on proposed mechanisms of ototoxicity. Finally, a discussion of the combined findings from the literature will be presented along with specific insights.

METHODS

Search Strategy

A comprehensive electronic search of PubMed/MEDLINE, Scopus, and Cochrane Library (both the Central Register of Controlled Trials and the Database of Systematic Reviews) was conducted on or before March 21, 2018. Before de-duplication, the PubMed search generated 114 articles, the Scopus search yielded 73 publications, and the Cochrane search resulted in eight studies. The PRISMA flow diagram was used to document de-duplication, exclusion, and inclusion (see Appendix, http://links.lww.com/MAO/A733).

Inclusion Criteria

- All English language articles including pediatric studies
- Basic science articles, epidemiological studies, randomized controlled trials, cohort studies, case reports, reviews, meta-analyses

Exclusion Criteria

- Press releases and newsletters.
- Studies with vague and/or undefined endpoints
- Non-English publications
- Studies with unavoidable selection bias

RESULTS

Case Reports

In the last decade, many case studies of PDE-5 inhibitor-induced ototoxicity appeared in the literature. In April 2007, Mukherjee and Shivakumar (3) published the first case study describing a patient who experienced SSNHL after taking sildenafil for 15 days. However, the FDA AERS demonstrates that ototoxic events were reported prior to 2007. Five years prior, in 2002, a case report described a 79-year-old man who experienced severe vestibular dysfunction, with bilateral tinnitus, two hours after taking sildenafil for the first time (2).

Since 2007, five additional case reports have been published (Table 1). There were a total of nine patients, all male, with an average age of 57.4 years (37–79 years, SD = 13.87 years). Of the cases of hearing loss, 25% (2/8 cases) were bilateral, 75% (6/8) were unilateral, 22% (2/9) reported tinnitus, and 33% (3/9) had accompanying vestibular symptoms (including vertigo and dizziness). When reported, treatments consisted of various modes of steroid therapy. Only 37.5% (3/8) of the cases reported in

TABLE 1. *Case studies documenting PDE-5 inhibitor use and ototoxicity*

Author	Year	Patient Demographic	Drug (Dosage)	Cochleotoxic Findings	Vestibulotoxic Findings	Audiometry Tests Used	Treatment (dosage)	Resolution of Symptoms
Hamzavi et al.	2002	One 79-year-old male	Sildenafil (50 mg one time)	Bilateral tinnitus	Vestibular-neuritis like symptoms	n/a	n/a	CR after 24 hours
Mukherjee et al.	2007	One 44-year-old male	Sildenafil (50 mg/day for 15 days)	Profound bilateral SSNHL	absent	PTA, OAE, EABR	Prednisolone (1 mg/kg/qd for 1 mo.)	No resolution
Maddox et al.	2009	Two males, one 62-year-old and one 54-year-old	Pt. 1: Cialis (10 mg) Pt. 2: Viagra (50 mg) and Cialis (10 mg)	Pt 1: Unilateral SSNHL Pt 2: Unilateral SSNHL	Pt 1: Initial vertigo	PTA	oral prednisone (1 mg/kg/qd for 7 days) for both pts, IT dexamethasone injection (0.5 ml [24 mg/mL] 3x qw) for pt. 2 only	No resolution of hearing deficits after >10 days
Snodgrass et al.	2010	One 57-year-old male	Vardenafil	Unilateral SSNHL	Absent	Repeat audiogram	IV dexamethasone and oral prednisone	CR after 4 to 10 days
Barreto et al.	2013	Two males; one 37-year-old and one 43-year-old	Unspecified PDE5 inhibitor	Both pts: unilateral SSNHL with tinnitus	Both pts: Initial vertigo	PTA, OAE, EABR	Oral prednisolone (1 mg/kg day for 10 days; tapered), IT injection methylprednisolone (0.7 ml, [40 mg/mL] 3x qad)	No resolution after >10 days
Skeith et al.	2013	One 77-year-old male	Sildenafil, furosemide and diltiazem	Bilateral SSNHL	Absent	n/a	n/a	n/a
Hayashi et al.	2017	One 64-year-old male	Tadalafil	Unilateral SSNHL	Absent	Repeat audiogram	Oral prednisolone (40 mg/qd for 5 days)	CR after >10 days

CR indicates complete resolution; EABR, Evoked Auditory Brainstem Response; IT, intratympanic; IV, intravenous; OAE, otoacoustic emissions; PTA, pure tone audiometry.

the literature displayed complete resolution of symptoms (2–8).

Retrospective and Prospective Studies

In addition to case reports, several reviews, clinical trials, cross-sectional and cohort studies have been published to quantify the incidence of ototoxic events. The characteristics of these studies, including study design, and patient demographics, are outlined in Table 2.

The earliest study was a seminal postmarketing report conducted by the FDA in 2007 that described 29 cases of SSNHL associated with the use of one of the three PDE-5 inhibitors. Many of these cases were associated with vestibular symptoms, tinnitus, or both (1). In 2009, Maddox et al. (4) formalized the FDA's findings by tabulating queried AERS data and reporting two additional patients. In this combined dataset, hearing loss occurred 12–24 hours after drug consumption for all patients. Among this group, 32% of patients suffered concurrent vertigo, and 32% had partial or complete improvement in hearing upon cessation of the drug. Only one patient in the cohort experienced bilateral hearing loss while the rest experienced unilateral deficits.

Another cohort of 47 patients was published in 2011 by Khan et al. (9). In this dataset, laterality was recorded in 70% of reports, and of these, 22% were bilateral. Hearing loss occurred within 24 hours of PDE-5 inhibitor use in 66.7% of reports. Only 38.3% confirmed the hearing loss as sensorineural. However, this cohort study included cases from previously published studies.

Three prospective observational studies have been published in the literature and none demonstrated SSNHL among subjects. In a study on 18 patients who were started on vardenafil for ED (10), four patients demonstrated clinically significant unilateral threshold deficits. The changes resolved completely upon cessation of the drug for the affected patients. Another prospective study followed 25 patients taking tadalafil for either ED or PH (11). The authors found no statistically significant difference between hearing thresholds at baseline or after initiating the drug. However, three patients who were taking 20 mg of tadalafil, rather than the standard 10 mg, demonstrated a significant change in hearing threshold at frequencies greater than 10 kHz. In 2017, Öntepeli et al. (12) randomized 30 patients to three types of PDE-5 inhibitor: sildenafil (50 mg twice weekly), tadalafil (20 mg twice weekly), and vardenafil (20 mg twice weekly). Transitory Evoked Otoacoustic Emissions (TEOAEs) and Distortion Product Otoacoustic Emissions (DPOAEs) were measured before and after treatment. Post-treatment amplitudes demonstrated a statistically significant improvement in hearing thresholds across all three groups. However, at one frequency (3 kHz), the vardenafil group demonstrated a significant decrease in DPOAE amplitude.

In 2010, the first epidemiological study evaluating the association between PDE-5 inhibitor use and audiological function was performed by McGwin (13). A cohort of over 2 million men was chosen from the Medical Expenditure Panel Survey and stratified to represent the American population. Over a period of two years, participants were interviewed and self-reported hearing loss was found to be 17.9%, and the incidence of PDE-5 inhibitor use was 2%. The results demonstrated that men who reported hearing impairment were twice as likely to also have reported the use of a PDE-5 inhibitor (OR = 2.23).

TABLE 2. *Characteristics of multipatient studies documenting PDE-5 inhibitor use and ototoxicity*

Author	Year	Study Design	Drug	Number of Patients	Mean Age	% Female
Maddox et al.[a]	2009	Case study and review	Sildenafil, tadalafil, vardenafil	25 patients	63 years	12%
Mazurek et al.[b]	2009	Randomized DBPC trial	Vardenafil	42	51.3 in vardenafil group, 46.7 in placebo group	29%
Okuyucu et al.	2009	Prospective study	Vardenafil	18 men	56.3 years	0%
Mcgwin G	2010	Cross-sectional study	Sildenafil, tadalafil, vardenafil	248,217,013 men (11,525 unweighted)	64.1 years in hearing-impaired group; 54.8 in non-hearing-impaired.	0%
Giuliano et al.	2010	Collated review of DBPC trials	Sildenafil	39,277 patients	(stratified by $\geq$ 65 and $\geq$ 75 years)	n/a
Khan et al.	2011	Case study and review	Sildenafil, tadalafil, vardenafil	47 patients	56.6 years	12.5%
Thakur et al.	2013	Prospective study	Tadalafil	25 patients	35.84 years	12%
Öntepeli et al.	2017	Prospective study	Sildenafil, tadalafil, vardenafil	30 men	50.9 years	0%
Khouri et al.	2017	Meta-analysis and disproportionality analysis	Sildenafil or tadalafil	2,979 patients	n/a	n/a
Liu et al.	2018	Retrospective cohort study	Sildenafil, tadalafil, or vardenafil	2,334,955 men	52.9 years among PDE5i users and 41.7 year among nonusers	0%

DBPC indicates double-blinded, placebo-controlled.
[a]Study consisted of two additional case reports outlined in Table 1.
[b]Discussed in molecular mechanisms section.

However, this association was strictly limited to sildenafil and no other PDE-5 inhibitor.

The most recent study published during the writing of this review is a retrospective cohort study of almost 2.5 million men that were randomly selected from the MarketScan Commercial Claims and Encounters database. The findings demonstrated that, compared with nonuse, the adjusted hazard ratio was statistically significantly among PDE-5 inhibitor users. The authors concluded that in their sample, the use of PDE-5 inhibitors was associated with a significant, albeit small, risk of SSNHL (14).

Our literature search also yielded two studies that evaluated PDE-5 inhibitor-induced ototoxicity as secondary endpoints. In a 2010 collated review of data from 67 double-blinded placebo-controlled (DBPC) trials (>14,000 men) and Pfizer's postmarketing safety database (39,277 men) analyzed hearing loss as one of several adverse events (15). In the DBPC database, there was only one case of severe unilateral deafness, which was presumed to be caused by an embolus and not by a PDE-5 inhibitor. In the postmarketing safety database, ototoxicity was exceedingly rare with sudden hearing loss occurring in only 3 (0.01%) patients and impaired hearing loss occurring in 26 (0.07%) patients out of a total of 39,277 patients (16). In 2017, a meta-analysis compared the safety profiles of sildenafil, tadalafil, and riociguat (a soluble guanylate cylase stimulator) indicated for PH (17). Among the three drugs, there was no significant impact on hearing/vestibular disorders. The disproportionality analysis showed that deafness as an adverse event was reported more frequently among PDE-5 inhibitor users compared to riociguat users. However, vestibular disorders were more frequently found among users of riociguat. Furthermore, among PDE-5 inhibitor users, the use of sildenafil was associated more strongly with vestibular/hearing disorders compared to tadalafil.

Molecular Mechanisms and Animal Studies

Several animal models have proposed multiple mechanisms behind PDE-5 inhibitor-induced ototoxicity (Table 3). The predominating theories all implicate various aspects of the NO/Prkg1/cGMP pathway. Nitric oxide (NO) is a soluble messenger synthesized and released from endothelial cells that promotes relaxation of vascular smooth muscle by up-regulating cyclic guanosine monophosphate (cGMP). cGMP is a second messenger that decreases smooth muscle tone via intracellular signals, notably Prkg1 (18,19). Inhibiting PDE-5 potentiates this effect as phosphodiesterase type 5 is responsible for the degradation of cGMP. In PH, PDE-5 inhibitors are used to promote pulmonary artery vasodilation (20).

NO has been demonstrated to exist in cochlear vascular endothelium and has been linked to cochlear damage (21–23). In 2008, Hong et al. investigated the effects of a prolonged high-dose of sildenafil on hearing impairment in mice. At the highest dose of sildenafil, the authors observed a delayed latency of auditory brainstem response (ABR), a significant shift in the hearing threshold of the brainstem response, and a significant difference in otoacoustic emissions between the sildenafil group and the control group (24). The authors proposed that this damage was due to excess NO as a direct result of sildenafil treatment. Bakir et al. suggested that NO might act as a cytotoxin by inducing apoptosis in cochlear cells and found that 30% of the samples in sildenafil group showed caspase 3 (marker for apoptotic cells) immunoreactivity compared to 0% in the control group (25).

Others hypothesize ototoxicity results from the prolongation of cGMP downstream of the NO effects (4,9). cGMP has been shown to increase levels of nuclear factor kappa beta (NF-κB) and mitogen-activated protein (MAP) kinase (26). NF-κB is found in the cochlea and is proposed as a causative agent in SSNHL (27). It has been postulated that variations of NF-κB levels, possibly caused by sildenafil's role in prolonging cGMP, can disrupt cellular homeostasis and promote pathological activation of cellular stress response pathways (4). MAP kinases have many physiologic roles in the body, including cellular stress response and regulation of proliferation, gene expression, cell survival, and apoptosis (28). Two important isoforms are C-Jun-K-terminal kinases (JNK proteins) and p38. Two studies demonstrated that the inhibition of JNK proteins (via JNK inhibitors CEP-1347 and D-JNK-1, respectively) was correlated with the attenuation of ototoxic stress and promotion of otoprotective effects (29,30).

Several animal studies have provided opposing or inconclusive evidence regarding ototoxicity. In 2012,

TABLE 3. *Studies proposing either a mechanistic explanation and/or molecular/histological evidence regarding PDE-5 inhibitor-induced ototoxicity*

Author	Year	Drug	Study Animal	Endpoints
Hong et al.	2008	Sildenafil	ICR mice	ABR, AMLR, TEOAE shifts
Maddox et al.	2009	Sildenafil	n/a	n/a
Bakir et al.	2012	Sildenafil	Wistar albino rats	Histopathological/morphological changes
Jaumann et al.	2012	Vardenafil	Wistar rats, mice	ABR, DPOAE shifts, protein expression
Au et al.	2013	Sildenafil	C57BL/6J and FV/BN mice	ABR shifts
Mahmood et al.	2014	Sildenafil	Sprague Dawley rats	ABR shifts
Liang et al.	2015	Sildenafil	Guinea pigs	ABR shifts, SEM changes

ABR indicates auditory brainstem response; AMLR, auditory middle latency response; DPOAE, distortion products of otoacoustic emissions; SEM, scanning electron microscope; TEAOE, transient evoked otoacoustic emissions.

Jaumann et al. (31) demonstrated both PDE-5 and Prkg1 are expressed in hair cells of murine cochlear tissues. Rats were then pretreated with vardenafil/ethanol solution and induced acoustic trauma with high frequency reverberating chambers. Compared to the control, vardenafil-pretreated rats demonstrated significantly better ABR thresholds and recovery of DPOAEs (31). The researchers then assayed for cochlear surface expression of Potassium Voltage-Gated Channel Subfamily Q Member 4 (Kcnq4), whose loss serves as a marker for acoustic damage (32). Compared to the control group, the vardenafil group had almost complete preservation of Kcnq4. The authors then studied cochlear poly ADP-ribose polymerase (PARP) activity, which has been demonstrated to mediate DNA repair mechanisms via the cGMP/Prkg1 pathway (33,34). Compared to the control, pretreatment of rats and wild-type mice with vardenafil caused a Prkg1-dependent up-regulation of PARP in hair cells, supporting cells, and spiral ganglion cells. These findings suggest that vardenafil prevents noise-induced hearing loss (NIHL) through activation of the cGMP/Prkg1/PARP pathway. Liang et al. also supported the otoprotective effect of PDE-5 inhibition against NIHL by exposing both sildenafil treated and control guinea pigs to a white noise of 110 dB. Results demonstrated that ABR threshold shifts in the sildenafil treatment group were significantly fewer than that in the control group (35). Au et al. proposed that PDE-5 inhibitors might potentiate age-related susceptibility to hearing loss instead of an immediate toxic effect (36). Either sildenafil citrate or saline was injected into two strains of mice, a control strain and an experimental strain which was susceptible to presbycusis. They found no significant difference in hearing between the two strains of mice after the treatment period (36).

The effects of PDE-5 inhibitors on tinnitus have also been studied. A murine model demonstrated that sildenafil citrate significantly reduced hearing impairment during the first week following blast exposure of 22 psi and also suppressed high-frequency tinnitus for the consecutive three to six weeks (37). However, this otoprotective effect against tinnitus has failed to manifest in human studies. A prospective, randomized double-blind placebo-controlled trial demonstrated that vardenafil had no superior efficacy compared to placebo for the treatment of subjective tinnitus (38).

DISCUSSION

In clinical practice, many commonly prescribed drugs possess ototoxicity as a noticeable adverse effect (39). Reports of ototoxicity have been linked to PDE-5 inhibitors since 2007. The current literature appears to be inconclusive regarding the significance of this association.

Most case reports of PDE-5 inhibitor-related ototoxicity (75%) exhibited unilateral hearing loss. Rates of unilaterality reported are as high as 96% (4,9). Although toxic hearing loss may be expected to be bilateral, Khan et al. noted that gentamicin-induced ototoxicity commonly induces unilateral hearing loss (9).

All prospective studies failed to find a significant association between PDE-5 use and ototoxicity (10–12,15,38). One study reported a significant improvement in auditory function in the treatment group (12). Among this cohort of papers, three were prospective observational studies (10–12). The authors of these papers had no funding sources to disclose. Furthermore, there was no detectable selection bias. However, these studies had a number of limitations including small sample sizes (ranging from 18 to 30 patients) and short follow-ups (72 hours to 1 month). Furthermore, though a formal meta-analysis of these studies would be optimal, the methodological heterogeneity between the papers was deemed to be too high; the dose stratification and final follow-up varied widely among each study.

The results of the retrospective studies are mixed. One retrospective disproportionality analysis demonstrated that PDE-5 inhibitors users were more likely to experience deafness as an adverse effect compared to riociguat (17). Another study showed a slight but significantly increased risk of SSNHL (14). Finally, the epidemiological study by McGwin demonstrated an increased risk of self-reported hearing loss with the use of sildenafil but not tadalafil or vardenafil. Although this study was robust in scope, it was a cross-sectional study thus it could not assess the temporal relationship between PDE-5 inhibitor use and the onset of the hearing loss. Also, it relied on self-reported hearing loss rather than a standard audiogram, introducing the potential for information bias (13). The sensitivity of self-reported hearing loss ranges from 41 to 65% (40).

Several studies have demonstrated that key molecules in the PDE-5 inhibitor pathway exist in the cochlea, including NO, cGMP, Prkg1, MAP kinase, NF-κB, and PARP (21,27,36,41,42). The proposed mechanisms have suggested both ototoxic or otoprotective effects. In two studies, PDE-5 inhibition was shown to have either an otoprotective effect or no effect, respectively (36,42). Despite contradictory findings, these studies provide crucial evidence that PDE-5 inhibitors enter the cochlea after introduction into the systemic circulation.

Two main proposed mechanisms of PDE-5 inhibitor-associated ototoxicity suggest either accumulation of NO/cGMP in the cochlea or caspase-3 activation (4,25). Part of the former mechanism relies heavily on the upstream cGMP-independent ototoxic effects of NO. PDE-5 inhibitors act specifically to increase the downstream of effects of NO, not the absolute amount of NO itself. In fact, sildenafil has not been shown to spontaneously induce NO release unless coupled with a NO synthase (43). To our knowledge, there is only one study demonstrating that sildenafil directly increases the release of NO, though this increase was only examined in rat cardiomyocytes (44). Additionally, even though PDE-5 inhibition does potentiate the effect of NO via downstream accumulation of cGMP, there has never been a formal study examining an explicit link between

NF-κB, MAP kinase, and PDE-5 inhibition. A study by Lang et al. demonstrated that mice lacking a subunit of NF-κB showed an accelerated hearing loss with age, suggesting that NF-κB might have a protective effect on primary auditory neurons (45). Bakir et al. supports the latter mechanism in their study, demonstrating caspase-3 upregulation in sildenafil-treated cochlear cells (25). However, it still relies on the assumption that NO is up-regulated by sildenafil administration.

These two mechanisms have been treated as independent. To unify these explanations and provide a cohesive model for future study, we examine the suggested pathogenesis of gentamicin, an established ototoxic drug. Gentamicin has been shown to cause cochlear cell death through phosphorylation of p38, activation of caspase-3 and cytochrome C release (41). Both p38 and caspase-3 are key mediators of apoptosis, with the former being a regulator of cytochrome C release and the latter serving as one of the major executioner caspases (41). cGMP has been shown to upregulate p38, a potent MAP kinase and sildenafil has been shown to upregulate caspase-3 (4,26). It is possible to conclude that sildenafil and other PDE-5 inhibitors may exert pro-apoptotic effects not through NO upregulation, but rather by promoting cGMP production in the cochlea and concomitant upregulation of p38 and caspase-3. Further studies are needed to establish whether or not there are any interactions between these key players.

It is important to note an increase in reported ototoxic events that occurred from 2007 to 2009 (Fig. 1). This aligns with the commencement of the FDA warning label requirement. The relative number of reported events fell after this two-year period across all three major drug formulations. Furthermore, the majority of ototoxic cases in the AERS database included patients demonstrating varying association between PDE-5 inhibitor use and hearing loss, hearing loss that predates drug use and gradual hearing loss over several years (1). Together, these findings suggest that the label change could have prompted an unintentional reporting bias and/or disseminated placebo effect.

Another cause for concern is that given the limited relative frequency of ototoxic events in the AERS database (0.018%, 0.020%, and 0.034% of all reported adverse events for Viagra, Levitra, and Cialis, respectively), it is possible that we simply seeing the natural incidence of hearing and vestibular disorders across the public. The incidence of SSNHL has been reported to be 5 to 20 per 100,000 (4).

For future inquiry, a double-blinded placebo controlled randomized trial with objective audiometric assessment as the primary endpoint is needed. This would provide stronger evidence as to whether an association between PDE-5 inhibitors and ototoxicity exists and could also delineate factors such as dosing and onset of symptoms as these two details have varied widely across studies (36). In addition, a reliable molecular model would provide greater insight to the mechanism of action. The PDE-5 inhibitor-induced up-regulation of PARP has demonstrated that there is a reason to believe that PDE-5 inhibition can affect cochlear function. Further study can examine the significance of this finding. We propose a novel mechanism linking PDE-5 inhibition, p38, and caspase-3. Only once consistent data is generated from both clinical and basic science studies can we begin to make statements regarding ototoxicity. Until then, data supporting ototoxicity are mixed at best.

CONCLUSION

Anecdotal reports and retrospective data suggest an association between PDE-5 inhibitors and ototoxicity. However, a review of both clinical and basic science literature demonstrates that this association is inconclusive as there are also studies that suggest potential protective effects associated with the drug. Future studies are needed to further elucidate this connection.

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