

## Viagra Deafness—Sensorineural Hearing Loss and Phosphodiesterase-5 Inhibitors

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**Background:** Viagra and PDE-5 inhibitors use has mushroomed since its launch over a decade ago. A growing body of evidence indicates significant morbidity associated with the side effect profile of this class of drug. Hearing loss associated with PDE-5 inhibitor use has recently been reported, but few studies have evaluated the causal link.

**Aim:** To review and scrutinise the current literature on the subject and propose possible physiologic mechanisms and to investigate the global reporting of this side effect.

**Methods and Materials:** Pharmacovigilance agencies around North America, Europe, and Australasia were contacted requesting reports of hearing loss associated with PDE-5 inhibitors. Reports were scrutinised to exclude those where other causes of hearing loss existed.

**Results:** Forty-seven cases of sensorineural hearing loss with a temporal association with PDE-5 inhibitor ingestion were obtained from both published literature and pharmacovigilance agencies. Cases had a mean age 56.6 years, male-to-female ratio of 7:1. Eighty-eight percent of reports were unilateral with an even left/right distribution. Hearing loss occurred within 24 hours of ingestion of PDE-5 inhibitor in 66.7% (n = 18) of cases. Sildenafil accounted for over 50% of cases.

**Conclusion:** There is increasing evidence that PDE-5 inhibitors may induce sensorineural hearing loss via plausible physiological mechanisms. There needs to be more awareness of this disabling side effect among healthcare professionals responsible for prescribing this drug.

**Key Words:** Hearing loss, deafness, sensorineural, sildenafil, viagra, phosphodiesterase inhibitors.

**Level of Evidence:** N/A.

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### INTRODUCTION

Phosphodiesterase-5 (PDE-5) inhibitors, originally developed for the treatment of angina, are the most commonly used drugs for the treatment of erectile dysfunction (ED). They are largely well tolerated in clinical practice and have recently also been used with proven usefulness in the treatment of pulmonary hypertension.<sup>1–3</sup>

Sudden sensorineural hearing loss (SSHL) is a distressing illness with up to one-third of patients left with permanent hearing impairment. It has an estimated incidence of 5–20 per 100,000 people per year. It is diagnosed to be mostly idiopathic, but viral or microvascular aetiologies are thought to be responsible.<sup>4</sup>

Recently, two authors have reported cases of SSHL occurring after PDE-5 inhibitor ingestion.<sup>5,6</sup> An epidemiologic study has also suggested a higher risk of

hearing loss with PDE-5 inhibitor use.<sup>7</sup> Two successive experimental studies also support a possible causal link.<sup>8,9</sup> Most reports of PDE-5 inhibitor related SSHL have come from the Food and Drug Agency (FDA) in the United States. To ascertain the global experience of this phenomenon we have surveyed pharmacovigilance agencies across America, Europe, and Australasia.

### METHODS AND MATERIALS

In an effort to assess the number of suspected cases, pharmacovigilance agencies in Europe, the Americas, East Asia, and Australasia were contacted for adverse events of sudden hearing loss in patients taking PDE-5 inhibitors as shown in Table I. Cases were individually analyzed and those with other causes of hearing loss present were excluded from the series. In addition, the temporality, PDE-5 inhibitor ingested and laterality of hearing loss was obtained.

### RESULTS

A total of 53 cases of hearing loss-associated with PDE-5 inhibitor use were reported to various pharmacovigilance agencies. After a review of individual case histories five were deemed to be related to other established causes of hearing loss such as otitis media or Meniere's and these were excluded. Of remaining 47 cases, 43 were submitted by pharmacovigilance agencies and four were from published literature (Table I). The mean age at presentation was 56.6 years with a male-to-

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TABLE I.  
Showing Details of All Reported Cases of PDE-5 Inhibitor-Associated Hearing Loss.

Country	Drug	Age(y)	Sex	Interval/Duration	Laterality	Hearing Loss Type
Canada	Vardenafil, Sildenafil	66	M	860 d, 145 d	Bilateral	NR
Canada	Sildenafil	NR	NR	NR	Unilateral	NR
Canada	Sildenafil	NR	M	NR	NR	NR
Canada	Sildenafil	37	M	NR	NR	NR
Canada	Sildenafil	70	M	NR	NR	NR
Germany	Sildenafil	44	M	42 d	NR	Sensorineural
Germany	Sildenafil	72	M	<6 hours	NR	NR
Germany	Sildenafil	54	M	NR	NR	NR
Germany	Sildenafil	NR	M	NR	NR	NR
Germany	Tadalafil	NR	M	NR	Right	NR
Germany	Vardenafil	NR	NR	NR	NR	NR
Germany	Vardenafil	43	M	NR	Left	NR
Germany	Vardenafil	72	M	NR	Right	NR
India	Sildenafil	44	M	15 d	Bilateral	Sensorineural
Ireland	Nil cases	Nil cases	Nil cases	Nil cases	Nil cases	Nil cases
United Kingdom	Tadalafil	NR	NR	4.5 hours	Bilateral	NR
United Kingdom	Sildenafil	NR	F	247 d	Unilateral	Sensorineural
United Kingdom	Sildenafil	NR	M	14 d	NR	Sensorineural
United Kingdom	Sildenafil	NR	M	7 d	NR	NR
United Kingdom	Tadalafil	NR	M	NR	Right	NR
United Kingdom	Sildenafil	NR	M	1 d	NR	NR
United Kingdom	Sildenafil, Tadalafil	NR	M	NR	NR	Sensorineural
United Kingdom	Tadalafil	NR	M	NR	Left	Sensorineural
Australia	Sildenafil, Tadalafil	57	M	18 months	Unilateral	Sensorineural
New Zealand	NIL FOUND	NR	NR	NR	NR	NR
USA	Sildenafil	72	M	<24 hours	Left	Sensorineural
USA	Sildenafil	55	M	<6 hours	Unilateral	NR
USA	Sildenafil	NR	NR	<12 hours	Left	NR
USA	Sildenafil	NR	NR	<12 hours	Left	Sensorineural
USA	Sildenafil	NR	NR	5 hours	Unilateral	NR
USA	Sildenafil	50	M	1 hour	Right	Sensorineural
USA	Sildenafil	NR	NR	<12 hours	Unilateral	NR
USA	Sildenafil	61	M	18 hours	Right	Sensorineural
USA	Sildenafil	72	NR	1 hours	Unilateral	Sensorineural
USA	Sildenafil	63	F	NR	Right	Sensorineural
USA	Sildenafil	50	F	NR	Unilateral	Sensorineural
USA	Sildenafil	36	F	NR	Unilateral	Sensorineural
USA	Tadalafil	71	NR	NR	Unilateral	NR
USA	Tadalafil	58	NR	6 hours	Unilateral	NR
USA	Vardenafil	74	NR	<12 hours	Unilateral	NR
USA	Vardenafil	59	NR	NR	Bilateral	NR
USA	Sildenafil	47	M	3 hours	Unilateral	NR
USA	Sildenafil	37	M	3 weeks	Unilateral	NR
USA	Tadalafil	64	M	1 hours	Left	Sensorineural
USA	Tadalafil	NR	M	48 hours	NR	NR
USA	Vardenafil	43	M	NR	Left	Sensorineural
USA	Tadalafil	62	NR	<12 hours	Unilateral	NR
USA	Tadalafil	54	NR	168 hours	Unilateral	NR

USA: United States of America, NR: Not recorded, d: Days, Y: Years.

female ratio of 7:1. Laterality was recorded in 70% (n = 33) of reports and of these hearing loss was unilateral in 88% (n = 29) and bilateral in 22% (n = 4). There was even distribution of hearing loss affecting the right and left sides. The interval between onset of hearing loss and PDE-5 inhibitor ingestion was recorded in 57.4% (n = 27) of reports. Hearing loss occurred within 24 hours of PDE-5 inhibitor use in 66.7% (n = 18) of reports. Only 38.3% (n = 18) of the total reports confirmed the hearing loss as sensorineural in nature. Sildenafil had the largest number of individual reports at 29 cases, followed by tadalafil (n = 10) and vardenafil (n = 7).

In addition to the 47 cases mentioned, raw data from the FDA's Adverse Events Reporting System (AERS) index yielded an additional 223 logged reports submitted after 2007 where hearing loss was reported with PDE-5 inhibitor ingestion. However, as there were no accompanying case histories these could not be included in the final analysis. The FDA also noted that in clinical trials of PDE-5 inhibitors, of the nearly 60,000 subjects across four trial studies, there were 17 cases of temporally associated sudden hearing loss. Again, no further case histories existed for these, and they were not included in final the analysis.

## DISCUSSION

PDE-5 inhibitors were first used to study cell and vascular physiology in the 1970s. However, it was not until 1995 that their physiologic importance in regulating vascular smooth muscle tone was understood.<sup>9a</sup> Sildenafil was the first drug in this class developed for commercial use. Synthesized at Pfizer's laboratories in Sandwich, Kent, it was initially studied for use in hypertension and angina pectoris. Phase two clinical trials showed that the drug had little effect on angina, but crucially observed that it could induce marked penile erections. Sildenafil citrate was patented in 1996, and approved for use by the FDA in 1998 as the first oral treatment for erectile dysfunction in the United States. Annual sales of Viagra in the period 1999–2001 exceeded \$1 billion. Since then, other PDE-5 inhibitors have been developed for use in ED with several countries producing generic versions.

It is estimated that over 20 million men in the United States have used Sildenafil, and over 40 million prescriptions have been issued worldwide since its launch.<sup>10</sup> In 2007, Sildenafil was the 65th most popular drug prescribed, exceeding such common drugs as Tylenol-codeine and albuterol in the United States. It is estimated that one in five men in the United States over the age of 40 have tried sildenafil.<sup>11</sup> In the United Kingdom, pilot "pharmacist led prescribing" schemes have lead to increased availability of Sildenafil, and the drug is frequently sold over the Internet.<sup>12</sup>

Sildenafil has proved to be an efficacious drug for treating for ED.<sup>1</sup> Its most common side effects are flushing, headache, blocked nose, dyspepsia, and dizziness with some studies showing that up to one-third of men taking the drug experience these with long-term use.<sup>1,2</sup> The frequency of these side effects appears to be fairly

dose dependent. More serious side effects are rare and include temporary loss of vision, retinopathy, seizures, myocardial infarction, ventricular arrhythmia, sudden cardiac death, cerebrovascular haemorrhage, and transient ischaemic attacks.<sup>13,14</sup> It was not until 2007 that a case of SSHL was reported as a potential side effect of this drug class.<sup>5</sup>

SSHL has been defined as hearing loss of at least 30 dB in three or more continuous frequencies that occurs within 72 hours of symptoms onset. It is a disturbing disorder that is usually unilateral with a varied incidence, with some authors estimating 15,000 cases diagnosed per year world wide.<sup>4</sup> The true incidence is thought to be far higher than reported in the literature, as only a fraction of cases present for medical assessment.

Its etiology is controversial and often labeled as idiopathic, because a cause is found in as little as 10% of patients.<sup>15</sup> Vascular disease, autoimmune conditions, labyrinthine membrane rupture, viral infection, and psychosomatic disorders are all contenders as potential causes.<sup>16</sup> The treatment of SSHL is no less controversial than its etiology and, in clinical practice, is often directed against a whole spectrum of possible causes. To cover possible vascular pathology vasodilators and rheologic agents have been used to reverse tissue hypoxia. As a significant proportion of patients report a recent viral illness, antiviral agents such as Acyclovir are frequently used despite uncertain hearing improvement. Hyperbaric oxygen has also been used and is thought to work by increasing oxygen tension in auditory tissue, but its clinical benefit is uncertain at present. Repairs of oval and round window perilymph fistulae can be performed for cases of SSHL with positive fistula tests or a history recent trauma, but diagnosis is difficult and the benefit uncertain.<sup>17</sup> Anti-inflammatory treatment with both oral and intratympanic corticosteroids has been studied in cases of SSHL and was previously considered as a gold standard in North America. However, a recent Cochrane review has shown that their clinical value is open to debate.<sup>18</sup> In fact, a meta-analysis recently stated no treatment for SSHL has been validated by large high-quality randomized controlled trials, probably due to the sparse presentation of cases.<sup>19</sup>

Mukherjee et al.<sup>5</sup> first reported a case of SSHL in a 44-year-old man occurring 15 days after taking Sildenafil, 50 mg daily, in 2007. The patient had taken the drug for 12 days continuously before developing profound bilateral hearing loss that was preceded by tinnitus but no other symptoms. Sensorineural hearing loss was subsequently confirmed on audiometric testing. Despite the initiation of high-dose steroid treatment and eight cycles of carbogen therapy, there was no improvement in his symptoms. This resulted in the FDA reviewing its postmarketing data on 113 cases of SSHL in patients taking PDE-5 inhibitors. Out of this, a total of 23 cases were deemed to have been potentially due to PDE-5 inhibitors. The FDA has since added SSHL onto the list of potential side effects for all PDE-5 inhibitors and is negotiating with manufacturers to feature this effect more prominently on its product labeling.<sup>14</sup>

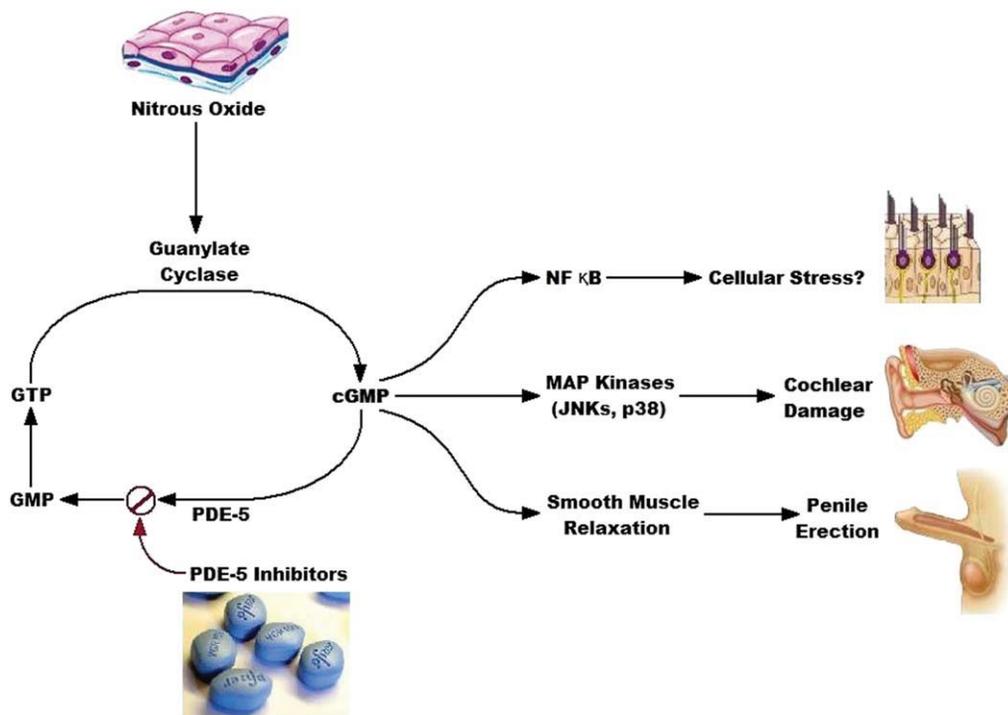


Fig. 1. Diagram illustrating potential physiologic pathways for PDE-5 inhibitor-mediated hearing loss. [Color figure can be viewed in the online issue, which is available at [wileyonlinelibrary.com](http://wileyonlinelibrary.com).]

Maddox et al.<sup>5</sup> subsequently combined these 23 cases with two novel reports in a review and found a strong temporal association between drug ingestion and the development of SSSL. They found that 88% (n = 15/17) of patients in their series who reported developing SSSL had ingested a PDE-5 inhibitor 24 hours prior to the development of symptoms. Of these 15 patients, 87% (n = 13/15) had symptoms beginning less than 12 hours postingestion.

In this current analysis we added a further 23 reports to the existing 26 in the literature. On further review of FDA data analyzed by Maddox et al.,<sup>5</sup> it was found that four cases had comorbid otologic disease that would account for the hearing loss. The patient demography in the current series was similar to those previously published. A temporal relationship was observed in 66.7% of cases, where hearing loss occurred within 24 hours of PDE-5 inhibitor ingestion. This is lower than that reported by Maddox et al. However, this difference is removed if the four suspect cases of hearing loss are excluded from the 15 cases they reported as having significant temporality. The overwhelming majority of hearing loss appears to be unilateral, consistent with both Maddox et al. as well as the FDA's own analysis of its postmarketing safety data. Sildenafil remains the most commonly implicated PDE-5 inhibitor with hearing loss, reflecting the fact that it is also the most popularly used drug in this class.

To date, only two studies have investigated the possibility of a direct causal association between PDE-5 inhibitor ingestion and hearing loss. A recent in vivo study assessed hearing thresholds in mice injected with

high-dose Sildenafil during a 135-day period. Hearing loss was evaluated by recording auditory middle ear latency responses and otoacoustic emissions. High doses of Sildenafil increased hearing thresholds as measured by auditory brainstem responses. It also delayed the latency of both auditory brainstem responses and auditory middle ear responses. This demonstrated that Sildenafil administration at high doses induces hearing impairment in mice.<sup>9</sup>

More recently, Okuyucu et al.<sup>8</sup> have performed the only prospective observational study in humans to date. Eighteen patients who had been using a PDE-5 inhibitor for ED were studied. Audiometric testing was carried out on all patients between frequencies 250 and 16,000 Hz prior to and after 1, 5, and 72 hours of 10 mg vardenafil ingestion. Four patients demonstrated a statistically significant unilateral decrease in hearing threshold compatible with ototoxic criteria within 72 hours of drug ingestion. In addition, all patients showed a significant unilateral threshold decrease at 10,000 Hz. However, all hearing loss resolved with discontinuation of the drug.

### Proposed Mechanisms

**Nitrous oxide–cyclic GMP pathway.** The nitrous oxide (NO)/cyclic guanosine monophosphate (cGMP) pathway is an established major regulatory system in cochlear physiology and has been implicated in the pathophysiology of hearing loss.<sup>20</sup> It is this pathway that is regulated by the PDE-5 inhibitor class of drugs (Fig. 1). It is the mechanism that induces smooth muscle relaxation in endothelial cells. NO activates guanylate

cyclase, which converts guanosine triphosphate (GTP) into to guanosine monophosphate (GMP). This depletes intracellular calcium stores to cause smooth muscle relaxation. Smooth muscle relaxation induces vasodilation in the corpus cavernosum vessels to result in penile erection. The production of cGMP is regulated by PDE-5, which recycles cGMP to GTP. Sildenafil and other PDE-5 inhibitors act to inhibit the breakdown of cGMP and hence potentiate the smooth muscle relaxation that leads to sustained penile erection.

NO and cGMP have been implicated in the literature to exert ototoxic effects via secondary messengers. Blasits et al.<sup>21</sup> (2000) conducted an experimental study into the effect of NO donor sodium nitroprusside on gap junction electrical coupling in Deiter's cells (cells supporting primary hair cells) in guinea pig cochlea. It was found that the introduction of sodium nitroprusside induced uncoupling of the gap junctions, a function necessary for maintaining normal cochlear sensory function. It was likewise observed that a cGMP analogue 8-bromo-cGMP also uncouples Deiter's cells, whereas an NO-synthase inhibitor blocked this effect. Known ototoxic drugs like gentamicin have also been known to cause uncoupling in Deiter cell gap junctions.<sup>22</sup> Hence, as a potentiator of the NO/cGMP pathway PDE-5 inhibitors can may induce ototoxicity in a similar fashion.

In an in vivo study Chung et al.<sup>23</sup> (2007) studied the effect of halothane and isoflurane, known NO-cGMP pathway inhibitors, in mice exposed to broad band white noise designed to simulate noise induced hearing loss. After 1 week of exposure, it was found that both anaesthetic agents had a protective effect, hence suggesting the involvement of cGMP in mediating ototoxicity.

### Secondary Messengers

The NO driven accumulation of intracellular cGMP activates various protein kinases and nuclear factors that act as secondary messengers, activating various cellular processes. Of interest is the activation of various mitogen-activated protein (MAP) kinases. These protein kinases respond to extracellular stimuli and regulate gene expression, mitosis, cell differentiation, and apoptosis. MAP kinase c-Jun N-terminal (JNKs) and the p38 isoforms have been shown to be involved in the cellular stress response.<sup>24,25</sup> The JNK proteins in particular have been shown to be activated within cochlear hair cells during cellular stress in vitro. Yilkoski et al.<sup>26</sup> (2002) conducted experiments in guinea pigs by injecting one group with gentamicin and another with gentamicin and CEP-1347, a nonprotein inhibitor of the JNK pathway. They found that CEP-1347 inhibition of JNK attenuated aminoglycoside induced cochlear hair cell damage. Wang et al.<sup>27</sup> (2003) reproduced these results with D-JNK-1, another inhibitor of JNKs, injected into guinea pig cochlear cell cultures. Once again, JNK inhibition provided an otoprotective effect against neomycin and noise-induced hair cell toxicity. Wei et al.<sup>28</sup> (2005) used minocycline, an inhibitor of MAP kinase p38, on rat cochlear explants treated with gentamicin. It was shown that p38 inhibition was otoprotective against cochlear hair cell death.

Nuclear factor-kappa beta (NF- $\kappa$ B) is another important regulator of the inflammatory cellular stress response, and apoptosis and is found in significant quantities in the cochlea. Based on this, it has been postulated as a possible etiologic agent in SSSL of all causes.<sup>29</sup> However, there are no physiologic studies that corroborate a causal ototoxic link. Lang et al.<sup>30</sup> (2006) showed that knock out mice lacking the gene for the p50 subunit of NF- $\kappa$ B, suffered accelerated auditory nerve degeneration induced by noise and aging. This suggests that NF- $\kappa$ B may in fact be otoprotective rather than a pathologic agent in ototoxicity.

### Critique

In our review we found 47 reports implicating PDE-5 inhibitors as a cause for SSSL. However, there are at least a further 240 potential cases from clinical and recent FDA adverse events reports where PDE-5 inhibitors may be related to hearing loss. However, due to incomplete data and case histories no further comment can be made with respect to these. In the course of our study we have noted a large variance in the detail and format of individual adverse event reports between the various pharmacovigilance agencies contacted. Overall, there also was a poor response rate from national pharmacovigilance agencies and transnational organizations such as the EMEA. The World Health Organization (WHO) Collaborating Centre for International Drug Monitoring based at Uppsala was also contacted. However, due to prohibitive administrative fees, in excess of £2,000 (Great British Pounds), this information could not be obtained.

In their case series Maddox et al.<sup>5</sup> considered that as SSSL is a relatively common condition and that, as PDE-5 inhibitors like Sildenafil are frequently prescribed drugs, it is possible that reported cases simply reflect the normal incidence of SSSL in this patient population. They extrapolated that if 4.4 million prescriptions of Sildenafil were issued in a year then based on an incidence of 10 per 100,000 one would expect 440 cases of SSSL in this population group yearly. They further asserted that if Sildenafil was taken once monthly then 15 cases of SSSL would occur within 24 hours of Sildenafil ingestion. However, this extrapolation is entirely speculative and based on assumptions about the true incidence of SSSL and PDE-5 inhibitor usage, both of which are poorly understood and recognized. Also, adverse drug reactions are frequently unrecognized and underreported. A recent systemic review estimated underreporting rates as high as 94%.<sup>31</sup>

Another important consideration is that although the original case reported by Mukherjee et al.<sup>5</sup> was of bilateral SSSL, 96% of subsequent cases of suspected PDE-5 inhibitor-induced SSSL have been unilateral. It is counterintuitive that a drug that has a systemic distribution should affect hearing asymmetrically. However, gentamicin, an established ototoxic drug, has been shown to induce unilateral and asymmetrical bilateral hearing loss.<sup>28</sup> Furthermore, in the only prospective study to look at PDE-5 inhibitor ingestion and SSSL, a

unilateral threshold decrease was observed in all four patients who suffered ototoxicity.<sup>8</sup> This implies that laterality of hearing loss may have little impact on excluding causality in drug induced ototoxicity.

The temporality between PDE-5 inhibitor ingestion and the onset of SSSL has been cited to support a causal relationship. In the aforementioned Korean study in mice, high-dose Sildenafil induced a significant decrease in brainstem responses to auditory stimuli after 15 days of continuous treatment. In humans this ototoxicity appears to manifest far earlier. In the case series by Maddox et al. 88% of patients developed SSSL within 24 hours of PDE-5 inhibitor ingestion. This may be an overestimation, as our analysis showed only 62% of patients developing hearing loss within this time. In support of this temporality, Okuyucu et al.<sup>8</sup> showed a significant decrease in hearing thresholds within 24 hours of drug ingestion in all affected patients.

It has to be acknowledged that there is a lack of direct causal evidence for SSSL induced by PDE-5 ingestion and the mechanisms by which they cause ototoxicity at the cellular level. However, drug-induced ototoxicity is poorly understood, and no one physiological pathway has been proven to be involved. The NO/cGMP pathway has been shown to mediate ototoxicity and regulate normal cochlear hair cell function. It is postulated that this occurs through the induction of specific MAP kinases such as JNKs and p38, which we have discussed (Fig. 1). However, there is no experimental study that demonstrates NO/cGMP potentiates ototoxicity via these mediators or that PDE-5 inhibitors significantly induce NO/cGMP and its secondary messengers in the auditory apparatus.

## CONCLUSION

Sildenafil and other PDE-5 inhibitors are commonly prescribed drugs for the treatment of a nonlife-threatening condition. Although side effects are commonly mild and transient, serious adverse reactions have been described. Sildenafil has been implicated as a causative agent in SSSL. There is a strong temporal association and plausible physiologic mechanisms described in the literature to account for this. Medical practitioners involved in the prescription of these drugs need to be vigilant about this potential side effect and its disabling consequences. Patients must be counseled appropriately before starting treatment. With patents for Sildenafil expiring between 2011–2013, cheaply available generic versions are likely to result in a significant increase in the usage of these drugs. The FDA in the United States has already taken steps to have this risk more prominently advertised. Healthcare professionals and organizations in the United Kingdom need to follow suit.

## BIBLIOGRAPHY

- McMahon C, Samali R, Johnson H. Efficacy, safety and patient acceptance of sildenafil citrate as treatment for erectile dysfunction. *J Urol* 2000; 164:1192–1196.
- Sergio G, Brannigan RE, Spitz A, Orejuela FJ, Lipshultz LI, Kim ED. Side effect profile of sildenafil citrate (Viagra) in clinical practice. *Adult Urol* 2000;56:474–476.
- Montani D, Chaumais MC, Savale L, et al. Phosphodiesterase type 5 inhibitors in pulmonary arterial hypertension. *Adv Ther* 2009;26: 813–825.
- Byl FM. Sudden hearing loss: eight years' experience and suggested prognostic table. *Laryngoscope* 1984;94:647–661.
- Mukherjee B, Shivakumar T. A case of sensorineural deafness following ingestion of sildenafil. *J Laryngol Otol* 2007;121:395–397.
- Maddox PT, Saunders J, Chandrasekhar SS. Sudden hearing loss from PDE-5 Inhibitors: a possible cellular stress etiology. *Laryngoscope* 2009; 119:1586–1589.
- McGwin G. Phosphodiesterase type 5 inhibitor use and hearing impairment. *Arch Otolaryngol Head Neck Surg* 2010;136:488–492.
- Okuyucu S, Guven OE, Akoglu E, Ucar E, Dagli S. Effect of phosphodiesterase-5 inhibitors on hearing. *J Laryngol Otol* 2009;123:718–722.
- Hong BN, Yi TH, Kim SY, Kang TH. High dosage sildenafil induces hearing impairment in mice. *Biol Pharm Bull* 2008;31:1981–1984.
- Coste H, Grondin P. Characterization of a novel potent and specific inhibitor of type V phosphodiesterase. *Biochem Pharmacol*, 1995;50: 1577–1585.
- CNN online (2007). Impotence drugs may increase risk for sudden hearing loss. Available at: [http://edition.cnn.com/2007/HEALTH/10/18/hearing\\_loss/](http://edition.cnn.com/2007/HEALTH/10/18/hearing_loss/). CNN site. Accessed: November 6, 2009.
- The Wall Street Journal Online. Viagra is misunderstood despite name recognition. [online]. Urological Sciences Research Foundation site. Available at: [http://www.usrf.org/breakingnews/bn\\_111202\\_viagra/bn\\_111202\\_viagra.html](http://www.usrf.org/breakingnews/bn_111202_viagra/bn_111202_viagra.html). Accessed on May 22, 2010.
- Mayor S. UK pilot allows pharmacists to supply sildenafil without prescription. *BMJ* 2007;334–387.
- Christiansen E, Guirguis WR, Cox D, Osterloh IH, Sildenafil Multicentre Study Group. Long-term efficacy and safety of oral Viagra® (sildenafil citrate) in men with erectile dysfunction and the effect of randomised treatment withdrawal. *Int J Impotence Res* 2000;12:177–182.
- U.S. Food and Drug Administration (2009). Information for Healthcare Professionals: Sildenafil (marketed as Viagra and Revatio), Vardenafil (marketed as Levitra), Tadalafil (marketed as Cialis) [online]. FDA site. Available from: <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrug-SafetyInformationforPatientsandProviders/ucm124841.htm>. Accessed on May 22, 2010.
- Loughan S. Management of sudden sensorineural hearing loss: a consultant survey. *J Otolaryngol Otol* 2000;114:837–839.
- Suckfull M. Perspectives on the pathophysiology and treatment of sudden idiopathic sensorineural hearing loss. *Dtsch Arztebl* 2009;106:669–676.
- Grundfast KM, Bluestone CD. Sudden or fluctuating hearing loss and vertigo in children due to perilymph fistula. *Ann Otol Rhinol Laryngol* 1978;87:761–771.
- Wei BPC, Mubiru S, O'Leary S. Steroids for idiopathic sudden sensorineural hearing loss. *Cochrane Database Syst Rev* 2006;CD003998. DOI: 10.1002/14651858.CD003998.pub2.
- Conlin AE, Parnes LS. Treatment of sudden sensorineural hearing loss. *Arch Otolaryngol Head Neck Surg* 2007;113:582–586.
- Fessenden JD, Schacht J. The nitric oxide/cyclic GMP pathway: a potential major regulator of cochlear physiology. *Hear Res* 1998;118: 168–176.
- Blasits S, Maune S, Santos-Sacchi J. Nitric oxide uncouples gap junctions of supporting Deiters cells from Corti's organ. *Eur J Physiol* 2000;440: 710–712.
- Santos-Sacchi J. Isolated supporting cells from the organ of Corti: some whole cell electrical characteristics and estimates of gap junctional conductance. *Hear Res* 1991;52:89–98.
- Chung JW, Ahn JH, Kim JY, et al. The effect of isoflurane, halothane and pentobarbital on noise-induced hearing loss in mice. *Int Anesth Res Soc* 2007;104:1404–1408.
- Zuo Z, Tichotsky A, Johns R. Halothane and isoflurane inhibit vasodilation due to constitute but not inducible nitric oxide synthase: implications for the site of anesthetic inhibition of the nitric oxide/guanylyl cyclase signaling pathway. *Anesthesiology* 1996;84:1156–1165.
- Wang J. A peptide inhibitor of c-Jun N-terminal kinase protects against both aminoglycoside and acoustic trauma-induced auditory hair cell death and hearing loss. *J Neurosci* 2003;23:8596–8607.
- Ylikoski J. Blockade of c-Jun N-terminal kinase pathway attenuates gentamicin-induced cochlear and vestibular hair cell death. *Hear Res* 2002; 166:33–43.
- Wei X, Zhao L, Liu J, Dodel RC, Farlow MR, Du Y. Minocycline prevents gentamicin-induced ototoxicity by inhibiting p38 MAP kinase phosphorylation and caspase 3 activation. *Neuroscience* 2005;131: 513–521.
- Fausti SA. Detection of aminoglycoside ototoxicity by high-frequency auditory evaluation: selected case studies. *Am J Otol* 1984;5:177–182.
- Lang H, Schultz BA, Zhou D, Smythe N, Spicer SS, Schmiedt RA. Nuclear factor-κB deficiency is associated with auditory nerve degeneration and increased noise-induced hearing loss. *J Neurosci* 2009;29:26: 3541–3550.
- Hazell L, Shakir SA. Under-reporting of adverse drug reactions: a systematic review. *Drug Safety* 2006;29:385–396.
- Merchant SN, Adams JC, Nadol JB. Pathology and pathophysiology of idiopathic sudden sensorineural hearing loss. *Otol Neurotol* 2005;26: 151–160.