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## Current Pharmacologic Otoprotective Agents in or Approaching Clinical Trials: How They Elucidate Mechanisms of Noise-Induced Hearing Loss

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### Abstract

Through understanding the underlying mechanisms of noise-induced hearing loss (NIHL), several promising pharmacologic otoprotective agents are in development. Conversely, the experimental results with these protective agents further elucidate NIHL mechanisms. This article reviews the major classes of otoprotective agents for NIHL that have undergone published peer reviewed clinical trials, or are currently in or approaching FDA approved clinical trials. Both prophylactic and rescue agents are included. The classes of agents include antioxidants, vasodilators, and glucocorticoids. Apoptotic pathway inhibitors are briefly mentioned. For antioxidants, some of the differences in the exact antioxidant mechanisms are included. Protective agents reviewed include D-methionine, N-acetylcysteine, ebselen, ACE Mg, Acuval, CoQ10, molecular hydrogen, magnesium as a single agent, and dexamethasone. The advantages, disadvantages, and state of development are included for each agent. Both safety and efficacy are considered as are considerations for specific patient populations if known. Further, results of animal and clinical trials are briefly described from the published literature.

Although no pharmacologic agent is yet approved by the FDA for clinical use to prevent or treat noise induced hearing loss at this time, it is hoped that within the next decade and perhaps within the next few years one or more agents will be available for clinical use. Further it is hoped that through an understanding of the underlying mechanisms and noise-induced hearing loss and otoprotection, even more safe and effective pharmacologic otoprotective agents will be developed.

**Keywords:** N-acetylcysteine; Ebselen; ACE Mg; Acuval; CoQ10; Molecular hydrogen; Magnesium; Dexamethasone

### Introduction

In the U.S., noise-induced hearing loss is estimated to affect 12.8% of adults aged 20–69 years (approximately 27 million) [1]. Currently no FDA-approved agent exists for protection against noise induced hearing loss, although there are many agents in or approaching clinical trials with promising results. Some agents may be used for prophylactic administration whereas others demonstrate efficacy in rescue, meaning they may be administered hours or even days after noise exposure and still prevent permanent noise-induced hearing loss.

Intense or prolonged noise exposure causes sensorineural hearing loss (SNHL) primarily by damaging cochlear auditory outer hair cells, sometimes with concomitant inner hair cell damage with subsequent degeneration of the spiral ganglion cells [2]. SNHL also occurs via vasoconstriction in the stria vascularis and damage to the reticular lamina [3]. Given recent advancements in our understanding of oxidative stress and its role in hair cell death, a multitude of antioxidants have emerged to defend against oxidation [4]. Antioxidant agents include D-methionine, N-acetylcysteine, ebselen, aspirin, a combination of beta-carotene, vitamin C and vitamin E, Acuval, Coenzyme Q10 and molecular hydrogen [5-11]. Magnesium is thought to exert its otoprotective effects partly via vasodilation [12]. Other agents in the prevention of cellular death category include inhibitors of apoptosis such as calcineurin inhibitors, caspase inhibitors, jun-N terminal kinase inhibitors, and calcium channel blockers [13-17]. The second pharmacologic category includes glucocorticoids, which have been widely used for otoprotection although their mechanisms remain largely unknown [18]. In 2012 Wang et al. demonstrated that one mechanism whereby dexamethasone exerts its otoprotective action involves encouraging dex-differentiation of supporting cells into outer hair cells [19]. However, systemic steroid administration presents risks such as impaired wound healing, hypokalemia,

hyperglycemia, hypertension, osteoporosis, myopathy, osteonecrosis and immunosuppression [20-27]. Therefore, their use would be better suited for rescue from severe acute acoustic trauma rather than prophylaxis. For common clinical use an oral agent with a very low risk of side effects is preferable. For this reason, agents approaching clinical trials tend to be of the antioxidant category. Antioxidants such as selenium, which is found in Brazil nuts, and D-methionine, which occurs naturally in cheese and yogurt, can survive the gastric system and first-pass metabolism to exert their effects. Such oral agents show promise for clinical use because of their ease of administration, safety and convenience in terms of portability and lengthy time window for administration [28,29].

### Antioxidants

The identification of oxidative stress within the cochlea advanced current understanding of auditory hair cell damage and subsequently provided a new target for novel therapeutic otoprotective agents. An overabundance of reactive oxygen species (ROS) and reactive nitrogen species (RNS) in auditory hair cells activate programmed cell death pathways [30]. ROS species include superoxide (O<sub>2</sub><sup>-</sup>) and hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>). RNS include nitric oxide (NO<sup>-</sup>) and peroxyxynitrate

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(ONOO<sup>-</sup>) [31]. These ROS/RNS species, termed “free radicals,” are created during normal cellular metabolism and by various noxious stimuli, including noise [32]. Free radicals are redox active molecules with an unpaired electron, making them highly reactive within cells. By oxidizing other stable molecules, free radicals can disrupt cellular components such as proteins, DNA and lipid membranes. Endogenous defense mechanisms exist to neutralize toxic free radicals, and they include superoxide dismutases (SODs), catalase, glutathione (GSH) and glutathione peroxidase (GPx), an enzyme that accelerates the oxidation of endogenous GSH. Overproduction of ROS and RNS may overwhelm antioxidant defenses, resulting in oxidative damage [4,33].

Evidence of free radical damage to hair cells and of increased susceptibility to hearing loss caused by antioxidant deficiency further supports the oxidation theory of ototoxicity. Application of paraquat, a superoxide generator, to the round window resulted in inner and outer hair cell damage and permanent threshold shifts (PTS) [34]. Deficiencies in glutathione, glutathione peroxidase and superoxide dismutase are correlated with greater susceptibility to noise-induced ABR threshold shifts. Thus, noise increases free radical formation while decreasing defense mechanisms [35-38]. Antioxidant supplementation provides varying levels of protection against noise-induced changes in cochlear function and morphology [5,7,9,39-42]. This finding is clinically important, as it suggests that antioxidants may be effective pharmacologic preventatives against NIHL.

### D-Methionine

D-methionine (D-met) can be administered as an oral suspension, as an injection or by direct application to the round window [5,43]. D-met provides virtually complete protection from PTS and cochlear hair cell loss in chinchillas and mice for the noise exposures tested [5,40-45]. Kopke et al. in 2002 demonstrated protection of both inner and outer hair cells by D-met. Temporary threshold shift (TTS) results have been mixed, showing virtually complete protection from TTS immediately postnoise and 1 day after noise in guinea pigs yet no significant protection from TTS at 1 day in chinchillas [40,46]. D-met has provided virtually complete protection from PTS and outer hair cell loss when administered every 12 hours beginning 2 days before noise exposure and continuing 2 days after noise exposure, starting 1 hour after noise exposure and then every 12 hours for 2 days, if given 1 hour before and 1 hour after noise exposure, or even if first administered up to 7 hours after noise cessation [5,40,44,45]. All studies thus far have shown D-met to be protective against NIHL with no studies demonstrating lack of protection or worsening of permanent NIHL. D-met has proven effective against noise exposures ranging from a 105-dB sound pressure level (SPL) octave band of noise centered at 4 kHz for 6 hours to a 110-dB SPL octave band of noise centered at 4 kHz for 4 hours and for a 105-dB SPL broad band of noise for 10 minutes [5,40,44-46]. In order to compare different otoprotective agents, studies are still needed using the same noise exposure conditions in the same species.

D-met most likely works as a direct and indirect anti-oxidant. Directly, it is reversibly oxidized [47]. Indirectly, methionine has been shown to increase intracellular glutathione, specifically mitochondrial glutathione [48,49]. This function is particularly significant, as the probability of hair cell survival after noise exposure correlates with mitochondrial function [50]. Additionally, methionine may prevent the efflux of glutathione from the cell that typically occurs after injury [51]. Thus methionine preserves or improves the ratio of reduced to oxidized glutathione in the cochlea. D-met is currently funded by

the US Department of Defense and approved by the FDA for Phase 3 clinical trials for PTS.

### N-Acetylcysteine

N-Acetylcysteine (NAC) is a glutathione precursor and ROS scavenger. Results of NAC's otoprotective capabilities have been variable. Most studies demonstrate partial protection from NIHL in animals when given either prior to or within 24 hours of noise exposure [6,52-55] but other studies have shown no protection or exacerbation of NIHL by NAC [56,57]. Kopke et al. found significant protection from NIHL only when NAC was combined with high-dose salicylate [58,59]. The protection may in fact be attributed to salicylate itself, which has otoprotective properties [8]. High dose salicylate, while potentially otoprotective, is contraindicated in many patient populations, including children (Reye's syndrome), patients with ulcers and those at high risk for bleeding, such as military personnel. However, some studies do show partial protection from NIHL using NAC as a single agent [41,60,61]. Two Phase 2 clinical trials were conducted by the Department of Defense but did not demonstrate clinically significant protection [41].

### Ebselen

Ebselen is a glutathione peroxidase mimetic which contains selenium and reduces hydroperoxide formation. Its clinical trial form is a dry blend capsule and it has demonstrated either partial or complete protection from PTS in rats and guinea pigs with no studies showing a lack of protection or exacerbation of NIHL [7,62-64]. One study showed significantly decreased TTS in the guinea pig. [63]. Ebselen was protective against PTS in the guinea pig after a 5-hour, 125-dB SPL, 4 kHz octave band noise exposure and against TTS after a 3-hour, 115-dB SPL, 4 kHz octave band exposure [63]. Significant partial protection from PTS was demonstrated in rats for a 4-hour, 4 to 16 kHz noise band exposure at 110-, 113-, or 115-dB SPL [7,64]. Ebselen is approaching Phase 2 clinical trials for TTS.

### ACE Mg

$\beta$  carotene, which metabolizes to form vitamin A, in combination with vitamins C and E plus magnesium (ACE Mg) can be delivered orally in capsule form and shows consistent protection from NIHL in animals [9,65-69]. While Le Prell et al. in 2007 found no otoprotection with either Mg alone or the ACE combination alone with treatments beginning 1 hour prior to noise, the combination of ACE Mg conferred significant partial protection from PTS in the guinea pig and the mouse [9,66,67]. ACE Mg also partially diminished TTS in the guinea pig after shorter, less intense exposure [65]. ACE Mg has demonstrated dose-dependent protection from NIHL in mice for noise exposures of 113- to 115-dB SPL, 8- to 16-kHz octave band noise for 2 hours [66]. In guinea pigs, TTS from a 110-dB SPL noise band centered at 4 kHz for 4 hours was decreased from ~20 dB to 5 to 10 dB [65].

This antioxidant combination, however, is contraindicated in smokers as there is evidence that  $\beta$  carotene may increase the risk of lung cancer [68,69]. Magnesium supplementation may have deleterious effects on chronic renal failure patients, including adynamic bone disease and mineralization defects [70]. Vitamin E and NAC have been shown to significantly increase the risk of prostate cancer among healthy men by encouraging prostate epithelial cell proliferation early in prostate tumorigenesis [71,72].

Because of the variety of patient comorbidities, medical histories and logistical considerations, there is clinical need for a variety of

pharmacological treatment and prophylaxis options. It is not likely that any one otoprotective agent will be appropriate or effective for every patient population. Only clinical trials for all otoprotective agents will delineate the proper patient populations, risks and appropriate use for optimal benefit. ACE Mg is approaching Phase 2 clinical trials for TTS.

### **Acuval, CoQ10**

Cascella et al. showed protection from NIHL using a specific multivitamin and mineral formulation combined with coenzyme Q10 (CoQ10) in Sprague Dawley rats [10]. Acuval 400R is a food supplement multivitamin containing vitamins A, E, B1, B2, B6 and B12, L-Arginine, Ginkgo biloba and minerals such as magnesium, selenium and zinc, as well as small amounts of Coenzyme Q10 (0.31 g/100 g). CoQ10 (2,3-dimethoxy-5-methyl-6-decaprenyl-1, 4 benzoquinone) assists in the proton and electron transport of the mitochondrial respiratory chain. This coenzyme is a free radical scavenger similar to antioxidant vitamins, but is minimally water soluble in its natural form [73]. A more water-soluble version recently developed – Q10 terclatrate (Qter) – improves the coenzyme's efficacy against oxidative injuries, lipid peroxidation and mitochondrial damage [74-76]. The study utilized fifty-five rats divided into 4 groups: A) noise-exposed animals; B) animals exposed to noise and treated with Acuval; C) animals exposed to noise and treated with Acuval plus Coenzyme Q10; D) animals only treated with Acuval and additional Coenzyme Q10 with no exposure to noise.

Animals from groups A and B showed significant threshold shifts for click and 4 kHz stimuli. For the same frequencies, animals from group C (CoQ10) demonstrated threshold levels similar to those from group D (no noise exposure). At higher frequencies (>8 kHz) the 2 Acuval groups both showed more otoprotection than the noise group A. Animals in group D showed no significant changes in hearing threshold throughout the experiment. It would be helpful to evaluate a fifth group of animals treated with only CoQ10 and noise to compare the results from this group to those of group C. This combination of nutraceuticals may not be appropriate for all patients because of the risk of side effects. Ginkgo biloba may present an increased risk of bleeding and its use would be inadvisable in soldiers, surgical candidates and patients with an increased risk of injury or a history of bleeding disorders [77]. CoQ10 was shown to impair cognitive and sensory functions in mice when taken at high levels (2.6 mg/g or greater, as in the Cascella study which used 3.1 mg/g) [10,78].

### **Molecular Hydrogen**

Lin et al. showed protection against TTS and accelerated recovery of distortion product otoacoustic emissions (DPOAEs), a measure of outer hair cell function, using molecular hydrogen [11]. Molecular hydrogen is a known therapeutic and preventive antioxidant that selectively reduces the hydroxyl radical, the most cytotoxic of the ROS [79]. To test its otoprotective abilities, guinea pigs received either plain water or hydrogen-rich water for 14 days prior to noise exposure. The animals then received 115 dB SPL 4 kHz octave band noise for 3 hours. All animals underwent auditory brainstem response (ABR) and DPOAE testing before treatment and then immediately, 1, 3, 7 and 14 days post noise exposure. Compared to plain water controls, the ABR thresholds at 2 and 4 kHz were significantly better in the hydrogen-supplemented animals on post-noise days 1, 3 and 14. The hydrogen-treated animals also showed greater amplitude of DPOAE input/output growth functions during recovery with statistical significance

on post-noise days 3 and 7. This study further supports the antioxidant theory of otoprotection and suggests that hydrogen can facilitate hair cell recovery following noise exposure and attenuate TTS.

### **Vasodilation of Cochlear Arterioles**

#### **Magnesium**

Severe or prolonged noise exposure decreases cochlear blood flow, resulting in diminished oxygen and nutrient delivery to hair cells and waste product buildup [12]. Magnesium may exert its otoprotective effects by inducing vasodilation of cochlear arterioles, thus minimizing ischemia [80]. Magnesium may also block the cellular apoptosis pathway in inner hair cells by reducing calcium influx into cells and may reduce ROS ototoxicity in outer hair cells [81]. Long-term administration of magnesium after gunshot impulse noise exposure was shown to improve hearing thresholds in guinea pigs [80]. Conversely, magnesium deficiency was found to increase susceptibility to NIHL in rats and guinea pigs [82,83]. However, Le Prell et al. in 2007 found no otoprotection from magnesium alone [9]. Two human trials demonstrated protection from permanent noise-induced threshold shifts in subjects administered supplemental oral magnesium [84,85].

### **Cochlear hes-1 Expression Suppression**

#### **Dexamethasone**

Corticosteroid therapy inhibits apoptosis, reduces inflammation and activates pro-survival pathways in the organ of Corti following noise exposure. Dexamethasone has been shown to target the trans-differentiation pathway to establish new outer hair cells [19]. Although auditory hair cells develop only during the embryonic stage and do not regenerate postnatally, supporting cells on the organ of Corti can trans-differentiate into hair cells when provided with the appropriate signals [86]. Positive basic helix-loop-helix (bHLH) transcription factors such as Math1 are required for inner ear hair cell differentiation [87]. The negative bHLH transcription factor hairy and enhancer of split 1 (Hes1) negatively regulates such differentiation [88]. The Wang study showed that dexamethasone suppresses cochlear Hes1 expression in guinea pigs after noise exposure by way of a glucocorticoid receptor mediated mechanism [19]. This suppression theoretically perpetuates auditory hair cell trans-differentiation and prevents overly diminished outer hair cell numbers and sensorineural hearing loss (SNHL). While steroids control inflammation and may cause regeneration of cochlear outer hair cells, these agents are not approaching clinical trials at this time. Further, systemic steroid administration presents serious risks such as hyperglycemia, immunosuppression and osteonecrosis, rendering it a less desirable choice for NIHL prophylaxis [22,26,27].

### **Apoptosis Pathway Inhibition**

Other agents such as calcium and calcineurin inhibitors, caspase inhibitors and inhibitors of the Jun-N terminal kinase have shown some protection against NIHL [13-17]. However, apoptosis pathway inhibitors present increased risks of infection and cancer. Calcineurin inhibitors have been associated with calcineurin pain syndrome, which appears to result from the interruption of the physiologic function of calcineurin [89]. While these agents may have other uses, they may not be safe for systemic, chronic administration for NIHL.

### **Conclusion**

Noise induced hearing loss affects millions of Americans in various industries, including military, construction, aeronautics,

music, manufacturing and law enforcement. It is the most common cause of hearing loss worldwide [90]. Auditory acoustic trauma from overstimulation of hair cells and mechanical damage leads to excessive production of ROS/RNS, followed by hair cell damage and SNHL [91]. Presently there is no FDA-approved agent for prevention of NIHL, but there are several agents in or approaching clinical trials with encouraging results. These pharmacologic agents exert their otoprotective effects by either preventing or minimizing hair cell death initially or through rescue, i.e., within a few hours after noise exposure before permanent hearing loss. Because the ideal agent for common clinical use is an oral agent with a known safety profile, the agents approaching clinical trials are typically of the antioxidant category (D-met, NAC, Ebselen, ACE Mg, Acuval, CoQ10 and molecular hydrogen). D-met is promising because of its safety profile, convenience, opportunity for rescue and efficacy against PTS. Ebselen also shows protection against PTS and is likewise available in oral form. NAC has demonstrated mixed results in trials. The combination of vitamins A ( $\beta$  carotene), C and E with magnesium has shown otoprotective efficacy, but  $\beta$  carotene is contraindicated in smokers because of increased lung cancer risk, magnesium should not be used in chronic renal failure patients and vitamin E (as well as NAC) increase the risk of prostate cancer. Another antioxidant formulation, Acuval, combined with CoQ10 has demonstrated protection against NIHL, but again, cannot be used in all patient populations. Ginkgo biloba, contained in Acuval, may increase the risk of bleeding and CoQ10 may impair cognitive functions. Molecular hydrogen may protect against NIHL, but the practicality of this agent is unclear. Dexamethasone has traditionally been employed as an otoprotective agent, however many unwelcome side effects accompany systemic steroid use, rendering these agents less than ideal options. Apoptosis pathway inhibitors offer otoprotective qualities, yet their risk profiles again prevent chronic, systemic administration from being a viable option strictly for NIHL prevention.

It should be noted that the majority of studies testing otoprotective agents have used steady state noise exposures below 126 dB SPL or impulse noise exposures simulating M-16 weapon fire (155 peSPL) [5,7,9,40]. However recent studies suggest that antioxidants may also provide at least partial but significant protection from blast-induced PTS and changes in DPOAEs [92]. Whether or not otoprotective agents will also protect against combined chemical and noise exposures that occur in many work environments has not yet been established [93]. However the potential of otoprotective agents to at least reduce the incidence and severity of noise-induced hearing loss appears to be high.

It is unlikely that any single agent will work for every scenario and every patient. Just as it is necessary to have a variety of agents capable of treating hypertension and diabetes, it would be similarly worthwhile to have a multitude of agents available to protect against NIHL in different patient populations. It is probable that in the future patients and providers will be afforded such options.

## References

- Mahboubi H, Zardouz S, Oliaei S, Pan D, Bazargan M, et al. (2012) Noise-induced hearing threshold shift among US adults and implications for noise-induced hearing loss: National Health and Nutrition Examination Surveys. *Eur Arch Otorhinolaryngol*.
- Yang WP, Henderson D, Hu BH, Nicotera TM (2004) Quantitative analysis of apoptotic and necrotic outer hair cells after exposure to different levels of continuous noise. *Hear Res* 196: 69-76.
- Seidman MD, Quirk WS, Shirwany NA (1999) Mechanisms of Alterations in the Microcirculation of the Cochlea. *Ann N Y Acad Sci* 884: 226-232.
- Clerici WJ, DiMartino DL, Prasad MR (1995) Direct effects of reactive oxygen species on cochlear outer hair cell shape in vitro. *Hear Res* 84: 30-40.
- Campbell KC, Meech RP, Klemens JJ, Gerber MT, Dyrstad SS, et al. (2007) Prevention of noise and drug-induced hearing loss with D-methionine. *Hear Res* 226: 92-103.
- Coleman JK, Kopke RD, Liu J, Ge X, Harper EA, et al. (2007) Pharmacological rescue of noise induced hearing loss using N-acetylcysteine and acetyl-L-carnitine. *Hear Res* 226: 104-113.
- Lynch ED, Gu R, Pierce C, Kil J (2004) Ebselen-mediated protection from single and repeated noise exposure in rat. *Laryngoscope* 114: 333-337.
- Yu N, Li X, Hu B (1999) The effects of salicylate on noise-induced hearing loss in the guinea pig. *Zhonghua Er Bi Yan Hou Ke Za Zhi* 34: 344-346.
- Le Prell CG, Hughes LF, Miller JM (2007) Free radical scavengers vitamins A, C, and E plus magnesium reduce noise trauma. *Free Radic. Biol Med* 42: 1454-1463.
- Cascella V, Giordano P, Hatzopoulos S, Petrucci J, Prosser S, et al. (2012) A new oral otoprotective agent. Part 1: Electrophysiology data from protection against noise-induced hearing loss. *Med Sci Monit* 18: BR1-BR8.
- Lin Y, Kashio A, Sakamoto T, Suzukawa K, Kakigi A, et al. (2011) Hydrogen in drinking water attenuates noise-induced hearing loss in guinea pigs. *Neurosci Lett* 487: 12-16.
- Miller JM, Ren TY, Dengerink HA, Nuttall AL (1996) Cochlear blood flow changes with short sound stimulation. *Scientific Basis of Noise-Induced Hearing Loss*. Thieme Medical Publishers, New York, USA.
- Uemaetomari I, Tabuchi K, Hoshino T, Hara A (2005) Protective effect of calcineurin inhibitors on acoustic injury of the cochlea. *Hear Res* 209: 86-90.
- Abaamrane L, Raffin F, Schmerber S, Sendowski I (2011) Intracochlear perfusion of leupeptin and z-VAD-FMK: influence of antiapoptotic agents on gunshot-induced hearing loss. *Eur Arch Otorhinolaryngol* 268: 987-993.
- Suckfuell M, Canis M, Strieth S, Scherer H, Haisch A (2007) Intratympanic treatment of acute acoustic trauma with a cell-permeable JNK ligand: a prospective randomized phase I/II study. *Acta Otolaryngol Sep*: 127: 938-942.
- Heinrich UR, Maurer J, Mann W (1999) Ultrastructural evidence for protection of the outer hair cells of the inner ear during intense noise exposure by application of the organic calcium channel blocker diltiazem. *ORL J Otorhinolaryngol Relat Spec* 61: 321-327.
- Shen H, Zhang B, Shin JH, Lei D, Du Y, et al. (2007) Prophylactic and therapeutic functions of T-type calcium blockers against noise-induced hearing loss. *Hear Res* 226: 52-60.
- Ghosh A, Jackson R (2005) Best evidence topic report. Steroids in sudden sensorineural hearing loss. *Emerg Med J* 22: 732-733.
- Wang B, Liu Y, Chi F, Zhang Y, Yang M, et al. (2012) Dexamethasone Suppresses Cochlear Hes1 Expression After Noise Exposure. *Acta Otolaryngol*.
- Li J, Wang X, Zhou C, Liu L, Wu Y, et al. (2012) Perioperative glucocorticosteroid treatment delays early healing of a mandible wound by inhibiting osteogenic differentiation. *Injury* 43: 1284-1289.
- Maddux JM, Moore WE, Keeton KS, Shull RM (1988) Dexamethasone-induced serum biochemical changes in goats. *Am J Vet Res* 49: 1937-1940.
- Rohrmeier C, Koemm N, Babilas P, Prahns P, Strutz J, et al. (2012) Sudden sensorineural hearing loss: systemic steroid therapy and the risk of glucocorticoid-induced hyperglycemia. *Eur Arch Otorhinolaryngol*.
- Nakamoto H, Suzuki H, Kageyama Y, Ohishi A, Murakami M, et al. (1991) Characterization of alterations of hemodynamics and neuroendocrine hormones in dexamethasone induced hypertension in dogs. *Clin Exp Hypertens A* 13: 587-606.
- Reid IR (1989) Pathogenesis and treatment of steroid induced osteoporosis. *Clin Endocrinol* 30: 83-103
- Kanda F, Okuda S, Matsushita T, Takatani K, Kimura KI, et al. (2001) Steroid myopathy: pathogenesis and effects of growth hormone and insulin-like growth factor-I administration. *Horm Res* 1: 24-28.
- Usher BW, Friedman RJ (1995) Steroid-induced osteonecrosis of the humeral head. *Orthopedics* 18: 47-51.

27. Craddock CG (1978) Corticosteroid-induced lymphopenia, immunosuppression and body defence. *Ann Intern Med* 88: 564-566.
28. Thomson CD, Chisholm A, McLachlan SK, Campbell JM (2008) Brazil nuts: an effective way to improve selenium status. *Am J Clin Nutr* 87: 379-384.
29. National Nutrient Database for Standard Reference, National Agricultural library, U.S. Department of Agriculture.
30. Yamane H, Nakai Y, Takayama M, Iguchi H, Nakagawa T, et al. (1995) Appearance of free radicals in the guinea pig inner ear after noise-induced acoustic trauma. *Eur Arch Otorhinolaryngol* 252: 504-508.
31. Evans P, Halliwell B (1999) Free radicals and hearing. Cause, consequence, and criteria. *Ann N Y Acad Sci* 884: 19-40.
32. Abi-Hachem R, Zine A, Van De Water TR (2010) The Injured Cochlea as a Target for Inflammatory Processes, Initiation of Cell Death Pathways and Application of Related Otoprotective Strategies. *Recent Pat CNS Drug Discov* 5: 147-163.
33. Ohlemiller KK, Wright JS, Dugan LL (1999) Early elevation of cochlear reactive oxygen species following noise exposure. *Audiol Neurootol* 4: 229-236.
34. Bielefeld EC, Hu BH, Harris KC, Henderson D (2005) Damage and threshold shift resulting from cochlear exposure to paraquat-generated superoxide. *Hear Res* 207: 35-42.
35. Yamasoba T, Nuttall AL, Harris C, Raphael Y, Miller JM (1998) Role of glutathione in protection against noise-induced hearing loss. *Brain Res* 784: 82-90.
36. Ohinata Y, Miller JM, Altschuler RA, Schacht J (2000) Intense noise induces formation of vasoactive lipid peroxidation products in the cochlea. *Brain Res* 878: 163-173.
37. Ohlemiller KK, McFadden SL, Ding DL, Lear PM, Ho YS (2000) Targeted mutation of the gene for cellular glutathione peroxidase (Gpx1) increases noise-induced hearing loss in mice. *J Assoc Res Otolaryngol* 1: 243-254.
38. Ohlemiller KK, McFadden SL, Ding DL, Flood DG, Reaume AG, et al. (1999) Targeted deletion of the cytosolic Cu/Zn-superoxide dismutase gene (Sod1) increases susceptibility to noise-induced hearing loss. *Audiol Neurootol* 4: 237-246.
39. Hu BH, Zheng XY, McFadden SL, Kopke RD, Henderson D (1997) R-phenylisopropyladenosine attenuates noise-induced hearing loss in the chinchilla. *Hear Res* 113: 198-206.
40. Kopke RD, Coleman JK, Liu J, et al. (2002) Enhancing intrinsic cochlear stress defenses to reduce noise-induced hearing loss. *The Laryngoscope* 112: 1515-1532.
41. Kopke RD, Jackson RL, Coleman JK, Liu J, Bielefeld EC, et al. (2007) NAC for noise: from the bench top to the clinic. *Hear Res* 226: 114-125.
42. Tanaka K, Sugahara K, Okuda T, Takeno K, Mikuriya T, et al. (2005) Post-exposure administration of edaravone attenuates noise-induced hearing loss. *Eur J Pharmacol* 522: 116-121.
43. Korver KD, Rybak LP, Whitworth C, Campbell KC (2002) Round window application of D-methionine provides complete cisplatin otoprotection. *Otolaryngol Head Neck Surg* 126: 683-689.
44. Campbell K, Claussen A, Meech R, Verhulst S, Fox D, et al. (2011) D-Methionine (D-met) Significantly Rescues Noise Induced Hearing Loss: Timing Studies. *Hear Res* 282: 138-144.
45. Samson J, Wiktorek-Smagur A, Politanski P, Rajkowska E, Pawlaczyk-Luszczynska M, et al. (2008) Noise-induced time-dependent changes in oxidative stress in the mouse cochlea and attenuation by D-methionine. *Neuroscience* 152: 146-150.
46. Cheng PW, Liu SH, Young YH, Hsu CJ, Lin-Shiau SY (2008) Protection from noise-induced temporary threshold shift by D-methionine is associated with preservation of ATPase activities. *Ear Hear* 29: 65-75.
47. Vogt W (1995) Oxidation of methionyl residues in proteins: tools, targets, and reversal. *Free Radic Biol Med* 18: 93-105.
48. Lu SC (1998) Regulation of hepatic glutathione synthesis: current concepts and controversies. *Faseb J* 13: 1169-1183.
49. Fernandez-Checa JC, Kaplowitz N, Garcia-Ruiz C, Colell A (1998) Mitochondrial glutathione: importance and transport. *Semin Liver Dis* 18: 389-401.
50. Hyde GE, Rubel EW (1995) Mitochondrial role in hair cell survival after injury. *Otolaryngol Head Neck Surg* 113: 530-540.
51. Ghibelli L, Fanelli C, Rotilio G, Lafavia E, Coppola S, et al. (1998) Rescue of cells from apoptosis by inhibition of active GSH extrusion. *FASEB J* 12: 479-486.
52. Ohinata Y, Miller JM, Schacht J (2003) Protection from noise-induced lipid peroxidation and hair cell loss in the cochlea. *Brain Res* 966: 265-273.
53. Lorito G, Giordano P, Petruccioli J, Martini A, Hatzopoulos S (2008) Different strategies in treating noise induced hearing loss with N-acetylcysteine. *Med Sci Monit* 14: 159-164.
54. Bielefeld EC, Kopke RD, Jackson RL, Coleman JK, Liu J, et al. (2007) Noise protection with N-acetyl-L-cysteine (NAC) using a variety of noise exposures, NAC doses, and routes of administration. *Acta Otolaryngol* 127: 914-919.
55. Fetoni AR, Ralli M, Sergi B, Parrilla C, Troiani D, et al. (2009) Protective effects of N-acetylcysteine on noise-induced hearing loss in guinea pigs. *Acta Otorhinolaryngol Ital* 29: 70-75.
56. Duan M, Qiu J, Laurell G, Olofsson A, Counter SA, et al. (2004) Dose and time-dependent protection of the antioxidant N-L-acetylcysteine against impulse noise trauma. *Hear Res* 192: 1-9.
57. Hamernik RP, Qiu W, Davis B (2008) The effectiveness of N-acetyl-L-cysteine (L-NAC) in the prevention of severe noise-induced hearing loss. *Hear Res* 239: 99-106.
58. Kopke RD, Weisskopf PA, Boone JL, Jackson RL, Wester DC, et al. (2000) Reduction of noise-induced hearing loss using L-NAC and salicylate in the chinchilla. *Hear Res* 149: 138-146.
59. Kopke RD, Coleman JK, Huang X, et al. (2001) Novel strategies to prevent and reverse noise induced hearing loss. Noise Research Network, London.
60. Kopke R, Bielefeld E, Liu J, Zheng J, Jackson R, et al. (2005) Prevention of impulse noise-induced hearing loss with antioxidants. *Acta Otolaryngol* 125: 235-243.
61. Kopke RD (2005) NAC for Noise: International Symposium-Pharmacologic Strategies for Prevention and Treatment of Hearing Loss and Tinnitus. Niagara Falls, Canada.
62. Pourbakht A, Yamasoba T (2003) Ebselen attenuates cochlear damage caused by acoustic trauma. *Hear Res* 181: 100-108.
63. Yamasoba T, Pourbakht A, Sakamoto T, Suzuki M (2005) Ebselen prevents noise-induced excitotoxicity and temporary threshold shift. *Neurosci Lett* 380: 234-238.
64. Lynch ED, Kil J (2005) Compounds for the prevention and treatment of noise-induced hearing loss. *Drug Discov Today* 10: 1291-1298.
65. Le Prell CG, Dolan DF, Bennett DC, Boxer PA (2011) Nutrient plasma levels achieved during treatment that reduces noise-induced hearing loss. *Transl Res* 158: 54-70.
66. Le Prell CG, Gagnon PM, Bennett DC, Ohlemiller KK (2011) Nutrient enhanced diet reduces noise-induced damage to the inner ear and hearing loss. *Transl Res* 158: 38-53.
67. Le Prell CG, Yamashita D, Minami S, Yamasoba T, Miller JM (2007) Mechanisms of noise-induced hearing loss indicate multiple methods of prevention. *Hear Res* 226: 22-43.
68. Omenn GS (1998) Chemoprevention of lung cancer: the rise and demise of beta-carotene. *Annu Rev Public Health* 19: 73-99.
69. Omenn GS (2007) Chemoprevention of lung cancers: lessons from CARET, the beta-carotene and retinol efficacy trial, and prospects for the future. *Eur J Cancer Prev* 16: 184-191.
70. Navarro-González JF, Mora-Fernández C, García-Pérez J (2009) Clinical implications of disordered magnesium homeostasis in chronic renal failure and dialysis. *Semin Dial* 22: 37-44.
71. Klein EA, Thompson IM Jr, Tangen CM, Crowley JJ, Lucia MS, et al. (2011) Vitamin E and the risk of prostate cancer: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). *JAMA* 306: 1549-1556.
72. Martinez EE, Anderson PD, Logan M, Abdulkadir SA (2012) Antioxidant treatment promotes prostate epithelial proliferation in nx3.1 mutant mice.

73. Turunen M, Olsson J, Dallner G (2004) Metabolism and function of coenzyme Q. *Biochim Biophys Acta* 1660: 171–179.
74. Fetoni AR, Piacentini R, Fiorita A, Paludetti G, Troiani D (2009) Water-soluble Coenzyme Q10 formulation (Q-ter) promotes outer hair cell survival in a guinea pig model of noise induced hearing loss (NIHL). *Brain Res* 1257: 108–116.
75. Corvi Mora P, Canal T, Fortuna F, Ruzzier F (2005) An Innovative Technology For Improving Solubility And Antioxidant Properties Of Coenzyme Q10. Oxygen Society of California Congress “Oxidants And Antioxidants In Biology”, Alba.
76. Corvi Mora P, Canal T, Fortuna F, Ruzzier F (2007) Composition containing micronutrients with improved anti-oxidant activity and the use there of.
77. Bent S, Goldberg H, Padula A, Avins AL (2005) Spontaneous bleeding associated with Ginkgo biloba: a case report and systematic review of the literature. *J Gen Intern Med* 20: 657-661.
78. Sumien N, Heinrich KR, Shetty RA, Sohal RS, Forster MJ (2009) Prolonged intake of coenzyme Q10 impairs cognitive functions in mice. *J Nutr* 139: 1926-1932.
79. Ohsawa I, Ishikawa M, Takahashi K, Watanabe M, Nishimaki K (2007) Hydrogen acts as a therapeutic antioxidant by selectively reducing cytotoxic oxygen radicals. *Nat Med* 13: 688–694.
80. Abamrane L, Raffin F, Gal M, Avan P, Sendowski I (2009) Long-term administration of magnesium after acoustic trauma caused by gunshot noise in guinea pigs. *Hear Res* 247: 137–145.
81. Sendowski I (2006) Magnesium therapy in acoustic trauma. *Magnes Res* 19: 244-254.
82. Joachims Z, Babisch W, Ising H, Günther T, Handrock M (1983) Dependence of noise-induced hearing loss upon perilymph magnesium concentration. *J Acoust Soc Am* 74: 104–108.
83. Ising H, Handrock M, Gunther T, Fischer R, Dombrowski M (1982) Increased noise trauma in guinea pigs through magnesium deficiency. *Arch Otorhinolaryngol* 236: 139–146.
84. Attias J, Weisz G, Almog S, Shahar A, Wiener M, et al. (1994) Oral magnesium intake reduces permanent hearing loss induced by noise exposure. *Am J Otolaryngol* 15: 26-32.
85. Joachims Z, Netzer A, Rebentisch E, Rebentisch E, Attias J et al. (1993) Oral magnesium supplementation as prophylaxis for noise-induced hearing loss: results of a double blind field study. *Schriftner Ver Wasser Boden Luftthyg* 88: 503-516.
86. Shou J, Zheng JL, Gao WQ (2003) Robust Generation of New Hair Cells in the Mature Mammalian Inner Ear by Adenoviral Expression of Hath1. *Mol Cell Neurosci* 23: 169-179.
87. Kageyama R, Nakanishi S (1997) Helix-loop-helix factors in growth and cell differentiation of the vertebrate nervous system. *Curr Opin Genet Div* 7: 659-665.
88. Zheng JL, Shou J, Guillemot F, Kageyama R, Gao WQ (2000) Hes1 is a negative regulator of inner ear hair cell differentiation. *Development* 127: 4551-4560.
89. Prommer E (2012) Calcineurin-inhibitor pain syndrome. *Clin J Pain* 28: 556-559.
90. National Institute on Deafness and Other Communication Disorders.
91. Forge A, Van De Water TR (2008) Hair Cell Regeneration, Repair and Protection. Protection and Repair of Inner Ear Sensory Cells. Springer Handbook in Auditory Research Series, USA.
92. Ewert DL, Lu J, Li W, Du X, Floyd R, et al. (2012) Antioxidant Treatment Reduces Blast-induced Damage and Hearing Loss. *Hear Res* 285: 29-39.
93. Leroux T, Klaeboe R (2012) Combined Exposures: An Update from the International Commission on Biological Effects of Noise. *Noise Health* 14: 313-314.

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