Pharmaceutical Interventions for Noise-Induced Hearing Loss–Acute Exposure Treatment (PINIHL-AET)

The University of Akron
School of Speech Language Pathology and Audiology
Polsky Building
225 South Main Street
Akron OH 44325-3001

Protocol#: PINIHL-UA
Version #: 7.0
Version Date: 23 MARCH 2022

ClinicalTrials.gov #: NCT04774250
IND: 147812

Signature Page:

Clinical Study Protocol No. PINIHL-UA v7.0

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I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol.

Kristine Sonstrom Malowski, AuD PhD		03/23/2022
Principal Investigator Name: (Printed)	Signature	Date

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Protocol Revision History

Version Date	Revision Summary
19 January 2021	Initial Approval Version
14 February 2021	Addition of Drs. Craig Buchman and Thomas Rench as sub-investigators.
19 February 2021	• Addition of baseline and follow-up blood draws that includes an electrolyte panel, BUN, Cr, ALT, and AST; serum pregnancy test at baseline • Addition of effective birth control instruction
10 June 2021	• Addition of NIOSH red flag guideline (an increase in hearing threshold level of 15 dB or more at any frequency (2, 3, 4, 6 kHz) in either ear for permanent threshold shift as a secondary endpoint. • Change in sample size • Removal of saliva collection and inclusion of blood draw for DNA analysis. • Inclusion criteria corrected. • Addition of primary and secondary efficacy measures to study design (section 4.0) • Added detail and updated modifications to tests within scheduled assessments (section 5.1) and follow-up assessments (5.5) • Updated cognitive test section to reflect specific measures being used (5.0) • Clarified wording for evaluability section (section 6.0) • Removed NEQ and HHIA Questionnaires from appendix and assessment (5.0) section • Added 1-Minute Noise Screen Questionnaire to appendix and assessment section (5.0) • Corrected timing of evaluation for post-dose drug related adverse events from 2 weeks to 30 days (6.0) • Delineated and updated study calendar to reflect each visit for when assessments and questionnaires are administered (9.0) • Clarified which assessments would be administered at what visit in each of the assessment sections (screening, baseline and follow-up visits) (5.0)

	• Removed PI and Sub-Investigator information (cover page) • List protocol version as a separate line (cover page) • Name change of form "Audiologic and Medical History" to "Case History". • Clarification of when clinical ear exam will be performed (5.0, 9.0) • Statistical Considerations section updated to match SAP (12.0)
21 October 2021	• Inclusion of stratification table for noise exposure (5.2) • Randomization language updated (4.0)
09 November 2021	• Clarification of language for secondary outcomes analysis criteria
21 January 2022	• Addition of section "Blood collection, transportation, and storage"
23 March 2022	• Addition of audiometry language in situations of an absence of a threshold.

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1.0 BACKGROUND AND SIGNIFICANCE

1.1 Noise-induced hearing loss (NIHL)

Noise-induced hearing loss (NIHL) is a serious problem. When a service member leaves the military, hearing loss can impact his or her quality of life and employability (Pfannenstiel, 2014). Service members are vulnerable to two types of NIHL: occupational NIHL due to continuous or intermittent noise exposure and acoustic trauma due to a sudden burst of sound. Because no form of hearing protection offers complete protection against noise of that intensity, repeated firing of weapons even with ear protection devices can subsequently lead to occupational NIHL (Chen and Brueck, 2011). Almost every member of the armed forces will be exposed to hazardous noise at some point in his or her career (McIlwain et al., 2008; Kirchner et al., 2012; Yankaskas, 2013), highlighting the urgent need for pharmaceutical intervention. Despite positive outcomes in preclinical studies, to date, no drugs have been approved by the U.S. Food and Drug Administration (FDA) for use in the amelioration of NIHL (Le Prell and Bao, 2012; Mukherjea et al., 2015).

1.2 NIHL and its Pathogenesis

After noise exposure, two phases of hearing loss can be measured. The first is a temporary threshold shift (TTS), which is greatest immediately after noise exposure, and gradually lessens within the first 24 hours. The second phase is a permanent threshold shift (PTS), which is measured two to three weeks after noise exposure (for recent review, Ryan et al., 2016; Liberman, 2016). These changes are typically monitored using behavioral pure-tone thresholds, distortion product otoacoustic emissions (DPOAE), or the auditory brainstem response (ABR) to generate an audiogram (a plot of threshold as a function of test frequency). The noise-induced damage is dependent on the noise pattern, intensity, and duration, with longer and louder noises being more hazardous than shorter or quieter sound exposures (Wang et al., 2002; Harding and Bohne, 2007; Chen et al., 2015). In addition, NIHL susceptibility differs markedly among individuals, resulting from the interaction of genetic and environmental factors (Clifford et al., 2016; Groth et al., 2016; Lavinsky et al., 2016). For example, in animals, the C57BL/6J mouse strain is more susceptible to noise than other mouse strains (Davis et al., 2001). In humans, individuals with specific single nucleotide polymorphisms (SNPs) in genes for certain antioxidant enzymes may be more susceptible to NIHL (Lin et al., 2009) and a recent study developed a genetic risk score for the likelihood of NIHL based on genetic markers (Zhang et al., 2019). Over 100 loci associated with syndromic and non-syndromic hearing loss provide excellent biomarkers for PGx studies and are easily surveyed in genetic screening protocols (e.g. Pawelczyk et al., 2009; Konings et al., 2009; Grondin et al., 2015). Furthermore, known genetic variation is associated with the metabolism of anti-epileptic drugs including zonisamide (Saruwatari et al., 2010) and could be used to predict patient populations that are both responsive and non-responsive to drug treatments.

Finally, methodologies are currently under development to predict genotypic variation based on audiographic profiles that could in practice be integrated with genetic data (https://audiogene.eng.uiowa.edu/) facilitating the statistical analysis of drug efficacy in clinical trials.

NIHL is caused by sensorineural damage, primarily to the sensory hair cells and primary auditory neurons of the cochlea (Liberman, 2017). Outer hair cells (OHCs) are particularly sensitive to noise. When OHCs are damaged, hearing thresholds increase due to a loss in amplification of the cochlear signal. Recently, Kujawa and Liberman (2006, 2009) have expanded on these classic findings with the observation that certain noise exposures at "benign" levels to rodents can result in only TTS, but no PTS. Nevertheless, the animals show selective synaptic loss between inner hair cells (IHCs) and spiral ganglion neurons (SGNs) with high thresholds, ultimately accelerating hearing loss over time. Because this cochlear synaptopathy does not change the hearing threshold immediately, the term "hidden hearing loss" has been used to label the hidden synaptopathic injury, and this term has also been used to describe corresponding functional deficits that are assumed to be hidden behind the normal hearing threshold.

Clinically, difficulties with understanding speech in noise have long been observed in older adults with normal audiometric thresholds (e.g. Frisina and Frisina, 1997). Loss of fidelity in the encoding of suprathreshold signals may provide one explanation for this deficit (Sergeyenko et al., 2013; Tremblay et al., 2015). Thus, there is the potential for profound functional consequences after a so-called benign noise exposure that led to only TTS. Of particular concern for military personnel with the potential for repeat exposure (Davis, 2016; Bramhall et al., 2017), further studies have found that benign noise exposures resulting in only TTS can also contribute to PTS after repeated exposure (Wang and Ren, 2012), underpinning the importance of developing pharmaceutical interventions to prevent noise-induced cochlear synaptopathy for military service members.

1.3 Molecular Pathways Underlying NIHL

Although mechanical destruction and decreased blood flow contribute to NIHL (Quirk et al., 1991; Mulroy et al., 1998), several key molecular mechanisms such as signaling mediated by an ATP receptor have been identified to contribute to TTS (for recent review, see Kurabi et al., 2017). Common mechanisms underlying both TTS and PTS have also been identified. One is the increase of mitochondrial free radical formation such as reactive oxygen species (ROS) due to noise-induced intense metabolic activity in the cochlea (e.g., Yamane et al., 1995; Ohlemiller et al., 1999; Ohinata et al., 2000; Henderson et al., 2006; Campbell et al., 2007; Darrat et al., 2007). Thus, it is not surprising that attempts to prevent NIHL with antioxidant agents have become the focus of much research in this field (Seidman et al., 1993; Hight et al., 2003; McFadden et al., 2005; Yamashita et al., 2005; for review, see Le Prell and Lobarinas, 2015). However, most of these interventions have been only partially effective or ineffective in preventing NIHL (Lynch and

Kil, 2005; Campbell et al., 2007; Kopke et al., 2007; Le Prell et al., 2007). The largely disappointing outcomes may be due to a narrow therapeutic window. As ROS signaling is also important for normal cellular function (for recent review, Sbodio et al., 2018), high doses of antioxidants may have less therapeutic benefit (for example, Kil et al., 2017). Recently, new signaling pathways underlying NIHL have been identified, including deregulation of calcium homeostasis (Guitton et al., 2004; Zine and Van De Water, 2004; Chen et al., 2012; Han et al., 2015; Chen et al., 2015). Deregulation of calcium signaling may contribute to development of both TTS and PTS. In addition, calcium signaling is upstream of many other cellular survival signaling pathways. For example, it can control ROS signaling by regulating the release of ROS from the mitochondrion (Estergerg et al., 2013, 2014). Calcium homeostasis in the cochlea can be regulated by several types of calcium channels, which include voltage-gated calcium channels (VGCCs) (Rodrigues Contreraz and Yamoah, 2001; Adamson et al., 2002; Fuchs, 2002; Schnee and Ricci, 2003). VGCCs can be divided into two groups: high-voltage-activated calcium channels and low-voltage-activated calcium channels (Igelmund et al., 1996; Lacinova et al., 2000; Perez-Reyes, 2003; Yunker and McEnery, 2003). The family of low-voltage-activated, or T-type, calcium channels (Cav3) is composed of three members (Cav3.1, Cav3.2, and Cav3.3) based on their respective main pore-forming alpha subunits: α 1G, α 1H, and α1I (Perez-Reyes, 2003; Yunker and McEnery, 2003). Our studies on drug repurposing have shown that a family of antiepileptic drugs blocking T-type calcium channels can prevent and treat NIHL (Shen et al., 2007; Bao et al., 2013). We have also determined the expression pattern of these calcium channels in the cochlea. All subtypes are present in SGNs, and α 1G and α 1I are expressed in the hair cells and supporting cells (Shen et al., 2007). Thus, it is not surprising that an antiepileptic drug (AED), zonisamide (ZNS), which blocks T-type calcium channels, has both prophylactic and therapeutic functions against NIHL (Bao et al., 2013). In addition, epidemiological studies show that ZNS is well-tolerated even for long-term treatment (Hashimoto et al., 1994; Leppik, 2006, White et al., 2010). These findings have led us to this project, which is the repurposing ZNS against NIHL for military service members.

1.4 NIHL and Pharmacogenetics

Preliminary results. Pharmacogenetics (PGx) is the study of how a person's genetic makeup determines his or her response to a therapeutic intervention. It offers the promise of utilizing genetic fingerprints to predict an individual's responses to drugs in terms of safety, efficacy, and pharmacokinetics. It can revolutionize the practice of medicine by individualizing treatment through the use of novel diagnostic tools.

Here, we provide three types of data from our PGx study of age-related hearing loss. They are highly pertinent because the same approaches will be applied to this project. First, we describe our recent clinical findings on the delay of ARHL in human subjects taking calcium channel blockers (CCBs). Second, we present our

preliminary human genetic studies of ARHL in the same population based on the continuous extreme phenotypes (CEP) and sequence kernel association test (SKAT) approaches. Third, we present an estimate of patient populations using the CEP-SKAT method.

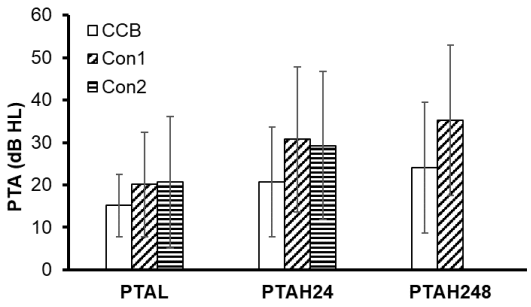

Fig. 1. CCB protection against ARHL. Participants taking CCBs show better hearing thresholds than participants taking no CCBs even at low frequency regions (0.25 to 1 kHz).

Delay of ARHL in patients taking CCBs. In our preliminary study, a total of 35 white female patients have completed their first visit, with 26 of them using amlodipine (74%) for more than one year. We compared this CCB group with two control cohorts, also of white females: control 1 group (Con 1) from the Rochester, NY, area (447 participants) and control 2 group (Con 2) from the St. Louis, MO, area (55 participants) (**Fig. 1**).

Since ARHL starts at higher frequencies in the cochlea, we divided audiograms into three pure tone averages (PTA): averages of 0.25, 0.5, and 1 kHz (PTAL); averages of 2 and 4 kHz (PTAH24); and averages of 2, 4, and 8 kHz (PTAH248). The means for the CCB group were: PTAL (15.1 dB HL), PTAH24 (20.7 dB HL), and PTAH248 (24.0 dB HL), and the means for the control 1 group were: PTAL (20.1 dB HL), PTAH24 (30.7 dB HL), and PTAH248 (35.2 dB HL). Since there were no data for 8 kHz for the control 2 group, the means for this group were PTAL (20.7, dB HL) and PTAH24 (29.3 dB HL). The two-tailed unequal variance t-test showed a significant difference between the CCB and the control 1 group for PTAL (p = 0.00067), PTAH24 (p = 0.00001), and PTAH248 (p = 0.00021), and a significant difference between the CCB and control 2 groups for PTAL (p = 0.02777) and PTAH24 (p = 0.00959). To correct for possible influences from both age and the three cohort sites, we used multivariate regression models with the Bonferroni correction method (**Table 1**, **2** and **3** for PTAL, PTAH24 and PTAH248, respectively). No significant difference was observed for PTAL between the CCB and control 1 or 2 groups (**Table 1**), or

Table 1. Least Squares Means with Bonferroni Correction Model 1

Cohort	LS Mean	Vs. Control 1 p-value	Vs. Control 2 p-value
CCB	19.77	1.0000	.9202
Control 1	20.28		.0784
Control 2	17.50		

Table 2. Least Squares means with Bonferroni Correction Model 2

Cohort	LS Mean	Vs. Control 1 p-value	Vs. Control 2 p-value
CCB	28.17	.0420*	1.0000
Control 1	35.19		.11
Control 2	28.54		

Table 3. Least Squares Means with Bonferroni Correction Model 3

Cohort	LS Mean	Vs. Control 1 p-value
CCB	32.41	.0145*
Control 1	39.28	

PTAH24 (**Table 2**) between the CCB and control 2 group. However, statistically significant differences were found for both PTAH24 and PTAH248 between the CCB and control 1 group (**Table 2** and **3**). These data indicate CCB had beneficial effects against peripheral ARHL.

The goal of this study is to increase the sensitivity of our clinical trial by identifying subgroups sensitive to NIHL prevention or treatment by ZNS. The expected high variability in individual responses to ZNS against NIHL is dependent on known factors such as age, sex, and previous hearing loss history, all of which are considered in the health survey during the initial screening process. However, unknown genetic variations in the participants can contribute to additional variable responses to ZNS against NIHL. PGx is the ideal approach to address this issue. Based on our preliminary studies, even with the sample size limitation, extreme ZNS protection phenotypes could still be identified, and sampling these individuals can enrich the presence of associated genetic variants. However, the dichotomization procedure used for most extreme phenotype sampling can reduce the analysis power due to a loss of sample size. The CEP-SKAT method can be used to avoid this issue by using continuous phenotypes in the analysis of extreme phenotype samples (Li et al., 2011; Barnett et al., 2012). Therefore, we will use this CEP-SKAT method to analyze our samples.

Pharmacogenetic testing will be performed by the Washington University School of Medicine Genome Technology Access Center.

1.5 NIHL in Police Officers

Both continuous and impulse-induced NIHL are sensorineural in nature. Unlike other injuries, sensorineural hearing loss will continue to progress with age (Kujawa and Liberman, 2006, 2009; Fausti et al., 2009). The incidence of hearing loss disability can increase four-fold after an average of only 4 years of active service among individuals with mild and moderate hearing loss prior to joining to the military (Gubata et al., 2013), suggesting NIHL from repeated noise exposure can cause more auditory damage in military service members with prior hearing loss. Similarly, police offices are repeatedly exposed to both continuous and impulse noises. A large population study of police officers (a total of 1880 subjects with 887 police officers) found that police officers were 1.4 times more likely to have a selective NIHL at 4 KHz than civil servants (Lesage et al., 2009). A subsequent study of 543 police officers found that of the officers identified with hearing loss, 93% presented with mild NIHL (26-40 dBA), 3.5% with moderate NIHL (41-60 dBA), and 3.5% with severe NIHL (61-80 dBA). Further analyses indicated a strong association of NIHL with age, duration of service and rank (Win et al., 2015). Several researchers have found NIHL across police populations. Lesage and colleagues (2009) found NIHL in 28% of police officers investigated, Shrestha and colleagues (2011) found NIHL in 66.4% of police personnel studied, and Gupta and colleagues (2015) found 22% of a police population presented with NIHL. Furthermore, tinnitus has been reported by several police officers across

studies (Singh & Mehta, 1999; Shrestha et al., 2011; Win et al., 2015; Thirugnanam et al., 2017). Based on this evidence, police officers are an ideal population for this project.

Hearing studies on police officers were performed by the current researchers in Northeast Ohio from 2017-2018 (Sonstrom Malowski & Steiger, 2020). Hearing assessments were performed on 30 police officers, ranging from 35-61 years of age. 40% of these individuals served in the military, 26% of these individuals were part of the SWAT team, and 10% of the population served for both the military and the SWAT team at some point of their career. Results indicated that 73% of the officers presented with some degree of permanent hearing loss. Specifically, 70% of the population presented with evidence of NIHL, as characterized by a sensorineural hearing loss with the greatest amount of loss at 4-6 kHz, seen as a notch or dip on the audiogram (McBride & Williams, 2001). Initial signs of NIHL may present as a distinct notch from 3-6 kHz even in the presence of "normal hearing," where thresholds fall at or above 25 dB HL, another observation observed from this study. Furthermore, evidence of NIHL was observed from absent otoacoustic emission recordings and absent high-frequency audiometric thresholds in the presence of normal audiometric results from .25-8 kHz. An increased sensitivity of OAEs in comparison to audiometric thresholds has been found whereby low-level OAEs indicate an increased risk of future hearing loss by as much as nine-fold (Marshall et al., 2009).

Hidden hearing loss was further investigated in a small sample of police officers in Rootstown, OH. Audiometric hearing thresholds were obtained from six graduate students and three campus police officers by using the Interacoustics® AD629 Diagnostic audiometer. Sennheiser HDA 200 headphones were used to obtain pure-tone air-conduction thresholds at 0.25, 0.5, 1, 3, 4, 6, 8, 10, 12, 14, and 16 kHz. For each test frequency, thresholds were assessed in 2 dB steps using ascending and descending runs in a modified Hughson-Westlake procedure (ANSI, 2009). The initial stimulus level for the ascending track was below the subject's audible threshold, whereas the initial stimulus level for the descending track was above the subject's behavioral threshold. Interestingly, two control subjects showed an increase of hearing thresholds only at 16 kHz, all three police officers showed an increase of hearing thresholds above 12.5 kHz, a sign of noise-induced hidden hearing loss (Liberman et al., 2016). In addition, all these three right-handed police officers have a notch at 6 kHz on their left ears. Asymmetric hearing losses were consistently observed across the officers tested. Thus, hidden hearing loss may be highly present for police officers.

One major obstacle to test drug candidates against NIHL is a lack of robust hearing loss (even as TTS) to testing possible drug protective effects (Le Prell et al., 2011). At the same time, a high percentage of police officers show permanent hearing loss after several years of service as seen with 70% of the officers tested in our preliminary studies. To further examine this paradox observation, we carried out a longitudinal study of police officers on our campus. One case, a female without

prior hearing loss, right-handed, demonstrated this phenomenon. Her audiogram performed in October 2017 was normal up to 12 kHz for both ears. However, a mild hearing loss was observed in her left ear at 6 kHz, and there are no obvious differences before and after one-hour shooting certification with 146 gun firing with M&P Shield and M&P 15 (about 156 dB SPL), which suggested a good hearing protection from her ear muffs, which offer a 34 dB SNR (Noise Reduction Rating) for noise cancelling. The only sign of noise-induced damage is a slight decrease of DPOAE amplitude near 3 kHz 5 minutes after the shooting. Thus, the repeated noise exposure during their service may contribute to a high incident of permanent hearing loss although the noise-induced damages are hard to detect immediately following each noise exposure.

The overarching goal of this study is to test whether ZNS can treat TTS and PTS in police officers on the range following training and certifications sessions. Participants will be randomized to receive either active treatment (ZNS) or placebo.

2.0 STUDY OBJECTIVES

2.1 Primary Objective

To determine if ZNS is more effective than placebo in preventing permanent threshold shift (PTS) in police officers identified with temporary threshold shift (TTS) following shooting range noise exposure.

2.2 Secondary Objectives

To determine if ZNS is more effective than placebo in the prevention of additional auditory dysfunction in police officers following shooting range noise exposure as measured by ultra-high frequency audiometry, distortion product otoacoustic emissions (DPOAE), electrocochleography (EcochG) and words-in-noise (WIN) scores, and to determine a PGx link between NIHL and ZNS treatment effect.

3.0 ELIGIBILITY CRITERIA

3.1a Screening Inclusion criteria

1. Police officers who are scheduled for firearm training and/or certification on the range.

2. At least 18 years of age.

3. Air conduction thresholds are to be no worse than 25 dB HL from 0.5 kHz to 3 kHz, no worse than 30 dB HL at 4 kHz, and no worse than 45 dB HL at 6 and 8 kHz prior to shooting range exposure.

4. Observed air-bone gap < 10 dB HL at .5, 1, 2 and 4 kHz, with normal tympanometry.

5. Ability to understand and willingness to sign an IRB approved written informed consent document.

3.1b Enrollment Inclusion Criteria

1. Observed audiometric TTS ≥ 10 dB HL at 2, 3, 4 and/or 6 kHz

3.2 Exclusion Criteria

1. History of known sulfa allergy or hypersensitivity to carbonic anhydrase inhibitors.

2. History of moderate-to-severe kidney or liver disease.

3. Acute viral, bacterial, fungal or parasitic infection.

4. History of seizures.

5. Currently pregnant or breast-feeding.

6. Any current or history of otologic disorder.

7. History of ototoxic drug use.

8. Current use of strong/moderate 3A4 inhibitor/inducer and grapefruit juice.

Note: For secondary outcomes analysis only, exclusion criteria is as follows:

a) DPOAE data will be used as a secondary outcome measure of TTS, and participants will be excluded if their DPOAE is absent at more than 4/10 frequencies. Criteria for a present response is any response that is > 5 dB SPL above the noise floor and replicable within ±5 dB SPL.
b) ECochG: Participants will be excluded if the ECochG/ABR wave I response is absent.
c) WIN test: Participants with WIN scores greater than moderate difficulty or 14.9 dB SNR will be excluded.

Participants will not be excluded from the study for not meeting secondary outcome criteria.

3.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

4.0 STUDY DESIGN

A randomized, double-blind, and placebo-controlled clinical trial has been designed.

Study participants will be recruited from the Akron Police Department, Summit County Police Department, and other local surrounding police departments. Police officers will be offered participation if they are training for firearm certification as part of their standard occupational requirements. These are officers that would be recommended and/or required to complete these trainings/certifications despite this investigation and this investigation will have no influence on audiologic recommendations.

The primary efficacy endpoint will be the proportion of PTS-positive subjects defined as the ratio of PTS-positive subjects to total number of subjects within each study arm/group. Subjects defined as PTS-positive will demonstrate an increase in threshold that is ≥10 dB HL at any frequency from 2-6 kHz post-shooting as compared to baseline audiogram.

The secondary efficacy outcome measures will be: (1) the proportion of PTS-positive subjects as defined above, but the definition of PTS will also include the NIOSH red flag guideline for permanent threshold shift: an increase in hearing threshold level of 15 dB or more at any frequency (2, 3, 4, 6 kHz). (2) The rate of temporary cochlear change as measured by a DPOAE amplitude shift at any frequency that is significantly greater than the stability of each measurement (i.e., 95% confidence interval of each measurement do not overlap). The rate of DPOAE shift is the ratio of DPOAE shift-positive subjects to total subjects within each arm.

Interested police officers will be consented and enrolled in the study. They will then undergo screening for TTS following shooting range noise exposure. Those officers identified with TTS will be randomized via an interactive randomization tool (IRT) and assigned to a study group. Once assigned the subject will be provided a kit that will contain either ZNS (100 mg PO) or a placebo. The ZNS and placebo capsules will look, taste, and smell the same. Participants will be instructed to take zonisamide without food. We will recommend that capsules be swallowed whole per the current approved labeling. Those without TTS will be finished with their study commitment.

The study will be “masked” or “blinded” in the sense that all the study participants and the study team members will be blinded to the assignment in the study groups. Only the pharmacist who will prepare the study drug kits and the unblinded statistician will have access to the kit assignments. The Medical Monitor will be contacted. A copy of the randomization list with study ID assignments will be saved in a limited access folder on a secure network server at Pharm-Olam. The Medical Monitor will

be contacted in emergent medical cases when knowing the treatments assignment is mandatory for clinical care of the study subject.

5.0 SCHEDULED ASSESSMENTS

5.1 Screening (Visit 1) and Baseline (Visit 2) Assessments

The screening assessment (Visit 1) will occur within 3 months of the first training session. The baseline assessment (Visit 2) will occur within one week of the first training following commencement of the study. These assessments will include the following tests or procedures:

1. Documentation of demographic information, including gender, age, allergies, and current medications (screening visit 1).

2. Clinical examination of the ears (screening and baseline visit 1 and 2).

3. Documentation of key clinical data such as confirmation of thresholds being $\leq$ 25 dB HL up to 4 kHz, $\leq$ 30 dB HL at 4 kHz, and $\leq$ 45 dB HL at 6 and 8 kHz, and the absence of any ear disorder (screening visit 1).

4. Blood draw for laboratory testing that include a serum pregnancy test*, electrolyte panel, BUN, Cr, ALT, and AST and DNA analysis will be collected (baseline visit 2).
   *Women capable of becoming pregnant will be asked to have a pregnancy test before beginning this study. Women capable of becoming pregnant will be instructed to use effective birth control methods and not to become pregnant while participating in this study as there may be unknown risks to the unborn child. There may be long-term effects of the treatment being studied that could increase the risk of harm to an unborn child. The study team must be notified if the birth control method fails while on the study and/or if the participant becomes pregnant while participating in this research study.

5. Audiogram, ECochG, DPOAE, and WIN testing to document baseline measurements (baseline visit 2).

   Audiometry: The audiogram will be performed to look for TTS and PTS. Earphones will be placed over the participant's ears and a series of tones at a soft volume will be played at varying frequencies. The participant indicates that they hear the tones by pressing a button. Thresholds will be measured from .025-16 kHz. If there is an absence of a threshold at the limits of the equipment, the threshold will be reported as equipment limits (in dB HL) + 10 dB HL. As with the DPOAE, all equipment and procedures are based on a clinically approved protocol. Each ear will be tested separately.

Electrocochleography (ECochG): An ECochG is an electrophysiological measurement of the cochlea in response to sound. It is a clinically-approved auditory evoked potential that is used to evaluate the status of both the cochlea and the auditory nerve fiber. This measurement is obtained by inserting a soft gold-foiled earphone into the participant's ear. This earphone serves to deliver a series of clicks, as well as an electrode to measure the electrophysiological response of the cochlea to the sound. The electrode montage is completed with a ground electrode on the forehead at midline and a gold-foil electrode in the contralateral ear to serve as the inverting electrode. The impedance between electrodes will be < 3 kΩ for all participants. The click stimuli at 90 dB nHL used for the study will be repeated 2000 times so that the recording signal can be averaged with artifact rejection. The measurement will be repeated three times. Testing time will take 45 minutes to 1 hour.

Distortion Product Otoacoustic Emissions (DPOAE): DPOAEs are a measure of outer hair cell function and will be used as an indicator of changes in cochlear health and possible PTS in the early period following noise exposure. A soft earphone will be inserted into the participant's ear and a series of tones at a comfortable volume will be played at varying frequencies. No participation is required of the participant as DPOAE are an objective assessment of cochlear health. The measurement system (Interacoustics Titan DPOAE440) will record the level of the emissions evoked by two primary tones, f1 and f2 (f2/f1 = 1.22) at levels 65 and 55 dB SPL respectively. The f2 primary tone will be swept from 1- 6 kHz, and will be repeated at least five times per session in order to calculate the stability of the emission at each session. All data will be identified and stored on a password protected computer. DPOAE recording will take about 20 minutes to complete.

Words in Noise Test (WIN): Earphones will be placed over the participant's ears and the WIN test will presented to each ear separately. The WIN test battery consists of 35 words that are presented in a background noise (speech babble) with varying degrees of signal-to-noise ratios (SNR) from 24 dB HL to 0 dB HL. The babble is set at 80 dB SPL, and the target word levels decrease from 104 dB SPL to 80 dB SPL. The SNR at 24 dB HL is the easiest, with words presented at 24 dB above the noise background, whereas the SNR of 0 dB is the most difficult with target words being presented at the same level as the background noise (Wilson and Burks, 2005; Wilson and Watts, 2012). The WIN will be repeated three times in order to assess test-retest reliability. The total number of words correctly identified will be used to calculate a dB HL S/N threshold by the Spearman-Karber equation at the mean of 50% correct points. All of speech testing will take 10-15 minutes to complete.

6. Baseline sound measurements will be obtained at the start of each test session, including the peak ambient noise level and the average noise level (screening and baseline visit 1 and 2).

7. Completion of participant questionnaires, including (screening visit 1):
   a. Case history form
   b. Life Exposure to Noise and Solvents (LENS-Q) (Full)
   c. Life Exposure to Noise and Solvents (LENS-Q) (Adapted)
   d. Tinnitus Functional Index (TFI)

8. Completion of baseline cognitive assessments, including (baseline visit 2):
   a. Digit-symbol substitution test: Measures processing speed
   b. List learning task/RBANS: Measures memory function.
   c. Verbal fluency test (word finding task): Measures working memory, speech/language.
   d. Stroop test: Measures executive functioning (vigilance, attention, inhibition).

All data will be identified and stored on a password protected computer.

5.2 Randomization

Following identification of TTS, eligible participants will be randomized via an interactive randomization tool (IRT) in a balanced fashion into one of two study groups: ZNS (100 mg PO) or placebo. Randomization will be based on a randomization list generated from the study statistician using a computer algorithm written in SAS using randomly selected blocks of sizes 2. Within each block of 2, there will be 1 subject assigned to each study group. To balance noise-exposure history across study arms we will employ stratified randomization. The subjects will be stratified based on noise exposure survey responses (see table below), and will then be randomized to study groups. The random assignment of subjects to the different study groups will be associated with consecutively assigned study identification numbers (Study ID) which will be unique for each study participant. The stratified randomization kit list will be provided to Advanced Rx who will package and label the drug for shipment to the pharmacist for each participant. Each bottle will be labeled with the kit number, study ID, and instructions on how to take the medication. The bottle will not contain any information of the treatment allocation.

- ZNS (100 mg PO) group

- Placebo PO group

Name	Description
1: High Noise	Screening: LENS-Q Adapted for Police Officer –

Name	Description
	1A Or 2A Or 3A = a.Daily, Or b.Less than daily/more than weekly, Or c.Weekly, Or d.Less than weekly/more than monthly Or e.Monthly OR 1C Or 2C Or 4C >= 5 Years
2: Low Noise	Screening: LENS-Q Adapted for Police Officer – 1A AND 2A AND 3A = f.Less than monthly/more than yearly, g.Yearly, h.Less than yearly Or i.Never OR 1C AND 2C AND 4C < 5 Years

5.3 Testing on the Range (Visit 3)

1. Duration of each shooting session and number of rounds fired by each participating officer will be documented.

2. Handedness will be documented.

3. Weapon type(s), including caliber and ammunition, used for each participating police officer will be documented.

4. Hearing protection device(s) including type, make, model and noise reduction rating (NRR) used by each participating police officer will be documented.

5.4 Follow-Up Assessments (Visits 3, 4 and 5)

The follow-up assessments will occur after training and include the following tests or procedures:

1. Audiogram and DPOAEs to measure for TTS and auditory changes, as soon as possible after the training session. The exact time of testing following training operations will be documented. A clinical ear exam will be completed prior to the audiogram and DPOAEs. (follow-up visit 3 and 5).

2. Baseline environmental/ambient sound measurements will be recorded at the start of each test session, including the peak ambient noise level and the average noise level (follow-up visit 3 and 5).

3. Collection of blood for laboratory testing to include an electrolyte panel, BUN, Cr, ALT, and AST. This will occur within 12-24 hours following drug intake (follow-up visit 4).

4. Cognitive assessments within 24 hours following drug intake, including (follow-up visit 4):
   a. Digit-symbol substitution test (processing speed)
   b. Verbal fluency (working memory, speech/language)
   c. Stroop (Executive function, inhibition)
   d. List Learning task/RBANS (memory)

   Additionally, after each officer is asked about potential study-related side effects for safety monitoring, they will be asked a question regarding their feeling of safety on the job, i.e. they will be asked *"if they feel safe partaking in required responsibilities associated with their job at this time or not?"*

5. Completion of LENS-Q 1-minute noise screening for noise exposure questionnaire (follow-up visit 5).

6. Audiogram, ECochG, DPOAE, and WIN testing 30 days (+/- 3 days) after each training session to assess for PTS and auditory changes, only if TTS is observed from #1 (visit 5).

7. Documentation of adverse events at all follow-up visits (5-30 minutes post, within 24 hours and at 30 day visit) (follow-up visit 3, 4 and 5).

Follow-up assessments will be planned at the stated time points; actual follow up times may vary due to patient logistics and compliance.

5.5 Blood collection, transportation, and storage

Blood samples will be collected from each participant during the baseline visit and the post-training visit within 24 hours. A phlebotomost will draw blood into a red-top tube (EDTA or citrate). Samples will be labeled with a study identification number. Samples to be used for safety labs will be sent to the lab by the phlebomtomist. PGx samples will be stored in a 2-8^{o}C degree refrigerator or a -

20ºC degree freezer at Akron. Samples will then be transported for extraction and stored in a -80ºC freezer at Gateway Biotechnology's lab.

6.0 EVALUABILITY

All participants are evaluable for the primary outcome – the proportion of patients who are PTS positive as defined by the ratio of the number of participants with $\geq$ 10 dB increase in PTS to the total number of participants tested 30 days (+/- 3 days) post-shooting – provided they have had the assigned study dose and undergone post study assessments.

Participants who receive the study medication are evaluable for toxicity related to the drug. Participants are evaluated from the time of dose administration through 30 days post dose for drug related adverse events.

The participant will be withdrawn from the study if:

- Participant withdraws consent
- Investigator removes the participant from study
- The Sponsor decides to close the study

7.0 PHARMACEUTICAL INFORMATION

7.1 Zonisamide (ZONEGRAN®)

7.1.1 Zonisamide Description

Molecular formula: $C_8H_8N_2O_3S$
Molecular weight: 212.23

7.1.2 Clinical Pharmacology

The precise mechanism(s) by which ZNS exerts its antiseizure effect is unknown. ZNS may produce these effects through action at sodium and calcium channels. In vitro pharmacological studies suggest that ZNS blocks sodium channels and reduces voltage-dependent, transient inward currents (T-type Ca^{2+} currents), consequently stabilizing neuronal membranes and suppressing neuronal hypersynchronization. Additional information can be found in the package insert.

7.1.3 Supplier

ZNS will be supplied through Advanced Rx (Washington, PA).

7.1.4 Dosage Form and Preparation

ZONEGRAN® is commercially available for oral administration as capsules containing 25mg, 50 mg, or 100 mg of ZNS.

Each 100 mg capsule contains the labeled amount of ZNS plus the following inactive ingredients: microcrystalline cellulose, hydrogenated vegetable oil, gelatin, and titanium dioxide.

7.1.5 Storage and Stability

Store at 25°C (77°F), excursions permitted to 15–30°C (59–86°F), in a dry place and protected from light.

7.1.6 Administration

Participants will receive one time dose of oral ZNS or matching placebo. Participants will be instructed to take study drug without food. We will recommend that capsules be swallowed whole per the current approved labeling.

7.1.7 Side Effects

Potential side effects from the administration of ZNS:

- Somnolence
- Anorexia
- Dizziness
- Ataxia
- Agitation/irritability
- Difficulty with memory and/or concentration

ZNS may rarely cause serious side effects, including:

- Serious skin rash that can cause death.
- Serious allergic reactions that may affect different parts of the body.
- Less sweating and increase in body temperature (fever).
- Suicidal thoughts or actions in some people.
- Increased level of acid in blood (metabolic acidosis).
- Problems with concentration, attention, memory, thinking, speech, or language.
- Blood cell changes such as reduced red and white blood cell counts.

7.1 Placebo

The placebo will contain microcrystalline cellulose which is the predominant filler in the generic capsule.

8.0 REGULATORY AND REPORTING REQUIREMENTS

The entities providing oversight of safety and compliance with the protocol require reporting as outline below. Please refer to Appendix A for definitions and Appendix B for a grid of reporting timelines.

Adverse events will be tracked for the Akron site post dose within 30 minutes, 24 hours, and at 30 days. All adverse events must be recorded on the AE tracking case report form (CRF). AEs related to study medication only will be tracked.

Reporting requirements for Washington University study team may be found in Section 8.1. Reporting requirements for secondary site study teams participating in Washington University-coordinated research may be found in Section 8.2.

In the event of a Serious Adverse Event determined by the PI to necessitate the breaking of the blind, the intervention assignment will be revealed by the independent programmer to the medical staff doctor caring for the patient. In the event the statistician is unable to be reached in a time needed, to assure the safety of the subject, the blind can be broken by Sara Kukuljan, RN and information will be shared with the medical staff assuming care for the research subject.

8.1 Sponsor-Investigator Reporting Requirements

8.1.1 Reporting to the Human Research Protection Office (HRPO) at Washington University

Reporting will be conducted in accordance with Washington University IRB Policies.

Pre-approval of all protocol exceptions must be obtained prior to implementing the change.

8.1.2 Reporting to the FDA

The conduct of the study will comply with all FDA safety reporting requirements. It is the responsibility of the Washington University principal investigator to report to the FDA as follows:

- Report any unexpected fatal or life-threatening suspected adverse reaction (refer to Appendix A for definitions) no later than **7 calendar days** after initial receipt of the information.
- Report a suspected adverse reaction that is both serious and unexpected (SUSAR, refer to Appendix A) no later than **15 calendar days** after it is determined that the information qualifies

for reporting. Report an adverse event (refer to Appendix A) as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event, such as:
    - A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure
    - One or more occurrences of an event that is not commonly associated with drug exposure but is otherwise uncommon in the population exposed to the drug
    - An aggregate analysis of specific events observed in a clinical trial that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group
- Report any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies that suggest a significant risk in humans exposed to the drug no later than **15 calendar days** after it is determined that the information qualifies for reporting.
- Report any findings from animal or in vitro testing that suggest significant risk in humans exposed to the drug no later than **15 calendar days** after it is determined that the information qualifies for reporting.
- Report any clinically important increase in the rate of a serious suspected adverse reaction of that listed in the protocol or IB within **15 calendar days** after it is determined that the information qualifies for reporting.

Submit each report as an IND safety report in a narrative format or on FDA Form 3500A or in an electronic format that FDA can process, review, and archive.

Each notification to FDA must bear prominent identification of its contents ("IND Safety Report") and must be transmitted to the review division in the Center for Drug Evaluation and Research (CDER) or in the Center for Biologics Evaluation and Research (CBER) that has responsibility for review of the IND. Relevant follow-up information to an IND safety report must be submitted as soon as the information is available and must be identified as such ("Follow-up IND Safety Report").

8.1.3 Reporting to Secondary Sites

The Washington University Sponsor-Investigator will notify the research team at the secondary site of all unanticipated problems involving risks to participants or others that have occurred at other sites within **10 working days** of the occurrence of the event or notification of the Sponsor-Investigator of the event. This includes events that take place both at Washington University and at other site, if applicable.

8.2 Secondary Site Reporting Requirements

The research team at each secondary site is required to promptly notify the Washington University Sponsor-Investigator of all serious adverse events (refer to Appendix A, Section D) within **1 working day** of the occurrence of the event or notification of the secondary site's PI of the event. This notification may take place via email if there is not yet enough information for a formal written report (using FDA Form 3500a (MedWatch) and Washington University's cover sheet (Appendix C). A formal written report must be sent to the Washington University Sponsor-Investigator and designee within **4 calendar days** (for fatal or life-threatening suspected adverse reactions) or **11 calendar days** (for serious unexpected suspected adverse reactions) of the occurrence of the event or notification of the secondary site's PI of the event.

The research team at the secondary site is responsible for following its site's guidelines for reporting applicable events to its site's IRB according to its own institutional guidelines. The research team at Washington University is responsible for reporting all applicable events to the FDA as needed.

Washington University pre-approval of all protocol exceptions must be obtained prior to implementing the change. Local IRB approval must be obtained as per local guidelines. Washington University IRB approval is not required for protocol exceptions occurring at secondary sites.

8.3 Exceptions to Expedited Reporting

Events that do not require expedited reporting as described in Section 1.1 include:

- planned hospitalizations
- hospitalizations < 24 hours
- respite care
- events related to disease progression

Events that do not require expedited reporting must still be captured in the EDC.

9.0 STUDY CALENDAR

	VISIT 1 Screening Assessment	VISIT 2 Baseline Assessment	Post-training		
			VISIT 3 Within 5-30 Minutes	VISIT 4 Within 24 Hours	VISIT 5 30 days (+/- 3 days)***
Informed Consent	X				
Demographic Info	X				
Current Meds	X				
Questionnaires	X				X
Cognitive Assessment		X		X	
Clinical ear exam	X	X	X		X
Audiogram	X	X	X		X
ECochG		X			X
DPOAE		X	X		X
WIN		X			X
Sound Measurements	X	X	X		
Randomization			X*		
Oral Dose* ZNS or Placebo			X*		
Blood draw**		X		X	
AE Assessment			X	X	X

* Dispensed after training if TTS is identified on audiogram 5-30 minutes after shooting.
** Blood draw: Electrolyte panel, BUN, Cr, ALT, and AST; DNA analysis and serum pregnancy test at baseline
*** If TTS is seen from pure tones after each training session

10.0 DATA SUBMISSION SCHEDULE

Case report forms with appropriate source documentation will be completed according to the schedule listed in this section.

Case Report Form	Submission Schedule
Original Consent Form	Prior to study activities
Eligibility Form	At time of consent; Prior to firearm training
Firearm Training Form	Time of firearm training
Adverse Event Form	Continuous

11.0 DATA AND SAFETY MONITORING

In compliance with the Washington University Institutional Data and Safety Monitoring Plan, an independent Data and Safety Monitoring Board (DSMB) will be specifically convened for this trial to review toxicity data. A DSMB will consist of no fewer than 3 members including 2 clinical investigators and a biostatistician. Individuals invited to serve

on the DSMB will disclose any potential conflicts of interest to the trial principal investigator and/or appropriate university officials, in accordance with institution policies. Potential conflicts that develop during a trial or a member's tenure on a DSMB must also be disclosed.

The DSM report for the DSMB will be prepared by the study team with assistance from the study statistician, will be reviewed by the DSMB, and will be submitted to the PI. The DSMB must meet at least every six months beginning six months after enrollment of the first participant at the secondary site, no more than one month prior to the due date of the DSM report to the PI. This report will include:

- HRPO protocol number, protocol title, Principal Investigator name, data coordinator name, regulatory coordinator name, and statistician
- Date of initial HRPO approval, date of most recent consent HRPO approval/revision, date of HRPO expiration, date of most recent QA audit, study status, and phase of study
- History of study including summary of substantive amendments; summary of accrual suspensions including start/stop dates and reason; and summary of protocol exceptions, error, or breach of confidentiality including start/stop dates and reason
- Study-wide target accrual and study-wide actual accrual
- Protocol activation date at each participating site
- Average rate of accrual observed in year 1, year 2, and subsequent years at each participating site
- Expected accrual end date, accrual by site, and accrual by cohort
- Objectives of protocol with supporting data and list the number of participants who have met each objective
- Measures of efficacy
- Early stopping rules with supporting data and list the number of participants who have met the early stopping rules
- Power analysis and/or interim analysis (if described in the protocol)
- Summary of toxicities
- Abstract submissions/publications
- Summary of any recent literature that may affect the safety or ethics of the study

The study principal investigator and coordinator will monitor for serious toxicities on an ongoing basis. Once the principal investigator or coordinator becomes aware of an adverse event, the AE will be reported to the HRPO according to institutional guidelines (please refer to Section 1.0).

11.1 Adverse Event Collection in the Case Report Forms

All adverse events that occur beginning with start of treatment must be captured in the AE Form.

12.0 STATISTICAL CONSIDERATIONS

12.1 Data analysis

Data will be analyzed using an intention to treat principle with patients analyzed in the groups they were randomized to. The primary outcome measure for assessing effectiveness of ZNS (100 mg PO) will be the proportion of officers experiencing PTS 30 days (+/- 3 days) after training in the ZNS group as compared to proportion of officers experiencing PTS in the placebo group (Group 2). The secondary outcome measures are key audiological and clinical assessments of hearing loss. OAE shift will be a secondary outcome measure and an early indicator of TTS and PTS.

Standard descriptive statistics will be used to describe distribution of demographic, clinical and audiometric characteristics as well as outcome measures for each study group. For continuous level characteristics Q-Q plots and Shapiro-Wilk test will be used to test assumption of normality. For normally distributed data mean and standard deviation will be used as descriptive stats of continuous level variables, and if the assumption of normality is violated we will report median and range for description of variables. Frequency and relative frequency will be used for description of categorical level variables.

12.2 Efficacy analysis

12.2.1 Analysis of primary outcome variable

Efficacy analysis at the end of the study

The primary outcome measure for assessing effectiveness of ZNS (100 mg PO) post-shooting compared to the placebo group will be the proportion of officers with TTS defined as PTS positive 30 days (+/- 3 days) after shooting range exposure.

Audiogram will be performed to look for PTS. Officers for whom the difference at any frequency from 2-6 kHz in hearing thresholds (30 days (+/- 3 days) post-shooting - Baseline) is ≥10 dB HL will be defined as PTS positive. Primary analysis and sensitivity analyses will be carried out on the primary endpoint.

Primary analysis.

Frequency and relative frequency will be used to describe the distribution of the primary outcome measure in each study group. To assess efficacy, Fisher's exact test will be used to compare the proportion of officers with PTS positive in ZNS group with the proportion of officers with PTS positive in the placebo group.

To provide an estimate of treatment effect a supportive logistic regression analysis will be done with covariates: age, pre-existing hearing loss dichotomized to normal to minimal hearing loss and slight to mild loss, noise exposure history dichotomized to high risk and low risk, average post-shooting

Sensitivity analysis of the primary endpoint

The potential impact of missing primary endpoint data will be explored in sensitivity analyses using multiple imputation. Two sensitivity analyses performed:

Sensitivity 1: MI analysis under the missing not at random assumption (MNAR)
Sensitivity 2: Logistic regression tipping point analysis under the assumption of data missing at random.

Sensitivity 1.
Proc MI procedure in SAS will be used to impute missing data for study treatment groups using the distribution implied by the non-missing officer data within the placebo group. The SAS code to impute data for Sensitivity analysis 1 under the MNAR assumption will be of the form:

```
PROC MI DATA=X SEED=<value> NIMPUTE=10  OUT=MI_OUT1 NOPRINT;
CLASS  GROUP;
VAR AGE PTA LSurg……;
FCS LOGISTIC(PTS);
RUN;
```

Post imputation each of the imputed 10 datasets will be analyzed using the same approach as for the primary outcome measure. The estimates of the analysis of the 10 imputed datasets will be then combined following Rubin's rules using PROC MIANALYZE procedure in SAS which will be of the form:

```
PROC MIANALYZE PARMS=GMPARMS COVB=GMCOVB PARMINFO=GMPINFO WCOV
BCOV
    TCOV; / *dataset "gmparms" contains the estimates and
associated standard errors for the mean parameters from each of
the M=10 imputed data sets.
dataset "gmcovb" contains the asymptotic covariance matrics
dataset "gmpinfo" contains parameter info*/

    MODELEFFECTS INTERCEPT AGE PTA LSurg……;
RUN;
```

Sensitivity 2.

Multiple imputation will be used to impute data in each of the study groups. A progressive penalty of $\delta_i = k_i \times \log(OR)$ will be added to imputed

values in ZNS arm where (i) OR is the Odds ratio estimate for ZNS as compared to Placebo from the primary logistic regression analysis and (ii) $k_i = 1, 0.95, 0.90, \ldots 0.05, 0, 1.05, 1.10, \ldots$ thus k ranges from 1 (equivalent to MI approach based on MAR) to 0 (or higher), until the conclusion of the primary analysis is overturned (i.e., p<0.05 is lost at, this value of k_i being the 'tipping point'). Rubin's method will be used to combine the primary endpoint treatment effects across imputations for each value, k_i, of the penalty. Forest plots will be used to graphically display the penalty value that results in loss of statistical significance.

SAS code sample for Sensitivity analysis is provided below:

```
**Step 1: Generate 10  datasets by imputing the missing data**;

PROC MI DATA=X SEED=<value> NIMPUTE=10  OUT=MI_OUT1 NOPRINT;
CLASS  GROUP;
VAR AGE PTA LSurg……;
FCS LOGISTIC(PTS);
RUN;

**Step 2: Generate 10 complete datasets from the 10 monotonized
datasetsin Step 1 for missing values in the drug arm,
subtract DELTA derived above from their imputed data.**;
proc mi data=YYY NIMPUTE=1 SEED=<value> OUT=YYY_shift;
by group;
class group;
var AGE PTA LSurg……;
monotone method=logistic;
mnar adjust(PTS / shift=DELTA adjustobs=(group='1'));
run;

**Step 3: Apply the primary MMRM to the 10 complete datasets in
Step 2**;
proc genmod data=YYY_shift descending;
by _imputation_;
class group;
model PTS = group AGE PTA LSurg……;
ods output GEEModPEst=gmparms;
run;



**Step 4: Obtain the pooled inference from 10 sets of estimates
from Step 3**;

PROC MIANALYZE PARMS=GMPARMS COVB=GMCOVB PARMINFO=GMPINFO WCOV
BCOV
    TCOV;
    MODELEFFECTS group;
RUN;
```

12.2.2 Analysis for secondary outcome measures.

The focus of the study is to determine efficacy of ZNS for treatment of acute hearing loss based on the testing of the hypothesis for the primary outcome. In addition, we will also conduct analysis to evaluate other important audiologic measures. The secondary outcome measures are key audiological and clinical assessments of hearing loss, and include: Audiometric TTS, DPOAEs, Ultra-high frequency audiometry, ECochG, and WIN testing 30 days (+/- 3 days) after shooting, and are measured as continuous level variables. We do not plan any adjustment of alpha error for multiple comparisons.

Analysis of variance (ANCOVA) will be used for comparison of outcome measures between each of the ZNS groups and placebo study group after controlling for baseline value, age, pre-op hearing dichotomized to: normal to minimal hearing loss and slight to mild loss, noise exposure history dichotomized to: high risk and low risk, average post-shooting TTS.

Statistical analyses will be conducted using the SAS software (SAS Institute Inc., Cary, N.C., USA).

Measurements will include (1) the average audiogram threshold shift between 3 and 6 kHz (sensitive region for NIHL) and 10 and 16 kHz (markers for hidden hearing loss), (2) DPOAE amplitudes, (3) ECochG changes (AP amplitude and latency, AP width), and (4) WIN scores.

Missing Data

Every attempt will be made to ensure data completeness. We do not anticipate much loss to follow-up because of the relatively short time follow-up interval. Conservatively, we would estimate that fewer than 5% of subjects will drop out/withdraw of the study. The participant will be withdrawn from the study follow-up and procedures if the participant withdraws consent, or the sponsor decides to close the study.

If any, the loss of data would almost certainly be due to the fact that the subjects refused to complete or did not show up for the assessment of PTS 30 days (+/- 3 days) after the baseline assessment on shooting day. If the subjects reschedule the follow-up appointment for a later date for any reason, and if this delay is within 30 days of the scheduled date, the data will be considered valid and used in the efficacy analysis. Any measure outside this time window of +30 days will be defined and considered missing data.

Missing PTS at 30 days will be imputed using SAS PROC MI procedure within each treatment group using the distribution implied by the non-missing data for the specific treatment group.

The SAS code below using MICE via the Fully Conditional Specification (FCS) statement will be used to impute the missing data under the missing at random (MAR) assumption.

```
PROC MI DATA=X SEED=<value> NIMPUTE=10  OUT=MI_OUT1 NOPRINT;
CLASS  GROUP;
VAR AGE PTA LSurg……;
FCS LOGISTIC(PTS);
RUN;
```

The estimates of the analysis of the 10 imputed datasets will be then combined following Rubin's rules using PROC MIANALYZE procedure in SAS which will be of the form:

```
PROC MIANALYZE PARMS=GMPARMS COVB=GMCOVB PARMINFO=GMPINFO WCOV BCOV
    TCOV; / *dataset "gmparms" contains the estimates and associated
standard errors for the mean parameters from each of the M=10 imputed
data sets.
dataset "gmcovb" contains the asymptotic covariance matrics
dataset "gmpinfo" contains parameter info*/

    MODELEFFECTS group;
RUN;
```

12.3 Sample size estimation

Sample size estimation for primary outcome measure.

Calculation of sample size for this study is based on a balanced design and a one-sided significance level of 0.025. We estimate that among officers identified as being at high risk for permanent hearing loss due to having TTS, the proportion of PTS positive officers 30 days (+/- 3 days) after shooting will be 50%. This is the proportion of PTS positive we expect to observe in the placebo group. Thus, for the primary outcome, we estimated that 66 subjects per group will provide us with 80.5% power to detect a 50% reduction in the proportion of PTS positive officers (from 50% to 25%) at the 1-sided alpha level of 0.025 and with 84% power to detect a 50% reduction in the proportion of PTS positive officers (from 50% to 25%) at the one-sided alpha level of 0.025. Our one-sided hypothesis is supported by animal studies, and lack of any evidence of hearing loss as a side effect of ZNS in human studies. A total of 132 subjects will be enrolled.

Using a number needed to treat estimate for the assumed proportion of officers with PTS positive in each study group, the absolute risk reduction of 25% tells us that we will need to treat 4 officers with TTS with ZNS to protect 1 from PTS. We do not expect to have any missing data in this short-term study, so no plan for missing data analysis is included.

Sample size for secondary outcome measures.

Blioskas et al. reported that 280 out of 344 (81%) military cadets had TTS. Thus, for TTS as secondary outcome measure, the estimated sample size of 63 subjects in each arm will provide us with 96.1% power to detect a 40% reduction in the proportion of subjects experiencing TTS (from 80% to 48%) at the 1-sided alpha level of 0.0235.

12.4 Interim analysis

A sponsor blinded interim analysis focused on the primary endpoint after 33% of the officers have completed participation in the study (22 in each group). The independent programmer will prepare the dataset using a pre-prepared SAS code and will freeze them for the interim analysis. To ensure the double blinding of the study the subjects will not be presented in the assigned groups. The blinded statistician will estimate the overall proportion of PTS positive subjects in each group.

With 33% information, the trial would be stopped for futility if the interim z-value <= 0.5233 (p=0.60 2-sided) corresponding to a conditional power less than 10%. This design would provide 79.4% overall power (i.e. the probability of passing futility and reaching p<0.025 for the comparison in the final analysis would be 79.4%).

Based on interim analysis the following actions may be taken:

- Stop the trial for futility
- Continue the trial as planned.

Early stopping rule related to serious adverse events: In the event of a serious adverse event, DSMB will evaluate the association of the serious adverse events with the study arm, break the blind if needed, and if found to be associated with treatment, DSMB will consider the study for revision or stopping.

Serious feasibility or design difficulties. If one year after the start of the trial, <50% of the planned accrual goals are met, DSM and study team will discuss difficulties in recruitment. Amount of remuneration will be revised, if needed. If there are not enough officers meeting inclusion/exclusion criteria, then the criteria will be revised without impacting study objectives. If there are recruitment difficulties, the DSM will discuss with the PI and research team what are the main reasons for these difficulties and will identify ways to deal with them. For example, if there are not enough police officers identified with a TTS $\geq$ 10dB, then the study inclusion criteria will be revised to include members of the Bomb squad. In order to preserve the balanced design and group representation, a stratified randomization strategy will be employed. If there are difficulties in recruitment related to length of

audiometric testing pre- and post-shooting, then the DSM and research team will discuss using OAE testing.

For this study, we have approximately 800 officers from Akron and Summit County, not including additional local police departments from which to screen and recruit, understanding a large percentage of the population may already present with significant NIHL, thus, may not meet the eligibility criteria. In a previous study by the investigators, 62-85% of police officers presented with evidence of NIHL (62.5% of canine police handlers and 85.7% of non-canine police handlers), therefore, we need a significantly larger sample size to recruit subjects that meet our eligibility criteria. We estimate that each year we will have at least 60 officers screened within 1 hour of shooting each year. If the rate of TTS after 1 hour of shooting is that of the study from Blioskas et al, we estimate that 48 officers will qualify to undergo randomization each year. If 70% of them consent to be randomized there will be 34 officers enrolled and completing the trial each year. Based on these estimates, we will be able to meet our accrual goals and complete the study with a sample size of 132 officers in approximately 4 years.

12.5 Pharmacogenetic analysis plan

This analysis will be performed at the end of the trial by Gateway Biotechnology. To identify genetic variants with ZNS protection against hearing loss, we will first use univariate logistic regression analyses to identify potential confounding variables: sex, age, Z-scores of drug concentration, Z-scores of noise intensity and duration, and Z-scores of hearing functions measured immediately following range shooting. Single-marker allelic association analyses will be conducted on the two imputed data sets in PLINK v1.07. The data will be analyzed with a logistic regression model on the additive continuous dosage of minor alleles from 0 to 2 to account for uncertainty of imputation. We will combine association results in the two cohorts by performing a genome-wide inverse-variance weighting meta-analysis using PLINK v1.07, and assuming a fixed-effect model. Functional annotation of top-associated markers will be performed with R package NCBI2R 1.4.6 (http://CRAN.Rproject. org/package=NCBI2R), and key regional association plots of meta-analyzed results will be generated. To confirm whether these variants are specific to ZNS response, we will apply CEP SKAT to analyze genetic associations based on Z-scores of audiogram average threshold shifts and DPOAE amplitudes. All genetic variants, including both common and rare variants, will be included in this association study. Age, gender, drug concentration, and noise duration and intensity will be adjusted for the analysis. The analysis will also be performed using hearing data collected two to four weeks after range shooting. The only differences will be a) using the Z scores of ECochG AP amplitude, latency, and width as well as WIN score, and b) using average audiogram threshold shifts and DPOAE amplitudes at 30 days (+/- 3 days) post-treatment. To control for confounding effects, these models will be adjusted for age, gender, drug concentration, and noise duration and intensity. Finally, the control and ZNS-treated comparisons will be performed using post-hoc comparisons with a Bonferroni adjustment for multiple comparisons of any ZNS versus none.

Statistical analyses will be performed using the CEP-SKAT method in R language, and the statistical software SAS version 9.4 for Windows will be used for additional analysis.

13.0 REFERENCES

1. Abtahi SH, Fazel A, Rogha M, Nilforoush M, Solooki R. *Effect of drill-induced noise on hearing in nonoperated ear.* Adv Biomed Res. 2016. 11;5:87.
2. Adamson CL, Reid MA, Davis RL. *Opposite actions of brain-derived neurotrophic factor and neurotrophin-3 on firing features and ion channel composition of murine spiral ganglion neurons.* J Neurosci. 2002.22(4):1385-96.
3. Ahn H, Fehlings MG. *Prevention, identification, and treatment of perioperative spinal cord injury.* Neurosurg Focus. 2008. 25(5):E15.
4. Bao J, Hungerford M, Luxmore R, Ding D, Qiu Z, Lei D, Yang A, Liang R, Ohlemiller KK. *Prophylactic and therapeutic functions of drug combinations against noise-induced hearing loss*. Hear Res. 2013. 304:33-40.
5. Bielefeld EC, Kopke RD, Jackson RL, Coleman JK, Liu J, Henderson D. *Noise protection with N-acetyll-cysteine (NAC) using a variety of noise exposures, NAC doses, and routes of administration.* Acta Otolaryngol. 2007. 127(9):914-9.
6. Blioskas S, Tsalighopoulos M, Psillas G, Markou K. *Utility of otoacoustic emissions and olivocochlear reflex in predicting vulnerability to noise-induced inner ear damage*. Noise Health. 2018. 20(94):101-111.
7. Bohne BA. In: Henderson D, Hamernik RP, Mills JH, Dosanjh DS Eds. *Mechanisms of noise damage in the inner ear. In Effects of Noise on Hearing.* NY, Raven Press, 1976. 41-68.
8. Bramhall NF, Konrad-Martin D, McMillan GP, Griest, SE. *Auditory brainstem response altered in humans with noise exposure despite normal outer hair cell function.* Ear Hear. 2017.
9. Brodie MJ, Ben-Menachem E, Chouette I, Giorgi L. *Zonisamide: its pharmacology, efficacy and safety in clinical trials*. Acta Neurol Scand Suppl. 2012. 194:19-28.
10. Cacace AT, Silver SM, Farber M. *Rapid recovery from acoustic trauma: chicken soup, potato knish, or drug interaction?* Am J Otolaryngol. 2003 24(3):198-203.
11. Campbell KC, Meech RP, Klemens JJ, Gerberi MT, Dyrstad SS, Larsen DL, Mitchell DL, El-Azizi M, Verhulst SJ, Hughes LF. *Prevention of noise- and drug-induced hearing loss with D-methionine.* Hear Res. 2007. 226(1-2):92-103.
12. Canlon B, Meltser I, Johansson P, Tahera Y. *Glucocorticoid receptors modulate auditory sensitivity to acoustic trauma.* Hear Res. 2007. 226(1-2):61-9.
13. Casto KL, Casali JG. *Effects of headset, flight workload, hearing ability, and communications message quality on pilot performance*. Hum Factors. 2013 Jun;55(3):486-98.
14. Chen, L. Brueck, S. *Noise and Lead Exposures at an Outdoor Firing Range California.* Health Hazard Evaluation Report. 2011. HETA 2011-0069-3140.
15. Chen FQ, Zheng HW, Hill K, Sha SH. *Traumatic noise activates Rho-family GTPases through transient cellular energy depletion.* J Neurosci. 2012. 32(36):12421-30.
16. Chen J, Yuan H, Talaska AE, Hill K, Sha SH. *Increased Sensitivity to Noise-Induced Hearing Loss by Blockade of Endogenous PI3K/Akt Signaling.* J Assoc Res Otolaryngol. 2015. 16(3):347-56.
17. Clifford, R E, Hoffer, M, Rogers, R. *The Genomic Basis of Noise-induced Hearing Loss: A Literature Review Organized by Cellular Pathways.* Otology & Neurotology. 2016. Volume 37 - Issue 8 - p e309–e316

18. Darrat I, Ahmad N, Seidman K, Seidman MD. *Auditory research involving antioxidants.* Curr Opin Otolaryngol Head Neck Surg. 2007. 15(5):358-63.
19. Davis RR, Kozel P, Erway LC. *Genetic influences in individual susceptibility to noise: a review*. Noise Health. 2003. 5(20):19-28.
20. Dodson, K.M., Sismanis, A. *Intratympanic perfusion for the treatment of tinnitus*. Otolaryngol Clin North Am. 2004. 37:991-1000.
21. Dodson, K.M., Woodson, E., Sismanis, A. *Intratympanic steroid perfusion for the treatment of Meniere's disease: a retrospective study.* Ear Nose Throat J. 2004. 83:394-8.
22. Du X, Chen K, Choi CH, Li W, Cheng W, Stewart C, Hu N, Floyd RA, Kopke RD. *Selective degeneration of synapses in the dorsal cochlear nucleus of chinchilla following acoustic trauma and effects of antioxidant treatment.* Hear Res. 2012. 283(1-2):1-13.
23. Earl BR, Chertoff ME. *Mapping auditory nerve firing density using high-level compound action potentials and high-pass noise masking.* J Acoust Soc Am. 2012. 131(1):337-52.
24. Esterberg R, Hailey DW, Coffin AB, Raible DW, Rubel EW. *Disruption of Intracellular Calcium Regulation Is Integral to Aminoglycoside-Induced Hair Cell Death.* 2013. Journal of Neuroscience. 33 (17) 7513-25.
25. Fausti SA, Wilmington DJ, Gallun FJ, Myers PJ, Henry JA. *Auditory and vestibular dysfunction associated with blast-related traumatic brain injury.* J Rehabil Res Dev. 2009;46(6):797-810.
26. Fernandez KA, Jeffers PW, Lall K, Liberman MC, Kujawa SG. *Aging after noise exposure: acceleration of cochlear synaptopathy in "recovered" ears.* J Neurosci. 2015. 35(19):7509-20.
27. Frisina DR, Frisina RD. *Speech recognition in noise and presbycusis: relations to possible neural mechanisms. Hear Res. 1997. 106(1-2):95-104.*
28. Fuchs P. *The synaptic physiology of cochlear hair cells.* Audiol Neurootol. 2002. 7(1):40-4.
29. Gould AL. *Interim analyses for monitoring clinical trials that do not materially affect the type I error rate.* Statistics in medicine. 1992;11(1):55-66.
30. Gould AL. *Sample size re-estimation: recent developments and practical considerations*. Statistics in Medicine. 2001 Sep 15;20(17-18):2625-43.
31. Gould AL, Shih WJ. *Modifying the design of ongoing trials without unblinding.* Statistics in Medicine. 1998 Jan 15;17(1):89-100.
32. Goyal, A., Singh, P., & Vashishth, A. *Effect of mastoid drilling on hearing of the contralateral ear.* 2013. The Journal of Laryngology & Otology. 127(10), 952-956.
33. Griffith SG, Dai Y. *Effect of zonisamide on the pharmacokinetics and pharmacodynamics of a combination ethinyl estradiol-norethindrone oral contraceptive in healthy women*. Clin Ther. 2004. 26(12):2056-65.
34. Grondin Y, Bortoni ME, Sepulveda R, Ghelfi E, Bartos A et al. *Genetic Polymorphisms Assoicated with Hearing Threshold Shift in Subjects during First Encounter with Occupational Impulse Noise.* 2015. 10(6): e0130827.
35. Groth JB, Kao SY, Briët MC, Stankovic KM. *Hepatocyte nuclear factor-4 alpha in noise-induced cochlear neuropathy.* 2016. Dev Neurobiol. 2016 Dec;76(12):1374-1386.
36. Gubata ME, Packnett ER, Feng X, Cowan DN, Niebuhr DW. *Pre-enlistment hearing loss and hearing loss disability among US soldiers and marines.* Noise Health. 2013. 15(66):289-95.

37. Guitton MJ, Wang J, Puel JL. *New pharmacological strategies to restore hearing and treat tinnitus.* Acta Otolaryngol. 2004.124(4):411-5.
38. Gupta D, Gulati A, Gupta U. *Impact of socio-economic status on ear health and behaviour in children: A cross-sectional study in the capital of India.* Int J Pediatr Otorhinolaryngol. 2015. 79(11):1842-50.
39. Hallmo P1, Mair IW. Drilling in ear surgery. *A comparison of pre- and postoperative bone-conduction thresholds in both the conventional and extended high-frequency ranges*. Scand Audiol. 1996. 25(1):35-8.
40. Han Y, Wang X, Chen J, Sha SH. *Noise-induced cochlear F-actin depolymerization is mediated via ROCK2/p-ERM signaling.* J Neurochem. 2015. 133(5):617-28.
41. Harding GW, Bohne BA. *Distribution of focal lesions in the chinchilla organ of Corti following exposure to a 4-kHz or a 0.5-kHz octave band of noise.* Hear Res. 2007 254(1-2):54-63.
42. Hashimoto Y, Odani A, Tanigawara Y, Yasuhara M, Okuno T, Hori R. *Population analysis of the dosedependent pharmacokinetics of zonisamide in epileptic patients.* Biol Pharm Bull. 1994. 17(2):323-6.
43. Hayball PJ, Cosh DG, Ahern MJ, Schultz DW, Roberts-Thomson PJ. *High dose oral methylprednisolone in patients with rheumatoid arthritis: pharmacokinetics and clinical response.* Eur J Clin Pharmacol. 1992. 42(1):85-8.
44. Helfer TM, Jordan NN, Lee RB, Pietrusiak P, Cave K, Schairer K. *Noise-induced hearing injury and comorbidities among postdeployment U.S. Army soldiers: April 2003-June 2009.* Am J Audiol. 2011. Jun;20(1):33-41.
45. Henderson D, Bielefeld EC, Harris KC, Hu BH. *The role of oxidative stress in noise-induced hearing loss.* Ear Hear. 2006. 27(1):1-19.
46. Henry, K.R. *Noise-induced auditory loss: influence of genotype, naloxone and methyl-prednisolone.* Acta Otolaryngol. 1992. 112:599-603.
47. Hickey SA, O'Connor AF. *Measurement of drill-generated noise levels during ear surgery.* J Laryngol Otol. 1991. 105(9):732-5.
48. Hickox AE, Liberman MC. *Is noise-induced cochlear neuropathy key to the generation of hyperacusis or tinnitus?* J Neurophysiol. 2014. 111(3):552-64.
49. Hight NG, McFadden SL, Henderson D, Burkard RF, Nicotera T. *Noise-induced hearing loss in chinchillas pre-treated with glutathione monoethylester and R-PIA.* Hear Res. 2003.179:21-32.
50. Hilmi OJ, Mckee RH, Abel EW, Spielmann PM, Hussain SS. *Do high-speed drills generate high-frequency noise in mastoid surgery?.* Otol Neurotol. 2012. 33(1):2-5.
51. Hinni ML, Zarka MA, Hoxworth JM. Margin mapping in transoral surgery for head and neck cancer. *Laryngoscope.* May 2013;123(5):1190-1198.
52. Hope AJ, Luxon LM, Bamiou DE. *Effects of chronic noise exposure on speech-in-noise perception in the presence of normal audiometry.* J Laryngol Otol. 2013 127(3):233-8.
53. Humes LE, Lee JH, Coughlin MP. *Auditory measures of selective and divided attention in young and older adults using single-talker competition*. J Acoust Soc Am. 2006 120(5 Pt 1):2926-37.
54. Igelmund P, Zhao YQ, Heinemann U. *Effects of T-type, L-type, N-type, P-type, and Q-type calcium channel blockers on stimulus-induced pre- and postsynaptic calcium fluxes in rat hippocampal slices.* Exp. Brain Res. 1996.109(1):22-32.

55. Jensen JB, Lysaght AC, Liberman MC, Qvortrup K, Stankovic KM. *Immediate and delayed cochlear neuropathy after noise exposure in pubescent mice*. PLoS One. 2015. 10(5):e0125160.

56. Jin DX, Lin Z, Lei D, Bao J. *The role of glucocorticoids for spiral ganglion neuron survival.* Brain Res. 2009. 24;1277:3-11.

57. Khimich D, Nouvian R, Pujol R, Tom Dieck S, Egner A, Gundelfinger ED, Moser T. *Hair cell synaptic ribbons are essential for synchronous auditory signalling.* Nature. 2005. 434(7035):889-94.

58. Kieser M, Friede T. *Simple procedures for blinded sample size adjustment that do not affect the type I error rate*. Statistics in medicine. 2003 Dec 15;22(23):3571-81.

59. Kil J, Lobarinas E, Spankovich C, Griffiths SK, Antonelli PJ, Lynch ED, Le Prell CG. *Safety and efficacy of ebselen for the prevention of noise-induced hearing loss: a randomised, double-blind, placebocontrolled, phase 2 trial.* The Lancet. 2017. 390(10098):969-79.

60. Kil J, Lynch ED, Griffiths S, Lobarinas E, Spankovich C, Antonelli PJ, Le Prell CG. *Efficacy of SPI-1005 for prevention of noise-induced hearing loss: phase 2 clinical trial results*. Otolaryngol Head Neck Surg 2014. 151:83–84.

61. Kirchner DB, Evenson E, Dobie RA, Rabinowitz P, Crawford J, Kopke R, Hudson TW. *Occupational noise-induced hearing loss: ACOEM Task Force on Occupational Hearing Loss.* J Occup Environ Med. 2012. 54(1):106-8.

62. Kochak GM, Page JG, Buchanan RA, Peters R, Padgett CS. *Steady-state pharmacokinetics of zonisamide, an antiepileptic agent for treatment of refractory complex partial seizures*. J Clin Pharmacol. 1998. 38(2):166-71.

63. Konings A, Van Laer L., Wiktorek-Smagur A., Rajkowska E., Pawelczyk M et al. *Candidate Gene Association Study for Noise-Induced Hearing Loss in Two Independent Noise-exposed Populations.* Ann Hum Genet. 2009. 73(2): 215-224.

64. Kopke RD, Jackson RL, Coleman JK, Liu J, Bielefeld EC, Balough BJ. *NAC for noise: from the bench top to the clinic.* Hear Res. 2007. 226(1-2):114-25.

65. Kopke R, Slade MD, Jackson R, Hammill T, Fausti S, Lonsbury-Martin B, Sanderson A, Dreisbach L, Rabinowitz P, Torre P 3rd, Balough B. *Efficacy and safety of n-acetylcysteine in prevention of noise induced hearing loss: a randomized clinical trial.* Hear Res 2015. 323:40–50.

66. Kothare SV, Kaleyias J. *Zonisamide: review of pharmacology, clinical efficacy, tolerability, and safety.* Expert Opin. Drug Metab. Toxicol. 2008. 4:4.493.

67. Kujawa SG, Liberman MC. *Acceleration of age-related hearing loss by early noise exposure: evidence of a misspent youth.* J Neurosci. 2006. 26(7):2115-23.

68. Kujawa SG, Liberman MC. *Adding insult to injury: cochlear nerve degeneration after "temporary" noiseinduced hearing loss.* J Neurosci. 2009. 29(45):14077-85.

69. Kujawa SG, Liberman MC. *Synaptopathy in the noise-exposed and aging cochlea: Primary neural degeneration in acquired sensorineural hearing loss.* Hear Res. 2015. 330(Pt B):191-9.

70. Kumar UA, Ameenudin S, Sangamanatha AV. *Temporal and speech processing skills in normal hearing individuals exposed to occupational noise*. Noise Health 2012. 14:100-5.

71. Kurabi A, Keithley EM, Housely GD, Ryan AF, Wong A. *Cellular mechanisms of noise-induced hearing loss.* Hearing Res. 2017. 349:129-37.

72. Lacinova L, Klugbauer N, Hofmann F. *Low voltage activated calcium channels: from genes to function.* Gen. Physiol. Biophys. 2000. 19(2):121-36.
73. Lamm, K., Arnold, W. *The effect of prednisolone and non-steroidal anti-inflammatory agents on the normal and noise-damaged guinea pig inner ear*. Hear Res. 1998. 115:149-61.
74. Lavinsky J, Ge M, Crow AL, Pan C, Wang J, Salehi P, Myint A, Eskin E, Allayee H, Lusis AJ, Friedman RA. *The Genetic Architecture of Noise-Induced Hearing Loss: Evidence for a Gene-by-EnvironmentInteraction.* G3 (Bethesda). 2016. 6(10):3219-3228.
75. Lei D1, Gao X, Perez P, Ohlemiller KK, Chen CC, Campbell KP, Hood AY, Bao J. *Anti-epileptic drugs delay age-related loss of spiral ganglion neurons via T-type calcium channel.* Hear Res. 2011. 278(1-2):106-12.
76. Leppik IE. *Practical prescribing and long-term efficacy and safety of zonisamide*. Epilepsy Res. 2006. 68 Suppl 2:S17-24.
77. Le Prell CG, Bao, J. *Prevention of noise-induced hearing loss: potential therapeutic agents. Noise-Induced Hearing Loss-Scientific Advances*. 2011. Ed by Le Prell CG, Henderson D, Fay RR and Popper AN. Springer, ISSN 0947-2657.
78. Le Prell CG, Brungart DS. *Speech-in-Noise Tests and Supra-threshold Auditory Evoked Potentials as Metrics for Noise Damage and Clinical Trial Outcome Measures*. Otol Neurotol. 2016. 37(8):e295-302.
79. Le Prell CG, Clavier O. *Effects of noise on speech recognition: Challenges for communication by service members.* Hear Res. 2016. Jun;349:76-89
80. Le Prell CG, Fulbright A, Spankovich C, Griffiths S, Lobarinas E, Campbell KCM, Antonelli PJ, Green GE, Guire K, Miller JM. *Dietary supplement comprised of β-carotene, vitamin C, vitamin E, and magnesium: failure to prevent music-induced temporary threshold shift*. 2016. Audiol Neurotol. 6: 20-39.
81. Le Prell CG, Hughes LF, Miller JM. *Free radical scavengers vitamins A, C, and E plus magnesium reduce noise trauma.* Free Radic Biol Med. 2007. 42(9):1454-63.
82. Le Prell CG, Johnson AC, Lindblad AC, Skjönsberg A, Ulfendahl M, Guire K, Green GE, Campbell KC, Miller JM. *Increased vitamin plasma levels in Swedish military personnel treated with nutrients prior to automatic weapon training*. Noise Health. 2011. 13(55):432-43.
83. Le Prell CG, Dell S, Hensley B, Hall JW 3rd, Campbell KC, Antonelli PJ, Green GE, Miller JM, Guire K. *Digital music exposure reliably induces temporary threshold shift in normal-hearing human subjects*. Ear Hear. 2012. 33(6):e44-58.
84. Le Prell CG, Lobarinas E. S*trategies for assessing antioxidant efficacy in clinical trials*. In: Miller, J.M., Le Prell, C.G., Rybak, L.P., (Eds.), Oxidative Stress in Applied Basic Research and Clinical Practice: Free Radicals in ENT Pathology. Humana Press, New York. 2015. pp.163-192.
85. Lesage FX, Jovenin N, Deschamps F, Vincent S. *Noise-induced hearing loss in French police officers.* Occup Med (Lond). 2009. 59(7):483-6.
86. Levy RH, Ragueneau-Majlessi I, Garnett WR, Schmerler M, Rosenfeld W, Shah J, Pan WJ. *Lack of clinically significant pharmacokinetic interactions between zonisamide and lamotrigine at steady state in patients with epilepsy.* Ther Drug Monit. 2005. 27(2):193-8.
87. Liberman MC. *Noise-induced and age-related hearing loss: new perspectives and potential therapies.* F1000Res. 2017. 6:927

88. Liberman MC. *Noise-Induced Hearing Loss: Permanent Versus Temporary Threshold Shifts and the Effects of Hair Cell Versus Neuronal Degeneration.* Adv Exp Med Biol. 2016
89. Lim DJ, Melnick W. *Acoustic damage of the cochlea. A scanning and transmission electron microscopic observation.* Arch Otolaryngol. 1971. 94(4):294-305.
90. Lin CY, Wu JL, Shih TS, Tsai PJ, Sun YM, Guo YL. *Glutathione S-transferase M1, T1, and P1 polymorphisms as susceptibility factors for noise-induced temporary threshold shift.* Hear Res. 2009. 257(1-2):8-15.
91. Lin HW, Furman AC, Kujawa SG, Liberman MC. *Primary neural degeneration in the Guinea pig cochlea after reversible noise-induced threshold shift*. J Assoc Res Otolaryngol. 2011. 12(5):605-16.
92. Lobarinas E, Scott R, Spankovich C, Le Prell CG. *Differential effects of suppressors on hazardous sound pressure levels generated by AR-15 rifles: Considerations for recreational shooters, law enforcement, and the military.* Int J Audiol. 2016. 55 Suppl 1:S59-71.
93. Lustig LR, Jackler RK, Chen DA. *Contralateral hearing loss after neurotologic surgery.* Otolaryngol Head Neck Surg. 1995. 113(3):276-82.
94. Lynch ED, Gu R, Pierce C, Kil J. *Ebselen-mediated protection from single and repeated noise exposure in rat.* Laryngoscope. 2004. 114(2):333-7.
95. Lynch ED, Kil J. *Compounds for the prevention and treatment of noise-induced hearing loss.* Drug Discov Today. 2005.10(19):1291-8.
96. MacArthur CJ, Kempton JB, DeGagne J, Trune DR. *Control of chronic otitis media and sensorineural hearing loss in C3H/HeJ mice: glucocorticoids vs mineralocorticoids.* Otolaryngol Head Neck Surg. 2008. 139(5):646-53.
97. MacDonald RL. *Zonisamide: mechanism of action. 2002.* Ed by Levy R, Mattson R, Meldrum B, Perucca E. Antiepileptic drugs. (5th ed). Philadelpia, PA: Lippincott, Williams & Witkins Healthcare; p. 867-72.
98. Mager DE, Lin SX, Blum RA, Lates CD, Jusko WJ. *Dose equivalency evaluation of major corticosteroids: pharmacokinetics and cell trafficking and cortisol dynamics*. J Clin Pharmacol. 2003. 43(11):1216-27.
99. Maison SF, Rauch SD. *Ethical considerations in noise-induced hearing loss research.* 2017. The Lancet.
100. Marshall L, Lapsley Miller JA, Heller LM. *Detecting incipient inner-ear damage from impulse noise with otoacoustic emissions.* J. Acoust. Soc. Am. 2009. 125 (2): 995-1013.
101. Matsubara A, Laake JH, Davanger S, Usami S, Ottersen OP. *Organization of AMPA receptor subunits at a glutamate synapse: a quantitative immunogold analysis of hair cell synapses in the rat organ of Corti. J Neurosci.* 1996. 16(14):4457-67.
102. Mattson MP. *Excitatory amino acids, growth factors, and calcium: a teeter-totter model for neural plasticity and degeneration.* Adv. Exp. Med. Biol. 1990. 268:211-20.
103. McBride DI, Williams S. *Audiometric notch as a sign of noise induced hearing loss.* Occup Environ Med. 2001. 58(1):46-51.
104. McCabe, B.F. *Autoimmune sensorineural hearing loss.* Ann Otol Rhinol Laryngol. 1979. 88, 585-9.

105. McFadden SL, Ohlemiller KK, Ding D, Shero M, Salvi RJ. *The Influence of Superoxide Dismutase and Glutathione Peroxidase Deficiencies on Noise-Induced Hearing Loss in Mice.* Noise Health. 2001. 3(11):49-64.
106. McFadden SL, Woo JM, Michalak N, Ding D. Dietary vitamin C supplementation reduces noise-induced hearing loss in guinea pigs. Hear Res. 2005. 202(1-2):200-8.
107. McIlwain DS, Gates K, Ciliax D. Heritage of army audiology and the road ahead: the Army Hearing Program. Am J Public Health. 2008. 98(12):2167-72.
108. Mehraei G, Hickox AE, Bharadwaj HM, Goldberg H, Verhulst S, Liberman MC, Shinn-Cunningham BG. Auditory Brainstem Response Latency in Noise as a Marker of Cochlear Synaptopathy. J Neurosci. 2016. 36(13):3755-64.
109. Mukherjea D, Ghosh S, Bhatta P, Sheth S, Tupal S, Borse V, Brozoski T, Sheehan KE, Rybak LP, Ramkumar V. *Early investigational drugs for hearing loss*. Expert Opin Investig Drugs. 2015. 24(2):201-17.
110. Mulroy MJ, Henry WR, McNeil PL. *Noise-induced transient microlesions in the cell membranes of auditory hair cells.* Hear Res. 1998. 115(1-2):93-100.
111. Nikonenko I, Bancila M, Bloc A, Muller D, Bijlenga P. *Inhibition of T-type calcium channels protects neurons from delayed ischemia-induced damage.* Mol Pharmacol. 2005. 68(1):84-9. NIOSH (National Institute for Occupational Safety and Health). *Work-Related Hearing Loss*. Pub 2001-103.
112. Nordmann AS, Bohne BA, Harding GW. *Histopathological differences between temporary and permanent threshold shift.* Hear Res. 2000. 139(1-2):13-30.
113. Ohlemiller KK. Recent findings and emerging questions in cochlear noise injury. Hear Res. 2008 245(1-2):5-17.
114. Ohlemiller KK, McFadden SL, Ding DL, Flood DG, Reaume AG, Hoffman EK, Scott RW, Wright JS, Putcha GV, Salvi RJ. *Targeted deletion of the cytosolic Cu/Zn-superoxide dismutase gene (Sod1) increases susceptibility to noise-induced hearing loss.* Audiol Neurootol. 1999. 4(5):237-46.
115. Ohlemiller KK, McFadden SL, Ding DL, Lear PM, Ho YS. *Targeted mutation of the gene for cellular glutathione peroxidase (Gpx1) increases noise-induced hearing loss in mice*. J Assoc Res Otolaryngol. 2000. 1(3):243-54.
116. Ohinata Y, Miller JM, Altschuler RA, Schacht J. *Intense noise induces formation of vasoactive lipid peroxidation products in the cochlea.* Brain Res. 2000. 878(1-2):163-73.
117. Ohinata Y, Miller JM, Schacht J. *Protection from noise-induced lipid peroxidation and hair cell loss in the cochlea.* Brain Res. 2003. 966(2):265-73.
118. Palva A, Sorri M. *Can an operation of deaf ear be dangerous for hearing?*. Acta Otolaryngol Suppl. 1979. 360:155-7.
119. Panusa A, Regazzoni L, Aldini G, Orioli M, Giombini A, Minghetti P, Tranquilli C, Carini M. *Urinary profile of methylprednisolone acetate metabolites in patients following intra-articular and intramuscular administration.* Anal Bioanal Chem. 2011. 400:255-67.
120. Park E, Bell JD, Baker AJ. *Traumatic brain injury: can the consequences be stopped?* CMAJ. 2008. 178(9):1163-70.
121. Pawelczyk M, Van Laer L, Fransen E, Rajkowska E, Konings A, et al. *Analysis of gene polymorphisms associated with K ion circulation in the inner ear of patients susceptible and resistant to noise-induced hearing loss.* Ann Hum Genet. 2009. 73 (Pt 4):411-21.
122. Paz, Z., Freeman, S., Horowitz, M., Sohmer, H. *Prior heat acclimation confers protection against noiseinduced hearing loss.* Audiol Neurootol. 2004. 9:363-9.

123. Perez-Reyes E. *Molecular physiology of low-voltage-activated t-type calcium channels*. Physiol. Rev. 2003. 83(1):117-61.
124. Pfannenstiel TJ. *Noise-induced hearing loss: a military perspective*. Curr Opin Otolaryngol Head Neck Surg. 2014. 22(5):384-7.
125. Puel JL, Ruel J, Guitton M, Pujol R. *The inner hair cell afferent/efferent synapses revisited: a basis for new therapeutic strategies*. Adv. Otorhinolaryngol. 2002. 59:124-30.
126. Quaranta A, Portalatini P, Henderson D. *Temporary and permanent threshold shift: an overview.* Scand Audiol Suppl. 1998. 48:75-86.
127. Quirk WS, Shapiro BD, Miller JM, Nuttall AL. *Noise-induced changes in red blood cell velocity in lateral wall vessels of the rat cochlea.* Hear Res. 1991. 52(1):217-23.
128. Rodriguez-Contreras A, Yamoah EN. *Direct measurement of single-channel Ca(2+) currents in bullfrog hair cells reveals two distinct channel subtypes.* J Physiol. 2001. 534(Pt 3):669-89.
129. Rogawski MA, Löscher W. *The neurobiology of antiepileptic drugs*. Nat Rev Neurosci. 2004. 5(7):553-64.
130. Rohde NN, Baca CB, Van Cott AC, Parko KL, Amuan ME, Pugh MJ. *Antiepileptic drug prescribing patterns in Iraq and Afghanistan war veterans with epilepsy.* Epilepsy Behav. 2015. 46:133-9.
131. Ryan AF, Kujawa SG, Hammill T, Le Prell C, Kil J. *Temporary and Permanent Noise-induced Threshold Shifts: A Review of Basic and Clinical Observations.* Otol Neurotol. 2016. 37(8):e271-5.
132. Saruwatari J, Ishitsu T, Nakagawa K. *Update on the Genetic Polymorphisms of Drug-Metabolizing Enzymes in Antiepileptic Drug Therapy.* Pharmaceuticals. 2010. 3(8): 2709-2732.
133. Saunders JC, Cohen YE, Szymko YM. *The structural and functional consequences of acoustic injury in the cochlea and peripheral auditory system: a five year update*. J Acoust Soc Am. 1991. 90:136-46.
134. Sbodio JI, Snyder SH, Paul BD. *Redox Mechanisms in Neurodegeneration: From Disease Outcomes to Therapeutic Opportunities.* 2018.
135. Schnee ME, Ricci AJ. *Biophysical and pharmacological characterization of voltage-gated calcium currents in turtle auditory hair cells.* J Physiol. 2003. 549(Pt 3):697-717.
136. Seidman MD, Shivapuja BG, Quirk WS. *The protective effects of allopurinol and superoxide dismutase on noise-induced cochlear damage.* Otolaryngol Head Neck Surg. 1993. 109:1052-6.
137. Sendowski, I., Abaamrane, L., Raffin, F., Cros, A., Clarencon, D. *Therapeutic efficacy of intra-cochlear administration of methylprednisolone after acoustic trauma caused by gunshot noise in guinea pigs.* Hear Res. 2006. 221, 119-27.
138. Sergeyenko Y, Lall K, Liberman MC, Kujawa SG. *Age-related cochlear synaptopathy: an early-onset contributor to auditory functional decline.* J Neurosci. 2013. 33(34):13686-94.
139. Shen H, Zhang B, Shin JH, Lei D, Du Y, Gao X, Wang Q, Ohlemiller KK, Piccirillo J, Bao J. *Prophylactic and therapeutic functions of T-type calcium blockers against noise-induced hearing loss.* Hear Res. 2007. 226(1-2):52-60.
140. Shimazaki T, Ichimiya I, Suzuki M, Mogi G. *Localization of glucocorticoid receptors in the murine inner ear.* Ann Otol Rhinol Laryngol. 2002. 111(12 Pt 1):1133-8.
141. Singh V, Mehta AK. *Prevalence of occupational noise induced hearing loss amongst police personnel.* Indian J Otolaryngol. 1999. 51: 23-26.

142. Slepecky N. *Overview of mechanical damage to the inner ear: noise as a tool to probe cochlear function*. Hear Res. 1986. 22:307-21.
143. Spoendlin H. *Primary structural changes in the organ of Corti after acoustic overstimulation.* Acta Otolaryngol. 1971. 71(2):166-76.
144. Stamper GC, Johnson TA. *Auditory function in normal-hearing, noise-exposed human ears.* Ear Hear. 2015.36(2):172-84
145. Shrestha I, Shrestha BL, Pokharel M, Amatya RC, Karki DR. *Prevalence of noise induced hearing loss among traffic police personnel of Kathmandu Metropolitan City.* Kathmandu Univ Med J (KUMJ). 2011. 9(36):274-8.
146. Sonstrom Malowski K, Steiger J. *Hearing loss in police K9 handlers and non-K9 handlers.* Int. J. Audiol. 2019.
147. Tabuchi, K., Murashita, H., Sakai, S., Hoshino, T., Uemaetomari, I., Hara, A. *Therapeutic time window of methylprednisolone in acoustic injury*. Otol Neurotol. 2006. 27:1176-9.
148. Tahera, Y., Meltser, I., Johansson, P., Bian, Z., Stierna, P., Hansson, A.C., Canlon, B. *NF-kappaB mediated glucocorticoid response in the inner ear after acoustic trauma.* J Neurosci Res. 2006a. 83:1066-76.
149. Tahera, Y., Meltser, I., Johansson, P., Canlon, B. *Restraint stress modulates glucocorticoid receptors and nuclear factor kappa B in the cochlea.* Neuroreport. 2006b. 17:879-82.
150. Tahera, Y., Meltser, I., Johansson, P., Hansson, A.C., Canlon, B. *Glucocorticoid receptor and nuclear factor-kappa B interactions in restraint stress-mediated protection against acoustic trauma.* Endocrinology. 2006c. 147:4430-7.
151. Ten Cate, W.J., Curtis, L.M., Small, G.M., Rarey, K.E. *Localization of glucocorticoid receptors and glucocorticoid receptor mRNAs in the rat cochlea.* Laryngoscope. 1993.103:865-71.
152. Thirugnanam I, Kumar A, Padmanabam P, Valarmathi V, Ramesh R. *Prevalence of Noise-Induced Hearing Loss in Police Personnel Coming for Health Checkup at Government Theni Medical College Hospitals.* J Evid Based Med. 2017. 4: 4175-4180.
153. Tos M, Lau T, Plate S. *Sensorineural hearing loss following chronic ear surgery*. 1984. Ann Otol Rhinol Laryngol. 93:1984 The American Journal of Otology: October 1984 - Volume 5 - Issue 6 - ppg 459-462
154. Tremblay KL, Pinto A, Fischer ME, Klein BE, Klein R, Levy S, Tweed TS, Cruickshanks KJ. *Self-Reported Hearing Difficulties Among Adults With Normal Audiograms: The Beaver Dam Offspring Study.* Ear Hear. 2015. 36(6):e290-9.
155. Trune DR, Canlon B. *Corticosteroid therapy for hearing and balance disorders.* Anat Rec (Hoboken). 2012. 295(11):1928-43.
156. Viana LM, O'Malley JT, Burgess BJ, Jones DD, Oliveira CA, Santos F, Merchant SN, Liberman LD, Liberman MC. *Cochlear neuropathy in human presbycusis: Confocal analysis of hidden hearing loss in post-mortem tissue*. Hear Res. 2015. 327:78-88.
157. Wan G, Corfas G. *Transient auditory nerve demyelination as a new mechanism for hidden hearing loss. Nat* Commun. 2017. 17;8:14487.
158. Wang, Y., Hirose, K., Liberman, MC. *Dynamics of noise-induced cellular injury and repair in the mouse cochlea*. JARO. 2002. 3:248-68.
159. Wang, Y, Ren C. *Effects of repeated "benign" noise exposures in young CBA mice: shedding light on agerelated hearing loss.* JARO. 2012.
160. Werling LL, Lauterbach EC, Calef U. *Dextromethorphan as a potential neuroprotective agent with unique mechanisms of action.* Neurologist. 2007. 13(5):272-93.

161. Wilson RH, Abrams HB, Pillion AL. *A word-recognition task in multitalker babble using a descending presentation mode from 24 dB to 0 dB signal to babble.* J. Rehabil. Res. Dev. 2003. 40:321-7.
162. Wilson RH, Burks CA. *Use of 35 words for evaluation of hearing loss in signal-to-babble ratio: A clinic protocol.* J. Rehabil. Res. Dev. 2005. 42:839-52.
163. Wilson RH, Burks CA, Weakley DG. *Word recognition in multitalker babble measured with two psychophysical methods*. J. Am. Acad. Audiol. 2005.16:622-30.
164. Wilson RH, Cates WB. *A comparison of two word-recognition tasks in multitalker babble: Speech Recognition in Noise Test (SPRINT) and Words-in-Noise Test (WIN)*. J. Am. Acad. Audiol. 2008.19:548-56.
165. Wilson RH, McArdle R. *Intra- and inter-session test, retest reliability of the Words-in-Noise (WIN) test*. J. Am. Acad. Audiol. 2007.18:813-25.
166. Wilson RH, McArdle R, Betancourt MB, Herring K, Lipton T, Chisolm TH. *Word-recognition performance in interrupted noise by young listeners with normal hearing and older listeners with hearing loss.* J. Am. Acad. Audiol. 2010. 21:90-109.
167. Wilson, R.H., McArdle, R.A., Smith, S.L. *An Evaluation of the BKB-SIN, HINT, QuickSIN, and WIN Materials on Listeners with Normal Hearing and Listeners With Hearing Loss*. J. Speech. Lang. Hear. Res. 2007. 50:844-56.
168. Wilson RH, Watts KL. *The Words-in-Noise Test (WIN), list 3: a practice list.* J. Am. Acad. Audiol. 2012. 23:92-6.
169. Win KN, Balalla NBP, Lwin MZ, Lai A. *Noise-Induced Hearing Loss in the Police Force.* Safety and Health at Work. 2015. 6: 134-138.
170. Xu J, Chen S, Chen H, Xiao Q, Hsu CY, Michael D, Bao J. *STAT5 mediates antiapoptotic effects of methylprednisolone on oligodendrocytes.* J Neurosci. 2009. 29(7):2022-6.
171. Yamane H, Nakai Y, Takayama M, Iguchi H, Nakagawa T, Kojima A. *Appearance of free radicals in the guinea pig inner ear after noise-induced acoustic trauma.* Eur Arch Otorhinolaryngol. 1995. 252(8):504-8.
172. Yamashita D, Jiang HY, Le Prell CG, Schacht J, Miller JM. *Post-exposure treatment attenuates noiseinduced hearing loss.* Neuroscience. 2005. 134(2):633-42.
173. Yamashita D, Jiang HY, Schacht J, Miller JM. *Delayed production of free radicals following noise exposure.* Brain Res. 2004. 1019(1-2):201-9.
174. Yamasoba T, Schacht J, Shoji F, Miller JM. *Attenuation of cochlear damage from noise trauma by an iron chelator, a free radical scavenger and glial cell line-derived neurotrophic factor in vivo.* Brain Res. 1999. ;815(2):317-25.
175. Yankaskas K. *Prelude: noise-induced tinnitus and hearing loss in the military.* Hear Res. 2013. 295:3-8
176. Yoshida, N., Kristiansen, A., Liberman, M.C., 1999. *Heat stress and protection from permanent acoustic injury in mice.* J Neurosci. 19, 10116-24.
177. Yu M, Liu T, Chen Y, Li Y, Li W. *Combination therapy with protein kinase inhibitor H89 and Tetrandrine elicits enhanced synergistic antitumor efficacy*. J Exp Clin Cancer Res. 2018. 37(1):114.
178. Yunker AM, McEnery MW. *Low-voltage-activated ("T-Type") calcium channels in review*. J. Bioenerg. Biomembr. 2003. 35(6):533-75.
179. Zecker SG1, Hoffman HJ, Frisina R, Dubno JR, Dhar S, Wallhagen M, Kraus N, Griffith JW, Walton JP, Eddins DA, Newman C, Victorson D, Warrier CM, Wilson RH. *Audition assessment using the NIH Toolbox.* Neurology. 2013. 80(11 Suppl 3):S45-8.

180. Zhang X., Ni Y., Liu Y., Zhang L., Zhang M. et al. *Screening of noise-induced hearing loss (NIHL)- associated SNPs and the assessment of its genetic susceptibility.* Environ Health. 2019. 18(1): 30.
181. Zhou Y, Zheng G, Zheng H, Zhou R, Zhu X, Zhang Q. *Primary observation of early transtympanic steroid injection in patients with delayed treatment of noise-induced hearing loss*. Audiol Neurootol. 2013. 18(2):89-94.
182. Zine A, van de Water TR. *The MAPK/JNK signalling pathway offers potential therapeutic targets for the prevention of acquired deafness.* Curr Drug Targets CNS Neurol Disord. 2004. 3(4):325-32.
183. Zipfel GJ, Babcock DJ, Lee JM, Choi DW. *Neuronal apoptosis after CNS injury: the roles of glutamate and calcium.* J Neurotrauma. 2000. 17(10):857-69.
184. Zuo J, Curtis LM, Yao X, ten Cate WJ, Bagger-Sjöbäck D, Hultcrantz M, Rarey KE. *Glucocorticoid receptor expression in the postnatal rat cochlea.* Hear Res. 1995. 87(1-2):220-7.

APPENDIX A: Definitions for Adverse Event Reporting

A. Adverse Events (AEs)

As defined in 21 CFR 312.32:

Definition: any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related.

Grading: the descriptions and grading scales that should be used are those provided by the Department of Health and Human Services' Office for Human Research Protections (OHRP). A copy of this guidance can be found on OHRP's website:
http://www.hhs.gov/ohrp/policy/advevntguid.html

Attribution (relatedness), Expectedness, and Seriousness: the definitions for the terms listed that should be used are those provided by the Department of Health and Human Services' Office for Human Research Protections (OHRP). A copy of this guidance can be found on OHRP's website:
http://www.hhs.gov/ohrp/policy/advevntguid.html

B. Suspected Adverse Reaction (SAR)

As defined in 21 CFR 312.32:

Definition: any adverse event for which there is a reasonable possibility that the drug caused the adverse event. "Reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. "Suspected adverse reaction" implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

C. Life-Threatening Adverse Event / Life Threatening Suspected Adverse Reaction

As defined in 21 CFR 312.32:

Definition: any adverse drug event or suspected adverse reaction is considered "life-threatening" if, in the view of the investigator, its occurrence places the patient at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

D. Serious Adverse Event (SAE) or Serious Suspected Adverse Reaction

As defined in 21 CFR 312.32:

Definition: an adverse event or suspected adverse reaction is considered "serious" if, in the view of the investigator, it results in any of the following outcomes:

- Death

- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Any other important medical event that does not fit the criteria above but, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

E. Protocol Exceptions

Definition: A planned change in the conduct of the research for one participant.

F. Deviation

Definition: Any alteration or modification to the IRB-approved research without prospective IRB approval. The term "research" encompasses all IRB-approved materials and documents including the detailed protocol, IRB application, consent form, recruitment materials, questionnaires/data collection forms, and any other information relating to the research study.

A minor or administrative deviation is one that does not have the potential to negatively impact the rights, safety, or welfare of participants or others or the scientific validity of the study.

A major deviation is one that does have the potential to negatively impact the rights, safety, or welfare of participants or others or the scientific validity of the study.

APPENDIX B: Reporting Timelines

Event	HRPO	FDA
Serious AND unexpected suspected adverse reaction		Report no later than 15 calendar days after it is determined that the information qualifies for reporting
Unexpected fatal or life-threatening suspected adverse reaction		Report no later than 7 calendar days after initial receipt of the information
Unanticipated problem involving risk to participants or others	Report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day.	
Major deviation	Report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day.	
A series of minor deviations that are being reported as a continuing noncompliance	Report within 10 working days.	
Protocol exception	Approval must be obtained prior to implementing the change	
Clinically important increase in the rate of a serious suspected adverse reaction of that list in the protocol or IB		Report no later than 15 calendar days after it is determined that the information qualifies for reporting
Complaints	If the complaint reveals an unanticipated problem involving risks to participants or others OR noncompliance, report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day. Otherwise, report at the time of continuing review.	
Breach of confidentiality	Within 10 working days.	
Incarceration	If withdrawing the participant poses a safety issue, report within 10 working days. If withdrawing the participant does not represent a safety issue and the patient will be withdrawn, report at continuing review.	

Event	HRPO	FDA
Adverse event or SAE that does not require expedited reporting	If they do not meet the definition of an unanticipated problem involving risks to participants or others, report summary information at the time of continuing review	The most current toxicity table from the DSM report is provided to the FDA with the IND's annual report.
Minor deviation	Report summary information at the time of continuing review.	
Complaints	If the complaint reveals an unanticipated problem involving risks to participants or others OR noncompliance, report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day. Otherwise, report at the time of continuing review.	
Incarceration	If withdrawing the participant poses a safety issue, report within 10 working days. If withdrawing the participant does not represent a safety issue and the patient will be withdrawn, report at continuing review.	

Event	WU (Coordinating Center)	Local IRB	FDA
Serious AND unexpected suspected adverse reaction	Report no later than 11 calendar days after it is determined that the information qualifies for reporting.	Report all applicable events to local IRB according to local institutional guidelines.	The research team at Washington University is responsible for reporting all applicable events to the FDA as needed.
Unexpected fatal or life-threatening suspected adverse reaction	Report no later than 4 calendar days after initial receipt of the information.		
Unanticipated problem involving risk to participants or others	Report no later than 4 calendar days after initial receipt of the information.		
Adverse event or SAE that does not require expedited reporting	As per routine data entry expectations		
Protocol exception	Approval must be obtained prior to implementing the change.		

APPENDIX C: Washington University Unanticipated Problem Reporting Cover Sheet

SAE COVER SHEET- Secondary Site Assessment

Washington University HRPO#:	Sponsor-Investigator:
Subject Initials:	Subject ID:
Treating MD:	Treating Site:
EVENT TERM:	Admission Date:
EVENT GRADE:	Date of site's first notification:

Treating MD Event Assessment:

Is this event **possibly, probably, or definitely** related study treatment?

☐ yes ☐ no

If yes, please list which drug (if more than one)_____

Explain _____

_____

_____ _____ _____

Physician's Name **Physician's Signature** **Date**

APPENDIX D: Questionnaire 1: Case History Form

Medical / Hearing History Questionnaire

Name: _____

Date of Birth: _____

Gender: _____

Length of time as a police officer: _____

Handedness: _____ Shoot with: _____

How often do you shoot for certification, annually (occupational)? _____

Communication radio location: _____

Do you have an existing hearing problem?	Yes No Unknown
If you have a hearing problem, has it been:	Gradual Lifelong Sudden
Have you ever had your hearing tested?	Yes No If yes, when? _____
Have you *recently* experienced pain in either ear?	Yes No Left Right Both
Have you *recently* experienced drainage from your ear?	Yes No Left Right Both
Have you *recently* experienced ear fullness of discomfort?	Yes No Left Right Both
Have you *recently* experienced dizziness?	Yes No Left Right Both
Do you experience tinnitus (ringing) in your ears?	Yes No Left Right Both Center
If yes, how often?	Rarely (few times a year) Several times a year Several times a month Several times a week Daily
Have you ever been to an ear specialist?	Yes No
Have you ever had ear surgery?	Yes No
Do you have frequent ear infections?	Yes No
Do you have sinus problems?	Yes No
Do you have allergies?	Yes No
Do you currently use prescription or over-the-counter drugs?	Yes No

Have you ever had kidney disease?	Yes No
Have you ever had meningitis?	Yes No
Do you have diabetes?	Yes No
Do you have high blood pressure?	Yes No
Do you experience headaches?	Yes No
Have you experienced head trauma?	Yes No
Do you have facial numbness?	Yes No
Do you shoot recreationally (i.e. hunting)?	Yes No
If yes, how often do you shoot recreationally?	Rarely (few times a year) Several times a year Several times a month Several times a week Daily
Is hearing protection used when you shoot recreationally?	Never (0% of time) Minimally (~25% of time or less) Moderately (~50% of time) Often (~75% of time) Always (100% of time)
Do you participate in loud activities (music, concerts, motorcycle)?	Yes No What types of activities? _____ _____ _____
If yes, how often do you participate in these activities?	Rarely (few times a year) Several times a year Several times a month Several times a week Daily
Is hearing protection used when you participate in these activities?	Never (0% of time) Minimally (~25% of time or less) Moderately (~50% of time) Often (~75% of time) Always (100% of time)
Do you operate chain or power tools?	Yes No
If yes, how often do you operate chain and/or power tools?	Rarely (few times a year) Several times a year Several times a month Several times a week Daily
Is hearing protection used when you operate chain/power tools?	Never (0% of time) Minimally (~25% of time or less)

	Moderately (~50% of time) Often (~75% of time) Always (100% of time)
Does any of your immediate family have a hearing loss?	Yes No
Do you, or have you previously worn hearing aids?	Yes No
Please rate your hearing	Very Good Good Average Poor Very Poor

PATIENT MEDICATION LIST

MEDICATION NAME	DOSAGE / STRENGTH	FREQUENCY (How often)	ROUTE (Oral, injection, spray)	REASON FOR USE

ALLERGY INFORMATION

ALLERGIC TO	REACTION

Please add or elaborate on any additional comments regarding your medical and hearing health that was not addressed:

APPENDIX E: Questionnaire 2: Life Exposure to Noise and Solvents (LENS-Q)

NOISE AND SOLVENT EXPOSURE QUESTIONNAIRE

We are interested in knowing about your noise exposure history over your entire lifetime.

This questionnaire is divided into 3 parts:
1) your **NON-MILITARY,OCCUPATIONAL** noise and solvent/chemical exposure;
2) your **MILITARY, OCCUPATIONAL** noise and solvent/chemical exposure;
3) your **NON-OCCUPATIONAL/RECREATIONAL** noise and solvent/chemical exposure.

NON-MILITARY, OCCUPATIONAL EXPOSURE HISTORY

The following questions are about your **NON-MILITARY, OCCUPATIONAL** noise and solvent/chemical exposure history. This includes all occupations **OUTSIDE** of your military career. Please answer the questions thinking only about occupational exposures you had during the time period **before**, **between** or **after** your military career.

To help you understand what we mean by "exposed to loud noise" see the "NOISE THERMOMETER" provided in your questionnaire packet for examples of loud sounds. You are most likely "exposed to loud noise" if you are around activities at or above 85 decibels. Another example of loud noise is noise that makes it hard to talk to or hear another person, or makes your ears ring after exposure.

Subject ID

Do not fill in - for office use only

Month/Day/Year

Lifetime Exposure to Noise and Solvents (LENS-Q)

Non-Military Occupational Noise

Please answer each question by circling or marking the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

Shade Circles Like This--> ●

Not Like This--> ⊗ ✓

Occupational Non-MILITARY 1. Did you work in any of these types of jobs? (Circle No or Yes)	*For each job you answer "Yes" please answer additional questions 2 - 6.* 2. Year Started (YYYY)	3. Year Ended (YYYY) If job is current, use this year	4. Length of time at job (#yrs/mos)	5. How often were you around loud noise? Never	Several times a year	Several times a month	Several times a week	Daily	6. How often did you use hearing protection while in loud noise? Never	Some of the time	Most of the time	Always
A. Automotive..... No Yes				○	○	○	○	○	○	○	○	○
B. Construction... No Yes				○	○		○	○	○	○	○	○
C. Industrial..... No Yes				○	○	○	○	○	○	○	○	○
D. Manufacturing. No Yes				○	○	○	○	○	○	○	○	○
E. Carpentry..... No Yes				○	○	○	○	○	○	○	○	○
F. Airport Staff.... No Yes				○	○	○	○	○	○	○	○	○
G. Agricultural/ Farming..... No Yes				○	○	○	○	○	○	○	○	○
H. Logging/Lumber Industry..... No Yes				○	○	○	○	○	○	○	○	○
I. Mining..... No Yes				○	○	○	○	○	○	○	○	○
J. Printing..... No Yes				○	○	○	○	○	○	○	○	○

Version 02/27/2018

Subject ID
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LENS-Q
Non-Military Occupational Noise

Month/Day/Year

Please answer each question by circling or marking the answer. If you are unsure about how to answer a question, give the best answer you can.

Occupational Non-MILITARY (Continued) 1. Did you work in any of these types of jobs? (Circle No or Yes)	*For each job you answered "Yes" please answer additional questions 2-6* 2. Year Started (YYYY)	3. Year Ended (YYYY) If job is current, use this year	4. Length of time at job (#yrs/mos)	5. How often were you around loud noise? Never	Several times a year	Several times a month	Several times a week	Daily	6. How often did you use hearing protection while in loud noise? Never	Some of the time	Most of the time	Always
K. Entertainment.. No Yes *(nightclubs, disco, concert, live show, sporting event)*				○	○	○	○	○	○	○	○	○
L. Musician..... No Yes *(band, orchestra, symphony)*				○	○	○	○	○	○	○	○	○
M. Transportation.. No Yes *(ship, train, plane, truck)*				○	○	○	○	○	○	○	○	○
N. Fisherman/..... No Yes Merchant Marine				○	○	○	○	○	○	○	○	○
O. Emergency ..... No Yes *(police, fire, EMT)*				○	○	○	○	○	○	○	○	○
Other type of jobs: P.				○	○	○	○	○	○	○	○	○
Q.				○	○	○	○	○	○	○	○	○
R.				○	○	○	○	○	○	○	○	○

Subject ID
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LENS-Q
Non-Military Occupational

Month/Day/Year

Please answer **"Yes"** to any chemicals you have been in contact with in your **NON-MILITARY** work environment.

Non-Military Occupational **1. Have you been in contact with any of the following chemicals?** (Circle No or Yes)	*For each chemical you answer "Yes" please answer questions 2 - 6.* **2. Year Started (YYYY)**	**3. Year Ended (YYYY)** If current, use this year	**4. Length of time exposed** (#yrs/mos)	**5. How often were you in contact with chemicals?** Never	Several times a year	Several times a month	Several times a week	Daily	**6. How often did you wear protective gear?** *(respirator, eye gear, mask, face shield, gloves clothes)* Never	Some of the time	Most of the time	Always
A. Ethyl benzene.. No Yes				○	○	○	○	○	○	○	○	○
B. Toluene..... No Yes				○	○	○	○	○	○	○	○	○
C. Xylene..... No Yes				○	○	○	○	○	○	○	○	○
D. Styrene..... No Yes				○	○	○	○	○	○	○	○	○
E. n-Hexane..... No Yes				○	○	○	○	○	○	○	○	○
F. Carbon monoxide..... No Yes				○	○	○	○	○	○	○	○	○
G. Trichloroethylene (TCE)..... No Yes				○	○	○	○	○	○	○	○	○
H. Lead..... No Yes				○	○	○	○	○	○	○	○	○
I. Acrylonitrile..... No Yes				○	○	○	○	○	○	○	○	○
J. N-Butylalchol... No Yes				○	○	○	○	○	○	○	○	○
K. Carbon disulphide..... No Yes				○	○	○	○	○	○	○	○	○

Version 03/13/2018

Subject ID
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LENS-Q
Non-Military Occupational

Month/Day/Year

Please answer **"Yes"** to any chemicals you have been in contact with in your **NON-MILITARY** work environment.

Non-Military Occupational (Continued)	*For each chemical you answer "Yes" please answer questions 2 - 6.*			**5. How often were you around chemicals?**					**6. How often did you wear protective gear?** *(respirator, eye gear, mask, face shield, gloves, clothing)*			
1. Have you been in contact with any of the following chemicals? (Circle No or Yes)	**2. Year Started (YYYY)**	**3. Year Ended (YYYY)** If current, use this year	**4. Length of time exposed** (#yrs/mos)	Never	Several times a year	Several times a month	Several times a week	Daily	Never	Some of the time	Most of the time	Always
L. Cyanide..... No Yes *(including hydrogen cyanide)*				○	○	○	○	○	○	○	○	○
M. n-Heptane..... No Yes				○	○	○	○	○	○	○	○	○
N. Mercury..... No Yes *(alkyl compounds)*				○	○	○	○	○	○	○	○	○
O. Mercury..... No Yes *(inorganic compounds)*				○	○	○	○	○	○	○	○	○
P. Mercury..... No Yes *(vapor)*				○	○	○	○	○	○	○	○	○
Q. x-Methyl-styrene..... No Yes				○	○	○	○	○	○	○	○	○
R. Welding fumes.. No Yes				○	○	○	○	○	○	○	○	○
S. Burn Pits..... No Yes				○	○	○	○	○	○	○	○	○

MILITARY, OCCUPATIONAL EXPOSURE HISTORY

The following questions are about your **MILITARY, OCCUPATIONAL** noise and solvent/chemical exposure history. This includes occupational exposures you had **DURING** your military career. Please answer the questions thinking only about noise exposures you had during your military career. Please list up to four Job Titles (with your Occupational Specialty Codes e.g. MOS, Rating), during your military career, beginning with the most recent Job Title.

To help you understand what we mean by "exposed to loud noise" see the "NOISE THERMOMETER" provided in your questionnaire packet for examples of loud sounds. You are most likely "exposed to loud noise" if you are around activities at or above 85 decibels. Another example of loud noise is noise that makes it hard to talk to or hear another person, or makes your ears ring after exposure.

Subject ID
Do not fill in - for office use only

LENS-Q
Military Occupational

Month/Day/Year

Shade Circles Like This--> ●
Not Like This--> ⊘ ⊘

Please answer each question by circling or marking the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

Occupational Noise during MILITARY Service	*For each job/activity you answer "Yes" please answer questions 2-6*			5. How often were you around loud noise?					6. How often did you use hearing protection while in loud noise?			
1. What jobs did you have during your MILITARY service? (Circle No or Yes)	2. Year Started (YYYY)	3. Year Ended (YYYY) If current, use this year	4. Length of time at job (#yrs/mos)	Never	Several times a year	Several times a month	Several times a week	Daily	Never	Some of the time	Most of the time	Always
JOB TITLE 1:				○	○	○	○	○	○	○	○	○
Occupational Specialty Code (MOS; Ranking):												
Were you exposed to any of the following during your time in this job?												
A. Artillery..... No Yes				○	○	○	○	○	○	○	○	○
B. Explosion..... No Yes				○	○	○	○	○	○	○	○	○
C. Planes Helicopters.. No Yes				○	○	○	○	○	○	○	○	○
D. Small arms... No Yes				○	○	○	○	○	○	○	○	○
E. Tanks, other heavy equipment.... No Yes				○	○	○	○	○	○	○	○	○
F. Aircraft carriers, ships submarines... No Yes				○	○	○	○	○	○	○	○	○
G. Other types of noise:				○	○	○	○	○	○	○	○	○
				○	○	○	○	○	○	○	○	○

Version 02/27/2018

Subject ID
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LENS-Q
Military Occupational

Month/Day/Year

Please answer each question by circling or marking the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

Occupational Noise during MILITARY Service 1. What jobs did you have during your MILITARY service? (Circle No or Yes)	*For each job/activity you answer "Yes", please answer questions 2-6* 2. Year Started (YYYY)	3. Year Ended (YYYY) If job is current, use this year	4. Length of time at job (#yrs/mos)	5. How often were you around loud noise? Never	Several times a year	Several times a month	Several times a week	Daily	6. How often did you use hearing protection while in loud noise? Never	Some of the time	Most of the time	Always
JOB TITLE 2:				○	○	○	○	○	○	○	○	○
Occupational Specialty Code (MOS; Ranking):												
Were you exposed to any of the following during your time in this job?												
A. Artillery..... No Yes				○	○	○	○	○	○	○	○	○
B. Explosion..... No Yes				○	○	○	○	○	○	○	○	○
C. Planes Helicopters.. No Yes				○	○	○	○	○	○	○	○	○
D. Small arms... No Yes				○	○	○	○	○	○	○	○	○
E. Tanks, other heavy equipment... No Yes				○	○	○	○	○	○	○	○	○
F. Aircraft carriers, ships submarines... No Yes				○	○	○	○	○	○	○	○	○
G.Other types of noise:				○	○	○	○	○	○	○	○	○
				○	○	○	○	○	○	○	○	○

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LENS-Q
Military Occupational

Month/Day/Year

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Not Like This--> ⊗ ✓

Please answer each question by circling or marking the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

Occupational Noise during MILITARY Service 1. What jobs did you have during your Military service? (Circle No or Yes)	*For each job/activity you answer "Yes" please answer questions 2-6* 2. Year Started (YYYY)	3. Year Ended (YYYY) If job is current use this year	4. Length of time at job (#yrs/mos)	5. How often were you around loud noise? Never / Several times a year / Several times a month / Several times a week / Daily	6. How often did you use hearing protection while in loud noise? Never / Some of the time / Most of the time / Always
JOB TITLE 3:				○ ○ ○ ○ ○	○ ○ ○ ○
Occupational Specialty Code (MOS; Ranking):					
Were you exposed to any of the following during your time in this job?					
A. Artillery..... No Yes				○ ○ ○ ○ ○	○ ○ ○ ○
B. Explosion..... No Yes				○ ○ ○ ○ ○	○ ○ ○ ○
C. Planes Helicopters.. No Yes				○ ○ ○ ○ ○	○ ○ ○ ○
D. Small arms... No Yes				○ ○ ○ ○ ○	○ ○ ○ ○
E. Tanks, other heavy equipment.... No Yes				○ ○ ○ ○ ○	○ ○ ○ ○
F. Aircraft carriers, ships submarines... No Yes				○ ○ ○ ○ ○	○ ○ ○ ○
G.Other types of noise:				○ ○ ○ ○ ○	○ ○ ○ ○
				○ ○ ○ ○ ○	○ ○ ○ ○

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LENS-Q
Military Occupational

Month/Day/Year

Please answer each question by circling or marking the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

Occupational Noise during Military Service **1. What jobs did you have during your Military service?** (Circle No or Yes)	*For each job/activity you answer "Yes", please answer questions 2-6* **2. Year Started (YYYY)**	**3. Year Ended (YYYY)** If job is current, use this year	**4. Length of time at job (#yrs/mos)**	**5. How often were you around loud noise?** Never	Several times a year	Several times a month	Several times a week	Daily	**6. How often did you use hearing protection while in loud noise?** Never	Some of the time	Most of the time	Always
JOB TITLE 4: _____ Occupational Specialty Code (MOS; Ranking):				○	○	○	○	○	○	○	○	○
Were you exposed to any of the following during your time in this job? A. Artillery..... No Yes				○	○	○	○	○	○	○	○	○
B. Explosion..... No Yes				○	○	○	○	○	○	○	○	○
C. Planes Helicopters.. No Yes				○	○	○	○	○	○	○	○	○
D. Small arms... No Yes				○	○	○	○	○	○	○	○	○
E. Tanks, other heavy equipment... No Yes				○	○	○	○	○	○	○	○	○
F. Aircraft carriers, ships submarines... No Yes				○	○	○	○	○	○	○	○	○
G.Other types of noise: _____				○	○	○	○	○	○	○	○	○
_____				○	○	○	○	○	○	○	○	○

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LENS-Q
Military Occupational

Month/Day/Year

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Please tell us about any solvent or chemical exposures that you have had in your **MILITARY** work environment.

MILITARY Occupational Chemical/Solvent Exposures **1. Have you been in contact with any of the following chemicals?** (Circle No or Yes)	*For each chemical you answer "Yes" please answer questions 2 - 6.* **2. Year Started (YYYY)**	**3. Year Ended (YYYY)** If current, use this year	**4. Length of time exposed** (#yrs/mos)	**5. How often were you around chemicals?** Never / Several times a year / Several times a month / Several times a week / Daily	**6. How often did you wear protective gear?** *(respirator, eye gear, mask, face shield, gloves, clothing)* Never / Some of the time / Most of the time / Always
A. Ethyl benzene.. No Yes				○ ○ ○ ○ ○	○ ○ ○ ○
B. Toluene..... No Yes				○ ○ ○ ○ ○	○ ○ ○ ○
C. Xylene..... No Yes				○ ○ ○ ○ ○	○ ○ ○ ○
D. Styrene..... No Yes				○ ○ ○ ○ ○	○ ○ ○ ○
E. n-Hexane..... No Yes				○ ○ ○ ○ ○	○ ○ ○ ○
F. Carbon monoxide..... No Yes				○ ○ ○ ○ ○	○ ○ ○ ○
G. Trichloroethylene (TCE)..... No Yes				○ ○ ○ ○ ○	○ ○ ○ ○
H. Lead..... No Yes				○ ○ ○ ○ ○	○ ○ ○ ○
I. Acrylonitrile..... No Yes				○ ○ ○ ○ ○	○ ○ ○ ○
J. N-Butylalchol... No Yes				○ ○ ○ ○ ○	○ ○ ○ ○
K. Carbon disulphide..... No Yes				○ ○ ○ ○ ○	○ ○ ○ ○

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LENS-Q
Military Occupational

Month/Day/Year

Please tell us about any solvent or chemical exposures that you have had in your **MILITARY** work environment.

MILITARY Occupational Chemical/Solvent Exposures (Continued)	*For each chemical you answer "Yes" please answered questions 2 - 6.*			**5. How often were you around chemicals?**					**6. How often did you wear protective gear?** *(respirator, eye gear, mask, face shield, gloves, clothing)*			
1. Have you been in contact with any of the following chemicals? (Circle No or Yes)	**2. Year Started (YYYY)**	**3. Year Ended (YYYY)** If current, use this year	**4. Length of time exposed (#yrs/mos)**	Never	Several times a year	Several times a month	Several times a week	Daily	Never	Some of the time	Most of the time	Always
L. Cyanide..... No Yes *(including hydrogen cyanide)*				○	○	○	○	○	○	○	○	○
M. n-Heptane..... No Yes				○	○	○	○	○	○	○	○	○
N. Mercury..... No Yes *(alkyl compounds)*				○	○	○	○	○	○	○	○	○
O. Mercury..... No Yes *(inorganic compounds)*				○	○	○	○	○	○	○	○	○
P. Mercury..... No Yes *(vapor)*				○	○	○	○	○	○	○	○	○
Q. x-Methyl-styrene..... No Yes				○	○	○	○	○	○	○	○	○
R. Welding..... No Yes fumes				○	○	○	○	○	○	○	○	○
S. Burn Pits..... No Yes				○	○	○	○	○	○	○	○	○

NON-OCCUPATIONAL NOISE EXPOSURE HISTORY

The following questions are about your **NON-OCCUPATIONAL** noise exposure history. Please answer the questions thinking about non-occupational noise exposures you have experienced over your **entire lifetime** both in and out of the military. This would include recreational and leisure activities that you have participated in over your lifetime.

To help you understand what we mean by "exposed to loud noise" see the "NOISE THERMOMETER" provided in your questionnaire packet for examples of loud sounds. You are most likely "exposed to loud noise" if you are around activities at or above 85 decibels. Another example of loud noise is noise that makes it hard to talk to or hear another person, or makes your ears ring after exposure.

Subject ID

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LENS-Q
Non-Occupational/Recreation

Month/Day/Year

Please answer each question by circling or marking the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

Shade Circles Like This--> ●
Not Like This--> ⊗ ✓

Non-Occupational/ Recreation Noise 1. Have you been exposed to noise during any of these non-job related activities? (Circle No or Yes)			*For each activity you answer "Yes" please answer additional questions 2 - 5.*		4. How often were you around loud noise?					5. How often did you use hearing protection while in loud noise?			
			2. Age first started	3. Approximate duration (# yrs/mos)	Never	Several times a year	Several times a month	Several times a week	Daily	Never	Some of the time	Most of the time	Always
GUNFIRE													
A. Pistol	No	Yes	___	___ ___	○	○	○	○	○	○	○	○	○
B. Revolver	No	Yes	___	___ ___	○	○	○	○	○	○	○	○	○
C. Rifle	No	Yes	___	___ ___	○	○	○	○	○	○	○	○	○
D. Shotgun	No	Yes	___	___ ___	○	○	○	○	○	○	○	○	○
Have you ever been:													
E. Hunting	No	Yes	___	___ ___	○	○	○	○	○	○	○	○	○
F. Target Shooting	No	Yes	___	___ ___	○	○	○	○	○	○	○	○	○
TRANSPORTATION													
Have you ever been on a:													
A. Motor Boat	No	Yes	___	___ ___	○	○	○	○	○	○	○	○	○
B. Motorcycle	No	Yes	___	___ ___	○	○	○	○	○	○	○	○	○
C. Snowmobile	No	Yes	___	___ ___	○	○	○	○	○	○	○	○	○

Version 3/08/2018

Subject ID

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LENS-Q
Non-Occupational/Recreation

Month/Day/Year

Please answer each question by circling or marking the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

Non-Occupational/ Recreation Noise (Continued) **1. Have you been exposed to noise during any of these non-job related activities?** (Circle No or Yes)	*For each activity you answer "Yes" please answer questions 2 - 5.* **2. Age first started**	**3. Approximate duration (#yrs/mos)**	**4. How often were you around loud noise?** Never / Several times a year / Several times a month / Several times a week / Daily	**5. How often did you use hearing protection while in loud noise?** Never / Some of the time / Most of the time / Always
MUSIC **Have you ever attended a:**				
A. Rock concert..... No Yes	___	___ ___	○ ○ ○ ○ ○	○ ○ ○ ○
B. Jazz concert..... No Yes	___	___ ___	○ ○ ○ ○ ○	○ ○ ○ ○
C. Discotheque/Night club..... No Yes	___	___ ___	○ ○ ○ ○ ○	○ ○ ○ ○
Have you ever played in a:				
D. Rock band..... No Yes	___	___ ___	○ ○ ○ ○ ○	○ ○ ○ ○
E. Orchestra..... No Yes	___	___ ___	○ ○ ○ ○ ○	○ ○ ○ ○
F. Symphony..... No Yes	___	___ ___	○ ○ ○ ○ ○	○ ○ ○ ○
Have you ever used:			**How often did you listen to your earphones?**	
G. Stereo headphones/ Earphones..... No Yes	___	___ ___	○ ○ ○ ○ ○	

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LENS-Q

Non-Occupational/Recreation

Month/Day/Year

Please answer each question by circling or marking the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

Non-Occupational/ Recreation Noise (Continued) **1. Have you been exposed to noise during any of these non-job related activities?** **(Circle No or Yes)**			*For each activity you answer "Yes" please answer questions 2 - 5.* **2. Age first started**	**3. Approximate duration (#yrs/mos)**	**4. How often were you around loud noise?** Never / Several times a year / Several times a month / Several times a week / Daily	**5. How often did you use hearing protection while while in loud noise?** Never / Some of the time / Most of the time / Always
POWER TOOLS **Have you ever used a:**						
A. Drill, electric.....	No	Yes	___	___ ___	○ ○ ○ ○ ○	○ ○ ○ ○
B. Drill, pneumatic.....	No	Yes	___	___ ___	○ ○ ○ ○ ○	○ ○ ○ ○
C. Hammer.....	No	Yes	___	___ ___	○ ○ ○ ○ ○	○ ○ ○ ○
D. Jointer.....	No	Yes	___	___ ___	○ ○ ○ ○ ○	○ ○ ○ ○
E. Lathe.....	No	Yes	___	___ ___	○ ○ ○ ○ ○	○ ○ ○ ○
F. Molder.....	No	Yes	___	___ ___	○ ○ ○ ○ ○	○ ○ ○ ○
G Planer.....	No	Yes	___	___ ___	○ ○ ○ ○ ○	○ ○ ○ ○
H. Router.....	No	Yes	___	___ ___	○ ○ ○ ○ ○	○ ○ ○ ○
I. Sander.....	No	Yes	___	___ ___	○ ○ ○ ○ ○	○ ○ ○ ○
J. Power saw.....	No	Yes	___	___ ___	○ ○ ○ ○ ○	○ ○ ○ ○

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LENS-Q
Non-Occupational/Recreation

Month/Day/Year

Please answer each question by circling or marking the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

Non-Occupational/ Recreation Noise (Continued) **1. Have you been exposed to noise during any of these non-job related activities?** (Circle No or Yes)	*For each activity you answer "Yes" please answer questions 2 - 5.* **2. Age first started**	**3. Approximate duration (#yrs/mos)**	**4. How often were you around loud noise?** Never / Several times a year / Several times a month / Several times a week / Daily	**5. How often did you use hearing protection while in loud noise?** Never / Some of the time / Most of the time / Always
RECREATION **Have you ever attended a Professional or College:**				
A. Basketball game..... No Yes	⌊_⌋⌊_⌋	⌊_⌋⌊_⌋⌊_⌋	○ ○ ○ ○ ○	○ ○ ○ ○
B. Football game..... No Yes	⌊_⌋⌊_⌋	⌊_⌋⌊_⌋⌊_⌋	○ ○ ○ ○ ○	○ ○ ○ ○
C. Hockey game..... No Yes	⌊_⌋⌊_⌋	⌊_⌋⌊_⌋⌊_⌋	○ ○ ○ ○ ○	○ ○ ○ ○
D. Baseball game..... No Yes	⌊_⌋⌊_⌋	⌊_⌋⌊_⌋⌊_⌋	○ ○ ○ ○ ○	○ ○ ○ ○
Have you ever attended an:				
E. Aerobic exercise class..... No Yes	⌊_⌋⌊_⌋	⌊_⌋⌊_⌋⌊_⌋	○ ○ ○ ○ ○	○ ○ ○ ○
F. Car race..... No Yes	⌊_⌋⌊_⌋	⌊_⌋⌊_⌋⌊_⌋	○ ○ ○ ○ ○	○ ○ ○ ○
G. Monster truck show..... No Yes	⌊_⌋⌊_⌋	⌊_⌋⌊_⌋⌊_⌋	○ ○ ○ ○ ○	○ ○ ○ ○
H. Demolition derby..... No Yes	⌊_⌋⌊_⌋	⌊_⌋⌊_⌋⌊_⌋	○ ○ ○ ○ ○	○ ○ ○ ○
I. Fireworks show..... No Yes	⌊_⌋⌊_⌋	⌊_⌋⌊_⌋⌊_⌋	○ ○ ○ ○ ○	○ ○ ○ ○

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LENS-Q
Non-Occupational/Recreation

Month/Day/Year

Please answer each question by circling or marking the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

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Non-Occupational/ Recreation Noise (Continued) 1. Have you been exposed to noise during any of these non-job related activities? (Circle No or Yes)	*For each activity you answer "Yes" please answer additional questions 2 - 5.* 2. Age first started	3. Approximate duration (#yrs/mos)	4. How often were you around loud noise? Never	Several times a year	Several times a month	Several times a week	Daily	5. How often did you use hearing protection while in loud noise? Never	Some of the time	Most of the time	Always
YARD AND GARDEN Have you ever used a:											
A. Chain saw..... No Yes	⌊⌋⌊⌋	⌊⌋⌊⌋⌊⌋⌊⌋	○	○	○	○	○	○	○	○	○
B. Tractor..... No Yes	⌊⌋⌊⌋	⌊⌋⌊⌋⌊⌋⌊⌋	○	○	○	○	○	○	○	○	○
C. Lawn mower, gas powered..No Yes	⌊⌋⌊⌋	⌊⌋⌊⌋⌊⌋⌊⌋	○	○	○	○	○	○	○	○	○
D. Edger/trimmer..... No Yes	⌊⌋⌊⌋	⌊⌋⌊⌋⌊⌋⌊⌋	○	○	○	○	○	○	○	○	○
E. Leaf blower..... No Yes	⌊⌋⌊⌋	⌊⌋⌊⌋⌊⌋⌊⌋	○	○	○	○	○	○	○	○	○
F. Weed whacker..... No Yes	⌊⌋⌊⌋	⌊⌋⌊⌋⌊⌋⌊⌋	○	○	○	○	○	○	○	○	○
G. Snow blower..... No Yes	⌊⌋⌊⌋	⌊⌋⌊⌋⌊⌋⌊⌋	○	○	○	○	○	○	○	○	○
Other Non-Occupational Noise:											
H. _____	⌊⌋⌊⌋	⌊⌋⌊⌋⌊⌋⌊⌋	○	○	○	○	○	○	○	○	○
I. _____	⌊⌋⌊⌋	⌊⌋⌊⌋⌊⌋⌊⌋	○	○	○	○	○	○	○	○	○

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LENS-Q
Non-Occupational/Recreation

Please answer each question by circling or marking the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

6. Have you ever undergone any non-occupational accidental exposure to sudden, intense noise?

○ No
○ Yes

IF NO, go to next page

IF YES:

a. Type of noise you were exposed to: _____

b. Your age when exposed: ☐☐ years old

c. Which ear or side of your head was exposed?

○ LEFT ear/side
○ RIGHT ear/side
○ BOTH ears/sides
○ Not sure

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LENS-Q
Non-Occupational/Recreation

Month/Day/Year

Please tell us about any solvent or chemical exposures that you have had in your **NON-Occupational/Recreation** activities.

Non-Occupational/ Recreation Solvent Exposures			*For each chemical exposure you answered "Yes" please answer questions 2 - 6.*			5. How often were you around chemicals?					6. How often did you wear protective gear? *(respirator, eye gear, mask, face shield, gloves, clothing)*			
1. Have you been in contact with any of the following chemicals? (Circle No or Yes)			2. Year Started (YYYY)	3. Year Ended (YYYY) If current, use this year	4. Length of time exposed (#yrs/mos)	Never	Several times a year	Several times a month	Several times a week	Daily	Never	Some of the time	Most of the time	Always
A. Ethyl benzene..	No	Yes				○	○	○	○	○	○	○	○	○
B. Toluene.....	No	Yes				○	○	○	○	○	○	○	○	○
C. Xylene.....	No	Yes				○	○	○	○	○	○	○	○	○
D. Styrene.....	No	Yes				○	○	○	○	○	○	○	○	○
E. n-Hexane.....	No	Yes				○	○	○	○	○	○	○	○	○
F. Carbon monoxide.....	No	Yes				○	○	○	○	○	○	○	○	○
G. Trichloroethylene (TCE).....	No	Yes				○	○	○	○	○	○	○	○	○
H. Lead.....	No	Yes				○	○	○	○	○	○	○	○	○
I. Acrylonitrile.....	No	Yes				○	○	○	○	○	○	○	○	○
J. N-Butylalchol...	No	Yes				○	○	○	○	○	○	○	○	○
K. Carbon disulphide.....	No	Yes				○	○	○	○	○	○	○	○	○

Version: 23 March 2022

APPENDIX F: Questionnaire 3: Tinnitus Functional Index (TFI)

TINNITUS FUNCTIONAL INDEX

Today's Date _____ Your Name _____
Month / Day / Year *Please Print*

Please read each question below carefully. To answer a question, select *ONE* of the numbers that is listed for that question, and draw a *CIRCLE* around it like this: (10%) or (1).

I **Over the PAST WEEK...**

1. What percentage of your time awake were you consciously **AWARE OF** your tinnitus?

Never aware ► 0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100% ◄ *Always aware*

2. How **STRONG** or **LOUD** was your tinnitus?

Not at all strong or loud ►0 1 2 3 4 5 6 7 8 9 10 ◄ *Extremely strong or loud*

3. What percentage of your time awake were you **ANNOYED** by your tinnitus?

None of the time ► 0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100% ◄ *All of the time*

SC **Over the PAST WEEK...**

4. Did you feel **IN CONTROL** in regard to your tinnitus?

Very much in control ►0 1 2 3 4 5 6 7 8 9 10 ◄ *Never in control*

5. How easy was it for you to **COPE** with your tinnitus?

Very easy to cope ► 0 1 2 3 4 5 6 7 8 9 10 ◄ *Impossible to cope*

6. How easy was it for you to **IGNORE** your tinnitus?

Very easy to ignore ► 0 1 2 3 4 5 6 7 8 9 10 ◄ *Impossible to ignore*

C **Over the PAST WEEK...**

7. Your ability to **CONCENTRATE**?

Did not interfere ► 0 1 2 3 4 5 6 7 8 9 10 ◄ *Completely interfered*

8. Your ability to **THINK CLEARLY?**

Did not interfere ► 0 1 2 3 4 5 6 7 8 9 10 ◄ *Completely interfered*

9. Your ability to **FOCUS ATTENTION** on other things besides your tinnitus?

Did not interfere ► 0 1 2 3 4 5 6 7 8 9 10 ◄ *Completely interfered*

SL **Over the PAST WEEK...**

10. How often did your tinnitus make it difficult to **FALL ASLEEP or STAY ASLEEP**?

Never had difficulty ► 0 1 2 3 4 5 6 7 8 9 10 ◄ *Always had difficulty*

11. How often did your tinnitus cause you difficulty in getting **AS MUCH SLEEP** as you needed?

Never had difficulty ► 0 1 2 3 4 5 6 7 8 9 10 ◄ *Always had difficulty*

12. How much of the time did your tinnitus keep you from **SLEEPING** as **DEEPLY** or as **PEACEFULLY** as you would have liked?

None of the time ► 0 1 2 3 4 5 6 7 8 9 10 ◄ *All of the time*

08.15.08

Please read each question below carefully. To answer a question, select *ONE* of the numbers that is listed for that question, and draw a *CIRCLE* around it like this: (10%) or (1).

A	**Over the PAST WEEK, how much has your tinnitus interfered with...**	*Did not interfere*										*Completely interfered*
	13. Your ability to **HEAR CLEARLY**?	0	1	2	3	4	5	6	7	8	9	10
	14. Your ability to **UNDERSTAND PEOPLE** who are talking?	0	1	2	3	4	5	6	7	8	9	10
	15. Your ability to **FOLLOW CONVERSATIONS** in a group or at meetings?	0	1	2	3	4	5	6	7	8	9	10

R	**Over the PAST WEEK, how much has your tinnitus interfered with...**	*Did not interfere*										*Completely interfered*
	16. Your **QUIET RESTING ACTIVITIES**?	0	1	2	3	4	5	6	7	8	9	10
	17. Your ability to **RELAX**?	0	1	2	3	4	5	6	7	8	9	10
	18. Your ability to enjoy "**PEACE AND QUIET**"?	0	1	2	3	4	5	6	7	8	9	10

Q	**Over the PAST WEEK, how much has your tinnitus interfered with...**	*Did not interfere*										*Completely interfered*
	19. Your enjoyment of **SOCIAL ACTIVITIES**?	0	1	2	3	4	5	6	7	8	9	10
	20. Your **ENJOYMENT OF LIFE**?	0	1	2	3	4	5	6	7	8	9	10
	21. Your **RELATIONSHIPS** with family, friends and other people?	0	1	2	3	4	5	6	7	8	9	10

22. How often did your tinnitus cause you to have difficulty performing your **WORK OR OTHER TASKS**, such as home maintenance, school work, or caring for children or others?

Never had difficulty ► 0 1 2 3 4 5 6 7 8 9 10 ◄ *Always had difficulty*

E	**Over the PAST WEEK...**

23. How **ANXIOUS** or **WORRIED** has your tinnitus made you feel?

Not at all anxious or worried ► 0 1 2 3 4 5 6 7 8 9 10 ◄ *Extremely anxious or worried*

24. How **BOTHERED** or **UPSET** have you been because of your tinnitus?

Not at all bothered or upset ► 0 1 2 3 4 5 6 7 8 9 10 ◄ *Extremely bothered or upset*

25. How **DEPRESSED** were you because of your tinnitus?

Not at all depressed ► 0 1 2 3 4 5 6 7 8 9 10 ◄ *Extremely depressed*

 08.15.08

APPENDIX G: Questionnaire 4: LENS-Q Adapted Survey for Stratification (High vs. Low Noise Exposure Group Stratification)

LENS-Q Adapted for Police Officer Study: By virtue of working in a career with required firearm use, all participants are automatically categorized as high noise. The point of this modified survey is to stratify participants into relatively higher and relatively lower exposure groups.

Noise Exposure History Interview Questions

1. In your role as a police officer:

   A. How often does your police officer job cause you to be exposed to loud noise(s) where you have to shout to be heard? (For example, loud equipment or trucks, loud ship or jet engines, exposure from the rifle range, sirens, K-9 noise, loud crowds, loud music (e.g. concert/band events), loud noise from construction sites)

   a. Daily
   b. Less than daily/more than weekly
   c. Weekly
   d. Less than weekly/more than monthly
   e. Monthly
   f. Less than monthly/more than yearly
   g. Yearly
   h. Less than yearly
   i. Never

   B. How likely are you to be wearing hearing protection when this occurs (circle one)?

   Never Rarely Sometimes Usually Always

   C. How many years have you worked in a police officer job? _____

2. Have you served in the military? If yes:

   A. How often did your military service cause you to be exposed to loud noise(s) where you had to shout to be heard? (For example, loud equipment or trucks, loud ship or jet engines, loud aircraft)

   a. Daily
   b. Less than daily/more than weekly
   c. Weekly
   d. Less than weekly/more than monthly
   e. Monthly
   f. Less than monthly/more than yearly
   g. Yearly
   h. Less than yearly
   i. Never

   B. How likely were you to be wearing hearing protection when this occurred (circle one)?

Never Rarely Sometimes Usually Always

C. How many years did you serve in the military? _____

3. In either your police officer position, your military service, or your recreational activities:

A. How often have you been exposed to sudden intense noise? (For example, shooting range, target practice, hunting, explosions, cannon fire, gun shot, music (e.g. drums), etc.)

a. Daily
b. Less than daily/more than weekly
c. Weekly
d. Less than weekly/more than monthly
e. Monthly
f. Less than monthly/more than yearly
g. Yearly
h. Less than yearly
i. Never

B. Were you wearing hearing protection when this occurred (circle one)?

Never Rarely Sometimes Usually Always

4. A. How often did or do non-police officer/non-military jobs or recreational activities cause you to be exposed to loud noise(s) where you would have to shout to be heard?

a. Daily
b. Less than daily/more than weekly
c. Weekly
d. Less than weekly/more than monthly
e. Monthly
f. Less than monthly/more than yearly
g. Yearly
h. Less than yearly
i. Never

B. Were you wearing hearing protection when this occurred?

Never Rarely Sometimes Usually Always

C. How many years did you work in a non-police officer/non-military job where you had to shout to be heard?

_____

Noise Exposure Group Assignment Based on Interview Questions

- Participants with a response to 1.A., 2.A., or 3.A. of monthly or more frequent exposure are assigned to the higher noise group. Participants with less than monthly exposure are assigned to the lower noise group.
- Participants with a response to 1.C., 2.C, or 4.C. of 5 years or more are assigned to the Higher Noise group.

APPENDIX H: Questionnaire 5: 1-Minute Noise Screen (30-day post follow-up visit)

1-Minute Noise Screen

ID Number: _____ Date: _____

DURING THE PAST 30 DAYS,	
1.	How often were you around or did you shoot firearms such as rifles, pistols, shotguns, etc.? ☐ Never ☐ Less than weekly ☐ Weekly ☐ More than weekly ☐ Daily
2.	How often were you exposed to loud sounds while working on a paid job? By loud sounds, we mean sounds so loud that you had to shout or speak in a raised voice to be heard at arm's length. ☐ Never ☐ Less than weekly ☐ Weekly ☐ More than weekly ☐ Daily
3.	How often were you exposed to any other types of loud sounds, such as power tools, lawn equipment, or loud music? By loud sounds, we mean sounds so loud that you had to shout or speak in a raised voice to be heard at arm's length. ☐ Never ☐ Less than weekly ☐ Weekly ☐ More than weekly ☐ Daily

Noise exposure score: _____