Discuss & Comment: List of Treatment Options for Hyperacusis

The Hyperacusis Masterdoc

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Introduction:

What is Hyperacusis?

Hyperacusis is a rare hearing condition, and involves an increased sensitivity to sound and a low tolerance for environmental noise. It can be a highly debilitating hearing disorder. People with hyperacusis often find ordinary noises too loud, while loud noises can cause discomfort and/or pain. The most common known causes of hyperacusis are exposure to loud noise, and aging. There are currently no tests for diagnosing hyperacusis. Hyperacusis is often coincident with tinnitus, the latter is more common and there are important differences between their involved mechanisms. Little is known about the prevalence of hyperacusis, in part due to the

degree of variation in the term's definition. Reported prevalence in children and adolescents ranges from 3% to 17%. While there are no exact numbers, several people have died by suicide due to the severe consequences of the disease.

Categories & Subtypes:

Definitions of hyperacusis can vary significantly; it can refer to normal noises being perceived as: loud, annoying, painful, fear-inducing, or a combination of those, and is often categorized into four subtypes: loudness, pain, annoyance, and fear. It is extremely common to have a combination of the subtypes, especially Noxacusis and Loudness.

Noxacusis (Pain Hyperacusis): In some instances, hyperacusis is accompanied by pain, which is known as noxacusis. Noxacusis is characterized by pain resulting from sounds, often initiated at certain volumes or frequencies; pain can be immediate or delayed, and sometimes persists for an extended period of time following exposure. Pain can be acute or chronic, and is often described as stabbing, burning, acid, or nerve pain, and is sometimes equated with the pain of a root canal or a broken tooth.

Loudness Hyperacusis: Hyperacusis is most often characterized by a sensitivity to sound, where the perception of loudness is much greater than for a typical person; it is often associated with certain volumes and/or frequencies. Hyperacusis can occur in children and adults, and can be either "short-term" in a duration of weeks to less than a year before recovery, or, less-commonly, "long-term", spanning years and in some cases becoming permanent. Sensitivity is often different between ears.

Annoyance Hyperacusis: Unrelated to Misophonia, Annoyance hyperacusis likely reflects the emotional reactions associated with hyperacusis. Annoyance hyperacusis is a reflection of the nuisance, unpleasantness, anxiety or irritation evoked by sounds. Although tinnitus and hyperacusis are thought to share common mechanisms, the annoyance associated with hyperacusis is poorly correlated with the annoyance associated with tinnitus.

Fear Hyperacusis: Fear Hyperacusis is when the flight or fight response produces a negative emotional reaction to sounds. It is an aversive response to sounds that results in an anticipatory response and avoidance behavior.

Noxacusis (Pain Hyperacusis)

Symptoms:

The more severe form of hyperacusis—pain hyperacusis, sometimes called noxacusis or auditory nociception—is a new diagnosis in the field. It has been recognized only in the last 10 years, largely through the efforts of the late Bryan Pollard, who founded the nonprofit Hyperacusis Research and coined the term “noise-induced pain.” “Pain has long been underrepresented—and often, completely overlooked—as a component of hyperacusis,” he wrote. The pain often worsens with ordinary noise exposure. In extremely severe cases, people feel ear pain even in silence. This pain is still quite under researched and unknown, however, researchers have been able to pinpoint two possible theories on where the pain could be occurring from: the middle ear and/or the inner ear. Symptoms of the pain can be different and crossover in both areas.

Inner Ear Symptoms:

- Baseline deep burning pain, often described as a feeling of acid, sunburn or sandpaper in the ear canal
- Itching and a wetness feeling in the inner ear
- Stabbing deep pain upon noise exposure
- Lingering deep aching pain after noxious noise exposure

Middle Ear Symptoms:

- Aural fullness — an uncomfortable feeling of pressure within the ear
- Headaches and pressure upon noise exposure
- Burning pain in middle ear from noise exposure
- Thumping or fluttering in the ear canal
- Aching pain in the middle ear after noise exposure
- Itching and a wetness feeling in the middle and outer ear
- Stabbing middle ear pain upon noise
- Rumbling in the ear when yawning or burping
- Sensitivity to speaking
- Pain in outer ear canal, neck, face, and mouth

Other symptoms, without any direct correlation to the inner or middle ear, could include tinnitus or ringing in the ears, exploding head syndrome, visual snow, photophobia, and a perception of sounds as distorted or echoing and perceived as extremely loud.

Treatment:

DISCLAIMER:

Multiple medications featured in this document are known to be Ototoxic. Ototoxicity is when a person develops hearing or balance problems due to a medicine. This can cause or worsen pre-existing tinnitus and/or hyperacusis, sometimes even permanently. Some medications listed could also be potentially addictive, and may result in severe, long-lasting withdrawal symptoms.

Always research these medications extensively before trying them. Know the side effects and consult a medical professional to ensure that this medication is right for you, and if there are other low-risk treatments you should try first.

First Treatments to Try:

Avoiding Sound Triggers: Avoiding sound triggers is a crucial component to recovery. As this condition is rare and misunderstood, medical professionals will advise that you do not "overprotect" as normal sound cannot hurt you, this is untrue. It is strongly advised that you protect your ears from any sound that causes pain, no matter how "normal" the sound is. If you do not have a fully controlled environment to stay in while you recover, high-decibel rated earplugs (over 30 NRR) and earmuffs (Peltors X5A) are recommended. Soundproofing your environment is also recommended. This can be done by soundproofing a room or rooms, using quiet versions of appliances, and using paper plates and wooden or plastic cutlery.

Time: Noise injuries heal very slowly, and the improvements are often non-linear. Users of forums, like Tinnitus Talk, reported seeing results from a few months to a few years, even up to four or more. Two years is reported to be the average amount of time for the symptoms to become dormant.

Adequate Rest and Healthy Lifestyle: Auditory, mental, and physical rest are incredibly important components in the recovery from hyperacusis. Like any other physical injury, rest is required to recover efficiently. Placing the body under stress will hinder progress. Ensure you're getting eight hours or more of sleep a night. Try to maintain stress levels by practicing meditation and mindfulness and keeping your mind occupied with quiet activities and hobbies, as stress can exacerbate symptoms. A healthy anti-inflammatory diet is strongly recommended. If possible, light exercise is recommended as well.

Applying Ice and/or Heat: A combination of ice and heat may help bring down swelling and inflammation in the ear. Omitting heat and only applying ice has also been reported to help with the nerve pain from hyperacusis.

ACE + Magnesium Combo: A study done in 2007 reported that the antioxidant agents, vitamins A, C, and E, acted in synergy with magnesium and effectively prevented noise-induced trauma. Neither the antioxidant agents nor the magnesium reliably reduced NIHL or sensory cell death with the doses they used when these agents were delivered alone. In combination, however, they were highly effective in reducing both hearing loss and cell death even with treatment initiated just 1 h before noise exposure. The study concluded that a high combination of Vitamins A, C, and E, along with Magnesium, were shown to reduce the damage of noise trauma.

Inner Ear:

Medication:

Trobalt/Retigabine: Retigabine or ezogabine is an anticonvulsant used as an adjunctive treatment for partial epilepsies in treatment-experienced adult patients. This is a Kv7.2, Kv7.3, Kv7.4, and Kv7.5 channel opener. A study published in 2015 found that opening the Kv7.2 and Kv7.3 potassium channels in mice "suppressed the type II fibre’s response to hair cell damage"

Flupirtine: Flupirtine is a medicine used to treat acute (short-lived) pain for up to 2 weeks, in patients who cannot use other painkillers such as opioids or nonsteroidal anti-inflammatory medicines (NSAIDs). Flupirtine works as a 'selective neuronal potassium channel opener'. Like Retigabine, a KNCQ channel opener, it suppresses the type II fibre’s response to hair cell damage.

Epidiolex: Cannabidiol (CBD) is a chemical in the Cannabis sativa plant, also known as cannabis or hemp. Epidiolex is the one specific form of CBD approved as a drug in the U.S. for seizures. Cannabidiol is a Kv7.2/7.3 channel opener, like retigabine and flupirtine.

Gabapentin: Gabapentin, sold under the brand name Neurontin among others, is an anticonvulsant medication primarily used to treat partial seizures and neuropathic pain. It is commonly used medication for the treatment of neuropathic pain caused by diabetic neuropathy, postherpetic neuralgia, and central pain. Previously thought to be a sodium channel blocker, it's instead been revealed to open potassium channels Kv7.2/7.3 & Kv7.5.

Rimegepant: Rimegepant, sold under the brand name Nurtec ODT among others, is a medication used for the acute treatment of migraine with or without aura in adults and the preventative treatment of episodic migraine in adults. It works by blocking CGRP receptors. Researchers believe there is a connection between the CGRP-alpha in the neurons and immune response of the inner ear; this may illustrate a role for type II neurons in pain and inflammation following tissue damage. There are other CGRP-blocker medications, such as Emgality and Nurtec.

P2Y12 Receptor Blockers: P2Y12 receptor blockers are another group of antiplatelet drugs. This group of drugs includes: clopidogrel, ticlopidine, ticagrelor, prasugrel, and cangrelor. In 2015, a study concluded that after a noise exposure, P2Y receptors became more active, affecting potassium channels and contributing to noxacusis. ATP released from the noise exposure activated P2Y receptors, which in turn closed the KNCQ channels. After noise damage, the ATP concentrations increased, which caused P2Y receptors to become more easily agonized, which in turn leads to a greater effect on the potassium channels. It is theorized that a P2Y4-6 antagonist could prevent ATP binding to its receptors and thereby reduce closure of the potassium channels. Unfortunately, the only drugs currently available that antagonize P2Y receptors act on P2Y12 specifically, though it's possible that P2Y12 Receptor Blockers could alleviate the pain from noxacusis as well.

Flunarizine: Flunarizine, sold under the brand name Sibelium among others, is a drug classified as a calcium antagonist which is used for various indications. It's a calcium channel blocker and prescribed in Parkinson's cases. It's theorized that dysfunctional Cav1.3 calcium channels may cause hyperacusis. Other diseases and conditions caused by dysfunctional Cav1.3 calcium channels are Parkinson's, which is sometimes treated with calcium channel blockers. Other medications that block these channels are Diltiazem.

Clonazepam: Clonazepam, sold under the brand names Klonopin and Rivotril, is a medication used to prevent and treat seizures, panic disorder, anxiety disorders, and the movement disorder known as akathisia. It is a tranquilliser of the benzodiazepine class.

Topiramate: Topiramate is used alone or with other medications to treat certain types of seizures including primary generalised tonic-clonic seizures (formerly known as a grand mal seizure; seizure that involves the entire body) and partial onset seizures (seizures that involve only one part of the brain). It is an AMPA antagonist. This may be effective in persons with hyperacusis due to irritable neural pathways. Like Gabapentin, it may help with chronic nerve pain.

Keppra: Levetiracetam, sold under the brand name Keppra among others, is a medication used to treat epilepsy. Like Gabapentin, it may help with the chronic nerve pain that sets in.

Flomax: Tamsulosin, sold under the brand name Flomax among others, is a medication used to treat symptomatic benign prostatic hyperplasia and chronic prostatitis and to help with the passage of kidney stones. Like Gabapentin, it is an Alpha-1 adrenergic receptor antagonist and relaxes smooth muscle. It also has anticholinergic properties, which is somewhat relevant to the Norena model. Acetylcholine (ACh) maintains muscle contraction, which is undesirable for an inflamed middle ear.

Ivabradine: Ivabradine is a HCN2 Ion Channel Blocker, used to treat adults who have chronic heart failure to reduce their risk of hospitalization for worsening heart failure. HCN2 channels are found in the nerve fibres of the auditory system, which carry information from the ear to the brain. These fibres are often damaged after exposure to loud noise, which can lead to tinnitus. Some preliminary studies carried out by researchers have shown that blocking HCN2 channels with Ivabradine significantly reduced tinnitus in animal models. HCN2 Blockers also help alleviate chronic neuropathic pain, which may help Noxacusis.

Multi-Modal Migraine Prophylaxis Therapy: Patients with hyperacusis were treated with a multi-modal step-wise migraine prophylactic regimen (nortriptyline, verapamil, topiramate, or a combination thereof) as well as lifestyle and dietary modifications. Pre- and post-treatment average loudness discomfort level (LDL), hyperacusis discomfort level measured by a visual analogue scale (VAS), and scores on the modified Khalfa questionnaire for severity of hyperacusis were compared. Twenty-two of the 25 patients (88%) reported subjective resolution of their symptoms following treatment. Post-treatment audiograms showed significant improvement in average LDL from 81.3 ± 3.2 dB to 86.4 ± 2.6 dB ($P < .001$), indicating increased sound tolerability.

Supplements:

Low-Histamine Diet: Histamine is a chemical, known as a biogenic amine. It plays a role in several of the body's major systems, including the immune, digestive, and neurological systems. The body gets all the histamine it needs from its own cells, but histamine is also found in certain foods. A chemical called ATP is released in the ear upon damage. It is speculated that it can keep triggering the nerve fibers leading to non-stop excitation. Histamine can cause ATP leak, inflammation, and nerve excitation. Lowering histamine can lower all that and allow healing.

Nicotinamide Riboside: Nicotinamide riboside is a member of the vitamin B3 family, which also includes niacin and niacinamide. It's found in fruits, vegetables, meat, and milk. It's changed in the body to a chemical called NAD+. The body needs NAD+ for many processes to work normally. Low levels can cause health problems. Nicotinamide riboside protects noise-induced hearing loss by recovering the hair cell ribbon synapses and has been proved to protect the

hearing. It also promotes oxidation resistance to protect the synapse and the inner ear morphology.

NAC: N-acetyl cysteine comes from the amino acid L-cysteine. Amino acids are building blocks of proteins. N-acetyl cysteine is an antioxidant and an anti-inflammatory. It's been theorized that this may help with setbacks from noise exposure. Whether this is a preventive measure or a corrective action remains unclear.

Vitamin B Complex: Vitamin B complex is a group of B vitamins that play a role in your body's functions, including cardiovascular and cell health. You typically get these vitamins from a nutritious diet. These complexes consist of B1, B2, B3, B5, B6, B7, B9, and B12. This supplement can help with nerve regeneration and health from damage.

Surgery:

Sphenopalatine Ganglion Block: Sphenopalatine ganglion block is a procedure that involves the delivery of a local anesthetic to the sphenopalatine ganglion (SPG)—a group of trigeminal nerve cells located in the back of the nasal passages—to relieve headache pain. It is a minimally invasive procedure used to treat head and facial pain.

Stellate Ganglion Nerve Block: A stellate ganglion block is an injection of medication into a collection of nerves at the bottom of the front side of your neck. It can help treat a variety of circulation and pain conditions, such as complex regional pain syndrome and peripheral artery disease. A stellate ganglion block has been effective for temporary pain relief in one ASD patient, confirming sympathetic nervous system involvement. This can help with the stabbing and lingering nerve pain from hyperacusis. It can also be injected with botox, this can give the nerve block a lasting effect.

Cochlear Implant: A Cochlear Implant is a string of electrodes inserted into the cochlea that electrically stimulates the nerves that would normally be stimulated by hair cells. This gives the person a useful representation of sound and helps them understand speech. A recent study led by Angel Macias analyzed the impact of cochlear implant surgery on 16 patients who had unilateral hearing loss and severe tinnitus. All patients presented hyperacusis symptoms before the surgery. Comparing Pre and post op results show all patients with a fully inserted cochlear implant reported a reduction in hyperacusis symptoms.

Cochlear Destruction (Labyrinthectomy): Labyrinthectomy is a surgical procedure of the temporal bone used to treat intractable and refractory vertigo. This procedure surgically removes the neuroepithelial elements of the semicircular canals and vestibule. In one case involving a musician with debilitating hyperacusis, a labyrinthectomy was suggested to abolish the residual hearing and consequently abolish the hyperacusis and diplacusis. After the operation, the hyperacusis patient was relieved of his hyperacusis and diplacusis symptoms.

However, since this procedure destroys the vestibular function of the inner ear, the patient was left with a persistent feeling of unsteadiness.

Doctors, Clinics, and Researchers:

Doctors:

Clinics:

Researchers:

Paul Fuchs: Paul Fuchs, Ph.D., is the David M. Rubenstein Research Professor of Otolaryngology-Head & Neck Surgery in the Johns Hopkins University School of Medicine, with secondary appointments in Biomedical Engineering and Neuroscience. He is co-director of the Center for Sensory Biology in the Institute for Basic Biomedical Sciences at Hopkins. His research centers on the cellular electrophysiology of the inner ear with particular attention paid to excitability and synaptic transmission between sensory hair cells, afferent and efferent neurons. These efforts have: 1.) discovered the molecular mechanisms by which acetylcholine release from efferent neurons inhibits hair cells, 2.) detailed the diversity of synaptic ribbon function among cochlear hair cells, 3.) cataloged the roles of gated ion channels in hair cells and 4.) provided the first evidence for the function of type II cochlear afferents.

Megan Beers Wood: Megan Beers Wood, Ph.D., is a postdoctoral research fellow in the laboratory of Dr. Paul Fuchs. Her research uses noise-induced hearing loss models to study the effect of damaging noise on the cochlea. High levels of sound can lead to cell death in the cochlea. Cochlear type II afferent neurons do not respond to sound, but do respond to cell damage. Recent work from Dr. Fuchs' laboratory suggests that type II afferent neurons report damage and may be responsible for nociception in the ear. Her work aims to shed light on the role of type II afferent neurons in the sensation of damage and pain. Wood's 2022 Emerging Research Grant is funded by Hyperacusis Research, which was renewed for a second year in 2023. This research is being conducted to understand the role of CGRP-alpha in the neurons and immune response of the inner ear, which may illustrate a role for type II neurons in pain and inflammation following tissue damage.

David Martinelli: David Martinelli received his doctorate in developmental biology from Johns Hopkins University and the Carnegie Institution for Science. He completed postdoctoral training at Stanford University and is now an assistant professor of neuroscience at the University of Connecticut Health Center. His 2019 Emerging Research Grant was funded by Hyperacusis Research Ltd. This research is to create and validate a genetically induced animal model for hyperacusis. While the presence of outer hair cell afferent neurons is known, it is not known what information the outer hair cells communicate to the brain through these afferents. This

project's hypothesis is that the function of these mysterious afferents is to communicate to the brain when sounds are intense enough to be painful and/or damaging, and that this circuitry is distinct from the cochlea-to-brain circuitry that provides general hearing. The hypothesis will be tested using a novel animal model in which a certain protein that is essential for the proposed "pain" circuit is missing. The absence of this protein is predicted to cause a lessening of the perception of auditory pain when high intensity sounds are presented.

Catherine Weisz: Dr. Weisz received a B.S. in neurobiology from Cornell University, an M.S. in biotechnology from Johns Hopkins University, and a Ph.D. in neuroscience from Johns Hopkins University School of Medicine. Her graduate work involved studies of synaptic inputs and electrical properties of cochlear type II spiral ganglion afferent neurons in the laboratories of Dr. Paul Fuchs and Dr. Elisabeth Glowatzki. Postdoctoral work in the laboratory of Dr. Karl Kandler at the University of Pittsburgh School of Medicine investigated the development of circuits between brainstem neurons involved in sound localization. In 2015, Dr. Weisz moved to the NIDCD where she became acting chief of the Section on Neuronal Circuitry. Dr. Weisz's laboratory investigates the synaptic transmission and electrical properties of descending neuronal circuitry in the auditory brainstem and cochlea.

Charles Liberman: Dr. Charles Liberman is the Director of the Eaton-Peabody Laboratories at Mass. Eye and Ear, where he studies the peripheral auditory system. The inner ear is connected to the brain by two kinds of sensory neurons and is controlled by two neuronal feedback systems. The Liberman Lab studies all four of these pathways, in normal hearing and in sensorineural hearing loss, particularly that caused by acoustic overexposure. His research interests include 1) the coding of acoustic stimuli as neural responses in the auditory periphery, 2) efferent feedback control of the auditory periphery, 3) the mechanisms underlying noise-induced and age-related hearing loss, 4) the signaling pathways mediating nerve survival in the inner ear, and 5) the application of cell- and drug-based therapies to the repair of a damaged inner ear. His work uses a variety of approaches from systems neuroscience to cell and molecular biology.

Trial Drugs:

XEN1101: XEN1101, created by Xenon Pharmaceuticals, is a differentiated Kv7 potassium channel opener, for the treatment of epilepsy, major depressive disorder (MDD), and potentially other neurological disorders. Instead of opening all of the potassium channels like Trobalt, it only opens the Kv7.2/7.3 channels, thereby avoiding any unwanted side effects. It is expected to be released by 2024/2025.

BHV-7000: BHV-7000, created by Biohaven, is an activator of Kv7.2, Kv7.3, and Kv7.4, which are key subunits involved in neuronal signaling and in regulating the hyperexcitable state in focal epilepsy.

RL-81: RL-81, created by Thanos Tzounopoulos, is a very potent and highly specific activator of Kv7.2/7.3 channels. In a 2021 study, he found that the transient administration of RL-81 one week after noise exposure did not affect hearing loss, but significantly reduced the number of mice with evidence of tinnitus. These results indicate that RL-81 is a promising drug candidate for further development for the treatment of noise-induced tinnitus.

QRA-244: QRA-244, created by QurAlis, is a Kv7.2/7.3 ion channel opener optimized for both safety and efficacy as a potential treatment for motor neuron hyperexcitability-induced neurodegeneration in ALS patients.

Research Papers & Theories:

Unmyelinated type II afferent neurons report cochlear damage

In this paper, researcher Paul Fuchs was able to find evidence that type II afferents, while not being damaged themselves, respond to the outer hair cells being damaged from acoustic shock, and emit pain signals to avoid the inner ear from being damaged more.

They were able to conclude that type II afferents remain intact in damaged regions of the cochlea, and that type II afferents are activated when outer hair cells are damaged. This response depends on both ionotropic (P2X) and metabotropic (P2Y) purinergic receptors, binding ATP released from nearby supporting cells in response to hair cell damage. Selective activation of P2Y receptors increased type II afferent excitability by the closure of KCNQ-type potassium channels, a potential mechanism for the painful hypersensitivity (that we term “noxacusis” to distinguish from hyperacusis without pain) that can accompany hearing loss.

They were also able to find that exposure to the KCNQ channel activator, retigabine, suppressed the type II fiber’s response to hair cell damage. And that type II afferents may be the cochlea’s nociceptors, prompting avoidance of further damage to the irreparable inner ear.

Acoustic Trauma Increases Ribbon Number and Size in Outer Hair Cells of the Mouse Cochlea

In this paper, researcher Megan Beers Wood conducted a study with mice on ribbon synapses of the outer hair cells and their response to acoustic trauma.

Mice of both sexes were subjected to acoustic trauma that produced a threshold shift of 44.2 ± 9.1 dB 7 days after exposure. Ribbon synapses of OHCs were quantified in post-trauma and littermate controls using immunolabeling of CtBP2. Visualization with virtual reality was used to determine 3-D cytoplasmic localization of CtBP2 puncta to the synaptic pole of OHCs. Acoustic trauma was associated with a statistically significant increase in the number of synaptic ribbons per OHC. Serial section TEM was carried out on similarly treated mice. This also showed a significant increase in the number of ribbons in post-trauma OHCs, as well as a significant

increase in ribbon volume compared to ribbons in control OHCs. An increase in OHC ribbon synapses after acoustic trauma is a novel observation that has implications for OHC:type II afferent signaling. A mathematical model showed that the observed increase in OHC ribbons considered alone could produce a significant increase in action potentials among type II afferent neurons during strong acoustic stimulation.

Prior Acoustic Trauma Alters Type II Afferent Activity in the Mouse Cochlea

In this paper, researchers Paul Fuchs and Megan Beers Wood set out to find more about the type II afferents, as the role of them remains unresolved. Limited recordings of type II afferents from cochlear apex of prehearing rats reveal they are activated by widespread outer hair cell stimulation, ATP, and by the rupture of nearby outer hair cells. Altogether, these lines of evidence suggest that type II afferents sense loud, potentially damaging levels of sound.

To explore this hypothesis further, calcium imaging was used to determine the impact of acoustic trauma on the activity of type II cochlear afferents of young adult mice of both sexes. Two known marker genes (Th, Drd2) and one new marker gene (Tac1), expressed in type II afferents and some other cochlear cell types, drove GCaMP6f expression to reveal calcium transients in response to focal damage in the organ of Corti in all turns of the cochlea. Mature type II afferents responded to acute photoablation damage less often but at greater length compared with prehearing neurons. In addition, days after acoustic trauma, acute photoablation triggered a novel response pattern in type II afferents and surrounding epithelial cells, delayed bursts of activity occurring minutes after the initial response subsided. Overall, calcium imaging can report type II afferent responses to damage even in mature and noise-exposed animals and reveals previously unknown tissue hyperactivity subsequent to acoustic trauma.

A Novel Mouse Model of Aminoglycoside-Induced Hyperacusis and Tinnitus

Researchers Rende Gu, Jennifer Homan, and Jonathan Kil set out to find the effects of the drug class, Aminoglycoside, on the cochlea.

They were able to conclude that amikacin, a medication from the Aminoglycoside class, caused peripheral damage to the cochlea leading to hearing loss that could fluctuate and become permanent over time or through multiple exposures. They also concluded using mice that amikacin can lead to fluctuating behavioral evidence of hyperacusis and tinnitus as assessed by the acoustic startle reflex. Additionally, electrophysiological assessments of hearing via auditory brainstem response demonstrate increased central activity in the auditory brainstem. These data together suggest that peripheral Aminoglycoside-induced dysfunction can lead to central hyperactivity and possible behavioral manifestations of hyperacusis and tinnitus.

They also found that ebselen, a novel investigational drug that acts as both an antioxidant and anti-inflammatory, can mitigate Aminoglycoside-induced hyperacusis.

Middle Ear:

Medication:

Ambroxol: Ambroxol is a secretolytic agent used in the treatment of respiratory diseases associated with viscid or excessive mucus. It is the active ingredient of Mucosolvan, Lasolvan or Mucoangin. This is reported to have helped trigeminal nerve pain in the facial area and the burning pain in the ear. It works as a middle ear surfactant, so it helps to drain middle ear fluid inflammatory molecules. It's also a potent NaV 1.7 blocker.

Muscle Relaxants: Muscle relaxers (also called muscle relaxants) are prescription medications that affect muscle function. They are prescribed to treat several symptoms, such as muscle spasms, spasticity and musculoskeletal pain. This may help relieve the muscles in the middle ear and subsequently help reduce the inflammation. It also promotes whole body relaxation, which may help relieve the surrounding area if tense.

Supplements:

Emoxypine: Emoxypine succinate regulates the antioxidant defense system by increasing the activity of the enzyme catalase as well as glutathione peroxidase, resulting in the neutralization of hydrogen peroxide radicals. One user of Tinnitus Talk reported that their symptoms of burning, fullness, and pressure went away after taking this medication.

DMSO and Magnesium Oil: DMSO, or dimethyl sulfoxide, is a by-product of paper making. It has been used as an industrial solvent since the mid-1800s. From about the mid-20th century, researchers have explored its use as an anti-inflammatory agent. DMSO has a number of healing qualities and characteristics, giving it the ability to increase circulation and reduce inflammation. However, there is a study that reports its ototoxicity to hair cells and can damage them.

CoQ10: Coenzyme Q10 (CoQ10) is an antioxidant that your body produces naturally. Your cells use CoQ10 for growth and maintenance. An 800mg dosage or more helps with ATP synthesis. We know from Arnaud Norena's body of work that the ATP energy crisis plays a big role in the chronic middle ear inflammation that sets in.

Ionic Liquid Magnesium: Relieves muscle cramps and relaxes the body. Magnesium plays a major role in major human body functions such as energy production, muscle strength, bone development, blood pressure and heart rate. Can help relax the stapedius and the tensor tympani.

Ginger: Ginger root comes from the Zingiber officinale plant. Antioxidants and other nutrients in ginger root may help prevent or treat arthritis, inflammation, and various types of infection. With high doses of raw ginger, it may help the inflammation that sets in from noise exposure.

Surgery:

PRP Injection: Platelet-rich plasma (PRP) therapy uses injections of a concentration of a patient's own platelets to accelerate the healing of injured tendons, ligaments, muscles and joints. In this way, PRP injections use each individual patient's own healing system to improve musculoskeletal problems. A chronically weak tensor tympani (or stapedius) might contribute to both pain and susceptibility to setbacks. This injection may help the middle ear heal from the constant inflammation.

Botox Injection: Fournier and Noreña recently released a paper following their 2018 acoustic shock study. In the study, one of the patients reported getting a botox injection into their tensor tympani muscle (TTM). One month later, the patient reported that the intervention was a complete success: he didn't experience pain in the ear after exposure to impulsive sound anymore. The study also showed that all 11 patients had abnormalities in the way their tensor tympani muscle and/or stapedius muscle behaved. This finding seems to support that TTM hyperactivity and subsequent inflammation are a crucial part of pain hyperacusis.

Round and Oval Window Reinforcement Surgery: A surgical procedure called reinforcement of round and oval window has been helping people with hyperacusis. This procedure uses temporalis fascia (tissue from behind the ear) to support proper movement of the ossicles (hearing bones). The technique being studied is the surgical reinforcement of the round and oval windows of the inner ear. It is theorised that a hypermobile stapes bone can contribute to pain hyperacusis.

Heavy Grommet Surgery: This surgery involves inserting heavy, gold grommets (custom tympanostomy tubes) into the eardrum to dampen incoming sound. It is reported that this increases loudness tolerance relative to the high frequency hearing loss that is intentionally introduced by the grommet. This can also help the treatment of an oval window fistula. They reduce input from higher pitches, like semi-permanent ear plugs. These tubes can also be easily taken out. This is a minimally invasive approach to hyperacusis.

Tenotomy of the Middle Ear Muscles: Tenotomy of the tendon of the stapedius and tensor tympani muscles causes a dramatic reduction in vertigo attacks and improves audiological function in definite Meniere's disease. It's theorized that cutting these muscles will stop the chronic spasming that occurs with hyperacusis.

Doctors, Clinics, and Researchers:

Doctors:

Herbert Silverstein: Dr. Silverstein is the President and Founder of the Silverstein Institute and the Ear Research Foundation. He has been a leader in Otology/Neurotology (science of the ear and skullbase) for more than 40 years, developing surgical and diagnostic procedures, inventing instruments (such as the facial nerve monitor/stimulator), teaching medical students, residents and fellows, and helping people improve their quality of life. Recently he has pioneered treating Hyperacusis with a minimally invasive procedure, round and oval window reinforcement which reduces the sound vibrations of the stapes and round window membrane.

Clinics:

The Silverstein Institute: The Silverstein Institute, located in Sarasota, Florida, is an internationally-respected physicians' practice dedicated to diseases and surgery of the Ears, Nose and Throat. The Silverstein Institute provides premier patient care for the treatment of head, neck and throat diseases consistent with the highest standard of medical excellence and the latest innovative technology. The Round and Oval window Reinforcement Surgery is performed here.

Researchers:

Arnaud Noreña: Currently a team leader at the Sensory and Cognitive Neuroscience Laboratory in Marseille, Arnaud Noreña works with numerous hearing health professionals, such as ENT doctors and hearing care practitioners. His main interest is to understand how acoustic stimuli are represented in the central auditory system in the "normal" case and when sensory inputs are modified. In particular, he's interested in the plasticity of the auditory system triggered by cochlear damages and/or manipulating the acoustic environment. In this context, it has been suggested that cochlear damages, together (or not) with central plasticity, can produce aberrant perceptions, such as tinnitus (ringing in the ears) and hyperacusis (auditory hypersensitivity). An important part of his research is devoted to understanding the mechanisms of these aberrant perceptions and to develop and test therapeutic approaches in tinnitus subjects. These questions are addressed from different methods, namely:– Compound action potential (response of the cochlear nerve)– Auditory brainstem responses (responses from the cochlear nerve to the inferior colliculus)– Multi-unit recording in auditory centers from matrix of electrodes– Voltage-sensitive dye imaging optical imaging (membrane potential from populations of cortical neurons)– Psychoacoustic (relationships between stimulus and perception)

Philippe Fournier: Philippe Fournier currently works at the audiology program of the Medicine Faculty at Laval University. Trained as an audiologist, his research focuses on various auditory pathologies, including tinnitus, hyperacusis, misophonia and acoustic shock syndrome. His research aims to better understand the pathophysiological mechanisms responsible for the

onset of these different auditory pathologies, to develop new diagnostic measures and to improve the management of his patients through the implementation of innovative therapies.

Trial Drugs:

N/A

Research Papers & Theories:

An Integrative Model Accounting for the Symptom Cluster Triggered After an Acoustic Shock

In this paper, researchers Arnaud Noreña and Philippe Fournier were able to develop a persuasive model on the aftermath of an acoustic shock, and what symptoms generate as a result from it. In the article, they elaborated on the hypothesis that the tensor tympani muscle (TTM), the trigeminal nerve (TGN), and the trigeminal cervical complex (TCC) play a central role in generating these symptoms. They argued that TTM overuse (due to the acoustic shock), TTM overload (due to muscle tension), and ultimately, TTM injury (due to hypoxia and “energy crisis”) lead to inflammation, thereby activating the TGN, TCC, and cortex. The TCC is a crossroad structure integrating sensory inputs coming from the head–neck complex (including the middle ear) and projecting back to it. The multimodal integration of the TCC may then account for referred pain outside the ear when the middle ear is inflamed and activates the TGN.

They concluded that the triggering event was the overuse of the tensor tympani muscle (TTM), which could be associated with a TTM injury of varying severity, and could possibly lead to TTM chronic contraction or spasms. The initial TTM wound causes pain, which could spread through inflammatory processes, up to the middle ear mucosa, and may be amplified and persist beyond the tissue damage when peripheral and central sensitization mechanisms are at stake. The main trigeminal nerve (TGN) relay in the brainstem is the trigeminal cervical complex (TCC), a crossroad structure that integrates sensory information from the head–neck complex. The broad integration of the TCC may account for referred pain outside the ear when the middle ear is injured. The sympathetic nervous system may also be involved in maintaining and amplifying pain, while the trigeminal-parasympathetic reflex may account for autonomic symptoms such as blocked nose and tympanum hyperemia. Finally, tinnitus may be modulated and result from the excitatory modulation exerted on the central auditory system or on the cochlea (stria vascularis) by the TGN activation.

Exploring the middle ear function in patients with a cluster of symptoms including tinnitus, hyperacusis, ear fullness and/or pain

In this paper, researchers Arnaud Noreña and Philippe Fournier followed up on their previous study, and investigated the middle ear function of 11 patients who reported TTTS symptoms.

The evaluation included either, admittancemetry, EAC air pressure measurement or both. While the former method measured the middle ear stiffness, the latter provided an estimate of the tympanic membrane displacement. Most patients in this study displayed results consistent with phasic contractions of the TTM and/or Eustachian Tube (ET) dysfunction. The MEM contraction or ET dysfunction could be evoked by acoustic stimulation, somatic maneuvers, or pressure changes in the ear canal. Spontaneous TTM contraction or ET opening could also be observed. Finally, voluntary contraction of MEM was also reported.

It was previously thought that in periods of auditory stress, the TTM did a long, sustained (tonic) contraction; staying contracted the entire time. However, in the results of this study, none of the patients had these contractions. Rather what happened was simply that their TTM had a lower volume threshold for contraction. These were much shorter (phasic) contractions, usually in response to a sound that caused them distress, like a pen dropping or a baby crying. By using the new ear sensor that the researchers developed, the study was able to conclude that all 11 patients had abnormalities in the way their tensor tympani muscle and/or stapedius muscle behaved. One patient in particular received a treatment consisting of a botulinum toxin injection in the tensor and levator veli palatini muscles. One month later the patient reported that the intervention was a complete success: he didn't experience pain in the ear after exposition to impulsive sound anymore. Following the intervention, he was not able to voluntarily contract his MEM. These results suggest that some muscle activity in the oro-facial area was responsible for the pain and was deactivated by the toxin.

Inner Ear and Middle Ear:

Medication:

Clomipramine: Clomipramine, sold under the brand name Anafranil among others, is a tricyclic antidepressant. It is used for the treatment of obsessive–compulsive disorder, panic disorder, major depressive disorder, and chronic pain. Like other TCAs, clomipramine weakly blocks voltage-dependent sodium channels. Sodium channel blockade is also thought to contribute to the analgesic effects of TCAs, for instance in the treatment of neuropathic pain. This is similar to Ambroxol, which blocks sodium channels but does not affect neurotransmitters.

Carbamazepine: Carbamazepine, sold under the brand name Tegretol among others, is an anticonvulsant medication used in the treatment of epilepsy and neuropathic pain.

Duloxetine: Duloxetine, sold under the brand name Cymbalta among others, is a medication used to treat major depressive disorder, generalized anxiety disorder, fibromyalgia, neuropathic pain and central sensitization.

Supplements:

DNRS: The Dynamic Neural Retraining System is a drug-free, self-directed program that uses the principles of neuroplasticity to help reverse limbic system impairment in the brain, and to regulate a maladapted stress response involved with many chronic illnesses such as Long Covid, Chronic Fatigue Syndrome, Multiple Chemical Sensitivity, Fibromyalgia, Chronic Lyme Disease, Food Sensitivities, Anxiety, Chronic Pain, Postural Orthostatic Tachycardia Syndrome and many other conditions. Instead of chasing symptoms, the DNRS approach directly targets brain function in order to regulate a maladapted stress response, which is often the missing piece for people suffering with chronic illness, and teaches you how to rewire the limbic system and change the structure and function of your brain. A user on Tinnitus Talk who had severe noxacusis was relieved of her symptoms with a combination of treatments, including DNRS.

Surgery:

Disconnection of Middle Ear Bones: Ossicular chain dislocation is a separation of the middle ear bones. It results in a hearing loss due to sound not being transmitted properly (conductive hearing loss). Ossicular chain dislocation is also called ossicular chain discontinuity. In one case involving a patient with severe hyperacusis, the doctors suggested the disarticulation of the ossicular chain. This would effectively disconnect the middle ear bones and worsen the deafness in the affected ear. After surgery, her hearing thresholds dramatically increased. The patient reported complete relief from hyperacusis and distortion symptoms. This surgery is the functional equivalent of adding a super ear plug into the ear (with 50+dB attenuation) and appears to work in cases where hearing loss is already significant in one ear.

Severing the Auditory Nerve: Severing the Auditory Nerve has never been performed before and is highly experimental. Not much is known about this surgery and its effectiveness for hyperacusis and its many forms. This would induce deafness in the ear that it was performed in. However, one of the potential pain mechanisms may still be intact and vulnerable to sound.

Doctors, Clinics, and Researchers:

Trial Drugs:

SPI-1005 (Ebselen): SPI-1005, created by Sound Pharmaceuticals, is an investigational new drug that contains Ebselen, a new chemical entity. Ebselen is a selenorganic compound that mimics and induces glutathione peroxidase (GPx) activity, and is effective in reducing neuroinflammation across the central and peripheral nervous system. GPx activity is critical to several cell types and tissues in the inner ear, retina, prefrontal cortex of brain, lung, and kidney, and is often reduced during exposures to environmental insults or aging. Loss of GPx activity

has been shown to result in sensorineural hearing loss in multiple animal models. SPI-1005 is being developed for several neurotologic indications including noise-induced hearing loss and two types of ototoxicity (hearing loss, tinnitus, dizziness, or vertigo) caused by aminoglycoside antibiotics (such as tobramycin or amikacin) or platinum-based chemotherapy (such as cisplatin or carboplatin).

Research Papers & Theories:

N/A

Loudness Hyperacusis

Symptoms: