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A New Method in Subjective Tinnitus Management: The Use of a Nutraceutical Formulation to Improve Patient Outcomes

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A NEW METHOD IN SUBJECTIVE TINNITUS MANAGEMENT: THE USE OF A NUTRACEUTICAL FORMULATION TO IMPROVE PATIENT OUTCOMES

by

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A capstone research project submitted to the Graduate Faculty in Audiology in partial fulfillment of the requirements for the degree of Doctor of Audiology, The City University of New York

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This manuscript has been read and accepted for the Graduate Faculty in Audiology in satisfaction of the capstone requirement for the degree of Doctor of Audiology.

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ABSTRACT

A New Method in Subjective Tinnitus Management:
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Jade H. Faulkner

Advisor: Dorothy Neave-DiToro, Au.D., CCC-A, FAAA

Objective: This project aims to implement an evidence-based clinical practice guideline at the International Hearing Centre (IHC) in Lagos, Nigeria for future research and data collection of their subjective tinnitus management using a nutraceutical formulation called 'NHANCED Hearing (NH). After learning the IHC had incomplete charting in regard to tinnitus questionnaires pre- and post-administration of the NH formula, this capstone project sought to apply evidence-based guidelines for proper diagnostic evaluations and charting to assist in future research of the NH formula.
Methodology: A review and synthesis of current clinical practice guidelines in the United States, Germany, the Netherlands, Sweden, Denmark, and Japan allowed this research to present a complete diagnostic evaluation template and suggested timelines for administering subjective measures of tinnitus disturbance. Future research with IHC will benefit from complete charting for a retrospective chart review including tinnitus-specific case history, audiologic pure tone thresholds, tympanometry and acoustic reflex thresholds, distortion product otoacoustic emissions, and completed Tinnitus Handicap Inventory (THI) administered at 3-month intervals.
Results: Future research will be analyzed for clinically significant changes ($p \leq 0.05$) in tinnitus disturbance as measured by the THI at baseline and 1-year post-initial administration. A roadmap for statistical analysis of the data is included in this project.
Discussion: Anecdotal reports from clinicians at the IHC suggest significant improvements in subjective tinnitus as per patients taking the NH formulation. A proper, evidence-based, framework for implementing and measuring subjective improvement in tinnitus percept is necessary for future research. In addition to subjective reports, the distance traveled and cost out of pocket for the nutraceutical reveal a strong indication of perceived benefit.
Conclusion: The goal of this project is to implement an evidence-based clinical protocol at the IHC to standardize patient care in order to evaluate and statistically analyze the efficacy of the NH formulation on subjective tinnitus sufferers in the future. Future research can use this project as a template to assess changes to tinnitus percept in patients taking the NH formulation.

Key words: audiology, tinnitus, antioxidants, nutraceutical, clinical practice guideline, subjective tinnitus, bothersome tinnitus

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INTRODUCTION

Tinnitus and Hearing Loss

Tinnitus is the conscious perception of an auditory sensation in the absence of a corresponding external stimulus (Baguley, McFerran, and Hall, 2013). Patients with tinnitus are heterogeneous in tinnitus experience. For example, tinnitus may be subjective or objective, high-pitched or low-pitched, ringing or hissing, or have other varied clinical presentations. According to the American Tinnitus Association (n.d.), subjective tinnitus, experienced by 99% of tinnitus sufferers, is the most common type and perceived by the patient only. Meanwhile objective tinnitus, experienced by about 1% of patients, can be perceived by the clinician by auscultation (American Tinnitus Association, n.d.). Generally, objective tinnitus comes in the form of pulsatile tinnitus, imitating the heartbeat (Baguley, McFerran, and Hall, 2013).

Risk factors for tinnitus are vast, adding to its heterogeneity. Hearing loss is the main risk factor for tinnitus, even though there are patients that present with tinnitus and normal audiometric data or others with hearing loss not reporting tinnitus (Baguley, McFerran, and Hall, 2013). Other factors Baguley et al. (2013) offer: environmental factors, such as noise exposure; medicinal factors including over-the-counter and prescription drugs that can be harmful to the ear and hearing, known as ototoxic drugs, including corticosteroids, loop diuretics, platinum based chemotherapy agents, and non-steroidal anti-inflammatory drugs (NSAIDs); and lastly pathologies of the ear such as otitis media, labyrinthitis, acoustic neuroma, Meniere's disease, and otosclerosis are often accompanied by tinnitus. Thus, an unknown pathogenesis in addition to a plethora of presentations, lead to a very difficult to manage chronic disability. Interestingly, according to Hobson, Chisholm, and El Refaie (2012), in 60% of patients that have had the auditory nerve severed secondary to tumor removal in acoustic neuroma, the presence of tinnitus

remained, suggesting “the fundamental importance of the central auditory pathways in the maintenance of the symptom, irrespective of the initial mode of generation being the cochlea or the vestibulo-cochlear nerve” (pg. 3).

Severity is highly variable across tinnitus sufferers. The research has shown no significant correlation between severity and the degree of hearing loss, nor has there been a correlation between the loudness of the tinnitus and how bothersome it is to the patient. Depression, however, is highly correlated with the severity of tinnitus (Udupi et al., 2013). The disability generated by tinnitus depends “on primary psychological factors, such as difficulty in dealing with the problem” (Pinto et al., 2010, pg. 21). The severity of annoyance due to tinnitus and the presence of psychiatric conditions is highly correlated as well. Most researchers agree, 10-15% of the population is affected by some form of tinnitus, and most are able to habituate to the sensation (Celik & Koyuncu, 2018; Ciorba et al., 2013). Researchers, however, do not agree on the number of tinnitus sufferers unable to habituate to the sound which has been shown to lead to increased anxiety, social isolation, and depression. This population is reportedly between 0.5% and 20% of patients (Baguley et al., 2013; Celik & Koyuncu, 2018; Pinto et al., 2010). Trevis, McLachlan, and Wilson (2018) reviewed the psychological effects in chronic tinnitus sufferers unable to adjust to the sensation. The systematic review analyzed chronic tinnitus and its effect on emotional well-being (i.e. quality of life, depression and anxiety) and cognitive functioning. Chronic tinnitus sufferers were found to have a clinically significant increase in depression and anxiety symptoms compared to healthy controls. Some of the most notable impacts of tinnitus include poor sleep, social withdrawal, interference with work, suicidal thoughts, confusion, and worry (Trevis, McLachlan, and Wilson, 2016).

Anatomy and Physiology of the Ear & Oxidative Stress

The ear is divided into three anatomic parts: outer, middle, and inner. The outer ear includes the external, visible part of the ear, known as the pinna, and the ear canal. The middle ear begins at the tympanic membrane, or ear drum, and houses the ossicles, or bones of the ear, the malleus, incus, and stapes. Together, the outer and middle ear "form the sound conducting mechanism" (Alberti, 2001, p. 54). The pinna collects sound and channels it into the ear canal. The sound is then directed to the tympanic membrane, causing vibration and movement of the ossicles. The inner ear "consists of the cochlea which transduces vibration to a nervous impulse and the vestibular labyrinth which houses the organ of balance" (p. 54). The cochlea is "a bony tube filled with perilymph in which floats the endolymph filled membranous labyrinth" (p. 56). The footplate of the stapes, in the middle ear, sits in the oval window of the cochlea. Vibration of the stapes footplate "vibrates the perilymph in the cochlea" (p. 56). The basilar membrane, one of the separating structures between the perilymphatic and endolymphatic spaces in the cochlea, "responds resonantly to highest frequencies at its basal end nearest the oval window and to progressively lower frequencies" at its apical end, furthest from the oval window (p. 58). "Four rows of hair cells lie on top of the basilar membrane, together with supporting cells": One row of inner hair cells (IHCs) and three rows of outer hair cells (OHCs). It has "an abundant nerve supply carrying messages to and from the brain" (p. 57). Therefore, vibration of the perilymph by the stapes footplate in the oval window is transmitted into a nervous impulse carried along the eighth cranial nerve, the vestibulocochlear nerve, "from the cochlea to the brainstem. Here the nerve fibers reach nuclei where they relay with other nerve fibers…The fibers pass up the hindbrain to the midbrain and the cerebral cortex" (p. 58, 61). "Any sound introduced at the oval window, by motion of the stapes, is transmitted along the basilar

membrane as a traveling wave until all of its frequency components reach their respective place of resonance where they stop and travel no further" (p. 60). The inner and outer hair cells play a pivotal role in sound perception and transmission. Damage to the cochlea via noise exposure or ototoxic medication, for example, will result in death of OHCs that are not regenerative. "If the OHCs are damaged, they no longer contract in response to slight sounds and the IHCs are not stimulated…producing a hearing loss for low intensity sounds" (p. 61).

As previously indicated, the pathogenesis of tinnitus is not yet clearly defined. In most patients, the development of tinnitus can be linked to damage to the cochlea. Neri et al. (2006) evaluated the oxidative stress of 44 patients with idiopathic tinnitus and 25 healthy volunteers. They reported patients with idiopathic tinnitus presented a significant increment ($p<0.05$) of oxidative damage marker concentrations and plasma scavenger activity in jugular blood, accompanied by increased free radical concentrations. Based on these findings, they concluded that oxidative stress is important in the pathogenesis of tinnitus.

According to Pham-Huy, He, and Pham-Huy (2008), free radicals, or unpaired electrons, are highly reactive and are generated through the use of oxygen in the metabolism of certain compounds in the body's daily processes. Excessive production of free radicals can damage normal cells. Environmental factors, including stress, smoke and pollution, and elevated iron and copper in the body can contribute to the creation of free radicals at an increased rate. This excessive production causes oxidative stress, an inflammation to the cells that causes damage to DNA, RNA, cell membranes, proteins, and lipids.

Koc et al. (2016) further explain reactive oxygen species (ROS) play a role in the pathogenesis of otlogic and neurologic diseases. High concentrations of ROS can have cytotoxic and neurotoxic effects, resulting in damage to the auditory hair cells of the labyrinth and the

acoustic system. Then, as Ciorba et al. (2013) suggest, it is reasonable to suppose "antioxidant drugs can reduce the amount of intracellular damages mediated by ROS" (p. 249). The role of oxidative stress in certain inner ear disorders, such as Meniere's disease, noise-induced hearing loss, labyrinthitis, cisplatin ototoxicity and aminoglycoside ototoxicity is well known (Calabrese et al., 2010; Fujimoto and Yamasoba, 2014; Haase et al., 2016; Koc et al., 2016). According to Haase et al. (2016), biochemical pathways are increasingly becoming the culprit for abnormalities "from the cortical level through the inner ear apparatus" (p. 56). By understanding the effects of oxidative stress and free radicals on the inner ear, new biological options may be proposed in the management of tinnitus, especially for patients debilitated by the symptoms.

Tinnitus Management

Over the years, the research has shown inconsistent findings validating the efficacy of over-the-counter (OTC) vitamins, minerals, and supplements for the reduction of tinnitus. Antioxidant therapies have included phospholipids, vitamins C and E, *Ginkgo biloba*, alpha lipoic acid, zinc, garlic, and lemon-bioflavonoid, among others (DiSogra, 2010). The myriad clinical management strategies in attempts to alleviate tinnitus symptoms have ranged from "education and advice, relaxation therapy, tinnitus retraining therapy (TRT), cognitive behavioral therapy (CBT), sound enrichment using ear-level sound generators or hearing aids, and drug therapies to manage comorbid symptoms like insomnia, anxiety and depression" (Person et al., 2016, pg. 6).

Drug therapies such as tricyclic antidepressants and serotonin-reuptake inhibitors have not been shown to reduce the tinnitus loudness or perception, but they have had a positive role in improving psychological distress (Baguley, McFerran, Hall, 2013). According to Pirodda, Raimondi, and Ferri (2010), melatonin, used with patients suffering from tinnitus-related

insomnia, improves sleep even though the effect on tinnitus severity is minimal. Increased intake of dietary components such as vitamin B, zinc, and magnesium have had poor quality of evidence and have been contradictory. For example, Savastano et al. (2007) and Gopal et al. (2015) both reported positive findings. Savastano et al. (2007) reported a decrease in reactive oxygen species (ROS) and tinnitus disturbance after 18 weeks of oral treatment with phospholipids and vitamins in a cohort of 31 patients reporting idiopathic tinnitus. They analyzed measured changes in tinnitus loudness matching and subjective disturbance using the visual analogue scale (VAS). Savastano et al. concluded patients experienced a decrease in ROS and tinnitus loudness and disturbance at the end of the trial (2007). Gopal et al. (2015) found not only a subjective improvement in tinnitus distress in a case study of a female taking acetyl L-carnitine (ALCAR) for thirty days, but they also noted improved post-treatment audiologic thresholds and a clinically significant decrease in tinnitus questionnaire scores on the THI, 14 points pre-treatment to 4 points post-treatment. On the other hand, Polanski et al. (2016) found no significant difference in pre- and 6-month post-treatment tinnitus questionnaires within subjects, nor between subjects in their four groups of patients taking either (1) *Ginkgo biloba*, (2) vitamin C with alpha lipoic acid, (3) papaverine hydrochloride with vitamin E, or (4) the placebo group.

The door for research is open in the use of antioxidant approaches to relieving tinnitus distress in patients. Although current research is still undecided on when and how to implement antioxidant therapy, there is strong data revealing a link between tinnitus and oxidative stress (Ciorba et al., 2013; Haase et al., 2011; Koc et al., 2016; Koca et al., 2018). According to Pham-Huy et al. (2008), oxidative stress can be counteracted naturally by antioxidants produced in the body, "endogenous antioxidants," or it can be supplied through foods and supplements,

"exogenous antioxidants" (p. 92). They state: "The roles of antioxidants are to neutralize the excess of free radicals, to protect the cells against their toxic effects and to contribute to disease prevention" (p. 92).

Reactive oxygen species (ROS), as described previously, in large amounts can be hazardous to the body causing pathological disease (Pawlak-Osinska et al., 2018). ROS are formed in the cochlear hair cells after exposure to cisplatin, aminoglycosides, salicylates, and noise, for example. However, if in a homeostatic state, ROS are essential to body function, specifically in signal transmission inside the cell. Endogenous antioxidants produced by the body, such as catalase, glutathione peroxidase, and glutathione S-transferase, can help to balance ROS activity. An imbalance between ROS and endogenous antioxidants leads to pathological disease, including, but not limited to, damage to the inner ear like hearing loss and tinnitus. Interestingly, in the Pawlak-Osinska et al. study (2018), the tinnitus subjects showed significantly lower levels of the endogenous antioxidants glutathione peroxidase and erythrocyte glutathione than the control group ($p=0.026$ and $p=0.00$, respectively).

Antioxidants obtained by food sources are known as exogenous antioxidants. Devasagayam et al. (2004) provide a comprehensive list of fruits, vegetables, legumes, oils, dairy products, and more that provide antioxidant support for flavonoids, polyphenols, carotenoids, and vitamins. Haase et al. (2011) suggest preventive and protective benefits of antioxidants such as vitamin E, α-Lipoic acid, Coenzyme Q10, vitamin C and magnesium. They further assert the combination of multiple antioxidants prevents the possibility of creating more free radicals in the body. Haase et al. reminds us that although single agents may provide some benefit, more likely, the oxidation of an antioxidant creates free radicals (2011).

Two therapies used in managing tinnitus are cognitive behavioral therapy (CBT) and tinnitus retraining therapy (TRT). CBT aims to alter the patient's response to tinnitus, not the volume or perception. Jun and Park (2013) explain the concept of CBT is to correct the negative perception, thoughts, and beliefs about the tinnitus, and replace them with "positive and realistic thoughts" (p. 101). CBT does not aim to reduce the acoustic features of the tinnitus, rather the distress and handicap induced by the tinnitus. TRT, on the other hand, uses a two-step process to reduce the perception, emotional associations, and negative reactions to the tinnitus. Step one, described by Formby and Scherer (2013), involves "directive counseling," similar to CBT, to "initiate the habituation process by neutralizing the negative and emotional reactions to the tinnitus" (p. 135). Step two, they continue, involves the use of ear-level sound generators to enrich the sound environment and decrease the difference between the level of the tinnitus and the level of the ambient environmental sounds.

Sound therapy, in its various forms, has been used in attempts to reduce tinnitus distress in chronic tinnitus patients. According to Baguley, McFerran, and Hall (2013), after a treatable pathology associated with tinnitus has been excluded, such as cerumen or infection, standard care is to give an explanation of the situation, followed by sound therapy and intervention to reduce the distress. Sound therapy includes hearing aids or sound generators to effectively mask the tinnitus. In a systematic review by Hobson, Chisholm, El Refaie (2012), six trials of sound therapy masking studied 553 participants. Hobson et al. found the studies failed to show strong evidence of the efficacy of sound therapy in changing the loudness or overall severity of tinnitus; however, some studies showed sound therapy devices were subjectively helpful in reducing levels of tinnitus annoyance and improved scores on questionnaires like the TRQ (2012). Baguley et al. (2013) also discuss emerging sound treatments that not only mask

perception of the tinnitus, but are also effective as a therapeutic relaxant like the Widex Zen program, or one that reduces emotional arousal like the Neuromonics device (see also Tyler et al., 2017; Hanley et al., 2008). At present, the evidence is still inconclusive on sound therapy as a tool to eliminate the perception of tinnitus; however, outcomes are strong for reducing its perception when in use.

'NHANCED Hearing Nutraceutical Formulation

The current study aims to delve into an antioxidant micronutrient formulation created by Dr. Gerald Haase of the New Age Beverages Corporation, and formerly of the Premier Micronutrient Corporation (PMC). The 'NHANCED Hearing (NH), formerly Hearing Health (HH), formula claims to decrease the amount of free radicals in the body to increase effective immune function. This NH formula includes Vitamins A, C, D, E, B_6, B_{12}, Calcium, Zinc, Magnesium, and other vitamins and antioxidants. It is referred to as a nutraceutical, defined by Gupta et al. (2010) as a product that is derived from food sources with extra health benefits in addition to the basic nutritional value found in foods. Gupta et al. (2010) elaborate: "Nutraceuticals are non-specific biological therapies used to promote general well-being, control symptoms, and prevent malignant processes" (p. 56). The difference between a nutraceutical and the average over-the-counter (OTC) antioxidants is the specific and deliberate formulation that has an exact dosing schedule for best patient outcomes (Jain and Ramawat, 2013).

The NH nutraceutical was created and marketed to preserve hearing status and combat free radicals in the hearing organ on a cellular level. Dr. Gerald Haase, creator of the NH formula, worked closely with the United States Military, Department of Defense, and NASA on the nutraceutical. According to Haase (2014), PMC formulations help reduce the amount of free radicals and inflammation, thereby increasing the immune system function. In a 2011

publication, Haase posits a proper "combination of antioxidant supplementation may improve efficacy of standard therapy for some hearing disorders" (p. 57). Singular antioxidants have their own positive properties for improving immune and hearing function; however, he notes, "single agents [antioxidants], when oxidized, act as a free radical" (p. 57), meaning, in an attempt to mitigate oxidative stress, one may be causing oxidative stress. An important factor in the efficacy of the micronutrient is its specific and exacting dosing schedule. Haase (2011) elaborates: "great fluctuations in antioxidant levels associated with only once a day or every other day dosing" may not be consistent enough to be effective (p. 57). Therefore, "twice a day dosing maintains more constant levels to increase biologic effectiveness, protect the genetic machinery of the cell, and decrease cellular stress" (p. 57). The pilot study for Hearing Health (now 'NHANCED Hearing) revealed 7 patients out of 11 experienced a "clinically significant reduction in tinnitus grade," monitored by scores on the Tinnitus Handicap Inventory, pre- and post-treatment (p. 59).

Measuring Tinnitus: Questionnaires

Baguley, McFerran and Hall (2013) point out since there is no objective test available for most tinnitus patients, except in the case of pulsatile tinnitus which can be detected by auscultation, other measures must be used to note changes in tinnitus perception and effects on a patient's well-being. They expand: Tests to match pitch and loudness of the tinnitus are difficult, relate poorly to the patient's distress, and offer little to the subsequent management plan. These perceptual measurements of tinnitus do not reflect how bothered the patient is. Additionally, there is no linear relationship between the intensity of the tinnitus and how bothered the patient is by its perception; therefore, a self-report questionnaire will be the most effective tool for the current study.

Handicap from tinnitus can present as any or all of the following: Stress, anxiety, depression, insomnia, concentration difficulty, and quality of life impairments (Baguley, et al., 2013). Questionnaires are generally used to assess the degree to which the patient is bothered and handicapped from the tinnitus (Fackrell and Hoare, 2014). Questionnaires also help to quantify and measure changes longitudinally. Improved scores on a tinnitus questionnaire can be used as a counseling method to show the patient how a management technique is working over time.

There are many tinnitus questionnaires available, but they do not all measure the same aspects of the patient's complaints (Fackrell and Hoare, 2014). The six most common questionnaires are described here:

1. Tinnitus Questionnaire (TQ) – created by Hallam, Jakes, and Hinchcliffe. Fackrell and Hoare (2014) explain, this validated 52-item questionnaire measures tinnitus severity change and the relationship between different aspects of complaints and other psychological variables. Answers are based on a 3-point scale of true, not true, or partly true. The negative features of the TQ are the high demand on time; the majority of questions focus on emotional and cognitive aspects of the handicap; the three-point scale makes it difficult to notice small changes, and there is no grading system or minimal clinically important change score. The Mini-TQ is a 12-question rapid version of the TQ. It shows greater treatment effects than indicated with the TQ. The Mini-TQ also shows high item-total correlations, reliability and sensitivity to change.
2. Tinnitus Handicap Questionnaire (THQ) -- Fackrell and Hoare (2014) continue, the THQ is a validated 27-item questionnaire that is sensitive to change in handicap over time. The answers are on a scale of 1-100 allowing patients to see small changes in

handicap, making the THQ a sensitive outcome measure. However, no grading scale has been developed and almost half of all statements relate to the psychological and emotional aspects of tinnitus handicap.

3. Tinnitus Reaction Questionnaire (TRQ) -- Described by Fackrell and Hoare (2014) as a validated 26-item questionnaire that was developed to assess the effects of psychological distress on tinnitus and distinguish between its levels. The TRQ lacks a recommended grading system or minimal clinically important change score. However, the five-point Likert scale makes it more sensitive than the THI or TQ. The TRQ measures similar constructs to those measured by more general questionnaires measuring depression or anxiety, making it an important tinnitus assessor due to the psychological effects it has on patients.
4. Tinnitus Handicap Inventory (THI) – Fackrell and Hoare (2014) explain the THI was originally designed as a companion to the Hearing Handicap Inventory (HHI) and Dizziness Handicap Inventory (DHI) to complete a set of tools to quantify perceived handicap in a variety of hearing related conditions. This validated 25-item questionnaire measures the impact of tinnitus on everyday function using a three-point scale, yes, sometimes, or no. In contrast to some other tinnitus questionnaires, the THI has a grading system categorizing tinnitus handicap based on the patient's responses: slight, mild, moderate, severe, or catastrophic. Additionally, a minimal clinically important change score of 7 points has been determined to measure treatment related changes. Similar to other tinnitus questionnaires, the THI focuses on the psychological and emotional aspects of the handicap.

5. Tinnitus Functional Index (TFI) – Fackrell and Hoare describe this 25-item questionnaire that discriminates between levels of distress, and provides a responsive measure of treatment related change. The answers are on a scale of 0-10, which allows for the detection of small changes over time. Like the THI, the TFI has a grading system and a minimal clinically important change score. Additionally, the questions in the TFI are more evenly weighted across different aspects of tinnitus handicap than in other questionnaires.
6. Self-efficacy for Tinnitus Management Questionnaire (SETMQ) – Smith and Fagelson (2011) describe this 40-item questionnaire that allows patients to rate their answers on a percentage scale from 0-100% in intervals of 10 percentage points. The questionnaire rates the patient's self-efficacy in various areas of tinnitus management. The areas include routine tinnitus management, emotional response to tinnitus, internal thoughts and interaction with others, tinnitus concepts, and use of assistive devices.

Tinnitus Management – An International Review

Fuller et al. (2017) performed a systematic review of current clinical guidelines for tinnitus in Denmark, Sweden, Germany, the Netherlands, and the United States. The review discusses both assessment guidelines across the countries and management guidelines. Fairly consistently, the guidelines suggest physical examination by an otolaryngologist or other related professional and a hearing examination which includes the complete audiologic evaluation (CAE). Some guidelines suggest other audiologic assessments like auditory brainstem response (ABR), loudness discomfort levels (LDL), and otoacoustic emissions (OAE), though these are not consistent across countries. A tinnitus questionnaire is always indicated, regardless of

country. The most popular questionnaires, according to the guidelines, are the THI and TQ. Also, a psychological assessment is indicated, to include investigations of how the tinnitus is affecting the patient's daily life and comorbid symptoms.

The tinnitus management recommendations similarly remain consistent across countries (Fuller et al., 2017). No medical treatments are indicated for tinnitus specifically; however, recommendations are present for comorbidities, like depression, sleep, or anxiety. Audiological interventions strongly recommend the use of hearing aids for tinnitus patients with hearing loss, while TRT is recommended as a sound therapy for patients without hearing loss in all guidelines except in Germany. Lastly, CBT is strongly recommended as a psychological therapy across the board.

Ogawa et al. (2019) released clinical practice guidelines for diagnosis and treatment of chronic tinnitus following the guidelines set forth in Fuller et al. (2017). They recommend the use of a validated tinnitus questionnaire, namely the THI which has been translated into Japanese, pure tone audiometry, pitch matching, and loudness balance testing. Imaging is recommended by Ogawa et al., particularly for patients suffering from unilateral or pulsatile tinnitus. Lastly, the Japanese guideline supports TRT and CBT as treatment and management techniques for chronic tinnitus. A disadvantage for CBT at this time in Japan is the minimal number of facilities offering CBT with trained experts, but they find it to be a cost-effective treatment with no side effects.

Tunkel et al. (2014) created a comprehensive clinical practice guideline for the American Academy of Otolaryngology - Head and Neck Surgery Foundation (AAO-HNSF). The audiologic test battery recommended includes pure tone air conduction thresholds 250Hz through 8000Hz including interoctave frequencies as deemed necessary by the clinician, bone

conduction thresholds 250-4000Hz, speech recognition thresholds, word recognition scores, immittance measures to include contralateral acoustic reflex thresholds (ARTs) 500-4000Hz, ipsilateral ARTs 500-4000Hz, and acoustic reflex decay at 500 and 1000Hz. Tunkel et al., similar to Ogawa et al. (2019), recommend sound therapy and CBT for patients with persistent, bothersome tinnitus. On the other hand, Tunkel et al. strongly advise against the use of dietary supplements including *Ginkgo biloba*, melatonin, zinc, or other supplements for patients with persistent, bothersome tinnitus. The authors report a lack of proven efficacy in randomized clinical trials.

The Tinnitus Research Initiative (TRI) provides a broad flow-chart for clinical use to assist in managing the chronic tinnitus patient (Biesinger et al., 2011). The guideline proposes not only the case history and audiologic test battery, but it suggests psychoacoustic measures including pitch matching, loudness matching, minimum masking levels, residual inhibition, and loudness discomfort/growth tests. Although the current research project has determined psychoacoustic measures to be difficult and poorly related to patient's distress, the TRI considers the psychoacoustic measures may offer diagnostic value in the counseling process for the chronic tinnitus patient (Baguley et al., 2013; Biesinger et al., 2011). Additionally, psychoacoustic measures may also aid in hearing device programming, specifically the loudness discomfort levels.

In all, the above guidelines for tinnitus management are important for developed and developing countries to implement for tinnitus patients. The current project proposes the adoption of recommendations to better manage tinnitus patients, especially those with bothersome tinnitus. Most importantly, the assessment of tinnitus patients must include a CAE,

tinnitus questionnaire and examination by an otolaryngologist. The management, as proposed by the current study, will include dispensing of the NH nutraceutical formulation.

METHODOLOGY

The aim of this research project will be to measure the subjective changes in tinnitus perception while using the NH nutraceutical. As seen in the literature review, the THI and TFI are the only tinnitus questionnaires that have a grading system and minimal clinically important change score; however, the TFI, according to Fackrell and Hoare (2014), has not undergone formal validation. Therefore, changes will be measured by comparing the responses to the Tinnitus Handicap Inventory (THI) at baseline, then in 3 month intervals at 3-, 6-, and 9-months' post-administration, and 1-year post-administration. This will make it possible for researchers to note changes in tinnitus perception and the level of distress for patients at periodic follow-up appointments. The research hypothesizes using the NH formula will decrease the perception of subjective tinnitus. Furthermore, the research will analyze if any change in tinnitus perception remains over an extended period of time, for example a 6-month or 1-year period, and if cessation of the nutraceutical has any positive or negative effects on the percept.

The study will be designed as a retrospective chart review. Data will be collected from the International Hearing Centre (IHC) in Lagos, Nigeria. Anecdotal evidence from Audiologists and Pharmacists at the IHC suggest improvements in subjective tinnitus severity as per patient report, therefore, the research will examine the charts of patients to whom the nutraceutical has already been administered. Data collected will be redacted patient files containing only the following information: Gender, age, audiometric data including type and degree of hearing loss, if any, description and duration of the tinnitus, the case history related to hearing and tinnitus, and a pre- and post-administration tinnitus handicap inventory (THI) questionnaire. A minimum of 30 patient charts will be reviewed in order to make statistically significant claims of correlative effects of the nutraceutical formulation on subjective tinnitus

perception. In light of the within-subjects design of the study, gender and age will not be controlled for in data collection. Furthermore, there are discrepancies in the literature whether gender or age have a significant effect on tinnitus. Seydel et al. (2011) found women to be more emotionally affected by tinnitus using the Tinnitus Questionnaire (TQ) and four other questionnaires investigating perceived stress, coping, and sense of coherence measures. Regardless of age, Seydel et al. found women to have less loud tinnitus, compared to their male counterparts, measured by tinnitus loudness matching (2011). The study found age and gender to be important factors in psychometric outcomes. On the other hand, Udupi et al. (2013) reported no significant differences between gender or age and tinnitus severity. The authors found correlation between depressive symptoms and tinnitus severity, as has been previously discussed.

The NH formula composition is seen below in Table 1. According to the specified dosing schedule, patients are advised to take two pills, two times daily. This, as suggested by Dr. Haase, will maintain antioxidant levels in the blood for increased efficacy and decreased cellular stress (2011). The dosage will remain constant, with no tapering instructions.

Table 1. List of ingredients New Age Beverages Corporation NH Formula.

Ingredient	**Amount Per Serving**	**% Daily Value**
Vitamin A	5500 IU	183%
Vitamin C	250 mg	278%
Vitamin D	200 IU	25%
Vitamin E	200 IU	935%
Thiamin	4 mg	333%
Riboflavin	5 mg	385%

Niacin	30 mg	188%
Vitamin B_6	5 mg	294%
Folic Acid	200 mcg	50%
Vitamin B_{12}	10 mcg	417%
Biotin	200 mcg	667%
Pantothenic Acid	10 mg	200%
Calcium	60 mg	5%
Magnesium	100 mg	24%
Zinc	15 mg	136%
Selenium	100 mcg	182%
Chromium	50 mcg	143%
Proprietary Blend – L-Cystine, L-Carnitine, Alpha Lipoic Acid, Co-Enzyme Q_{10}	575 mg	Unspecified

Inclusion criteria for patient data will include healthy adults age 18 and above. Since tinnitus can affect both normal hearing and hearing impaired patients, the audiometric criteria will be inclusive of both. In order to be a candidate, the patient must have a history of chronic tinnitus lasting 6 months or longer. Although it has been established that tinnitus symptoms are heterogeneous in presentation and percept, the research will be inclusive of the following percepts: “ringing,” “buzzing,” “hissing,” “crickets,” “roaring.” The patient must be taking the nutraceutical formulation for 3 months or longer, as recommended. The dosing schedule is specific and imperative to follow; therefore, patients who have not taken two pills, twice daily, will be excluded. Appendix 1 is a checklist for use by the clinician to abide by the inclusion/exclusion criteria.

Exclusion criteria will include any patients younger than 18 years old. A tinnitus described as "pulsatile" or "clicking" will be excluded. Additionally, any previous or current use of tinnitus treatment, including, but not limited to, antioxidants, antidepressants, melatonin, TRT or CBT, will be cause for exclusion. The patient must also complete the informed consent form, if the patient refuses, s/he will be excluded from the study.

Further audiologic exclusion criteria include abnormal otoscopic evaluation, including perforated tympanic membrane or a mass observed through the tympanic membrane. Patients with active middle ear disease or conductive hearing loss are excluded, including abnormal tympanograms classified as Type B, meaning no peak due to perforation, effusion, or otherwise. Additionally, any confirmed retrocochlear pathology (e.g. acoustic neuroma) or diagnosis of Meniere's Disease will be cause for exclusion. Lastly, any treatment with aminoglycoside antibiotics, platinum-based chemotherapy, quinine, or otherwise ototoxic medication will lead to exclusion from the study. As seen in Baguley, McFerran, and Hall (2013), the above mentioned otologic findings can be accompanied by tinnitus, which may or may not resolve with treatment. A patient with impacted cerumen upon otoscopy will be excluded from the study if the tinnitus resolves after cerumen removal, otherwise they will be included. Patients with any of the above will be excluded from the current study to minimize confounding factors.

After approval by the International Review Board (IRB) at the City University of New York (CUNY), the pharmacist employed at the International Hearing Centre in Lagos, Nigeria indicated to the researchers a lack of consistent charting for the NH tinnitus patients. The redacted charts received by the researchers included audiograms, general case history forms, and a formal report by the lead audiologist. However, a majority of the charts did not include a pre-administration tinnitus questionnaire or any follow-up visit questionnaires. Due to the

inconsistent charting and lack of protocol for tinnitus patient charts, this Capstone project will propose an evidence-based guideline for audiologists and pharmacists to follow at the IHC, as well as, for future use by clinicians and healthcare professionals involved with the administration of the NH nutraceutical formulation.

The case history form (Appendix 2) to be used for future patients to whom the NH formula will be administered must contain the following information, suggested by the American Speech-Language-Hearing Association (n.d.), completed by the Audiologist and patient at the initial visit:

- Tinnitus description -- the patient will be asked to describe their tinnitus in the following ways:
    - Presentation - referring to a description such as a ring, buzz, click, hiss, heartbeat, chirp, or any other sound it may be akin to.
    - Onset and duration of the tinnitus
    - Pitch - patient may describe as high- or low-pitch, or relate it to a household sound
    - Loudness - patient can confirm if the tinnitus is louder than conversation, noticed only in the quiet of the home, or otherwise
    - Maskability – an account of any sounds or activities that dampen the tinnitus
- Medical history – other diagnoses and lab results from other health professionals
- Provoking and alleviating factors for tinnitus percept
- History of noise exposure or trauma
- Otologic or vestibular issues

- Other concerns including anxiety and depression - A patient scoring greater than 36 on the THI will be administered the Beck Anxiety Inventory (BAI) -- a 21-item questionnaire used in the clinical setting to measure anxiety levels in adolescents and adults. A score ≥ 16 on the BAI signifies a moderate level of anxiety or greater and will lead to referral to a medical professional, i.e. psychiatrist or clinical psychologist (Grant, 2011; Biesinger et al. 2011). Salviati et al. (2013) determined a score greater than 36 points on the THI was correlated with a psychiatric disorder in tinnitus patients. Almost half of the tinnitus patients in their study were found to have either anxiety disorder, adjustment disorder, bipolar disorder, or other mental health disorders (Salviati et al., 2013).

At the initial visit, audiometric data must include the following objective and subjective test measures:

- **Pure tone air conduction thresholds: Octave frequencies 250-8000Hz and interoctave frequencies 3000 and 6000Hz.** Langguth et al. (2007) state pure tone audiometry up to 8kHz is necessary for all patients, with recommendations of high frequency audiometry (HFA) thresholds up to 12kHz. In studies of noise induced hearing loss, the highest percentage of hearing loss is present between 3000 and 8000 Hz, including 6000Hz (Hwang et al., 2009). For this reason, 3000 and 6000 Hz will be included in audiologic assessment, due to the close link between noise exposure, hearing loss, and tinnitus. Interoctave frequencies between 500 and 2000Hz will be assessed only if a difference of 20dB or more is present between adjacent frequencies (Schlauch and Nelson, 2009). The IHC does not have the equipment necessary to perform high

frequency audiometry, therefore, HFA will not be part of the recommended audiologic evaluation.

- **Pure tone bone conduction thresholds: Octave frequencies 500-4000Hz** - unmasked bone conduction thresholds will be measured at the four octave frequencies between .5-4kHz. An air-bone gap of more than 10dB will require masking to determine the nature of the hearing loss (Schlauch and Nelson, 2009).
- **Immittance results**: Rosowski and Wilber (2015) recommend 226 Hz tympanograms as determined by the ANSI S3.36 standard; ipsilateral and contralateral acoustic reflex thresholds (ARTs) measured at 500, 1000, and 2000 Hz in 5 dB steps with a 0.02 mmho stimulus-related immittance change [4000 Hz will not be assessed as ARTs at this frequency are often elevated (Gelfand, 2009)]; and reflex decay measured at 500Hz for 10 seconds at 10dB SL above the ART in the contralateral stimulus mode (Gelfand, 2009).
- **Distortion product otoacoustic emissions results - 1.5-12kHz** - Langguth et al. (2007) recommend OAEs as part of the audiologic assessment. Since HFA is not possible at IHC, DPOAE results up to 12kHz will be implemented as part of the proposed protocol to assess cochlear outer hair cell function in the ultra-high frequencies.

The audiological evaluation will be completed at 6-months and 1-year post-initial administration of the NH formula to measure stability of hearing levels. Any significant decreases in auditory thresholds (15 dB HL or more) will result in temporary cessation of the NH formula, until medically cleared by an otolaryngologist. Haase et al. (2011) report the formulation to have neuroprotective properties, and deny any adverse side effects due to toxicity. The NH formula, as mentioned, has a specified dosing schedule meant to maintain antioxidant levels in the blood

at safe levels. As in other research of ototoxic medications, cessation of therapy is indicated if significant health changes occur (e.g. changes in hearing), therefore, the recommendation for the clinical protocol at the IHC is to regularly monitor hearing thresholds and to stop use of the nutraceutical if any significant changes are noted (Wilcox and Artz, 2007).

The Tinnitus Handicap Inventory (THI), seen in Appendix 3, must be filled out by the patient at the first visit to determine the severity of tinnitus. Additional questions that may be included for informational purposes will be answered with yes, sometimes, or no. The final question will be answered with a percentage score. See the following:

- My tinnitus has led me to avoid social situations (Wilson et al., 1991)
- My tinnitus has led me to think about suicide (Wilson et al., 1991)
- My tinnitus contributes to a feeling of general ill health (Kuk et al., 1990)
- I have a healthy outlook on tinnitus (Kuk et al., 1990)
- I have support from my friends and family regarding my tinnitus (Kuk et al., 1990)
- What percentage of your time awake were you consciously aware of your tinnitus? (Meikle et al., 2012)

The THI and additional questions will then be re-administered at the 3-month, 6-month, 9-month and 1-year follow up visits. In other studies of antioxidant usage for treatment and maintenance of disease, researchers followed up with patients every three months to monitor status. For example, Gutzmann and Hadler (1998) and Weyer et al. (1997) followed patients with Alzheimer's Disease for two years with follow up visits every 3 months to reassess results on the Alzheimer's Disease Assessment Scale (ADAS), the Mini-Mental State Evaluation (MMSE) and the Digit Symbol Substitution Test (DSS).

RESULTS

Pre-treatment and 1-year post-treatment audiologic results will be compared in a table including pure tone audiometric thresholds, distortion product otoacoustic emission results, tympanometry and acoustic reflex testing. It is important to note, although the patient will have had an audiologic evaluation at the 6-month interval, post-treatment, the results section will only assess the 1-year post-treatment results. The purpose of the research is to assess the clinical implications of the NH formula on tinnitus perception. Audiologic evaluations at 6-month intervals are explicitly for monitoring hearing status in patients taking the formula. As previously indicated in ototoxic drug administration research, it is important to monitor stability of auditory thresholds and cease therapy if adverse health changes occur (Wilcox and Artz, 2007). Here, any significant decrease in auditory thresholds of 15 dB HL or more will be cause for temporary cessation of antioxidant therapy until medically cleared by an otolaryngologist.

The primary outcome measure will be the THI, which will be administered at 3-month intervals. The THI score will be compared to the baseline, pre-treatment score at each interval. The use of pre-administration and post-administration questionnaires allows for each patient to serve as their own control. The hypothesized expectation is a statistically significant improvement in THI score and subjective improvement in tinnitus percept to the patient after 1-year of NH administration. The null hypothesis is no improvement in THI score or subjective improvement after 1-year NH administration. The research will aim to assess if the results at 3-, 6-, 9-months, and 1-year post-administration have a cumulative effect, suggesting the percept continues to decrease in severity to the patient; or if there is a ceiling effect to the treatment that will plateau at a point in time.

Statistical analysis will be used to determine any differences in pre- and post-administration THI scores. Clinical significance, as discovered by Zeman et al., is defined as a change in the THI of 7 points or greater (2011). For comparison of serial measurements, i.e. before and after, within patients, the non-parametric Wilcoxon Signed Ranks Test will be used. Statistical significance will be defined as a p-value ≤ 0.05.

The research outcomes will also be analyzed for any significant differences between subjects. Of particular interest could be age, gender, or description of tinnitus percept. To assess any between-subjects results, the researchers would use an independent samples / unpaired t-test. Age may be divided into an older and younger group in order to make the analysis. These groups may be determined once participants have been identified. The tinnitus percepts, too, may be separated into groups dependent on patient reports. Statistical significance, again, will be determined with a p-value ≤ 0.05.

DISCUSSION

Implementing a clinical protocol for dispensing the NH formulation to patients reporting subjective tinnitus is necessary to provide an evidence-based guideline for clinicians at the IHC. Such guidelines could serve to improve patient care and create a uniform evaluation of tinnitus patients. The anecdotal reports of clinicians and pharmacists at the IHC indicate subjective improvement in tinnitus severity for patients suffering from tinnitus. A mandated clinical protocol will allow patients to receive the same standard of care, as well as allow researchers to quantitatively assess this particular management strategy. The present research evaluated a systematic review of clinical practice guidelines for Denmark, Germany, the Netherlands, Sweden, and the United States "Different teams, same conclusions," "Clinical practice guideline for diagnosis and treatment of chronic tinnitus in Japan," and "Clinical practice guideline: Tinnitus," (Fuller et al., 2017; Ogawa et al., 2020; Tunkel et al., 2014). Additionally, the Tinnitus Research Initiative lends a flowchart for patient management to be implemented on an international level (Biesinger, 2011). Across the diverse guidelines, the most common recommendations were highlighted in this project: a comprehensive evaluation including pure tone air and bone audiometry, acoustic reflex thresholds and reflex decay, speech reception thresholds, word recognition scores, and tympanometry; a complete case history to determine onset and duration of tinnitus, description of tinnitus percept, how bothersome it is to the patient, and the ability to mask the tinnitus; a completed Tinnitus Handicap Inventory and Beck Anxiety Inventory (if indicated); and evaluation by an otolaryngologist if case history or audiological evaluation indicate.

According to Murad (2017), clinical practice guidelines can assist clinicians in making appropriate decisions in regards to patient assessment and management. One of the most

important benefits of using systematically reviewed guidelines, such as the "Clinical practice guideline: Tinnitus," is improved patient care. Murad reports guidelines aim to encourage proven interventions and discourage ineffective ones, thereby improving quality of care (2017). He further posits guidelines can lessen disparities and reduce unnecessary variations in care. It is important to recall the heterogeneity in chronic tinnitus patients. Clinical practice guidelines help to introduce an evidence-based standard of care across the field created by professionals who have considered the benefits and risks of diagnostic measures and management techniques. Therefore, the protocol proposed to the IHC for use with their tinnitus patients is meant to create a consistent level of quality care by the healthcare professionals. The protocol aims to implement consistent charting efforts to aid in differential diagnosis and outcome measurement. For instance, the current charting contained incomplete tinnitus questionnaires and scant case history responses. With the complete aforementioned information, the current study could have analyzed the tinnitus questionnaires pre- and post-administration of the NH nutraceutical to investigate if the anecdotal reports of patients and clinicians equated to clinically significant improvements. Although the consensus across published clinical practice guidelines is negative toward dietary supplements and nutraceutical formulations, Woolf et al. (1999) reminds us of some limitations to guidelines. They suggest only a small number of studies are well-designed with good generalizability. The evidence is sometimes lacking or misinterpreted. Therefore, and perhaps ironically, it is imminent the IHC implements consistent charting so research may analyze the outcomes of the NH nutraceutical and its seemingly positive effects on chronic tinnitus patients.

Research indicates positive outcomes in tinnitus resolution when the primary disease is treated. For instance, in cases of tinnitus secondary to cerumen impaction, otitis media, or

temporomandibular joint disorder, removal of cerumen, antibiotics, or neuromuscular splints have shown improvement in subjective tinnitus, respectively (Attanasio et al., 2015; Baguley et al., 2013). However, in cases of acoustic neuroma patients, subjective tinnitus improved in 16% of patients and worsened in 29% of patients after resection of the tumor (Fahy et al., 2002). Additionally, tinnitus symptoms secondary to ototoxic drug administration have been shown to reduce in severity with drug cessation (Attanasio et al., 2015). The current study aims to implement clinical practice guidelines at the IHC, where health professionals have taken a therapeutic approach to tinnitus with uncertain etiology. Elgoyhen and Langguth (2011) mention, there is an unmet need for a drug therapy aiming to eliminate, or at the very least, to produce a small, but significant change to the tinnitus percept. The NH formula, described by Haase et al. (2011) as the HH formula, provides a broad spectrum of antioxidants and their derivatives combined to impact oxidative damage and inflammation and to provide neuroprotection in hearing disorders. Previous research of antioxidants and tinnitus has revealed contradictory findings. As previously reviewed, the most efficacious pharmacotherapies, thus far, have been those combating comorbidities such as insomnia, depression, and anxiety. Here, the NH formula incorporates a comprehensive, multiple micronutrient strategy, rather than the single, limited combination approaches used in the past. Therefore, controlled clinical research must be completed to investigate the proposed benefits of the NH formula. Furthermore, a complete, clinical protocol needs to be implemented to allow for this research. The implications of positive findings secondary to the proper use of the NH formula are tinnitus relief for sufferers of chronic tinnitus and limited side effects. Some previous drug therapies that have had adverse side effects include: anti-epileptic drugs, benzodiazepines, intratympanic gentamicin and steroid injections, lidocaine, and vasodilators (Smith, Zheng & Darlington, 2005). Additionally, *Ginkgo*

biloba, particularly when taken with drugs like aspirin, can increase the risk of bleeding due to its vasodilatory effects (Smith, Zheng & Darlington, 2005). Haase et al. (2011) reviewed the dosage of the ingredients in the NH, formerly HH, formula. Toxicity was reported in Vitamins A and D and the mineral selenium at high doses; however, the dosage in the NH formula is below levels associated with adverse side effects. The remaining ingredients are all considered to be non-toxic (Haase et al., 2011). Thus, the nutraceutical formulation has the ability to be a positive incorporation into the tinnitus management portfolio for clinicians. The benefits outweigh the risks of the NH formula and as Elgoyhen and Langguth (2010) mention, patients are desperate for a drug therapy that could reduce or completely stop this subjective sound.

This desperation has led patients to search tirelessly for treatments, both medicinal and behavioral, that can help alleviate the negative associations brought on by the tinnitus. According to the IHC in Lagos, Nigeria, patients have reported subjective benefit to tinnitus perception associated with taking the NH formula. This has placed a high demand on the nutraceutical. Even though the nutraceutical sells for 14,000 Naira (N14,000), patients will come from distant states or neighboring countries, as far as eighteen hours' drive, to acquire the formulation (I. Okeke, personal communication, January 20, 2020). This amounts to about $40 according to the most current exchange rates (XE Currency Converter, 2020). However, it does not take into account the cost of living and salary differential between the United States and Nigeria. The average Nigerian monthly salary, according to Trading Economics (2018) is about N43,000, while the average American monthly salary is about $3600, according to the Bureau of Labor Statistics (2020). Therefore, if one bottle of NH costs N14,000, this is about ⅓ of the average Nigerian's monthly salary, which then amounts to almost $1200, ⅓ of the average American's salary, for one bottle, or one month's supply. The distance traveled and the cost

paid, in tandem, lend themselves as strong indicators that this nutraceutical is helping patients to deal with a chronic problem. Unfortunately, there is no health insurance system in place that covers the cost of a supplement such as NH, nor does one exist that covers the cost of diagnostic evaluations.

There is currently a dysfunctional health insurance system in Nigeria called the Nigerian Health Insurance Scheme (NHIS). Created about 10 years ago, the NHIS attempted to provide prepayment plans to Nigerian citizens (Nsofor, 2018). According to Okpani and Abimbola (2015), only about 5% of Nigerians have prepaid healthcare through social and voluntary private insurance; an additional 20% of Nigerians receive healthcare through the federal government if they are federal employees or the family members of federal employees; and the remaining 70% of Nigerians are uninsured and pay out of pocket for healthcare. They further explain: public sector healthcare facilities in Nigeria are located in each of the 36 states and are considered not-for-profit organizations. Even though the cost is significantly less than private sector facilities, Okpani and Abimbola note a perception of poorer quality care in the public sector facilities (2015). The IHC is considered part of the private sector health facilities and sees a majority of its patients paying out of pocket. The cost, according to Dr. Okeke, founder and lead audiologist at the IHC, for a basic hearing evaluation including pure tone air conduction and bone conduction thresholds, speech reception thresholds, word recognition scores, and tympanometry including acoustic reflex thresholds, is N14,000 (I. Okeke, personal communication, January 20, 2020).

The IHC and other healthcare facilities and practitioners are regulated by the Nigerian government. Okpani and Abimbola (2015) explain the structure and responsibilities of the government as it pertains to healthcare and pharmaceuticals. The government is separated into

three branches: federal, state, and local. Of note, the federal government provides support to state and local government on health program planning and implementation, health policy making and priority setting, and setting minimum standards for training and licensing of health workers. The Federal Ministry of Health (FMOH) notably regulates activities of healthcare practitioner groups and regulates pharmaceutical and food products. The NHIS, an agency of the FMOH, regulates healthcare and accredits HMOs.

A separate entity from the federal government is the National Agency for Food and Drug Administration and Control (NAFDAC). The NAFDAC, similar to the United States Food and Drug Administration (FDA), imposes guidelines on food, drugs, medical devices, herbals and cosmetics, among other items (NAFDAC, 2016). According to Dr. Okeke, the registration process for proper licensing and distribution of the NH nutraceutical formulation requires compliance with several directives: evidence and scientific studies of NH, inspection of the manufacturer's location, and presence of a superintendent pharmacist for dispensation of the nutraceutical (I. Okeke, personal communication, January 20, 2020). The professional role of pharmacists in Nigeria has evolved from a focus on preparation, dispensing, and sale of medications to one where the pharmacists are present to assist the public in education and patient monitoring for the best possible results (Erah, 2003). Therefore, the role of the pharmacist at the IHC helps to ensure proper protocol in dispensing the NH formula for all patients seen. The above evidence of patients traveling from afar and paying up to ⅓ their salary to obtain the NH nutraceutical is important to remember when considering perceived benefit from the formula. It appears there is a benefit that far outweighs the cost and accessibility.

A recent randomized, single-blind clinical trial by Petridou et al. (2019) assessed the use of antioxidant supplementation in a group of chronic tinnitus sufferers compared to matched

placebo controls in Greece. Although the authors do not name the supplement, the ingredient list, found in Appendix 4, is very similar to that of NH. The study added a supplement of alpha-lipoic acid (ALA) to participants' daily intake, which is also found in the proprietary formula of NH. Participants were followed for three months, assessing pre-treatment and post-treatment results on pure tone audiometry 250-12,000Hz, pitch and loudness psychoacoustic matching measurements, and three questionnaires: THI, Tinnitus Functional Index (TFI), and the visual analogue scale (VAS) for tinnitus disturbance. After three months, the antioxidant group was found to have significantly lower scores on THI, VAS, and TFI compared to the placebo group. This, the authors suggest, means the antioxidant supplementation was effective in alleviating patients from tinnitus-related distress compared to the placebo group. It is promising to see a formula with a similar list of ingredients has proven effective in a well-designed clinical trial.

In October 2019, a press release from New Age Beverages Corporation announced the launch of the NH formula in Japan, following a test-market release in Korea (New Age Beverages Corporation, 2019). It appears Japan does have a regulatory body, similar to the U.S. FDA, called the Pharmaceutical and Food Safety Bureau (PFSB), which is part of the larger Ministry of Health and Welfare (MHW) (Nagata & Rafizadeh-Kabe, 2002). The PFSB, according to Nagata and Rafizadeh-Kabe, is responsible for approval review and regulation and decision-making for the MHW (2002). On the report of the authors, western medicines are seen as potentially dangerous by the Japanese public. This indicates there may be some positive outcomes derived in clinical trials that have encouraged the public to adopt the NH formula for tinnitus management.

For patients suffering from bothersome, chronic tinnitus, a combination of the NH antioxidant nutraceutical with another form of therapy may also prove efficacious. For example,

the addition of tinnitus retraining therapy may help to combine a central auditory therapy with the peripheral auditory therapy of the nutraceutical. Of the many theories surrounding the pathophysiology of tinnitus, one that has continued to be particularly interesting is the involvement of the limbic system. Rather than a peripheral auditory system dysfunction, limbic system involvement proposes central dysfunction. Michel et al. (2015) suggest the limbic system has an important role in learning and memory function, as well as generation, integration, and control of emotions and behavioral responses. It seems reasonable that a system involved with behavioral responses has an effect on a patient's awareness and disturbance by this phantom auditory percept. Michel et al. explain further the dysfunction of the limbic regions are implicated in etiology of mental disorders like anxiety and depression (2015). The link between chronic tinnitus and anxiety or depressive symptoms has been repeatedly investigated, and in their 2018 systematic review and meta-analysis, Trevis, McLachlan, and Wilson found 64% and 62% of studies investigating depression and anxiety showed a significant increase in depressive or anxiety symptoms in chronic tinnitus sufferers compared to healthy controls, respectively. Consequently, a positive association between limbic system dysfunction and chronic tinnitus may be present. This migrates the focus away from a wholly peripheral auditory dysfunction and allows the introduction of central factors.

Other studies of limbic system involvement in chronic tinnitus examined brain imaging in tinnitus patients and healthy controls. Leaver et al. (2012) discovered reduced grey matter volume in the ventromedial prefrontal cortex (vmPFC), which has also been linked to depression and anxiety. They suggest this causes a failure to suppress aberrant activity in the auditory system. Additionally, Besteher et al. (2019) report grey matter alterations in tinnitus patients are highly influenced by comorbid psychiatric disorders. They implicate the parahippocampal

cortex in memory mechanisms related to phantom percept persistence. A 2011 study by Leaver et al. also found robust differences between chronic tinnitus patients and healthy controls in limbic areas. Specifically, they point to reduced grey matter volume in the vmPFC and hyperactivity in the nucleus accumbens (NAc). They suggest chronic tinnitus is caused by a compromised limbic corticostriatal circuit. This lends itself to a "disordered evaluation of the tinnitus sensation's perceptual relevance and an increased gain control of the percept" (p. 37). In other words, the dysfunctional system has difficulty determining which sensations are important and how they are experienced, making the sound perhaps perceptually louder than if measured in decibels.

Jastreboff and Jastreboff (2001) indicate TRT avoids further excitation of the limbic system to prevent changing the tinnitus signal. The aim is not to mask the signal, but rather to allow the patient to habituate. They further suggest a sound therapy that enhances the activation of the limbic system will enhance the tinnitus annoyance. TRT combines interactive teaching and counseling sessions with sound use that is significantly above the threshold of tinnitus perception. In the case of introducing a nutraceutical formulation, the percept, in theory, will gradually decrease as the patient follows the proper dosing schedule. TRT will continue to use sound that limits activation of the limbic system, but the threshold above tinnitus perception will, again in theory, decrease as the peripheral and central auditory systems improve.

CONCLUSION

Initially this project sought to investigate patient records from the International Hearing Centre in Lagos, Nigeria after learning patients reported subjective improvement in bothersome tinnitus. Incomplete charting transformed this research into a review of clinical practice guidelines for diagnostic evaluation and suggested timelines for assessing subjective validation measures of change to the tinnitus, i.e. the Tinnitus Handicap Inventory. The goal of this project is to implement an evidence-based clinical protocol at the IHC to standardize patient care in order to evaluate and statistically analyze the efficacy of the NH formulation on subjective tinnitus sufferers in the future. Future research can use this project as a template to assess changes to tinnitus percept in patients taking the NH formulation.

Appendix 1
Inclusion/Exclusion Checklist
For use by the clinician

Characteristics	**Responses**	**Necessary Response for Inclusion**
18 years of age or older	YES/NO	YES
Chronic tinnitus for 6 months or more	YES/NO	YES
Pulsatile or clicking tinnitus?	YES/NO	NO
Taken NH for 3 months or more?	YES/NO	YES
Current or previous use of other tinnitus treatment?	YES/NO	NO
Tinnitus resolved after cerumen removal?	YES/NO	NO
Perforated tympanic membrane?	YES/NO	NO
Mass observed behind the tympanic membrane?	YES/NO	NO
Type B tympanograms?	YES/NO	NO
Conductive hearing loss or active middle ear disease?	YES/NO	NO
Retrocochlear pathology?	YES/NO	NO
Meniere's Disease?	YES/NO	NO
Use of ototoxic medications?	YES/NO	NO

Appendix 2
Case History Form

Age _____
Gender _____
Occupation _____

Medical History (mark "X" to all that apply)
___Diabetes
___Hypertension
___Cancer (if yes, please specify _____)
___Chemotherapy
___Temporomandibular Disorder (TMJ)
___Ear surgery
___Heart problems (please specify _____)
___Kidney disease
___Thyroid disorder
___Autoimmune disease
___HIV/AIDS
___Head or neck trauma
___Depression, anxiety, sleep disorder
___Other (please specify _____)

Please list all medications you are currently taking:
_____
_____
_____

Any history of recreational or occupational noise exposure?
_____
_____

Any history of hearing loss, ear issues, or vestibular/balance disorder?
_____

Tinnitus History

1. What does it sound like? (e.g. buzz, click, ring, hiss, chirp, other) _____
2. When did it begin? _____
3. How often does it occur? (e.g. intermittent, constant) _____
4. What pitch is the tinnitus? (e.g. high, low, mid) _____
5. How loud is the tinnitus? (e.g. louder than conversation, only in quiet, other)_____
   _____
6. Do any sounds effectively mask the tinnitus? _____
7. Does anything provoke or exacerbate the tinnitus? _____
   _____

8. Does anything alleviate the tinnitus? _____
9. Does the tinnitus stop you from performing daily activities? _____

Answer the following questions with yes, sometimes, or no:

1. My tinnitus has led me to avoid social situations _____
2. My tinnitus has led me to think about suicide _____
3. My tinnitus contributes to a feeling of general ill health _____
4. I have a healthy outlook on tinnitus _____
5. I have support from my friends and family regarding my tinnitus _____

What percentage of your time awake are you consciously aware of your tinnitus? _____

Appendix 3
Tinnitus Handicap Inventory (Newman et al., 1996)

1. Because of your tinnitus, is it difficult for you to concentrate? Yes (4) Sometimes (2) No (0)
2. Does the loudness of your tinnitus make it difficult for you to hear people? Yes (4) Sometimes (2) No (0)
3. Does your tinnitus make you angry? Yes (4) Sometimes (2) No (0)
4. Does your tinnitus make you feel confused? Yes (4) Sometimes (2) No (0)
5. Because of your tinnitus, do you feel desperate? Yes (4) Sometimes (2) No (0)
6. Do you complain a great deal about your tinnitus? Yes (4) Sometimes (2) No (0)
7. Because of your tinnitus, do you have trouble falling asleep at night? Yes (4) Sometimes (2) No (0)
8. Do you feel as though you cannot escape your tinnitus? Yes (4) Sometimes (2) No (0)
9. Does your tinnitus interfere with your ability to enjoy your social activities (such as going out to dinner, to the movies)? Yes (4) Sometimes (2) No (0)
10. Because of your tinnitus, do you feel frustrated? Yes (4) Sometimes (2) No (0)
11. Because of your tinnitus, do you feel that you have a terrible disease? Yes (4) Sometimes (2) No (0)
12. Does your tinnitus make it difficult for you to enjoy life? Yes (4) Sometimes (2) No (0)
13. Does your tinnitus interfere with your job or household responsibilities? Yes (4) Sometimes (2) No (0)
14. Because of your tinnitus, do you find that you are often irritable? Yes (4) Sometimes (2) No (0)
15. Because of your tinnitus, is it difficult for you to read? Yes (4) Sometimes (2) No (0)
16. Does your tinnitus make you upset? Yes (4) Sometimes (2) No (0)
17. Do you feel that your tinnitus problem has placed stress on your relationships with members of your family and friends? Yes (4) Sometimes (2) No (0)
18. Do you find it difficult to focus your attention away from your tinnitus and on other things? Yes (4) Sometimes (2) No (0)
19. Do you feel that you have no control over your tinnitus? Yes (4) Sometimes (2) No (0)
20. Because of your tinnitus, do you often feel tired? Yes (4) Sometimes (2) No (0)
21. Because of your tinnitus, do you feel depressed? Yes (4) Sometimes (2) No (0)
22. Does your tinnitus make you feel anxious? Yes (4) Sometimes (2) No (0)
23. Do you feel that you can no longer cope with your tinnitus? Yes (4) Sometimes (2) No (0)
24. Does your tinnitus get worse when you are under stress? Yes (4) Sometimes (2) No (0)
25. Does your tinnitus make you feel insecure? Yes (4) Sometimes (2) No (0)

The sum of all responses is your THI Score _____
0-16 points – Slight or no handicap
18-36 points – Mild handicap
38-56 points – Moderate handicap
58-76 points – Severe handicap
78-100 points – Catastrophic handicap

Appendix 4
Petridou et al (2019) Antioxidant Ingredients

Ingredient	**Amount Per Serving**	**% Daily Value**	**Difference**
Vitamin A	2600 IU	98%	~ half less than NH
Vitamin C	150 mg	188%	100mg less
Vitamin D_3	400 IU	200%	*Vitamin D in NH
Vitamin E	150 IU	833%	50IU less
Thiamin	25 mg	2272%	5x as much
Riboflavin	25 mg	1786%	5x as much
Niacin	25 mg	156%	Same
Vitamin B_6	10 mg	714%	2x as much
Folic Acid	200 mcg	100%	Same
Vitamin B_{12}	10 mcg	400%	Same
Biotin	150 mcg	300%	About half as much
Pantothenic Acid	25 mg	417%	2x as much
Calcium	62 mg	8%	Same
Iron	14mg	100%	Not found in NH
Magnesium	50 mg	13%	About half as much
Zinc	15 mg	150%	Same
Selenium	100 mcg	200%	Same
Chromium	200 mcg	500%	Almost 4x as much
Molybdenum	500 mcg	1000%	Not found in NH
Iodine	150 mcg	100%	Not found in NH
Choline, Inositol, PABA	25mg each	Not specified	Not found in NH
Grapeseed extract	500 mg	Not specified	Not found in NH

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