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# **CRS** SCIENTIFIC JOURNAL Otology & Audiology Article Review

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Alterations in regional homogeneity in patients with unilateral chronic tinnitus Comparison of satisfaction between patients using percutaneous and transcutaneous bone conduction devices Hearing protection, restoration, and regeneration: an overview

# CONTENT

- TINNITUS SEVERITY CHANGE FOLLOWING STAPEDOTOMY IN PATIENTS WITH OTOSCLEROSIS Dziendziel B., Skarżyński H., Gos E. & Skarżyński P. Otology & Neurotology (2019): 40(5), 578-83. 41 ALTERATIONS IN REGIONAL HOMOGENEITY IN PATIENTS WITH UNILATERAL CHRONIC TINNITUS Gentil A., Deverdun J., Menjot de Champfleur N., et al. Trends in Hearing (2019): 23, 1-12. 42 TRACKING OF NOISE TOLERANCE TO PREDICT HEARING AID
- SATISFACTION IN LOUD NOISY ENVIRONMENTS Seper E., Kuk F., Korhonen P. & Slugocki C. J. Am. Acad. Audiol. (2019): 30, 302-14.
- ΔΔ COMPARISON OF SATISFACTION BETWEEN PATIENTS USING PERCUTANEOUS AND TRANSCUTANEOUS BONE CONDUCTION DEVICES

Svagan M., Povalej Brzan P. & Rebol J. Otology & Neurotology (2019): Vol. 40(5), 651-57.

- 45 SENSORINEURAL HEARING LOSS AND VOLATILE ORGANIC COMPOUND METABOLITES IN URINE Pudrith C. & Dudle WN. Am j Otolaryngol (2019): 40, 409-12.
- 46 MALFORMATIONS OF THE LATERAL SEMICIRCULAR CANAL CORRELATED WITH DATA FROM THE AUDIOGRAM Venkatasamy A., Le Foll D., Eyermann C., et al. European Archives of Oto-Rhino-Laryngology (2019): 276, 1029-34.
- 47 AUDIOLOGICAL EVALUATION OF INFANTS USING MOTHER'S VOICE Saito O., Nishimura T., Morimoto C., et al.

International Journal of Pediatric Otorhinolaryngology (2019): 121, 81-7.

48 THE CLINICAL OUTCOMES AFTER INTRATYMPANIC GENTAMICIN INJECTION TO TREAT MENIERE'S DISEASE: A **META-ANALYSIS** 

> Zhang Y., Fu J., Lin H., et al. Otology & Neurotology, 2019: 40(4), 419-29.

49 HEARING PROTECTION, RESTORATION, AND REGENERATION: AN OVERVIEW OF EMERGING THERAPEUTICS FOR INNER EAR AND CENTRAL HEARING DISORDERS

Schilder AGM., Su PM., Blackshaw H., et al. Otology & Neurotology (2019): 40(5), 559-70.

51 CHARACTERISTICS OF MID-FREQUENCY SENSORINEURAL **HEARING LOSS PROGRESSION** 

Birkenbeuel J., Abouzari M., Goshtasbi K., et al. Otology & Neurotology (2019): 40(5), e497-e502.

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# **EDITORIAL**



#### WARM WELCOME TO READERS OF THE CRS SCIENTIFIC JOURNAL!

am Reddy Sivaprasad, Head of training and clinical development at Amplifon India. Even as a student I always felt a strong interest for audiology and ENT journals, and I used to spend a great deal of time reading them. For me, the CRS journal offers a unique blend of audiology and ENT topics. It provides much needed updates and continues to advance our field thanks to the fine analyses its editors provide in their critical notes of these readings. I personally love being able to contribute to this fabulous journal, and the platform it has given me for sharing my own observations.

This CRS issue lays out a feast of ten reviews of articles relevant to our clinical work and published in leading peer-reviewed journals. Among the articles presented in this issue, I would like to mention the following:

A comprehensive review providing a unique directory of therapeutics for hearing protection, restoration and regeneration. Clinicians may only have a vague idea on this topic. This article provides a solid understanding of how to view emerging therapeutics, the progress achieved thus far and on what fronts.

Another unique article provides extensive data on new volatile organic compounds, detectable in urine samples, found in people with hearing loss but not exposed to noise. The authors found that a subgroup called mercapturic acids, when present at higher levels, was shown to be associated with 3-4 dB higher thresholds.

On another topic, one of the articles highlights that the lateral semicircular canals, which are part of the vestibular system, presented malformation in 61% of the subjects with childhood/congenital hearing loss of any type.

Also worthy of note are the great efforts of Francis Kuk and his team in developing an adaptive tracking test for noise tolerance which can be useful in predicted hearing aid success/satisfaction even before a hearing aid fitting.

These are just some of the gems we have picked for you. They are sure, as always, to tease your curiosity and advance your audiology knowledge. Happy reading!

Dr Reddy Sivaprasad, Head – Training & Clinical Development Amplifon India





### TINNITUS SEVERITY CHANGE FOLLOWING STAPEDOTOMY IN PATIENTS WITH OTOSCLEROSIS



Dziendziel B., Skarżyński H., Gos E. & Skarżyński P. Otology & Neurotology (2019): 40(5), 578-83. By Mark Laureyns Italy / Belgium The study shows that stapedotomy does not only improve hearing in subjects with otosclerosis, but also reduces the severity of tinnitus, particularly when the pre-operative tinnitus is classified moderate or severe.

Stapedotomy is one of the most frequently-used surgical procedures to improve hearing in Otosclerosis. This study evaluates the impact of stapes surgery on tinnitus severity in subjects with otosclerosis and chronic tinnitus.

#### • SUBJECTS

In total 389 adult subjects underwent stapedotomy, of whom 248 (64%) reported chronic tinnitus. Of these, 187 subjects returned the Tinnitus Functional Index questionnaires (TFI) correctly completed, 19 of whom had to be excluded since they had undergone surgery on the contralateral ear before the end of the study. This left 168 subjects (74% female/26% male), with an average age at surgery of 49 (SD 12y). 67% had bilateral hearing loss, 55% had bilateral tinnitus, and an average duration of hearing loss of ten years (SD 8y) and average duration of tinnitus of seven years (SD 6y).

#### • METHOD

All subjects underwent stapedotomy. Hearing loss was measured for both air and bone conduction pre- and six months post-surgery. In addition, patients were required to fill in the Tinnitus Functional Index questionnaire (TFI) and the Tinnitus Classification Questionnaire (Meikle *et al.*), where tinnitus is classified in five levels (No-, Small-, Moderate-, Big-, Very Big- problem) pre-, three months post- and six months post-surgery.

#### • RESULTS

Audiometric results.

132 subjects were evaluated after six months (34 failed to attend their follow-up for audiometry).

The average air conduction hearing loss (average HL at 500, 1000, 2000 and 4000Hz) was 59 dB (HL) pre- and 37 dB (HL) post-surgery, the average improvement was 22 dB (p < 0.001).

The average bone conduction hearing loss was 27dB (HL) pre- and 25dB (HL) post-surgery.

#### • TFI RESULTS

168 subjects were evaluated.

The average TFI score was 35 pre- and 18 post-surgery (three-month survey). This change was significant (p<0.001) There was no significant difference between the threeand six- month post-surgery TFI score.

There was a weak positive correlation between the amount of TFI improvement and the change in the air-conduction threshold improvement pre- versus six- months post-surgery (r=0.2/ p=0.01).







#### • TINNITUS CLASSIFICATION RESULTS

55% reported improvement; 38% reported no change; 7% reported more problems.

#### • CONCLUSIONS

The authors conclude that stapedotomy not only improves hearing in subjects with otosclerosis, but also reduces tinnitus severity, particularly when the pre-operative tinnitus is classified moderate or severe. •

#### **CRITICAL NOTE**

One of the limitations of this study, as reported by the authors themselves, is the fact that of the 248 subjects who reported chronic tinnitus, 80 (32%) dropped out as they failed to fill in the TFI questionnaire correctly. This could have influenced the outcome of this study.

The authors only briefly touch upon the eventual benefit of counselling in combination with stapedotomy for subjects with chronic tinnitus, but they do not report whether any counselling was provided during this study.

The fact that the TFI and Tinnitus Severity Classification were used, could certainly have had an impact on the intervention, since the use of questionnaires can lead to discussion and counselling.

A positive feature of this study is the fact that it covered a large cohort of 168 subjects.

The results outlined in this study, with 64% of the subjects with otosclerosis reporting chronic tinnitus and 55% reporting a reduction in tinnitus severity when hearing is improved, are in line with other studies on the impact of amplification with Cochlear Implants and Hearing Aids on tinnitus. Overall, this is certainly a very interesting study.

## ALTERATIONS IN REGIONAL HOMOGENEITY IN PATIENTS WITH UNILATERAL CHRONIC TINNITUS

Trends in HEARING

Gentil A., Deverdun J., Menjot de Champfleur N., et al. Trends in Hearing (2019): 23, 1-12. By Tine De Boodt This study uses resting-state fMRI with patients with chronic subjective tinnitus to provide a better understand of the brain areas involved. Results show that tinnitus can negatively alter a number of cerebral networks and brain areas.

The brain areas which are stimulated or inhibited in subjective tinnitus remain poorly understood. This is because existing research has proved very variable due to the data treatment methods employed, together with the lack of a homogeneous research population.

Belgium

The present study uses resting-state fMRI with patients

with chronic subjective tinnitus in order to understand better the brain areas involved. In total, 19 patients with unilateral chronic tinnitus and 16 healthy non-tinnitus control subjects were selected for the study; none of the tinnitus patients received tinnitus treatment prior to or during the study.

The following psychoacoustical and psychosocial tests were conducted in order to corelate with the results of the fMRI:

- Psychoacoustical tests: tinnitus Pitch Matching (PM); loudness matching; Minimal Masking Level (MML); and Residual inhibition

- Psychosocial tests: Subjective loudness of tinnitus (Visual Analogue Scale – V.A.S.) and Tinnitus Handicap Inventory (THI)

The researchers used a Regional Homogeneity (ReHo) technique to compare the differences in stimulation of the brain areas involved in tinnitus.

#### • MAIN RESULTS:

- Results show that tinnitus can negatively alter the functioning of various cerebral networks and brain areas, such as the auditory cortex, the limbic system and the attentional network. The disorganisation of the neuronal activity is measured in the auditory cortex contralateral to the tinnitus ear.

The greater the distress or perceived loudness, the more the contralateral auditory cortex is desynchronised.
This desynchronisation is paralleled by an increased

#### **IMPLICATIONS FOR OUR PRACTICE:**

Education about tinnitus during tinnitus treatment is one of the most important aspects when treating tinnitus patients. Patients need to understand why they have tinnitus and which mechanisms are involved. By showing patients evidence that their brain displays differences in stimulation compared to people without tinnitus, we are thereby demonstrating that their tinnitus can be measured objectively.

We can explain to our patients why they find it so difficult to focus on difficult tasks. MRIs show that tinnitus has an effect on the attentional network. Furthermore, the plasticity of the brain will always try to compensate for 'loss', and it may be possible to exploit these factors for retraining purposes. When communicating this to our patients, we should use a positive message, which is generally important during counselling.

connectivity in the ipsilateral primary and associative auditory cortex. This could be due to compensatory mechanisms of the auditory cortex of the no tinnitus ear. •



## TRACKING OF NOISE TOLERANCE TO PREDICT HEARING AID SATISFACTION IN LOUD NOISY ENVIRONMENTS



Seper E., Kuk F., Korhonen P. & Slugocki C. Journal of the American

Academy of Audiology (2019): 30, 302-14. By Katrien Hoornaert Belgium This study assesses the objective correlation between Tolerable Noise Level (TNL) and hearing aid (HA) satisfaction. The authors found no significant correlation between overall HA satisfaction which would help predict wearer satisfaction.

It would be very interesting to know, at the time of the fitting, the potential real-life satisfaction with hearing aids (HA), particularly in loud, noisy environments.

In this article, the authors question the reliability and clinical efficiency of (a variation of) an existing method which evaluates aided Tolerable Noise Level (TNL) over



time while maintaining subjective speech intelligibility. There are several reasons why Loudness Discomfort Level (LDL) – a very widespread method to used assess listeners' comfort level in response to sounds – is a poor predictor of hearing aid satisfaction in loud, noisy environments: it is often measured unaided; it uses pure tones; and it fails to take account of speech intelligibility. Another test which does use speech stimuli is the Acceptable Noise Level (ANL). However, this method too presents some limiting factors: the speech material is presented at a comfortable level; people are only expected to understand 80%; there is not sufficient evidence to prove a positive correlation between noise tolerance and subjective hearing aid satisfaction; and it offers very low test-retest reliability.

TheTracking of NoiseTolerance test (TNT, as first presented by Kuk *et al.*, 2017) is another test which accounts for both noise tolerance and speech intelligibility. This test uses speech at 85 dB SPL, with continuous speech-shaped noise over a four-min. period. Listeners are requested to increase the noise level until they can no longer "put up with" the noise or if there is a decrease in speech understanding <90%. This test shows a 2.2 dB withinsession test-retest variability.

The authors made a few modifications to the original TNT test:

1) It was made more active: the noise level automatically changes at a specific rate while the listener controls the changes in noise levels using a computer keyboard. This could give more stable results more quickly.

2) It was made less time-consuming: two minutes instead of four minutes, with an adaptive scoring method which estimated the stability of the noise tolerance level once a stable estimate was possible.

3) It was adapted to simulate a realistic communication situation, using a consistent topic as speech material.

#### **CRITICAL NOTE:**

TNL is probably a useful test in clinical practice but further studies with more participants and with a greater variety of satisfaction levels are necessary.

The study was carried out on a group of 17 subjects. All were experienced, adult hearing aid wearers and completed the MarkeTrak questionnaire.They performed four TNT tests over time, with speech (0°) at 82 dB SPL and noise (180°) starting at a level of 72 dB SPL: two tests with babble noise and two tests with continuous speech-shaped noise.Two scoring methods were used: the average noise level after two minutes; and the estimated noise level, as soon as the noise level was stable.

No significant difference was found between the averaged and the estimated noise level. However, it is important to mention that not all participants were able to reach a stable noise level in the two-minute test.

Noise type has a significant impact: participants tolerated 2.2 dB less continuous speech-shaped noise than babble noise. Both types of noise have their own value: babble noise is more representative of daily listening; speech-shaped noise is more useful for evaluating specific hearing aid features.

The modified version of the test proposed by the authors offers a high test-retest reliability: 1.5 dB for babble noise; 2.8 dB for speech-shaped noise.

There is no significant correlation between overall HA satisfaction and TNL level, but all participants in this study were satisfied HA users. When only the questions concerning satisfaction in noisy situations are taken into account, there is a correlation with the TNL value.





### COMPARISON OF SATISFACTION BETWEEN PATIENTS USING PERCUTANEOUS AND TRANSCUTANEOUS BONE CONDUCTION DEVICES



Svagan M., Povalej Brzan P. & Rebol J. Otology & Neurotology (2019): Vol. 40 (5), 651-7. By Mark Laureyns Italy / Belgium Although one would expect that since the Transcutaneous BAI group have less skin problems, better cosmetics and lower complexity compared to the Percutaneous BAI group, the satisfaction would be higher, this was not the case. Both satisfaction (GBI score) and daily usage time was better for the Percutaneous BAI group.

Bone Anchored Implants (BAI) have become a widely used solution for conductive hearing loss, single sided deafness (transcranial cross) and even for mixed hearing loss. They have replaced bone conduction hearing aids in many cases. Traditional "Percutaneous" Bone Anchored Implants are connected to an abutment that is fixed on the mastoid bone which can lead to skin problems. In recent years "Transcutaneous" Bone Conduction Implants have been developed. They do not use an abutment but rather magnets to transmit the vibration to the bone. The study under review compares user-satisfaction between the Percutaneous Cochlear BAHA Connect and the Transcutaneous Cochlear BAHA Attract.

#### • SUBJECTS

In total, 72 subjects participated in this study, 45 (63%) female and 27 (67.55) male, with an average age of 46 years. Overall, 44 (61%) used Percutaneous BAI (average processor use: 3.3 years) and 28 (39%) usedTranscutaneous BAI (average processor use: 1.5 years).

The cohort comprised 26 subjects with single sided deafness (SSD), 33 with mixed hearing loss (Mixed) and 13 with conductive hearing loss (Conductive).

	Percutaneous	Transcutaneous
SSD	13	13
Mixed	21	12
Conductive	10	3
TOTAL	44	28

#### • METHOD

Daily usage time was evaluated by a questionnaire, and satisfaction evaluated with the Glasgow Benefit Inventory (GBI) with the following subscales: general; social support; and physical health.

#### • RESULTS

- Daily median usage time.
- 12 hours for the Percutaneous BAI
- 7 hours for the Transcutaneous BAI

- The Percutaneous BAI group used the device significantly more hours per day than the Transcutaneous BAI group (U=196.5; p<0.001)

- Total GBI satisfaction score for total group.
- 40 for the Percutaneous BAI





#### - 17 for the Transcutaneous BAI

- The Percutaneous BAI group is significantly more satisfied than the Transcutaneous BAI group (U=306; p<0.001); the subscale social support shows the largest difference.

• Total GBI satisfaction score for specific groups.

- The total GBI score is higher for the Percutaneous BAI group for both the Single Sided Deafness (SSD) group and the Mixed Hearing Loss group

- The sample size for the Conductive groups was too small.

#### • CONCLUSIONS:

Although one would expect that since the Transcutaneous BAI group have less skin problems, better cosmetics and lower complexity compared to the Percutaneous BAI group, the satisfaction would be higher. This, however, was not the case in this study. Both satisfaction (GBI score) and daily usage time were better for the Percutaneous BAI group. The authors explain this by the fact that Transcutaneous transmission leads to an energy loss of about 7dB, which cannot be fully corrected by adding more gain in the fine-tuning.

The authors suggest including a longer trial period with a non-surgical bone conduction solution before deciding which type of BAI should be used. •

#### **CRITICAL NOTE:**

The selection of the type of BAI was based upon user preference, but no information is available on how this choice was guided or how the user was informed.

The authors do not refer to earlier publications by Snik and other authors, on the fact that Transcutaneous BAI result in 10dB lower maximum output compared to Percutaneous BAI. In super power traditional hearing aids, the maximum output can go up to 140 dBSPL; in Percutaneous BAI this is reduced to +/- 80 dBFI (force level measured in a skull simulator) and in Transcutaneous BAI this is at +/- 70 dBFI.

The authors suggest a longer trial with the nonsurgical bone conduction before any decisions being made, as they will have maximum output levels which will be as low as or even lower than Transcutaneous BAI.

*This study is very interesting and particularly relevant for clinical practice.* 

#### Reference for the critical note:

Hol M., Nelissen R., Agterberg M., et al. Comparison Between a New Implantable Transcutaneous Bone Conductor and Percutaneous Bone-Conduction Hearing Implant. Otol Neurotol (2013): 34, 1071-5

### SENSORINEURAL HEARING LOSS AND VOLATILE ORGANIC COMPOUND METABOLITES IN URINE

American Bremain of OTOLARYNGOLOGY OTOLARYNGOLOGY CONTRACTOR OTOLARYNGOLOGY Pudrith C. & Dudle, WN. American Journal of Otolaryngology (2019): 40, 409-12.

By Reddy Sivaprasad India This retrospective study examined the urinary concentration of 21 VOCs and their possible association with acquired SNHL in adults. Results demonstrate the correlation between new VOCs and hearing loss in individuals not exposed to noise.

Oxidative stress is a condition at the molecular level which results in acquired Sensorineural Hearing Loss (SNHL). Oxidative stress produces reactive oxygen species which break down the lipids of inner-ear hair cells, damages DNA and finally causes cell death, thereby damaging the cochlea. Oxidative stress can be caused by a number

of aetiologies including noise, ototoxic drugs, cigarette smoke, injury, etc. A biological marker for oxidative stress is Volatile Organic Compounds (VOC). There are three specific VOC metabolites which are associated with SNHL: mandelic acid, phenylgloxylic acid and hippuric acid.

Increased urinary concentration of VOC metabolites caused by toxic chemicals and noise is observed in people with hearing loss. This study was designed to examine the association among different urinary VOC metabolites in acquired SNHL in adults. In addition to the three VOCs mentioned above, this study also explored whether mercapturic acids are associated with hearing loss.

This extensive retrospective study included 557 adult subjects with hearing loss with no noise exposure and 292 adults with hearing loss and noise exposure. Audiogram data was averaged at pure tone Hearing Threshold Levels (HTLs) 4, 6 and 8 kHz (PTA<sub>4,6,8</sub>). 21 VOC metabolites were measured using mass spectrometry and liquid chromatography. Five of the 21 VOC metabolites (all are mercapturic acids) were significantly associated with increased HTLs (PTA<sub>4,6,8</sub>). Thresholds were 3-4 dB

#### **CRITICAL NOTE**

Thanks to the robust design of this study, new evidence suggests that VOCs in urine are a direct indication of oxidative stress leading to acquired SNHL in adults.

higher in those individuals with five of these elevated VOCs compared those with lower VOCs.

The elevated mercapturic acids are usually seen in smokers/those exposed to toxins. This elevation was seen in the group with no noise exposure. This is another significant finding. In addition, the study did not find any correlation between hearing loss and elevated mandelic and phenylgloxylic acids. Further analysis demonstrates a complex interaction between different VOCs in different etiologies.

Because of the inclusion of new VOCs and large data sample, this study was able to demonstrate a 3-4 dB threshold shift associated with elevated levels of five mercapturic acids in urine. •



## MALFORMATIONS OF THE LATERAL SEMICIRCULAR CANAL CORRELATED WITH DATA FROM THE AUDIOGRAM



Venkatasamy A., Le Foll D., Eyermann C., et al.

European Archives of Oto-Rhino-Laryngology (2019): 276, 1029-34. By Reddy Sivaprasad India In this retrospective study, the relation between lateral semicircular canal anomalies and hearing loss was analysed across a large group of subjects using CT scan and audiometric findings. The authors conclude that most subjects with a LSCC anomaly also presented with hearing loss.

Congenital hearing loss is known to be associated with vestibular malformation along with cochlear malformations. Amongst other manifestations, lateral semicircular canal (LSCC) malformations are more common as this structure is one of the earliest to develop in the embryo. LSCC malformations can be identified via CT scans and have been reported in both normal hearing and all types of hearing loss. However, these findings have only been reported in small subject groups.

The purpose of the study was to identify the prevalence



of LSCC malformations in people with hearing loss and specifically in different types of HL across a larger sample population, compared against a cohort of normal-hearing subjects.

In this retrospective study, the researchers carried out a data search based on specific criteria. Based on data spanning a two-year period, 109 patients (166 ears) were included in the experimental group. The control group had data from 24 subjects. All subjects went through nonenhanced CT scans on a 128-section CT scanner. The two parameters measured were width of medial part of LSCC and the surface of the bony island at the centre of the LSCC. Audiological data included in the study included findings from pure tone audiometry.

Results showed that 52% of subjects had bilateral LSCC malformations, whereas the rest had monaural malformations. The medial portion of the LSCC was significantly wider (mean of 1.84 mm) in the experimental group compared to that of the control group (mean 1.42 mm). The average surface of the bony island was lesser in the experimental group compared to that of the control group (<7 mm<sup>2</sup>).

#### **CRITICAL NOTE**

This study included a large cohort of subjects with a known LSCC malformation, whose associated audiogram findings were studied. However, the study did not examine possible underlying mechanisms leading to hearing loss. Furthermore, the correlation between degree of hearing loss and LSCC abnormality was not studied.

In the experimental group, 61% subjects had confirmed hearing loss. SNHL was seen in 40% of subjects, mixed hearing loss in 13% and 9% of the subject showed a conductive hearing loss. 81% of bilateral LSCC malformations were associated with hearing loss. The majority of subjects with a unilateral LSCC malformation had normal hearing. In the control group where no LSCC malformation was found, only three subjects presented with hearing loss. 81% subjects showed a contralateral LSCC malformation which is another significant finding.

The authors conclude by calling upon the relevant professionals to conduct a LSCC study in all individuals with congenital hearing loss. •



# **AUDIOLOGICAL EVALUATION** OF INFANTS USING MOTHER'S VOICE



### Saito O., Nishimura T., Morimoto C., et al.

International Journal of Pediatric Otorhinolaryngology (2019): 121, 81-7.

By Reddy Sivaprasad India The authors of this study experimented with recorded phrases in mother's voice so as to measure infants' hearing threshold. These results were compared with previous test results and that of the warble tones used in the same session. Reliability of responses improved significantly and correlated very well with ABR thresholds.

Early detection of hearing loss is crucial in the rehabilitation of children with hearing loss so that they acquire normal speech and language. Established timelines for this process suggest that they be implanted/aided with hearing aids before their first birthday. While most infant assessment protocols are based on objective tests, behavioural audiometry should play a greater role in providing more accurate unaided testing and aided testing. Narrowband noise and warble tones used in behavioural audiometry do not elicit thresholds closer to actual thresholds, so these are termed as minimum response levels by some professionals.

Studies recommend the use of human voices, especially mother's voice, to elicit better responses. The objective of the study was to measure thresholds for mothers' voices (MvTh) and compare these with those of warble tones.

The study group comprised 30 infants (age: 3-39 months), for 24 of whom brainstem response testing (ABR HTLs 37+21) was already performed. Visual Reinforcement Audiometry (VRA) was used to measure thresholds. The stimuli used were warble tones (250-4000 Hz) and recorded mothers' voice samples. Infants' responses were classified as: no response; uncertain response; possible positive response; and positive response.

Results showed that the number of positive responses at first response, and even the responses at the threshold level, were clearly considerably better for mothers' voice when compared to those of any warble tone. Correlation analyses showed a positive correlation between MvTh and warble tone thresholds. A significant and moderately

#### **CRITICAL NOTE**

The authors ingeneously used an existing idea of mother's voice to elicit hearing thresholds. However, they used a phrase which lacks frequency specificity. The better usage of mother's voice needs to be verified against Ling's six sounds (in mother's voice) so that frequency specificity improves and can be useful even in HA fitting.

strong positive correlation was found between  $M\nu Th$  and ABR thresholds.

Reliable thresholds which matched almost perfectly were obtained for almost all infants with previous hearing test results. •

## THE CLINICAL OUTCOMES AFTER INTRATYMPANIC GENTAMICIN INJECTION TO TREAT MENIERE'S DISEASE: A META-ANALYSIS



Zhang Y., Fu J., Lin H., et al. Otology & Neurotology (2019): 40(4), 419-29. By Reddy Sivaprasad

India

In this paper, the authors studied the safety and effectiveness of intratympanic gentamicin injection as a treatment option for Meniere's disease. Both qualitative and quantitative analyses showed ITG is a safe and effective regime.

Meniere's Disease (MD) or Endolymphatic Hydrops is a clinical condition manifested by episodic vestibular and audiological symptoms, ranging across fluctuating hearing loss, tinnitus, aural fullness, and spontaneous vertigo. Several working definitions of this condition are available with no single diagnostic test for confirming the condition.

Generally, the first line of management of this condition includes lifestyle modifications and symptomatic management. Although surgical options are available, intratympanic injections using gentamicin, due to its well-known vestibulotoxicity (ITG), has been the treatment of choice for some as it was considered to be safe and effective. However, two meta-analyses on this topic published in 2004 failed to find compelling evidence to support this claim. The objectives of the present study were to: 1) offer a systematic review of existing evidence on ITG effectiveness and toxicity; 2) to aggregate clinical outcomes quantitatively; and 3) to verify whether there had been changes in ITG efficacy/toxicity/evidence-based medicine since the last two meta-analyses.

The authors carried out a systematic literature search covering studies published between 1990 and 2018 with several criteria satisfying the AAO-HNS (1985 or 1995) guidelines. Based





on these guidelines, two classes of treatment effectiveness were considered: complete (class A) and substantial (classes A and B) vertigo control. Four ITG treatment protocols were included in the meta-analysis: low-dose (21), weekly (17), multiple daily (9), and continuous microcatheter delivery (5). Both qualitative and quantitative analyses were used. Two types of statistical analysis methods were employed: combining continuous variables from different experiments so as to explore differences in outcomes; and the second, combining rates of all included studies. Out of the 1,062 citations retrieved over the defined search period, 49 were ultimately selected for the analysis.

The results showed that vertigo was studied in 47 studies (n=2185 patients). The overall rate of vertigo improvement for substantial vertigo control (classes A and B) was 89% and that of complete control (class A) was 71%. Hearing threshold change (PTA) was found in 1,494 patients, with an overall increase of 3.09 dB. Word discrimination was measured in 1,076 patients, and this score fell by 4.85%.

#### **CRITICAL NOTE**

This meta-analysis of 49 published studies found ITG to be an effective and safe regimen for treating Meniere's disease. Although the meta-analysis proposed by the authors shows moderate to significant improvement, many of the studies relied on poor data and design. Therefore, further studies are required to gain more clinically significant insight as to the safety and effectiveness of ITG for intractable MD.

Tinnitus was studied in 540 patients and there was an improvement rate of 50%. Aural fullness data indicated an improvement by 60% in about 345 patients. Functional levels improved significantly in 547 patients. Among the different treatment protocols, the multiple daily program resulted in higher threshold loss. Overall, the study found ITG to be an effective regime to deal with intractable Meniere's disease. The additional significant finding of the study was tinnitus relief as reported in many studies.

# HEARING PROTECTION, RESTORATION, AND REGENERATION: AN OVERVIEW OF EMERGING THERAPEUTICS FOR INNER EAR AND CENTRAL HEARING DISORDERS



Schilder AGM., Su PM., Blackshaw H., et al. Otology & Neurotology (2019): 40(5), 559-70. By Reddy Sivaprasad India This study reviews and summarises recent research in inner ear related pharmacological, genetic and cell therapies, and offers an overview of the companies working within the field.

Sensorineural hearing loss is caused by several genetic and non-genetic etiologies. A number of studies have proposed therapies for the treatment of SNHL. The objective of this study was to review recent research in the field of inner ear therapeutics to provide a map of the companies involved in developing therapeutic approaches and products, and to report on their stage of clinical development.

The authors carried out an exhaustive search using specific criteria on different types of search engines and

also using company websites, leveraging professional networks and contacting industry stakeholders in order to map out emerging inner ear therapeutics. The metaanalysis covered studies featuring data on novel hearing therapeutics at any stage of development, as well as the biotechnology or pharmaceutical company driving this development. The authors found 43 companies with pre-clinical or clinical programs in this field. They are based in the US, the UK, France, Germany, Japan, Israel, Switzerland, Denmark, Belgium, Sweden and The Netherlands. The authors identified seven areas of research these companies are working on:

1. Otoprotection agents: developing therapeutics to prevent hearing loss and preserve hearing. This is indicated for drug- or noise induced, age-related or sudden onset SNHL, and cochlear implant users. At time of publication of the study, 24 companies were working on this approach, most (15) of them were in pre-clinical phase, some in phase I, phase II and phase III.

2. Regenerative therapeutics: the purpose of these drugs or agents is to help regenerate lost cells and other structures of the inner ear in acute/chronic/age-related SNHL. At time of writing, 15 companies are working on this approach, most (12) in pre-clinical phase, some in phase I and phase I/II.

3. Therapeutics to reduce tinnitus: 12 companies are working in this field. However not much progress has yet been achieved.

#### **CRITICAL NOTE**

This article provides a comprehensive review and a directory for the field of ototherapeutic products, companies and publications. Summarised in a useful manner for further reference.

4. Central hearing disorders: only one company is working at pre-clinical level to develop drugs which selectively stimulate the central auditory pathways.

 Balance: a total of five companies are working to improve inner ear problems associated with Meniere's disease.
 Some of these programs are in advanced clinical phase.
 Gene correction therapies: four companies are working on correcting genetic mutations leading to HL and deafness. Three of them are working on adeno-associated virus (AAV) delivery methods.

7. Drug delivery systems: two companies are working on developing drug delivery routes to the inner ear in SNHL, cochlear implantation and Meniere's disease.

Overall, 31 companies are developing drug-based regimes, seven are working on gene therapies and one is using cell-based therapy. The article offers many more details on these companies and their work spanning into seven tables. The authors call for more work and projects to be carried out in this field. •





### CHARACTERISTICS OF MID-FREQUENCY SENSORINEURAL HEARING LOSS PROGRESSION



Birkenbeuel J., Abouzari M., Goshtasbi K., et al. Otology & Neurotology (2019): 40(5), e497-e502. By Reddy Sivaprasad India The authors collected serial audiograms and other audiological tests of patients with mid-frequency sensorineural hearing loss (MFSNHL) in order to study its long-term clinical outcomes. Most of the subjects were paediatric with early childhood onset. The study suggests that thresholds do not worsen with age for this subset of audiograms.

Mid-frequency sensorineural hearing loss (MFSNHL) can be defined as an audiogram with a higher PTA of 1, 2 and 4 kHz than the PTA of 0.5 and 8 kHz by at least 10 dB. This is a rare but significant audiogram pattern which has etiologies ranging fromTurner syndrome, congenital familial deafness, to small vestibular schwannomas. The TECTA gene (involved in the development of the tectorial membrane) mutation has also been reported to be associated with this audiogram. The objective of this study was to report long-term outcomes of this condition.

The study covered a cohort of 37 patients (20 males) who were diagnosed with MFSNHL in the first appointment. The subjects' age ranged from eight months to 70 years old. All their audiological test results from different appointments were studied. Five of the subjects had a family history of hearing loss, and another five had a history of otitis media. Most subjects were paediatric with onset dating back to early childhood.

#### **CRITICAL NOTE**

This is a preliminary study but it addresses an important topic of mid-frequency SNHL. While most clinicians appreciate that the condition is not progressive, this study provides good empirical evidence to support this presumption.

The average mid-frequency PTA was 47 dB as against 27 dB for 500 and 8,000 Hz. Average Word Recognition Score (WRS) was 92%. Serial audiograms were available for 23 patients. Further analysis showed that only one subject showed significant increase in mid-frequency PTA over time. For the remaining 22 subjects, threshold change over time was insignificant.

The study clearly shows that MFSNHL does not worsen over time and mostly remains stable, indicating probable genetic origins set at birth or early childhood. •







