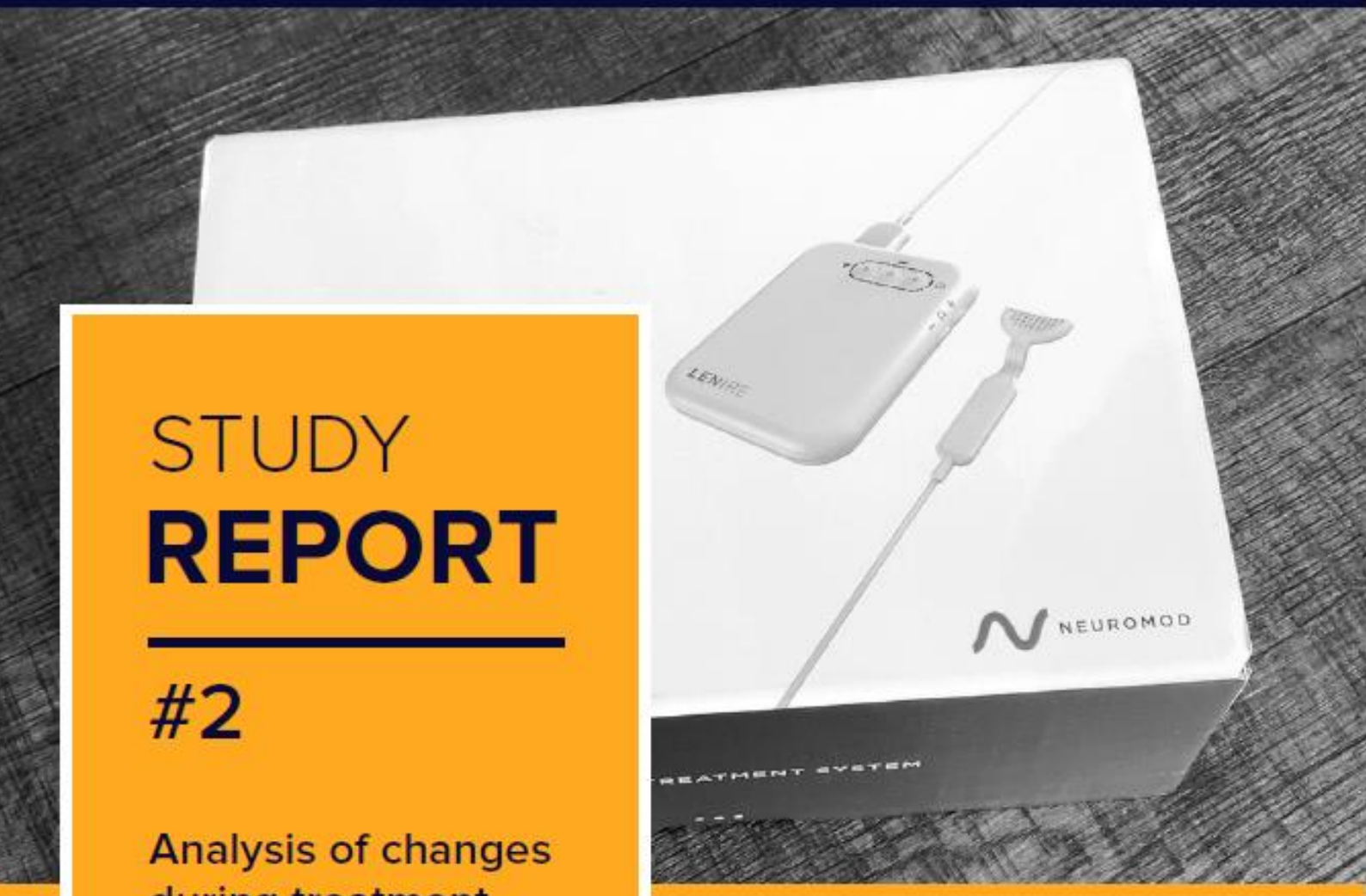
Lenire **User Experience Group**

May 2020



STUDY REPORT

#2

Analysis of changes during treatment

Written by @PeterPan

A total of **43 patients**

Independently created by patients for patients

TinnitusHub

Revision History

Date	Version	Change
21/5/2020	1.0	Version published on Tinnitus Talk
14/6/2020	1.1	Added “Last Value Carried Forwards Appendix” and this revision history section

Introduction

The Lenire User Experience Group (LUEG) Study is a patient-lead study aimed at helping to understand the effectiveness of a recently released device for treating tinnitus known as the Lenire. Lenire is a "bi-modal" device meaning that it delivers both sounds and electrical impulses to patients as its method of action in treating tinnitus. It is sold by Neuromod devices, a small company with a head office located in the Republic of Ireland. Neuromod have conducted their own extensive trials on the efficacy of the device, and information about the design of these trials may be found in [1] and [2]. The results of the trials have, at the time of writing, not been published.

Data for this LUEG study has been mostly obtained from volunteer members of Tinnitus Talk, a popular online tinnitus forum. Participants in the study have been asked to complete an online questionnaire that captures their baseline characteristics at the commencement of the treatment and their experiences at 6 and 12 weeks from this date. The study was conducted over the period between July 2019 to May 2020 and consists of 43 patients.

Two reports have been completed for this study. The first report [3] was completed in January 2020 and represented an analysis of the baseline characteristics of the 43-user cohort using data collected during the above-mentioned survey (a summary may be found in Appendix 8).

This report (Report 2) examines the changes in patients' tinnitus during the Lenire treatment. To get the most out of this report, it is worthwhile reading report 1.

The intended audience for these reports is Tinnitus Talk members and others interested in tinnitus, particularly persons afflicted with tinnitus. This report does include statistical techniques that may be difficult to understand for those without a statistics background, and as such, we recommend:

- **Those readers who would just like see the summary of the report findings, can just read Section 1: Executive Summary.** This section does contain some summary statistics.
- Those readers who would like some additional information about the change in patient's tinnitus during the treatment but who do not feel comfortable with statistics can also read Section 3, Section 4, Section 5 and Section 7. Section 3 describes the completion rates and the reason for patient drop-outs from the study (if known). Section 4 describes the contents of the questionnaire presented to patients at the 6 and 12-week milestones and the related top-level results. Section 5 provides information on factors which correlate with the amount of tinnitus change during the Lenire treatment where those results are statistically significant. Section 7 provides a discussion of the results presented in the report and provides some observations and draws some conclusions.
- Those who would like to tackle the statistics sections in order to get a better understanding of the statistical significant results mentioned in the Executive Summary can read Section 6. If you do not have a statistics background, to get the most out of these sections we recommend you read Appendix 2 and the references in Appendix 4 in advance.

This study is managed and staffed by volunteers from Tinnitus Hub, a not-for-profit patient organization that is passionate about improving the lives of tinnitus patients.

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Thanks

Tinnitus Hub would like to offer thanks to the following personnel who contributed to this report:

@Hazel and @Markku: Hazel and Markku participated in the design of the questionnaire, invited university researchers to review the questionnaire prior to release, helped with reminding members to complete their surveys, and provided overall guidance and assistance.

Tinnitus Talk forum members: for offering their valuable time to respond to the survey and share their experiences.

University Researchers for reviewing the questionnaire and providing valuable feedback.

Expert Forum Members and their relations who have donated their valuable time in reviewing the statistical component of this report.

@PeterPan: Yours truly, the author of this report and project manager of the study.

Section 1: Executive Summary

There are many caveats related to this study. Refer to Appendix 3 for details.

Background

Tinnitus is a common problem and can have substantial negative impacts on the quality of life. For such a common problem, there are remarkably few (if any) effective treatment options [7]. Although there is a dearth of treatment options that work, there is a regular stream of new treatments being announced (some more credible than others). Persons afflicted with tinnitus have several resources available to assess the likelihood of success when using a new treatment. Amongst these alternatives, the outcome of Patient-led research is a becoming increasing popular. Patients will often have a better understanding of their condition than medical professionals and can provide valuable insight into study design and the research process. In addition, studies led by patients are often not burdened by the multitude of stakeholders that are common in large studies undertaken by institutions.

The Lenire is a new tinnitus treatment option that does have a high degree of credibility. Tinnitus Talk has conducted a patient-led study of this treatment, the outcome of which is represented by this report. This report contains a detailed analysis of the change in tinnitus that patients have experienced during their treatment, with emphasis on examining the patient characteristics correlated with tinnitus improvements.

What we found

- Amongst patients that completed the treatment and who provided TFI (29 patients), there was an overall average reduction in TFI of approximately 13.9 after 12 weeks of Lenire treatment. This change is statistically significant (Paired t-test, p=0.001, 95% CI [-6.5,-21.2]). This result compares favourably with the mean TFI reduction of approximately 13 after 4 weeks of treatment of a competing bimodal device [5].
- Amongst patients who completed the treatment and who provided TFI, 48% of patients experienced a clinically significant change in TFI (a TFI reduction of 13 points or more is clinically significant). 50% of patients in the study described in [5] experienced this benefit.
- Six patients or about 17% of participants reporting results (36 patients) dropped out of the study prior to the elapsed 12 weeks due to adverse outcomes. One of these outcomes was the painful condition of trigeminal neuralgia and in one case the severity of tinnitus increased significantly.
- There were statistically significant differences (One Way Anova, Tukey HSD) in TFI reduction between groups within a factor for these factors:
    - Hyperacusis (None/Moderate, Delta 31.75, p = 0.026),
    - Hearing Loss (None/Mild, Delta 18.00, p = 0.020),
    - Combined Hyperacusis/Hearing Loss (Hyperacusis+No Hearing Loss/No Hyperacusis+Hearing Loss, Delta 29.43, p=0.024),
    - Pitch (Very High/High, Delta 18.54, p=0.048)

- We saw that there was a statistically significant (Wilcoxon Signed-Rank Test) change in patients' self-assessed tinnitus severity at the 12-week milestone (p=0.001)
- When comparing patients who experienced a clinically significant change in their tinnitus against those who did not, we saw statistically significant dependencies (Fisher Exact Test) for the Hyperacusis (p=0.038) and Hyperacusis/Hearing Loss (p=0.022) factors.

Study Weaknesses

While we have seen some significant statistical results from this study, it's important to point out some of the weaknesses:

- Our sample size of 43 is very small. It's difficult to reach sound conclusions with the sample size.
- We had no control arm, or an arm with an alternative treatment. The placebo effect can be very strong for tinnitus sufferers, and we have not been able to control for this effect during the study.

Further caveats and weakness may be found in Appendix 3.

COVID19

The latter part of this study was conducted during the beginning of the COVID19 pandemic. This has had an impact on this study as international travel was extremely limited during this period and patients, in the normal course of events, were required to visit Neuromod at each of the treatment milestones for consultation and possible tuning of the Lenire. In addition, in many countries people's lifestyles were changed significantly and this may have had an impact on their tinnitus.

Section 2: Some Terminology

This report frequently mentions factors and groups, and it is important to understand how they are used.

A factor is a characteristic of the patient population that is of interest. In this report, examples of factors are age, tinnitus duration, gender, hyperacusis etc.

Within each factor, patients are divided into groups, dependent on how they respond to questionnaires, or how we have divided them up as part of this study. Thus, for example, within the "Gender" factor there are Male and Female groups. Within the "Hyperacusis" factor there are None, Mild, Moderate, Severe groups. For the "Age" factor, we have, for the purposes of some tests, divided patients into <30, 30-39, 40-49, >50 groups.

Understanding how these terms are used should help with interpreting this report.

Section 3: Survey Completion Rates and Adverse outcomes

Survey Completion Rates

We enrolled 43 patients in this study. Provision of TFI[1] information was optional, however in most cases this was provided. The charts and tables below provide information on the survey completion rates of these patients.

Completion Code	#
Completed Successfully	30
Registered , purchased the device, but did not proceed with any treatment	1
Failed to respond at 6 week survey	3
Failed to respond at 12 week survey	1
Dropped out prior to 12 week survey due to adverse outcomes	3
Dropped out prior to 6 week survey due to adverse outcomes	3
Device Failed after 6 weeks and before 12 weeks and unable to replace	1
Delayed treatment commencement and unable to complete in time	1
Totals	43

Table 1 - Response Rates for Patients

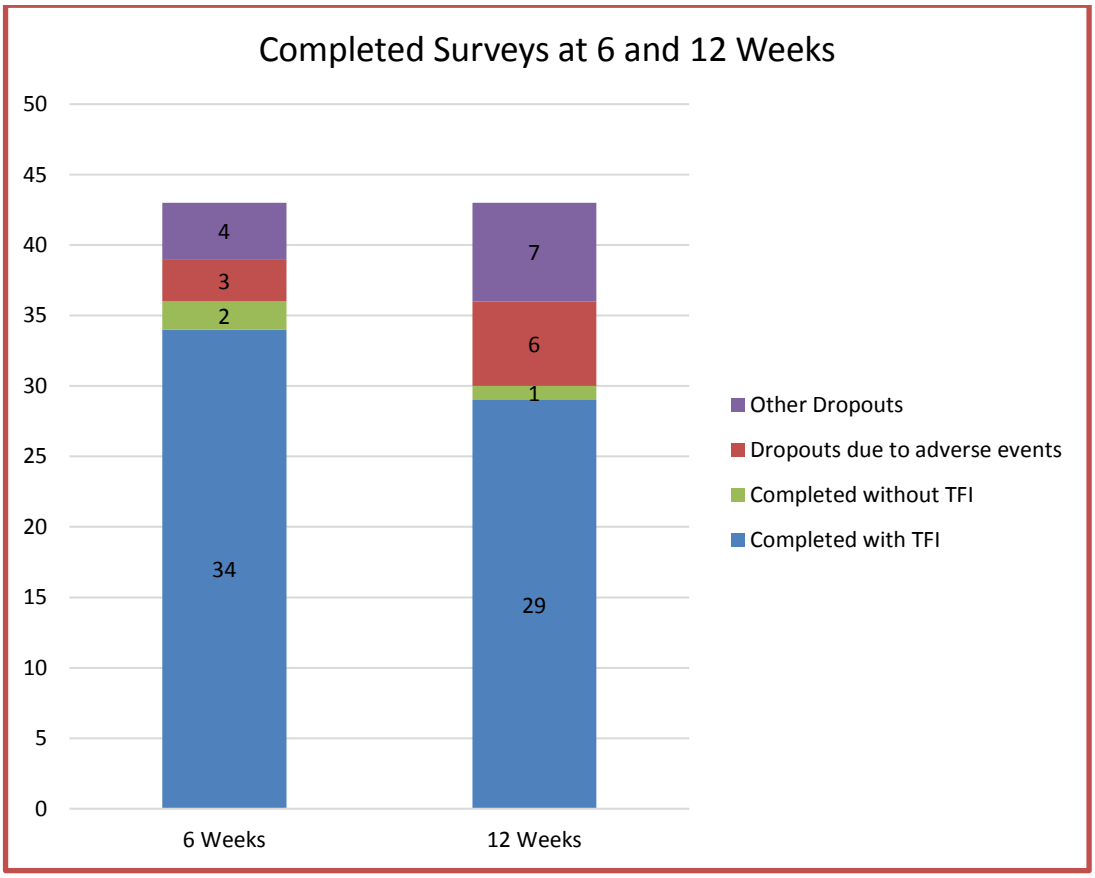


Figure 1 – Breakdown of types of responses to surveys at 6 and 12 weeks

[1] Information on TFI may be found in Report 1 of this series [3].

Adverse Outcomes

The table below provides information on the patients who dropped out due to an inability to continue using the device or adverse outcomes.

#	Symptoms	Prior to	Hyperacusis	Hearing Loss (Right)	Hearing Loss (Left)
1	Got a while new tinnitus tone in left eat a pulsating hiss. Quit after 9 days.	6 weeks	No	Mild hearing loss	Mild hearing loss
2	Each 30 minute session is torture so not going to use it anymore.	12 weeks	Mildly	Mild hearing loss	Mild hearing loss
3	Developed trigeminal neuralgia and has stopped using.	6 weeks	Moderately	No hearing loss	No hearing loss
4	Stopped as tinnitus has got louder as a result of it. Not happy with it.	12 weeks	No	Mild hearing loss	Mild hearing loss
5	Stopped due to ear spams	6 weeks	Mildly	No hearing loss	No hearing loss
6	Reported that tinnitus was a lot worse. Had to suspend treatment.	12 weeks	Mildly	Mild hearing loss	Mild hearing loss

Table 2 - Characteristics of Patients with Adverse Outcomes

We have also included some pertinent characteristics of these patients. We will see later in the report that those patients with hyperacusis and good hearing seem to have better success with the Lenire than others. We can see that some of these patients have the characteristics which would otherwise make them good candidates for success.

Section 4: The Questionnaire and Top-Level Results

In this section we present the questions that patients were asked to respond to during their 6 week and 12-week milestones, and an analysis of the responses. The questions that patients were asked to respond to during the baseline survey and the analysis of these responses may be found in [3].

How do you rate the severity of your tinnitus?

This question was also asked during the baseline survey. Patients could respond with one of Borderline Tinnitus, Mild Tinnitus, Moderate Tinnitus, Severe Tinnitus, Substantial Tinnitus or Catastrophic Tinnitus.

The diagrams below show how the response to this question changed at the 6 week and the 12 weeks milestones:

		6 Weeks					
AFTER	Catastrophic Tinnitus	0	0	0	0	1	0
	Severe Tinnitus	0	0	0	0	3	0
	Substantial Tinnitus	0	0	2	3	2	1
	Moderate Tinnitus	0	2	7	7	1	0
	Mild Tinnitus	0	2	3	0	1	0
	Borderline Tinnitus	0	0	1	0	0	0
		Borderline Tinnitus	Mild Tinnitus	Moderate Tinnitus	Substantial Tinnitus	Severe Tinnitus	Catastrophic Tinnitu
		BEFORE					

Table 3 - Change in Tinnitus Severity at 6 Weeks

To help with understanding this diagram, refer to the yellow 7. This number indicates that there are 7 people who rated their tinnitus as substantial at baseline and moderate at 6 weeks.

		12 Weeks					
AFTER	Catastrophic Tinnitus	0	0	0	0	0	0
	Severe Tinnitus	0	0	0	0	2	0
	Substantial Tinnitus	0	0	1	5	0	0
	Moderate Tinnitus	0	1	4	4	1	1
	Mild Tinnitus	0	2	4	1	1	0
	Borderline Tinnitus	0	1	2	0	0	0
		Borderline Tinnitus	Mild Tinnitus	Moderate Tinnitus	Substantial Tinnitus	Severe Tinnitus	Catastrophic Tinnitu
		BEFORE					

Table 4 - Change in Tinnitus Severity at 12 Weeks

You can see that in general, patients have rated their tinnitus less severe at the treatment milestones. We will see later in the statistics section, that there is a statistically significant change in severity.

These diagrams can be further simplified and augmented with data that includes dropouts due to adverse outcomes.

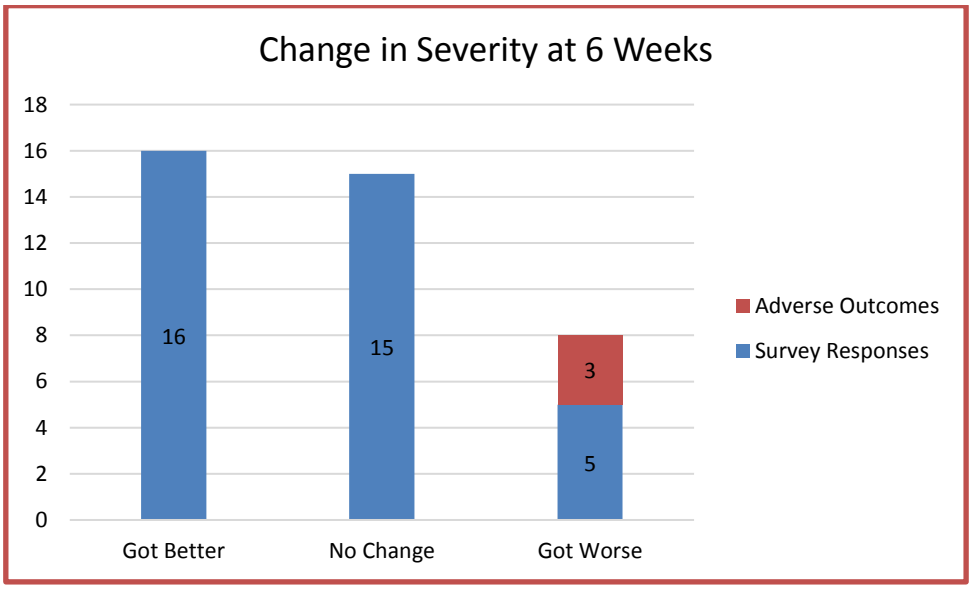


Figure 2 - Simplified Change in Severity at 6 weeks

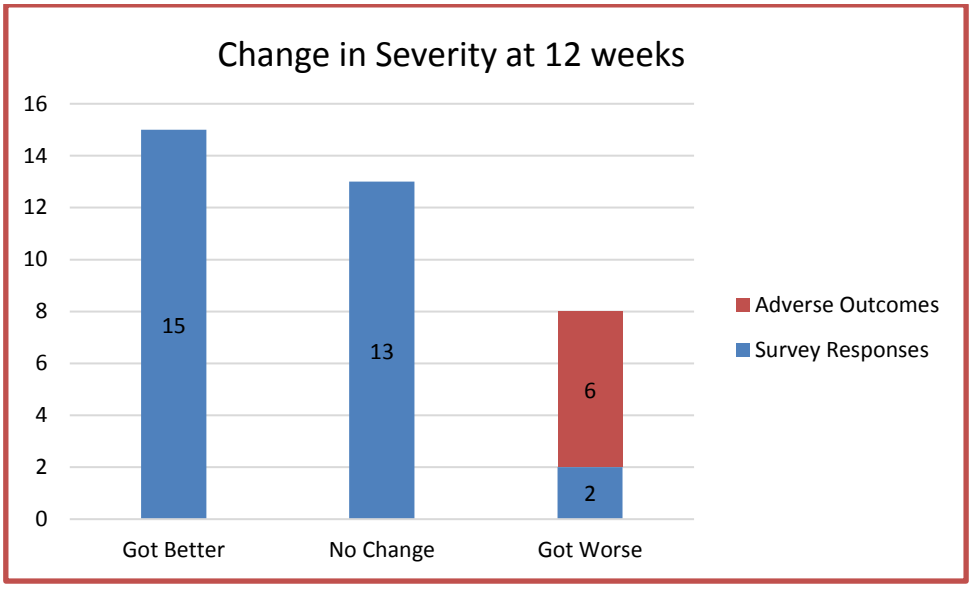


Figure 3 - Simplified Change in Severity at 12 weeks

At 12 weeks, approximately 42% got better, 36% stayed the same and 22% either got worse or dropped out due to adverse outcomes.

How do you rate the loudness of your tinnitus over the last week compared with the loudness during the week preceding the device fitting appointment?

The responses at the 6 and 12-week milestones are shown in the below chart:

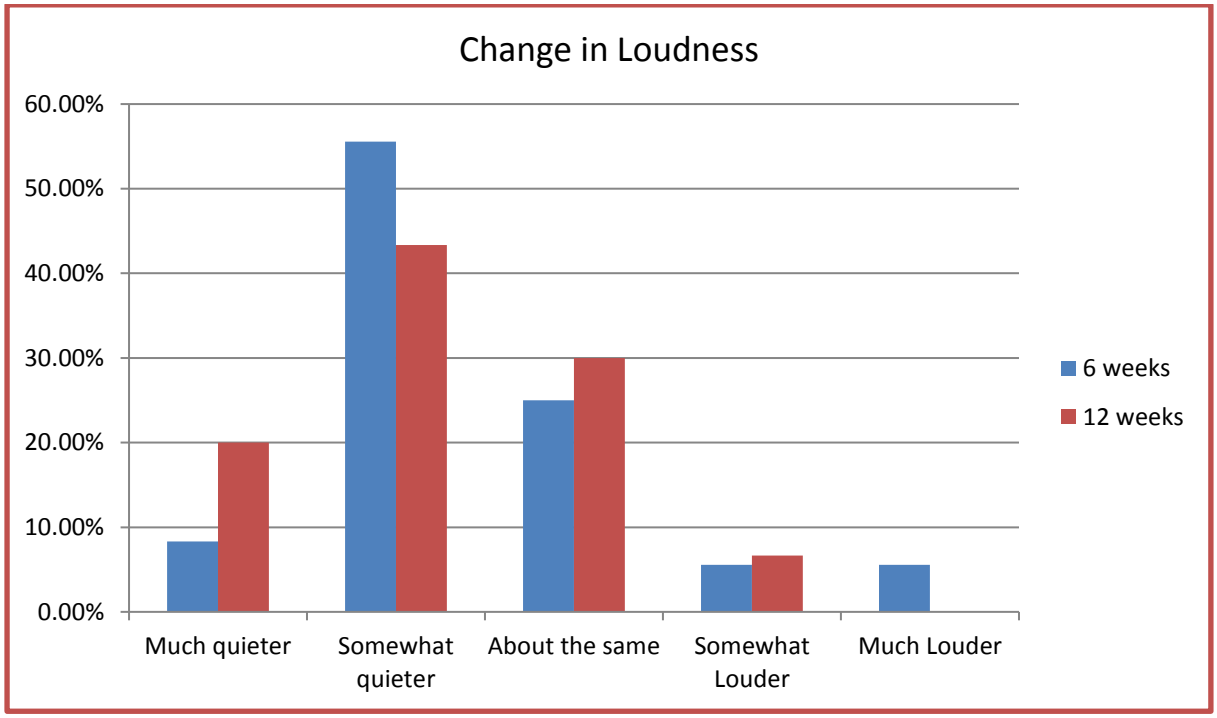


Figure 4- Change in Loudness

Have you experienced any changes to the bothersomeness of your tinnitus since the device fitting appointment?

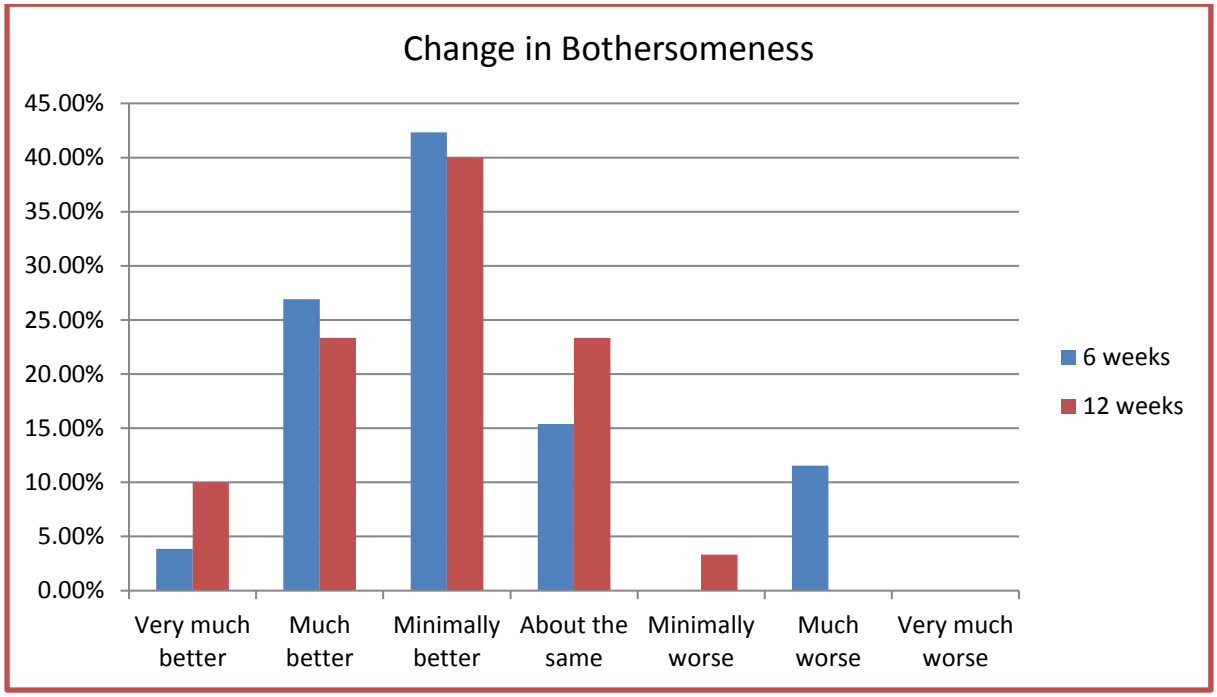


Figure 5 - Change in Bothersomeness

Did you complete your TFI (Tinnitus Functional Index) in the part of the survey you filled in before you started treatment? If so, we would like you to click "Yes" and repeat the TFI. This will take about 5 minutes and will help to assess whether your tinnitus severity has changed.NB: If you did NOT fill in the TFI last time, then please click "No."

Of the 36 completed 6-week surveys, 34 patients provided TFI information. Of the 30 completed 12-week surveys, 29 provided TFI information.

The TFI scores at the 6 and 12-week milestones compared with baseline are shown in the below chart.

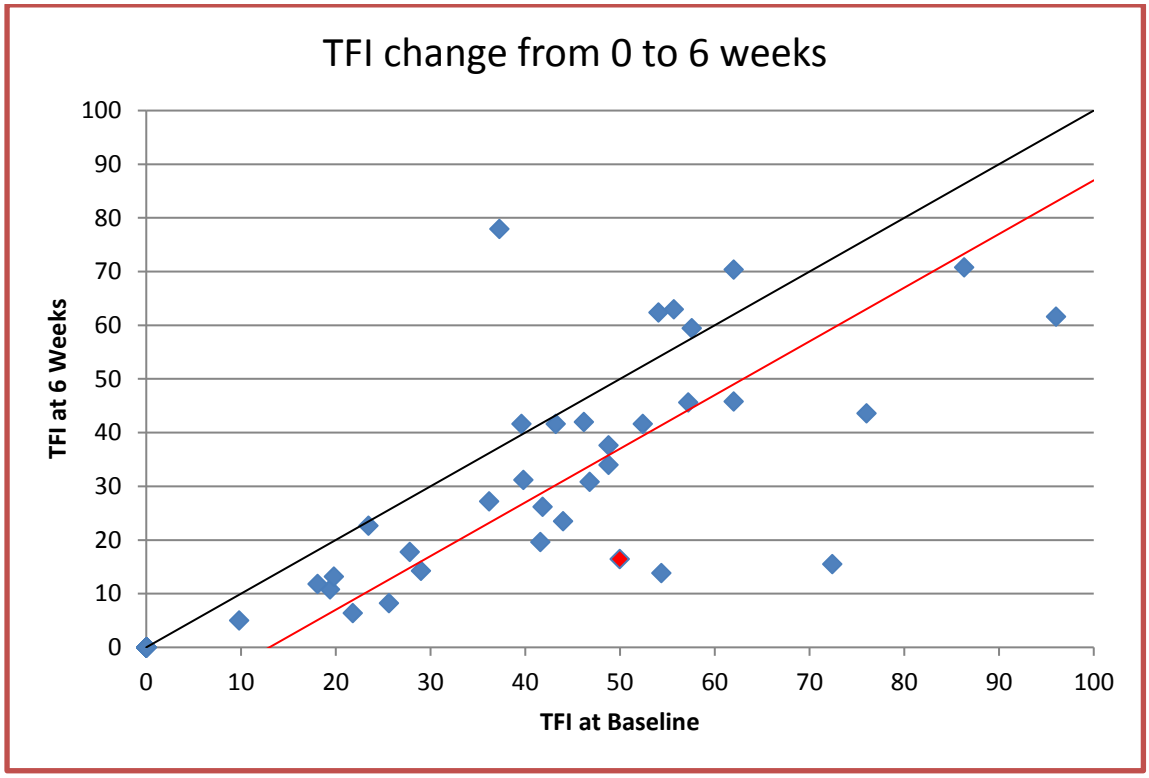


Figure 6 - TFI changes from baseline at 6 weeks

To help understand this diagram, note that the dot in red represents a patient who had a TFI of about 50 at baseline (draw a vertical line down to the baseline axis) and about 16 at 6 weeks (draw a horizontal line to the 6 weeks axis), quite an improvement.

The black diagonal line represents a line of no change, while the red line represents the minimally clinical important difference (MCID). The MCID is the minimal difference that can be considered significant to a patient. For TFI, this is 13 points. Data points below the red line represent patients with a clinically significant change.

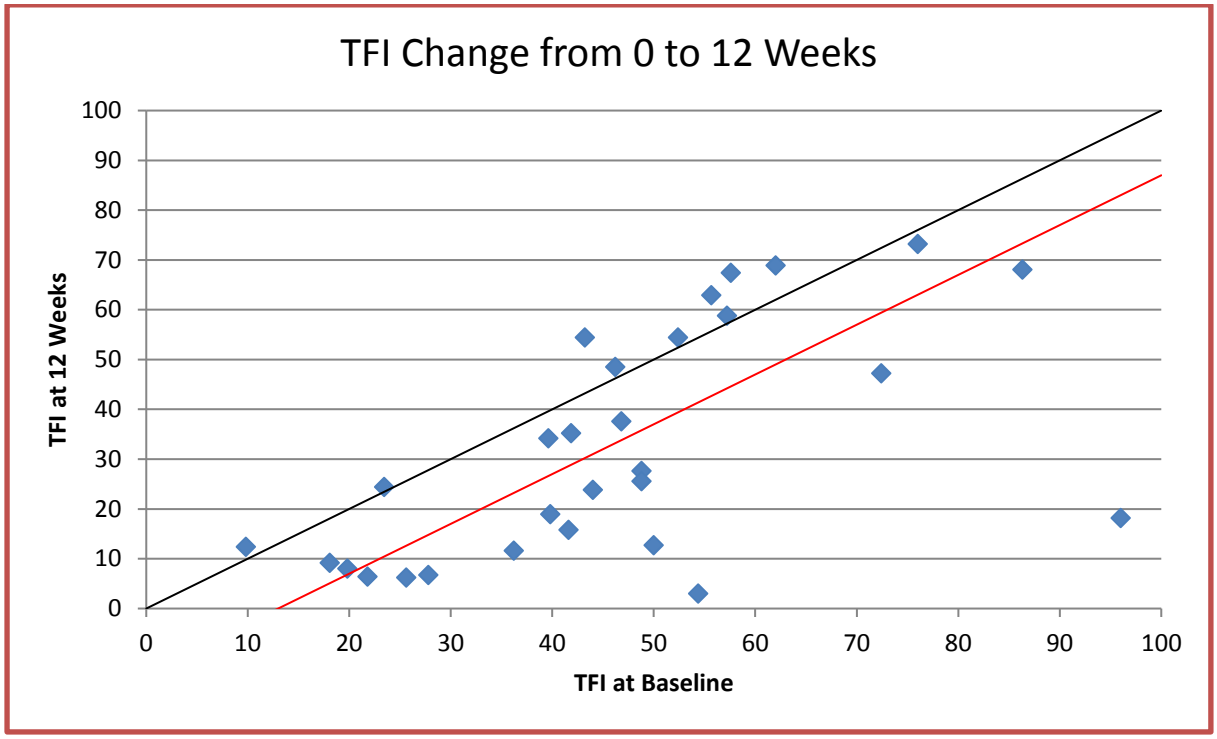
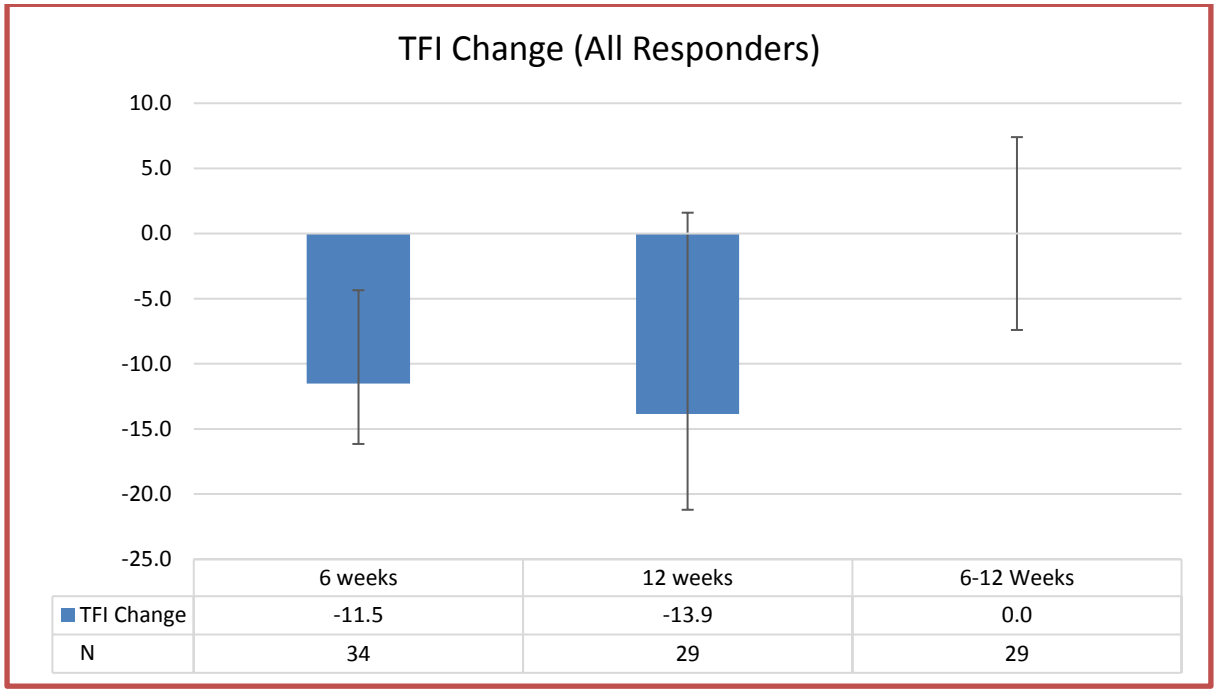


Figure 7 - TFI changes from baseline at 12 weeks

You can see that, in general, there are improvements, although this is not the case for all people (and in fact some people have experienced worsening).

This chart shows the average change in TFI for all responders (i.e. those that either completed the 6 week or 12-week surveys):



	6 weeks	12 weeks	6-12 Weeks
TFI Change	-11.5	-13.9	0.0
N	34	29	29

Figure 8 – Average TFI Change for all responders

The error bars represent the 25 and 75% percentiles.

This chart shows the same information, but this time only for those patients who completed both 6 and 12-week surveys:

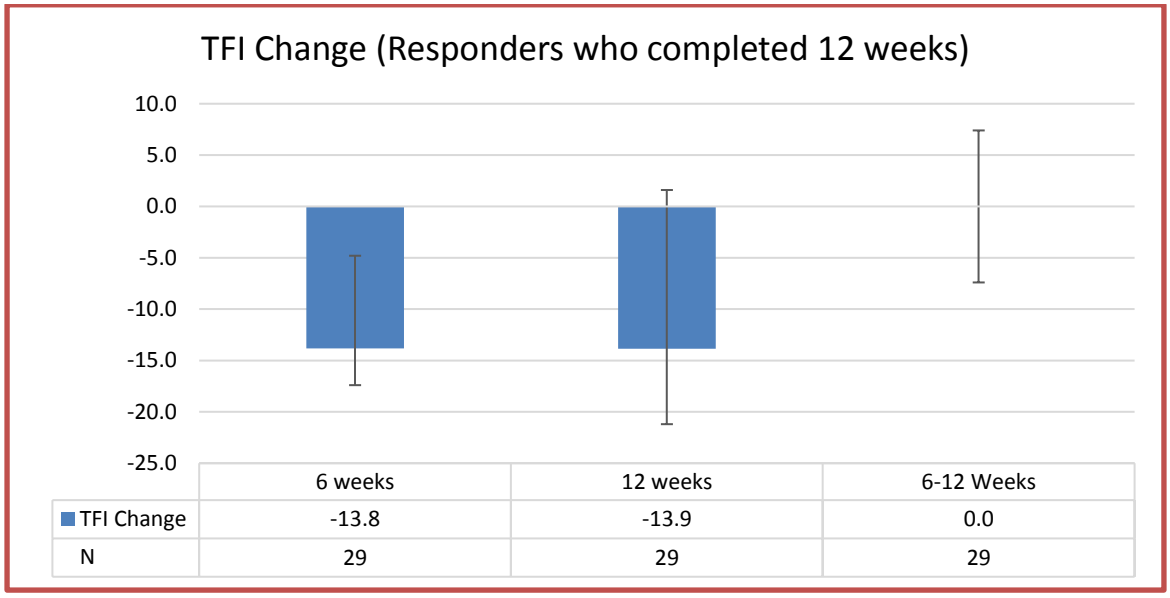


Figure 9 - Average TFI Change for patients who completed their 12-week surveys

We will see in the statistics section later that the changes in TFI from 0 to 6 weeks and 0 to 12 weeks are statistically significant.

The percentage of patients with a clinically significant change (13 points or more) was 48%. When adding in those patients who dropped out due to adverse outcomes, this percentage reduces to about 40%.

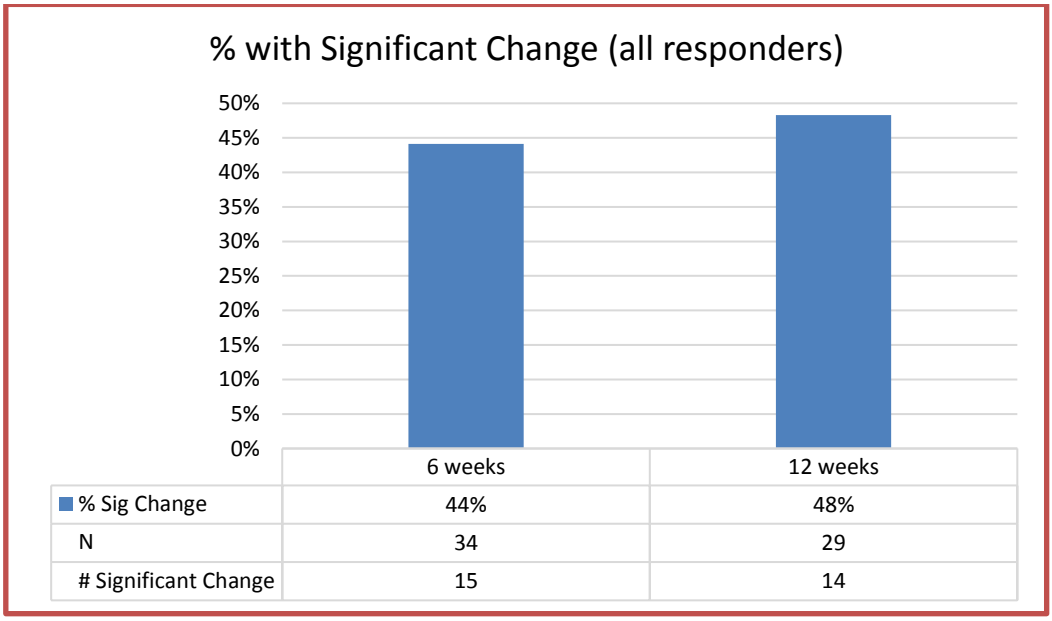


Figure 10 - Percentage of patients with clinically significant change

This chart shows the TFI trajectory of each patient from 0 to 6 to 12 weeks (for patients that completed the full 12 weeks only):

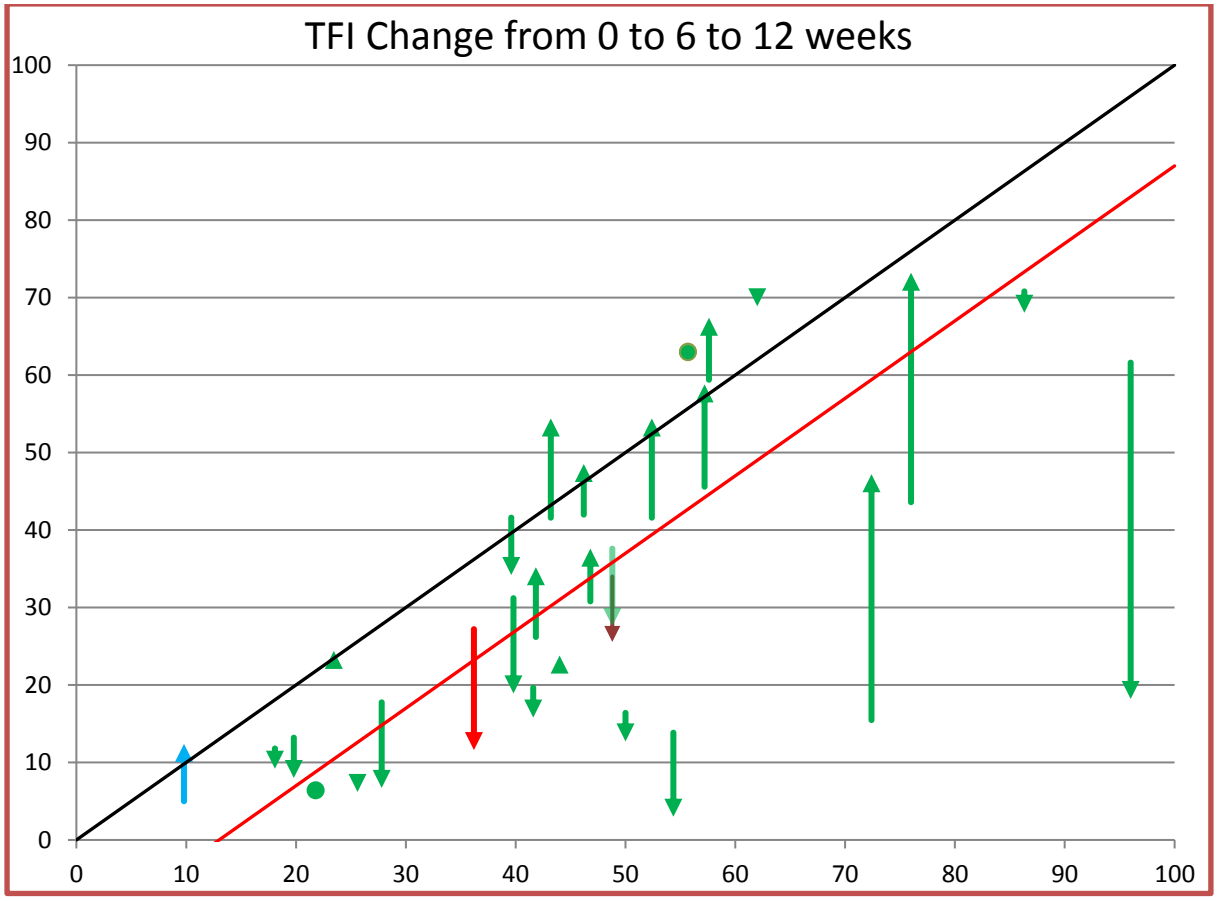


Figure 11- TFI Trajectory of each patient from 0 to 6 to 12 weeks

To help explain this chart, each patient is represented by an arrow (or a dot if their TFI does not change from 6 to 12 weeks). The baseline TFI of a patient can be obtained by finding out where the arrow intersects with the x-axis (by extending the arrow if necessary). Thus, the baseline TFI for the patient represented by the blue arrow is about 10. For the patient represented by the red arrow is it about 36. The patient's TFI at 6 weeks is the value of TFI on the y-axis on the blunt side of the arrow. Thus, for the patient represented by the blue arrow, it is about 5 and for the person represented by the red arrow it is about 27. And the patient's TFI at 12 weeks is the value of TFI on the y-axis on the pointy side of the arrow. So, again the TFI at 12 weeks of the patient represented by the blue arrow is about 12, and for the person represented by the red arrow it is about 12 also. An arrow pointing up means that there is a worsening of TFI from 6 to 12 weeks, and an arrow starting below the black line means there is an improvement from 0 to 6 weeks.

This chart shows the change in the distribution of TFI at each of the milestones:

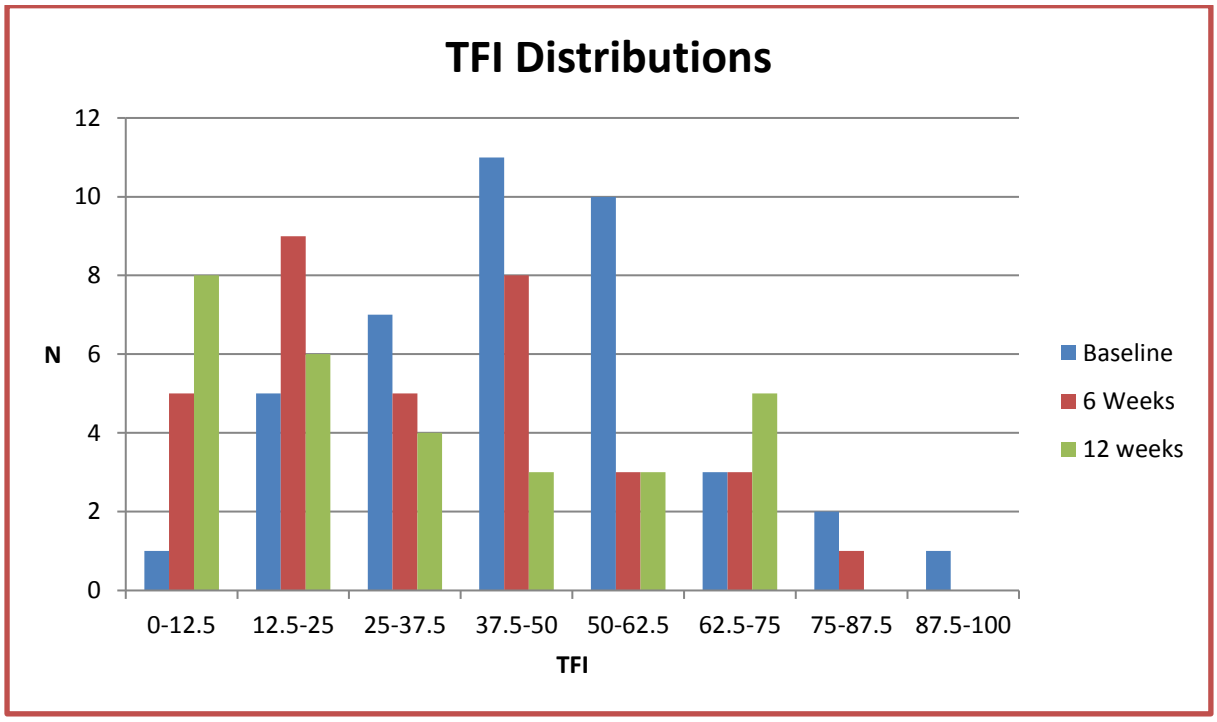


Figure 12 - TFI Distributions at treatment milestones

How compliant were you with treatment during the last 6 weeks? NB: Neuromod's instructions state to use the device for 1 to 2 sessions per day of 30 minutes.

Patients were asked to respond with Fully compliant (followed instructions exactly), Mostly compliant (>90%), Partially compliant (>50%), Not very compliant (<50%).

At 6 weeks, all but 2 were either Fully Compliant or Mostly compliant, and at 12 weeks all but 1 were Fully Compliant or Mostly compliant. There were no statistically significant relationships between compliance and TFI reduction in our analysis of variance tests.

How do you rate your experience with Neuromod during this appointment?

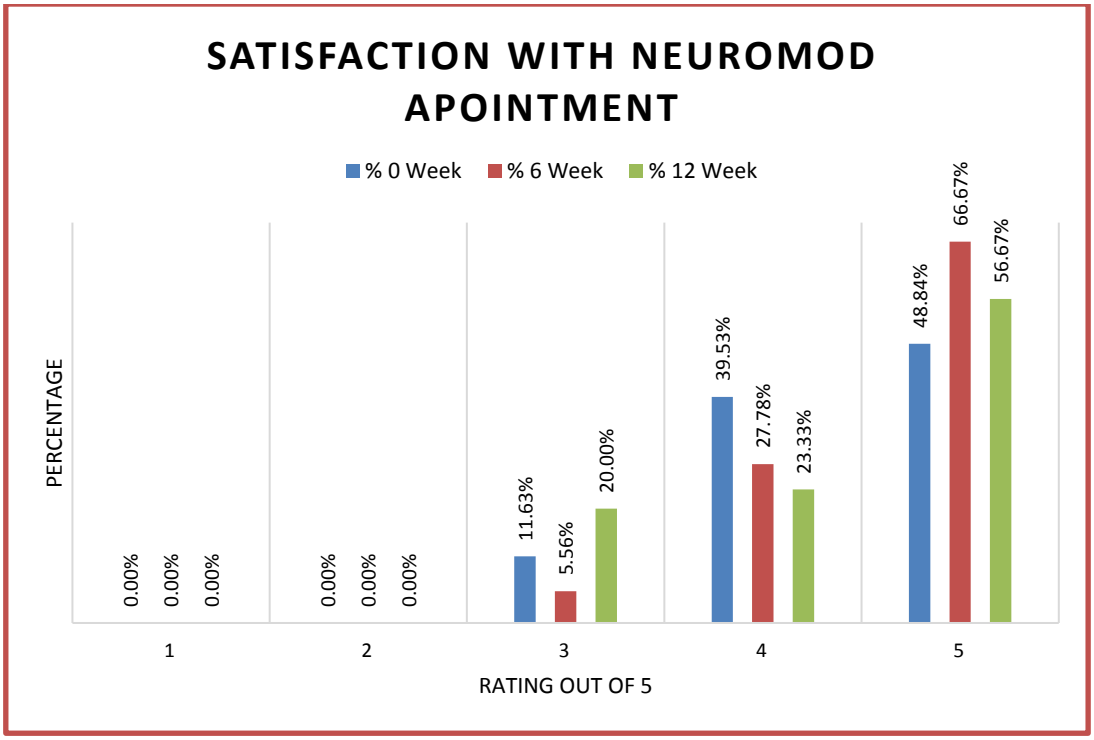


Figure 13- Satisfaction with Neuromod - Ratings Breakdown

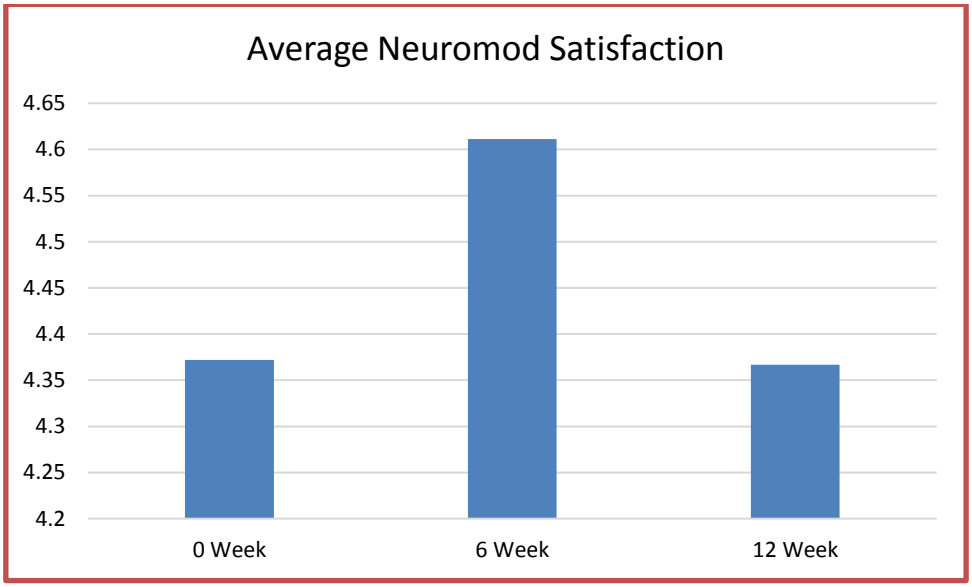


Figure 14 - Average Satisfaction with Neuromod by visit

Patients expressed a high degree of satisfaction with their Neuromod appointments.

Has the nature of your tinnitus changed since the device fitting appointment? If it has changed, describe how it is changed.

Refer to "Appendix 5 – Free Text Patient Responses" for a list of response to this question.

Please provide some feedback about your experience of tinnitus during the last week and how it is affecting your life.

Refer to “Appendix 5 – Free Text Patient Responses” for a list of response to this question.

Section 5: Impact of factors on TFI changes

We saw in the previous section that Lenire users experienced an overall average decline in TFI (and in section 6, we will see this is statistically significant). In this section we look at factors which correlate with this reduction. Potential users of the Lenire may find this section interesting as it will help to determine if their individual characteristics match those in the sample who have had the most success with the Lenire.

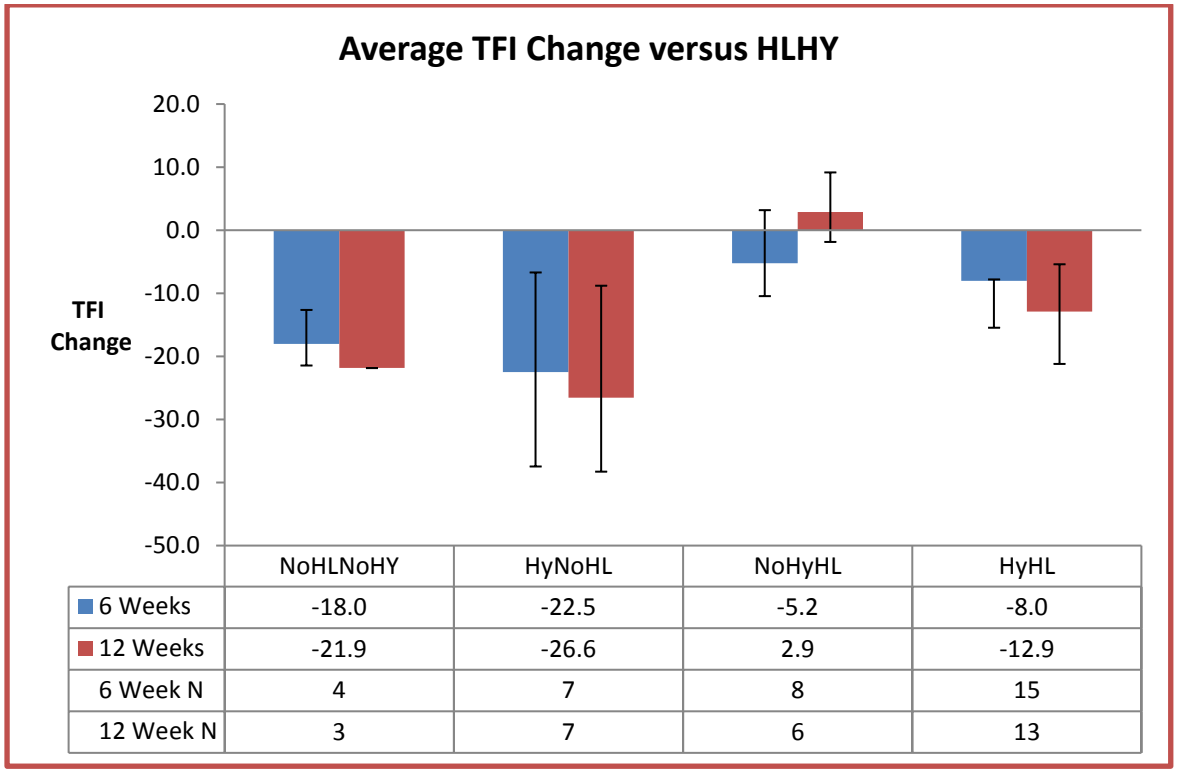
As mentioned in the introduction section, we will only show charts in this section that are associated with data that has shown some statistical significance at 12 weeks. We will not discuss the actual statistics in this section; this will be done in subsequent sections.

Hyperacusis and Hearing Loss

Our main findings were that the Lenire appears to have the most effect on patients with either hyperacusis or no hearing loss or both. We investigated the effect in combination and separately.

Let's look at them in combination first. When looking in combination, I decided to make each of the factors binary. That is, those who rated themselves as having no hyperacusis were scored as such, and all others were rated as having some hyperacusis (and same for hearing loss). Using this approach, we get a reasonable sample size for each combination and we also remove the subjectivity around patients describing their condition as mild or moderate, for example.

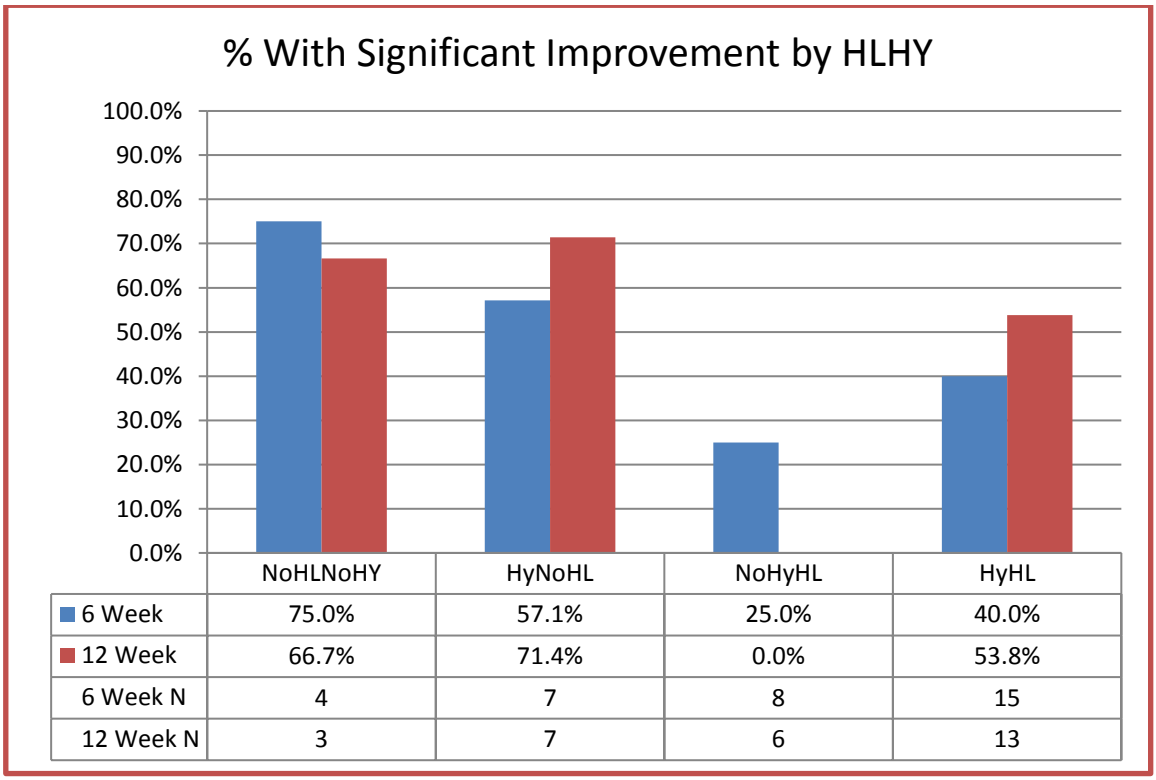
The charts below provide a summary of the TFI loss for each combination. So, for example, at 12 weeks those with Hyperacusis and No hearing loss averaged a TFI reduction of -26.6 points, which is quite high. A large reduction was also experienced by those with no hyperacusis and no hearing loss. The difference between the Hyperacusis No Hearing Loss group and the No Hyperacusis and Hearing Loss group was statistically significant.



	NoHLNoHY	HyNoHL	NoHyHL	HyHL
6 Weeks	-18.0	-22.5	-5.2	-8.0
12 Weeks	-21.9	-26.6	2.9	-12.9
6 Week N	4	7	8	15
12 Week N	3	7	6	13

Figure 15 - Average TFI change by Hearing Loss and Hyperacusis combinations

We can also look at the number of patients who experienced a significant improvement (13 or more TFI points). This pattern is again statistically significant.



	NoHLNoHY	HyNoHL	NoHyHL	HyHL
6 Week	75.0%	57.1%	25.0%	40.0%
12 Week	66.7%	71.4%	0.0%	53.8%
6 Week N	4	7	8	15
12 Week N	3	7	6	13

Figure 16 - Percentage of patients with Significant change by Hyperacusis and Hearing Loss combinations

We can see that 71.4% of patients with Hyperacusis and no hearing loss experienced a significant improvement (although the sample size is very small). Those with no hyperacusis and hearing loss fared particularly badly.

This chart shows more details:

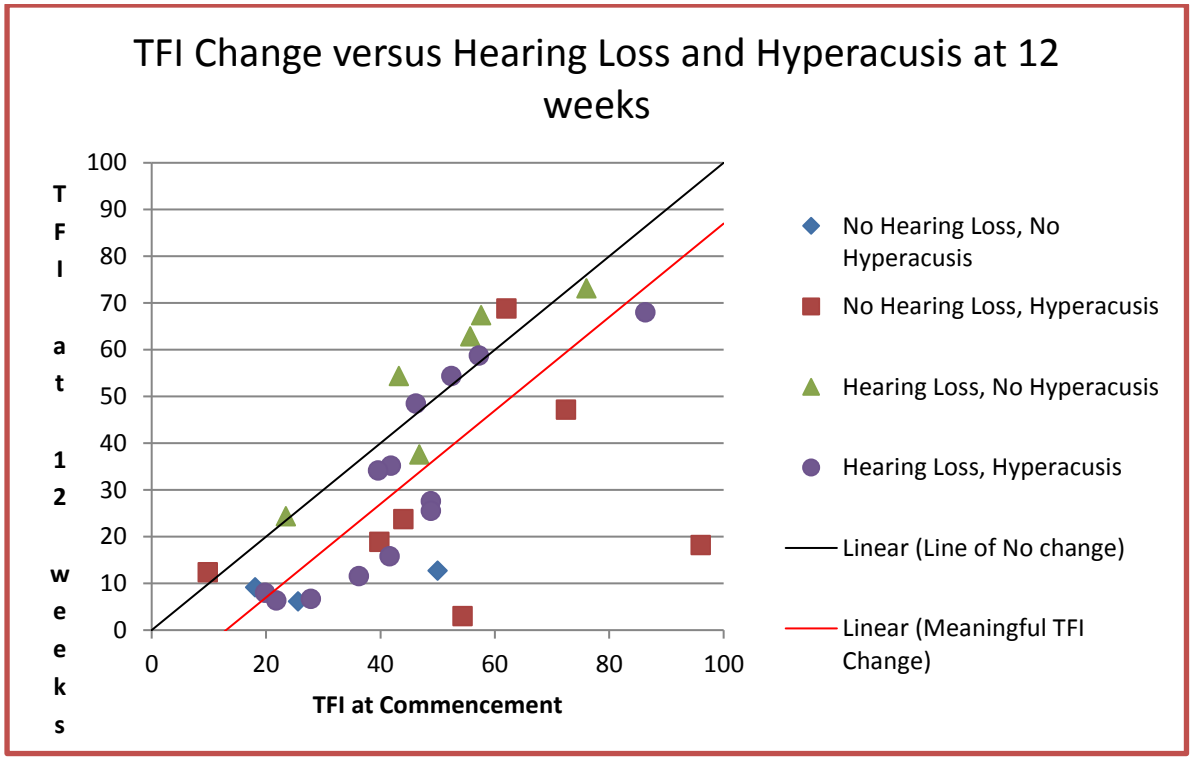


Figure 17 - TFI Change Scatter Plot showing Hearing Loss and Hyperacusis Combinations

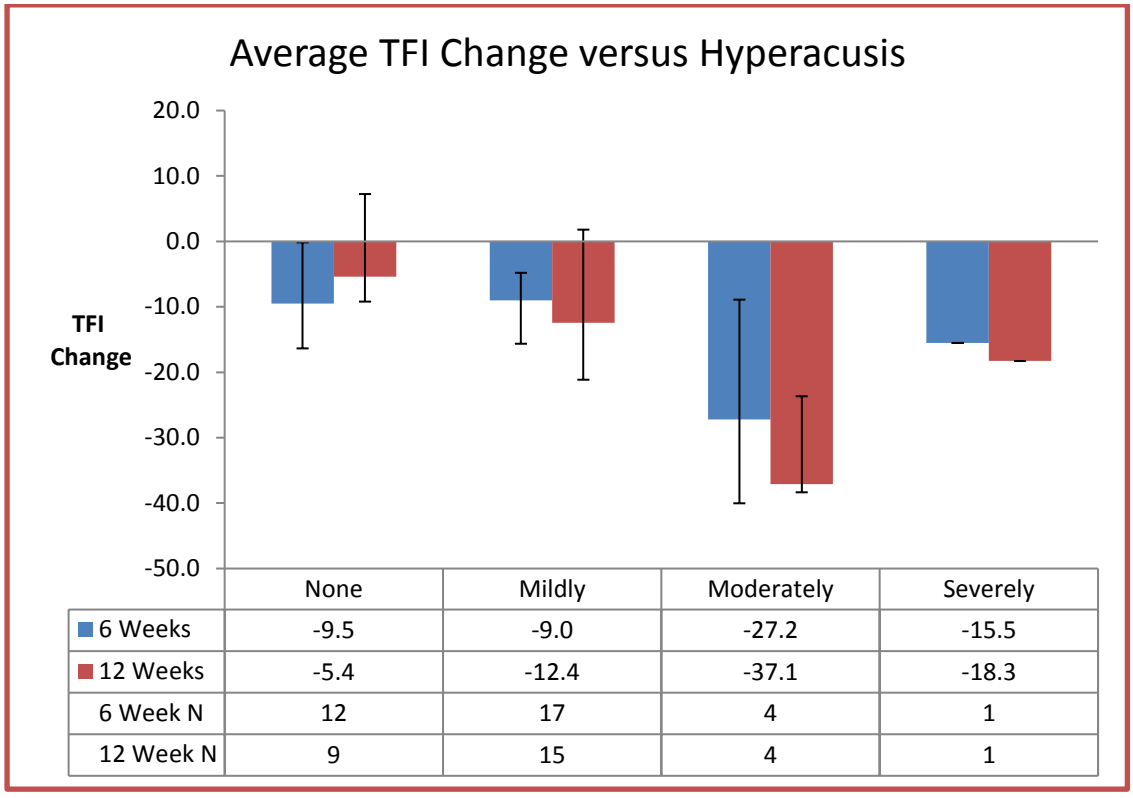
Severity

We saw significant differences in TFI changes in the groups within the Severity factors, however this was due to some large reductions in groups with small sample sizes. These won't be shown here.

Hyperacusis

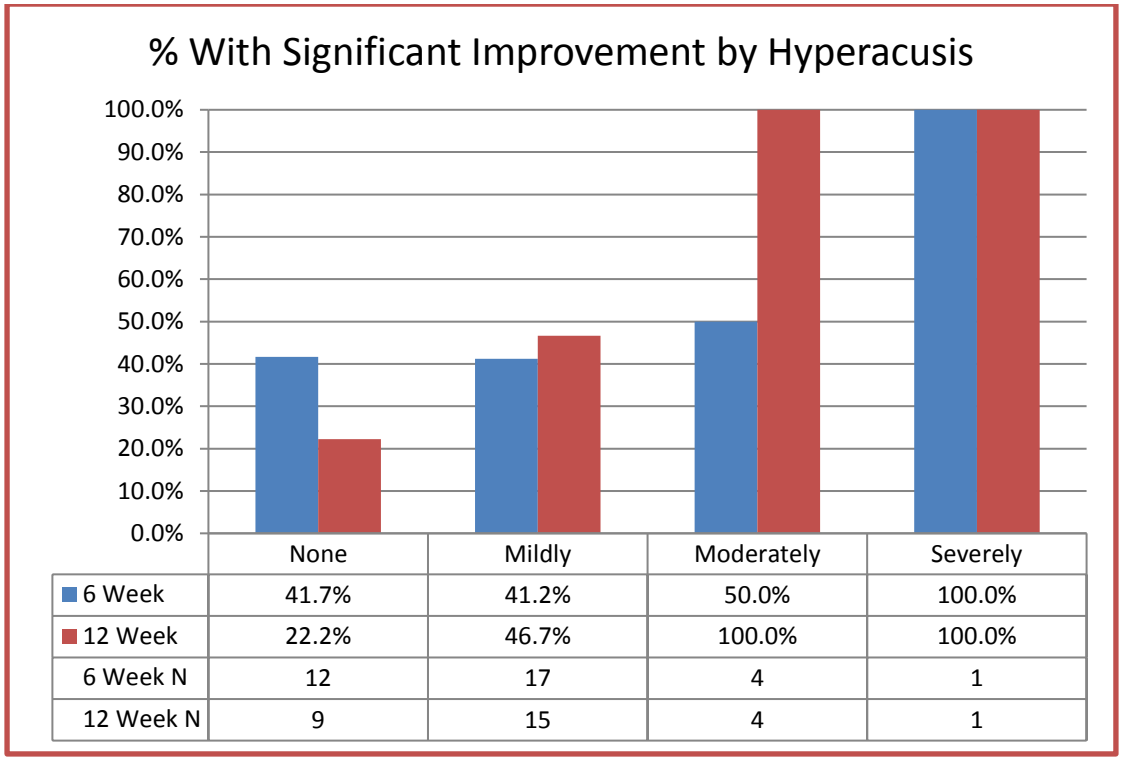
We saw some significant changes in the TFI groups within the Hyperacusis factor. The change in TFI when comparing those with no Hyperacusis and those with moderate hyperacusis was statistically significant.

In addition, when comparing the patients who obtained a clinically meaningful change, and their group membership, this pattern was also statistically significant.



	None	Mildly	Moderately	Severely
6 Weeks	-9.5	-9.0	-27.2	-15.5
12 Weeks	-5.4	-12.4	-37.1	-18.3
6 Week N	12	17	4	1
12 Week N	9	15	4	1

Figure 18 - Average TFI changes by Hyperacusis

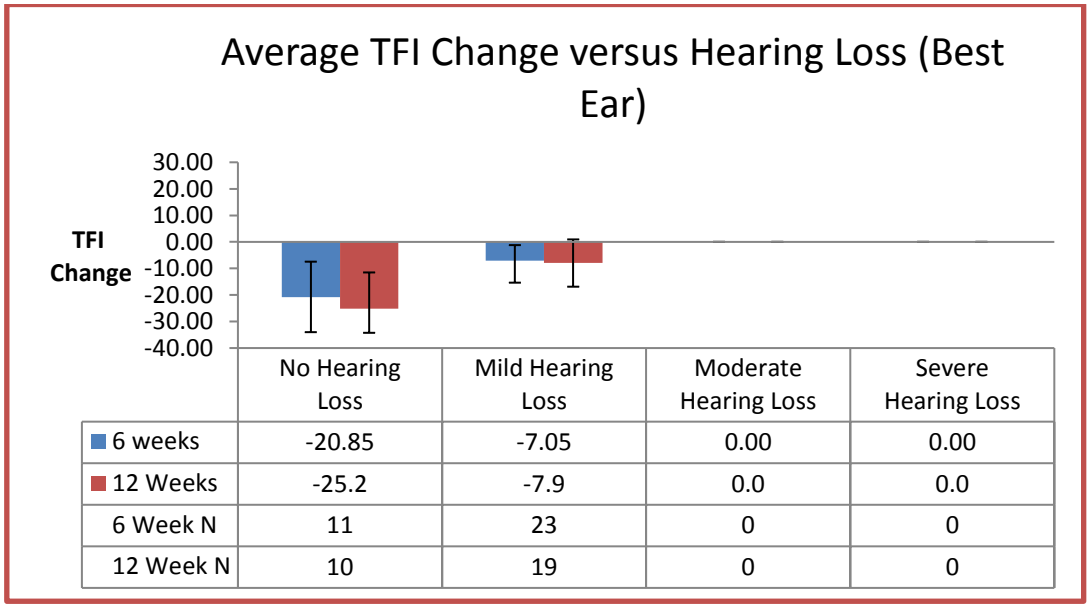


	None	Mildly	Moderately	Severely
6 Week	41.7%	41.2%	50.0%	100.0%
12 Week	22.2%	46.7%	100.0%	100.0%
6 Week N	12	17	4	1
12 Week N	9	15	4	1

Figure 19 - Percentage of Patients with Significant Change by Hyperacusis

Hearing Loss

We looked at Hearing Loss in several ways (e.g. worst hearing of each ear, best hearing of each ear, average hearing loss, no hearing loss at all versus some hearing loss). All showed significant difference in TFI reduction between some groups except Average Hearing Loss. Here are the diagrams for best ear (which showed the most significance when comparing group differences):

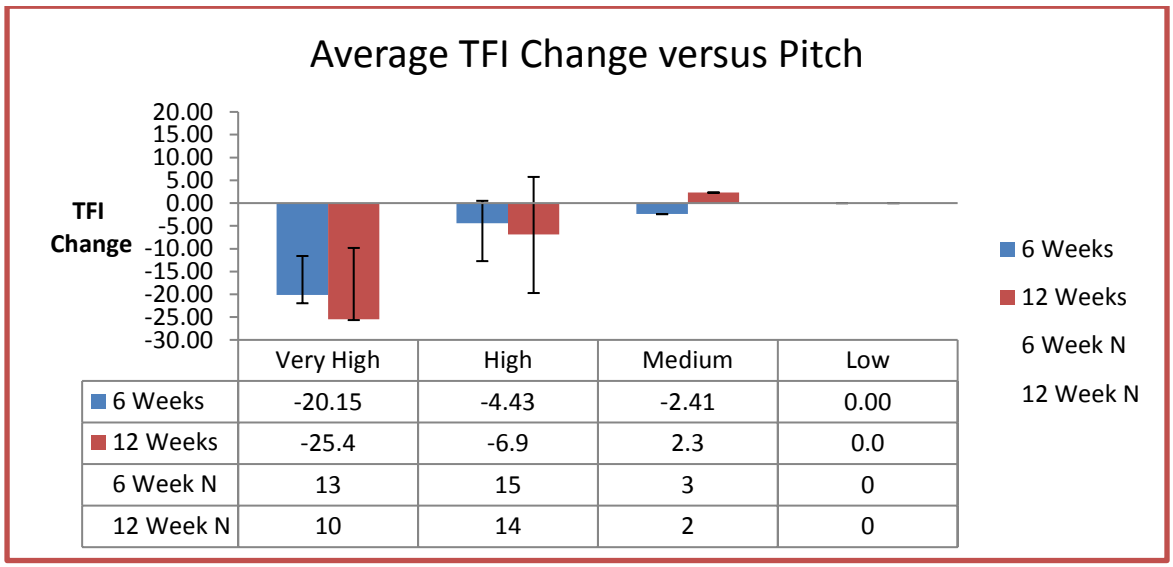


	No Hearing Loss	Mild Hearing Loss	Moderate Hearing Loss	Severe Hearing Loss
6 weeks	-20.85	-7.05	0.00	0.00
12 Weeks	-25.2	-7.9	0.0	0.0
6 Week N	11	23	0	0
12 Week N	10	19	0	0

Figure 20 - Average TFI change by Hearing Loss

Pitch

We saw statistically significant changes in TFI reduction between the High and Very High groups in the Pitch factor. This question was not specific about frequencies which represented high and very high.

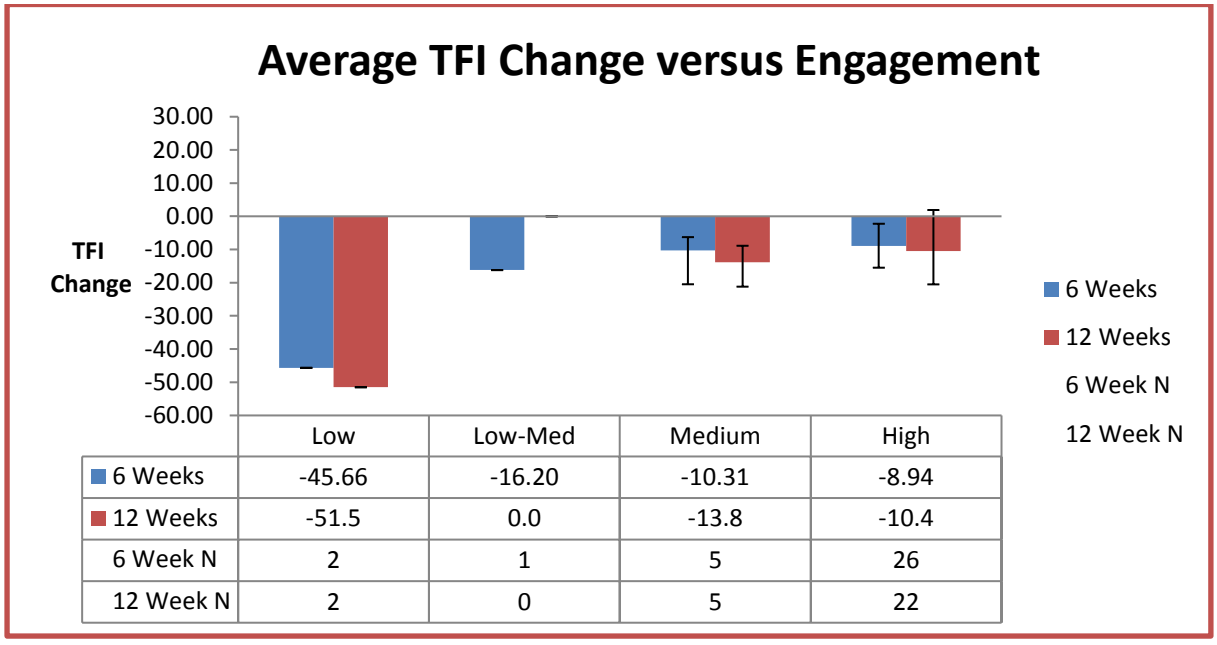


	Very High	High	Medium	Low
6 Weeks	-20.15	-4.43	-2.41	0.00
12 Weeks	-25.4	-6.9	2.3	0.0
6 Week N	13	15	3	0
12 Week N	10	14	2	0

Figure 21 - Average TFI change by Pitch

Engagement

Engagement is a measure of how much the patient interacted with the forum during the treatment. Quite a bit more is said about engagement in Appendix 7. We saw statistically significant differences in TFI reduction between the High and Low groups and between the Medium and Low groups, however the number of data points in the low group is very small.



	Low	Low-Med	Medium	High
6 Weeks	-45.66	-16.20	-10.31	-8.94
12 Weeks	-51.5	0.0	-13.8	-10.4
6 Week N	2	1	5	26
12 Week N	2	0	5	22

Figure 22- TFI Change Versus Engagement

Section 6: Statistical Analysis

WARNING Now Entering the Statistics Zone **WARNING**

In this section we perform a statistical analysis on the data we have collected during this study. At the outset it is important to again emphasize that we have a **very small sample**, and many of the tests described here are normally used on larger sample sizes. In addition, we **do not have a control arm**, so it's difficult to make conclusions from the results. It's possible the results we are seeing are related to the placebo effect.

Paired t-tests

Paired t-tests[2] are used to find if there is any difference in means of a sample of matched pairs. The matched pairs in this instance are the collection of patients' TFI at baseline and at 6 weeks, TFI at baseline and 12 weeks and TFI at 6 weeks and 12 weeks.

	Average Change	Paired t test p score (One Tailed)	Paired t test p score (Two Tailed)	Lower 95% confidence interval	Upper 95% confidence interval
0 to 6 weeks	-11.5	0.000	0.000	-5.7	-17.4
0 to 12 weeks	-13.9	0.001	0.001	-6.5	-21.2
6 to 12 weeks	0.0	0.99			

Table 5 - TFI Paired t-tests

We can see that there was a significant reduction in TFI both at the 6 and 12-week milestones. There is no significance result from 6 to 12 weeks. All the average benefits accrued during the first 6 weeks.

Note that the decrease in TFI from 0-12 weeks is greater than for 0-6 weeks, yet the change from 6-12 weeks is very small. The reason for this is we are included all patients in the 0-6 weeks results, including those that dropped out and did not proceed to the 12-week milestone.

One-Way Anova

The table below shows the one-way ANOVA results on the change in TFI for each factor. ANOVA is a means of determining if there is any significant difference in the changes in group means within a factor. Items shaded in green are significant.

[2] The Wilcoxon signed-rank test should be used where the distribution of differences between the TFI scores cannot be assumed to be normally distributed. Our sample size is small, so it is difficult to determine if this is the case, although the distribution *appears* to be roughly normal. Using this Wilcoxon signed-rank test, we get very similar p-scores to those generated by the student t-test. If we complete a Kolmogorov-Smirnov test for normality, the can reject the null hypothesis that the differences in scores is normally distributed. However, because the p-scores are very similar and our sample size is so small it will be difficult to pass this test, we have used the student t-test.

	One Way Anova p score	
Factor	6 Weeks	12 Weeks
Hyperacusis	0.255	0.042
Duration	0.090	0.215
Age	0.467	0.602
Hearing Loss (Average)	0.076	0.061
Hearing Loss (Worst Ear)	0.035	0.020
Hearing Loss (Best Ear)	0.022	0.019
Pitch	0.029	0.032
Loudness	0.558	0.052
Intermittency	0.628	0.264
Engagement	0.021	0.010
Source	0.611	0.719
Reactivity to Noise	0.459	0.530
Variation within a Day	0.989	0.998
Variation between Days	0.364	0.779
Compliance	0.302	0.911
Gender	0.081	0.054
Somatic Modulation	0.790	0.589
Hearing Loss Binary	0.022	0.019
Hyperacusis Binary	0.612	0.113
HL and Hy Binary	0.145	0.033
TFI	0.269	0.282
Severity	0.311	0.001

Table 6 - One Way Anova Results

We can see from the above results, that the main significant results were related to Hyperacusis, Hearing Loss, Pitch and Engagement. It's also interesting to see what is not significant; Age, Duration, TFI, Loudness and Intermittency are all not significant.

The relevant Tukey HSD results (providing information on which group means were significantly different within each factor) are shown below. We've missed out severity factor here as this was due to one data point in the "Catastrophic" group.

Factor	Group 1	Group 2	p	Delta	Lower CI	Upper CI
Hyperacusis	None	Moderately	0.026	31.75	3.10	60.39
Hearing Loss (Worst Ear)	No Hearing Loss	Mild Hearing Loss	0.020	18.00	3.15	32.85
Hearing Loss (Best Ear)	No Hearing Loss	Mild Hearing Loss	0.019	17.24	3.08	31.40
Pitch	Very High	High	0.048	18.54	0.15	36.93
Engagement	Low	High	0.007	41.06	10.36	71.76
Engagement	Low	Medium	0.032	37.66	2.88	72.44
Hearing Loss Binary	No He	H	0.019	17.24	3.08	31.40
HL and Hy Binary	HyNoHL	NoHyHL	0.024	29.43	3.18	55.68

Table 7 - Tukey HSD results

In the ANOVA table, we've added some additional factors from those in the original report. Some of the original patient questions asked for a grading of the extent of a condition. For example, the patient was asked to rate hearing loss as one of None, Mild, Moderate or Severe. Because distinguishing between some of these (say Mild and Moderate) may be somewhat subjective, we've also chosen to rate these as either Hearing Loss or No Hearing Loss (Hearing Loss Binary).

The possible options for the factors that originate directly form the questionnaire are shown in Appendix 1. An explanation of the derivative factors is shown below:

Hearing Loss

Hearing Loss is rated from 1 to 4 (None, Mild, Moderate, Severe) for each ear. The derivative factors for hearing loss were explained in report 1 [3] and shown below:

#	Description	Method
1	Average	Add up left and right scores, divide by 2
2	Worst Ear	Take the maximum of the left and right score. This corresponds to the worst ear.
3	Best Ear	Take the minimum of the left and right score. This corresponds to the best ear.
4	Binary	1 for no hearing loss in both ears, 2 for some hearing loss in either ear.

Hyperacusis Binary is rated as 1 for no Hyperacusis and a 2 for at least some Hyperacusis.

HL and HY Binary is rated as per the below table:

	No Hearing Loss (NoHL)	Hearing Loss (HL)
No Hyperacusis (NoHy)	1	3
Hyperacusis (Hy)	2	4

Table 8 - Rating combinations of Hyperacusis and Hearing Loss

Engagement is a factor that is meant to represent the extent to which the patient engages with the study and the Tinnitus Hub forum. It's also a measure of the amount of evidence provided by the patient that supports the proposition that they are a genuine user of the Lenire. Information on how the Engagement scores are derived may be found in Appendix 7. Because this survey was conducted over the Internet and all communications were via email and forum communications, we thought it would be prudent to collect this information for further analysis and correlations.

Tinnitus Rating at Baseline

We rated TFI at baseline according to the below table:

	TFI Rating
<25	1
<50, >=25	2
<75, >=50	3
>=75	4

Table 9 - Computing TFI Rating

Fisher Exact Test

We looked at the number of patients who experienced a significant improvement (TFI reduction of at least 13 points) and conducted a Fisher Exact Test to test for independence of variables.

For example, for the Hyperacusis factor, this table provides information on the number of patients who experienced significant changes in TFI against those who did not:

	None	Mildly	Moderately	Severely
Significant change	1	6	4	1
Not Significant	7	8	0	0

Table 10 - Hyperacusis - Group membership frequency for patients with significant and not significant change

The Fisher Exact Test will tell us if there is if the difference in distribution across the various groups when comparing the patients with Significant Change and the patients with No significant change is by chance, or if there is a dependency. In this particular case, p=0.038 indicates that there is a dependency.

The table below considers all factors. A significant p-value indicates that there is a dependency:

	Fisher Test p score	
Factor	6 Weeks	12 Weeks
Hyperacusis	0.880	0.038
Duration	0.212	0.160
Age	0.932	0.106
Hearing Loss (Average)	0.187	0.129
Hearing Loss (Worst Ear)	0.273	0.105
Hearing Loss (Best Ear)	0.151	0.128
Pitch	0.028	0.099
Intermittency	0.490	0.228
Engagement	0.321	0.310
Reactivity to Noise	0.570	0.584
Variation within a day	0.888	0.510
Variation between days	0.908	0.688
Compliance	0.416	1.000
Gender	0.672	0.215
Somatic Modulation	0.697	0.682
Loudness	0.215	0.376
Hyperacusis Binary	1.000	0.109
Hearing Loss Binary	0.151	0.128
Hearing Loss and Hyp Binary	0.399	0.022
TFI	0.155	0.416
Severity	0.710	0.141

Table 11 - Fisher Exact Test Results

We can again see that we are seeing results around Hyperacusis and Hearing Loss.

Wilcoxon Signed Rank Test for Severity

We used the Wilcoxon Signed Rank test to see if we could see a change in the self-assessed severity rating provided by patients from 0 to 6 weeks, from 0 to 12 weeks and from 6 to 12 weeks. This test is similar to a paired t-test, however it makes no assumptions about the distribution of differences between the samples.

	Delta Median	p-value
0-6 Weeks	-1	0.01
0-12 Weeks	-0.5	0.00
6-12 weeks	0	0.15

Table 12 - Wilcoxon Signed Rank Test for Severity Changes

This test rejects the hypothesis that the distribution of differences follows a symmetric distribution around zero.

Chi Square Test for Severity

We also performed a Chi-Squared test on the change in Severity. The Chi-squared test is similar to the Fisher Exact test, with the "rows" this time being the 0, 6 and 12 week milestones. It's not possible to user the Fisher Exact test here due to the number of groups in the severity factor.

Factor	6 Weeks	12 Weeks
Severity	0.315	0.036

Table 13- Severity Chi Square Test

Linear Regressions

For factors with ordinal or ratio data types we also performed Linear Regressions comparing how changes in TFI vary with groups within factors. Where there were groupings (e.g. in Age, TFI and Duration) which could be removed, we did so for greater fidelity.

So, for example, here is a graphical representation of the linear regression for the Hyperacusis factor:

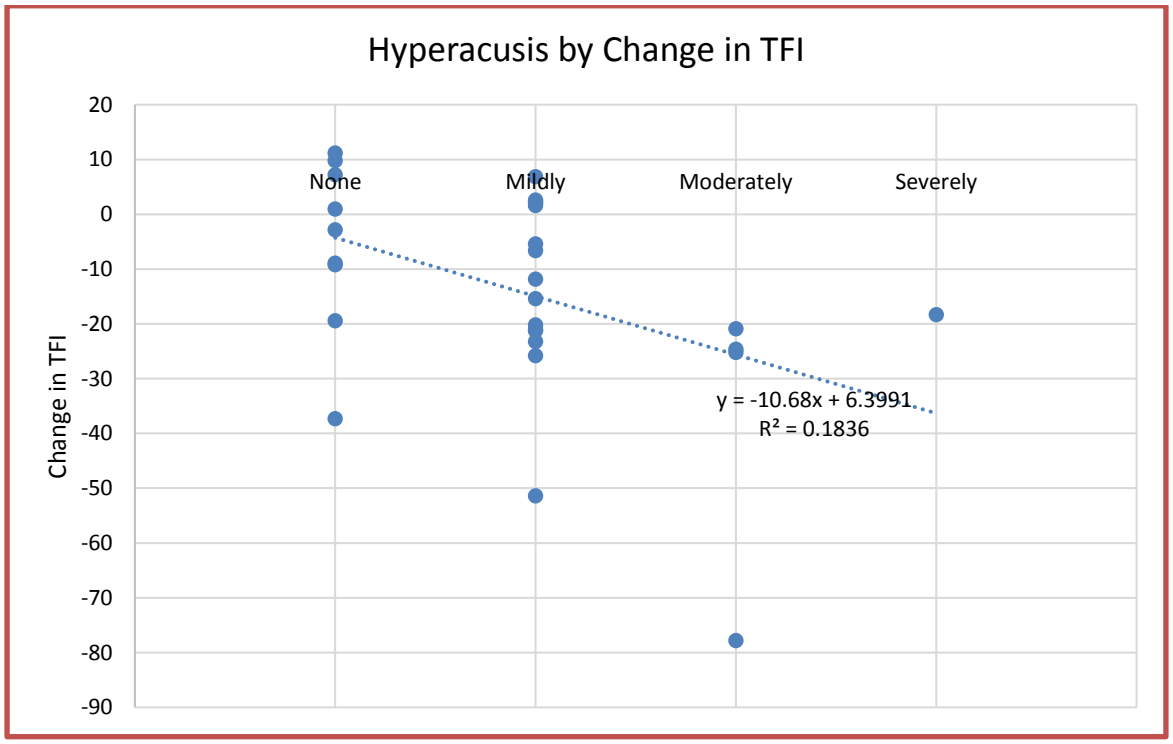


Figure 23 - Linear Regression - Hyperacusis and Change in TFI

The extent to which Hyperacusis is correlated with changes in TFI is measured by the p-value, and the extent to which the variation in the data is explained by the model is measured by the R^2 value. As mentioned in Appendix 2, Spearman's rank correlation or Kendall's Tau may be more appropriate for testing ordinal data, but results are similar. We also included the slope. A positive slope indicates that TFI is reducing as the factor is increasing (so, for example, engagement, which has a negative slope, indicates that the higher the level of engagement the lower the TFI reduction).

The table below summarised these numbers for different factors. P-values shaded in green are significant.

Linear Regressions	P Score		R2 (Adjusted)		Slope	
	6 Weeks	12 Weeks	6 Weeks	12 Weeks	6 Weeks	12 Weeks
Hyperacusis	0.198	0.020	0.022	0.153	5.021	10.680
Duration	0.006	0.076	0.188	0.079	-1.031	-0.918
Age	0.317	0.873	0.001	-0.036	-0.252	-0.049
Hearing Loss (Average)	0.033	0.058	0.108	0.094	-11.131	-11.883
Hearing Loss (Worst Ear)	0.063	0.148	0.076	0.042	-7.876	-7.311
Hearing Loss (Best Ear)	0.022	0.019	0.126	0.158	-13.802	-17.240
Intermittency	0.234	0.521	0.014	-0.021	-3.676	2.591
TFI	0.040	0.089	0.098	0.070	0.304	0.308
Pitch	0.019	0.011	0.134	0.187	-10.689	-15.132
Severity	0.951	0.010	-0.031	0.193	0.179	8.909
Loudness	0.275	0.057	0.007	0.096	3.945	8.391
Engagement	0.006	0.005	0.187	0.234	-9.451	-11.992
Compliance	0.326	0.032	0.000	0.128	4.183	-12.330

Table 14 - Linear Regression Results

We can see that Hyperacusis, pitch and engagement are again significant.

Group paired t-tests

In these tests we assumed that the only participants in the study were those that had a group characteristic. That is, for example, we assumed that only Males were permitted, or only those with Moderate Hyperacusis etc. We then looked to see if there was a significant change in their TFI via a pair-wise t-test (the same as in this section, except we are now filtering by group). The problem with this approach in that typically our sample size will be small, but it can be instructive. We should also note that as there is an overall significant change in TFI, it should not be unusual to see significant changes (the smaller sample sizes, however, will mitigate against this).

The table overleaf shows the groups which are significant. Each cell is shaded if the result is significant, and the colour of the shading indicates the sample size (Dark Green > =15, Light Green between 10 and 14, Pink between 5 and 9).

Factor	p-values				Description					
Somatic Modulation	0.00	0.14			Somatic	NonSomatic				
Gender	0.01	0.04			Male	Female				
Engagement	0.30		0.08	0.01	Low	Low-Med	Medium	High		
Compliance			0.18	0.00	Not very compliant (<50%)	Partially compliant (>50%)	Mostly compliant (>90%)	Fully compliant (followed instructions exactly)		
Variation within a day	0.33	0.05		0.08	It doesn't change at all	It's less bothersome in the mor	It's less bothersome in the ever	It fluctuates but there is no pattern		
Variation between Days	0.30	0.00	0.05		Constant	Some	Significant	0		
Reactivity	0.08	0.44	0.01	0.38	Sounds don't really affect me	Some sounds make it a little w	Mixture - some sounds make it	Some sounds make it a lot worse		
Source	0.01	0.38	0.17	0.07	Single Ear	Both Ears	Inside Head	Other		
Intermittency	0.24	0.03	0.24	0.05	I heard it occasionally	I heard it about 50%of the time	I heard it most of the time	I heard it all the time		
Pitch	0.01	0.07	0.08		Very High	High	Medium	Low		
Hearing Loss (B)	0.01	0.01			No He	H				
Min Hear Loss	0.01	0.01			No Hearing Loss	Mild Hearing Loss	Moderate Hearing Loss	Severe Hearing Loss		
Max Hear Loss	0.01	0.02	0.78		No Hearing Loss	Mild Hearing Loss	Moderate Hearing Loss	Severe Hearing Loss		
Hearing Loss	0.01	0.02	0.39		No Hearing Loss	Mild Hearing Loss	Moderate Hearing Loss	Severe Hearing Loss		
Severity		0.15	0.34	0.02	Borderline Tinnitus	Mild Tinnitus	Moderate Tinnitus	Substantial Tinnitus	Severe Tinnitus	Catastrophic Tinnitus
Age	0.22	0.05	0.10	0.10	< 30	30-39	40-49	>50		
Duration	0.04	0.01	0.70	0.21	< 1 year	1-3 years	3-5 years	> 5 years		
Hyperacusis (B)	0.33	0.00			No Hyperacusis	Hyperacusis				
Hyperacusis	0.33	0.01	0.07		None	Mildly	Moderately	Severely		
HLHY	0.12	0.06	0.42	0.00	NoHLNoHY	HyNoHL	NoHyHL	HyHL		
TFI	0.14	0.00	0.24	0.29	0<=TFI<25	25<=TFI<50	50<=TFI<75	75<=TFI<=100		

Table 15 - Group-wise t-test results

The diagram below provides confidence intervals for all significant results that have a sample size of at least 15:

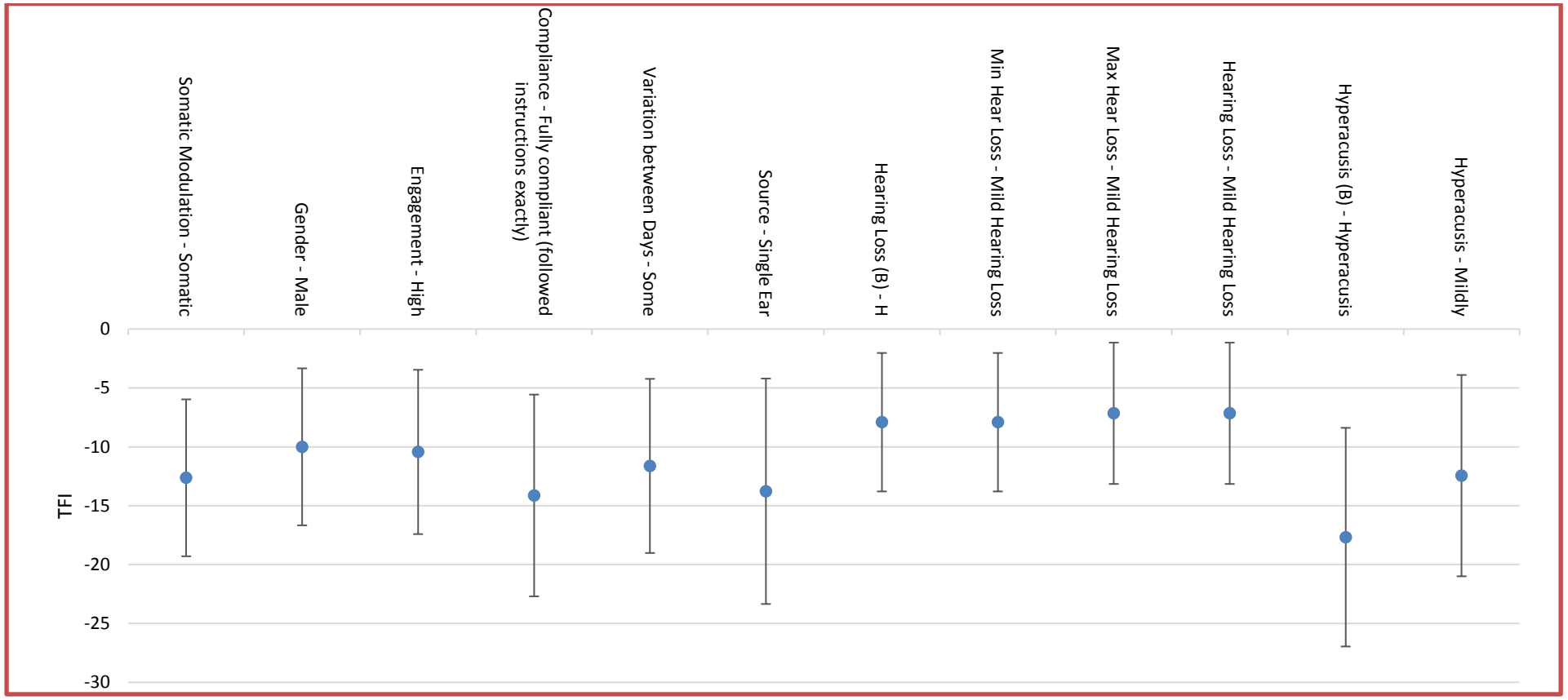


Figure 24 - Reduction in TFI by Group for groups with significant changes and sample size 15 or over

You can see that Hyperacusis again is a significant factor, but we are also seeing some significant results not showing up in the ANOVA (e.g. Somatic modulation).

Multiple Linear Regression

In the Linear Regressions section we saw that certain factors were correlated with TFI reduction. In this section we see if we can combine some of these factors in a linear model to get a better fit to the data (the extent to which the variation in the data is explained by the model is measured by the adjusted R^2 value) using multiple regression.

I chose some factors based on their linear regression correlations and taking into account the inter-factor correlations we saw in report 1.

Combination	1	2	3	4	5	6
	Age					
	Duration			Duration	Duration	
	Intermittency	Duration	Duration	Intermittency	Hearing Loss	
	Hearing Loss	Intermittency	Hearing Loss (Best)	Hearing Loss	Hyperacusis	Hearing Loss
	Hyperacusis	Hyperacusis	Hyperacusis	Hyperacusis	TFI	Hyperacusis
R^2 Adjusted	0.36	0.26	0.39	0.37	0.38	0.13
p-values	0.008	0.015	0.001	0.004	0.003	0.080
PeterPan Prediction	12.3	16.5	12.0	9.0	9.0	11.8

Table 16 - Multiple Regression Combinations p and R^2 values

In addition to the p-values and R^2 values, I've also included each model's prediction for my own tinnitus. The predictions range from a reduction of 9 to a reduction of 16.5, with the best fit model predicting 12.

We chose the combination with the highest R^2 value for further analysis (Combination 3). We can work out the predicted TFI reduction for each patient, and the confidence intervals.

If we do this, we find that of the 29 patients, 27 fall into the 95% confidence intervals (which are admittedly quite large, given our sample size).

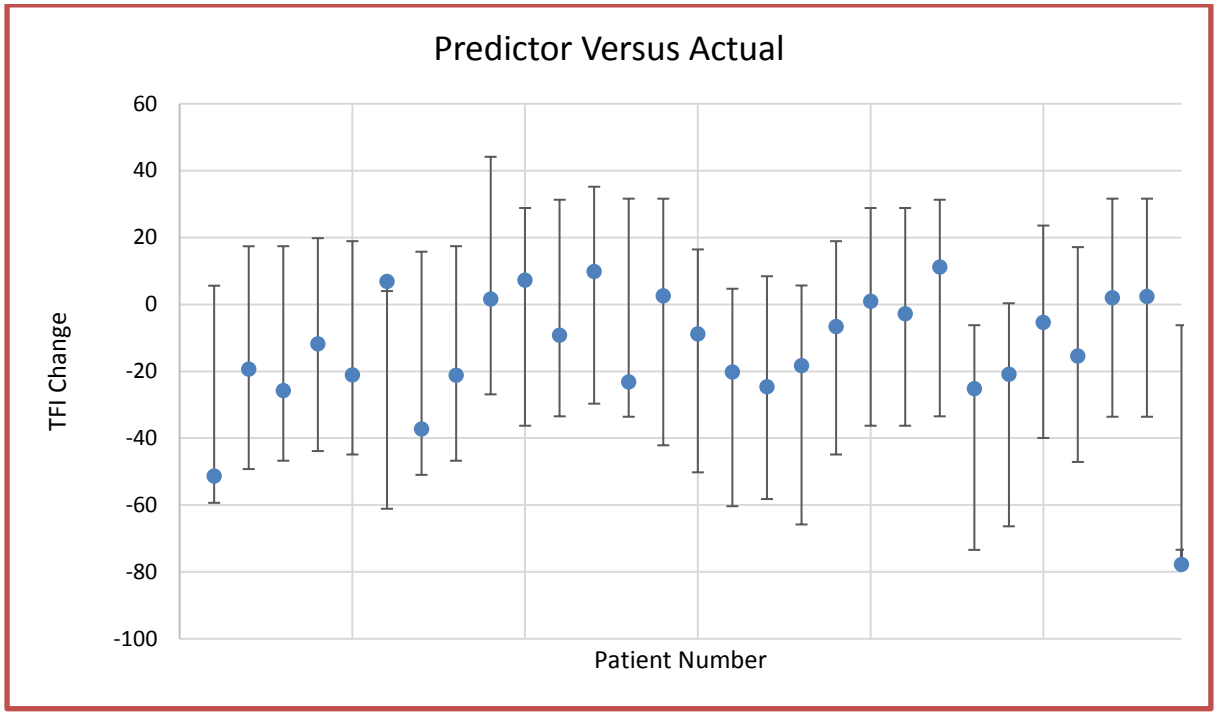


Figure 25 - Predictor versus actual for Duration, Hyperacusis and Hearing Loss model

Each dot represents a patient and the 95% confidence interval for the predictor (which is generated by the model) is represented by the corresponding error bar. You can see that in most (but not all) cases, the patient datapoint is near the middle of the confidence interval.

The formula for the predicted change in TFI is:

$$P = 21.26 + D*(-0.96) + HL*(-13.88) + HY*(10.94)$$

Where D is the duration in years, HL is a measure of Hearing Loss (Best Ear) as shown in Appendix 1 (1=None, 4 = Severe), and HY is a measure of Hyperacusis using the same scale (a positive value represents a reduction).

The confidence interval is P +/- INT, where

$$INT = 2.06 * \sqrt{225.41 * (1 + \begin{bmatrix}1 & D & HL & HY\end{bmatrix} * \begin{bmatrix}0.73 & 0.00 & -0.27 & -0.13\\ 0.00 & 0.00 & 0.00 & 0.00\\ -0.27 & 0.00 & 0.16 & 0.01\\ -0.13 & 0.00 & 0.01 & 0.06\end{bmatrix} * \begin{bmatrix}1\\ D\\ HL\\ HY\end{bmatrix})}$$

(Note there is some rounding in the above numbers)

An individual's parameters can then be entered to generate the predictor and the confidence interval. More data is likely to reduce the size of the confidence intervals.

If I use this on myself (Mild Hyperacusis, Mild Hearing Loss in Best ear, Duration 3.5 years, or D=3.5,HL=2,HY=2), I get a prediction of a TFI loss of 12, with the upper 95% limit of an increase in TFI of 19.8 and the lower a reduction of 43 (a very wide band, admittedly!).

You can also do this for yourself with the (shared) online calculator here.

Logistic Regressions

The last statistical test performed was logistic regression. In these tests, each patients' outcome is a pass or fail (pass if TFI reduction of 13 or more points and fail otherwise). By using Logistic Regression, we can create a model to predict the probability of a significant change in tinnitus. This model has the advantage that it tends to discount large changes in TFI. The patient circled in red below, for example, can have a large effect on a multiple regression model, but only a minimal effect on a Logistic Regression model.

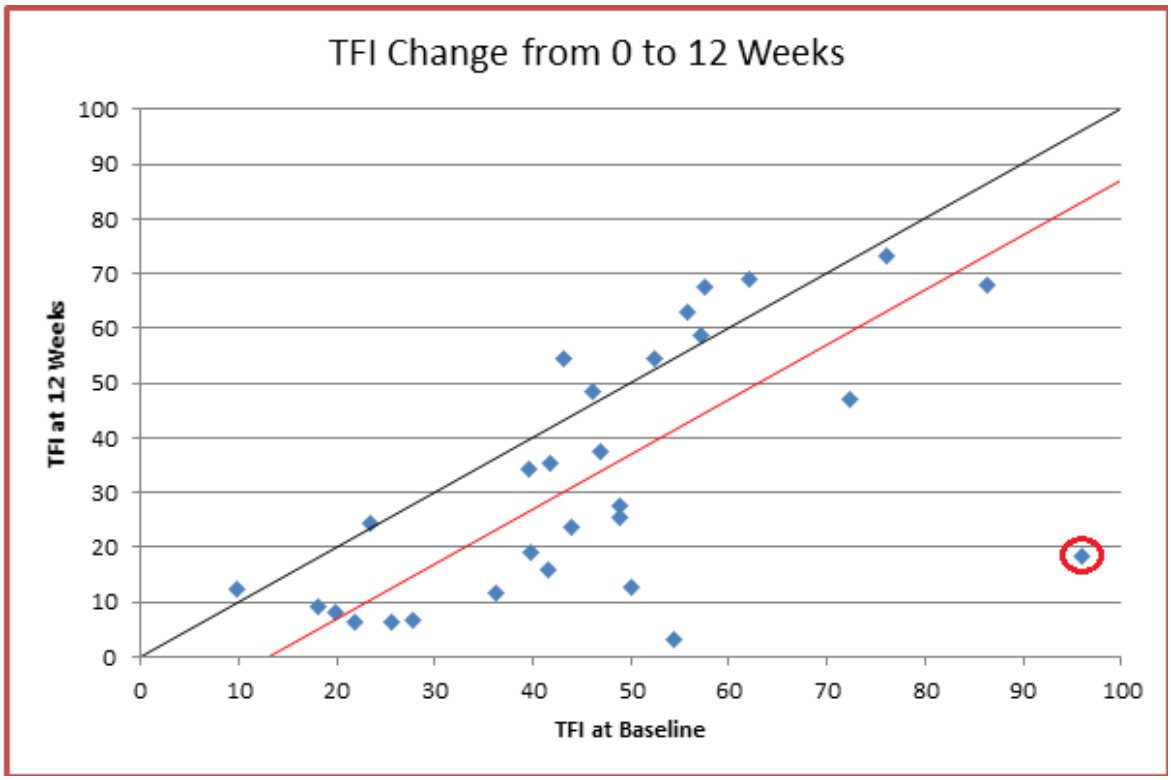


Figure 26 - Outliers can distort a multiple regression

We looked at the below combinations and chose combinations 1 and 2 for further analysis. I've included the prediction for treatment success for myself in the table (it ranges from 50% to 75%).

Combination	1	2	3	4	5
				Age	TFI
		Duration	Age	Duration	Duration
	Hyperacusis	Hyperacusis	Duration	Hyperacusis	Hyperacusis
	Hearing Loss	Hearing Loss (Best Ear)	Hyperacusis	Hearing Loss	Hearing Loss
R^2 (CS)	0.27	0.40	0.38	0.42	0.40
p- values	0.010	0.002	0.003	0.003	0.005
% Correct Predictions	62%	79%	79%	76%	76%
PeterPan prediction	50%	60%	67%	75%	64%

Table 17 - R^2 and p-values for various Logistic Regressions

Hyperacusis and Hearing Loss

The numbers for this model aren't as good as the others, but it does have the advantage of simplicity.

This model comes up with a probability of success according to the table below:

		Hyperacusis			
		None	Mildly	Moderate	Severely
Hearing Loss	None	24%	67%	93%	99%
	Mild	14%	50%	86%	98%
	Moderate	7%	33%	76%	95%
	Severe	4%	20%	61%	91%

Table 18- Logistic Regression Model - Probabilities of Significant Change

The actual results from our patients is shown below:

		Hyperacusis			
		None	Mildly	Moderate	Severely
Hearing Loss	None	67%	50%	100%	NA
	Mild	0%	40%	NA	100%
	Moderate	0%	100%	100%	NA
	Severe	NA	NA	NA	NA

Table 19 - Actual results for patients by Hyperacusis and Hearing Loss

With N values shown below:

		Hyperacusis			
		None	Mildly	Moderate	Severely
Hearing Loss	None	3	4	3	0
	Mild	5	10	0	1
	Moderate	1	1	1	0
	Severe	0	0	0	0

Table 20 - N values for number of patients in each combination of hearing loss and hyperacusis

If I compare the actual patient outcomes with the prediction from the model, the model is correct 62% of the time (which is not that high!). If I use this model on myself (mild hyperacusis, mild hearing loss), the model predicts a 50% chance of success (TFI reduction of more than 13 points).

Hyperacusis, Hearing Loss (Best) and Duration

This model has an R^2 value quite a bit higher than the previous one, so should be a better fit for the data. If we use this model and test the prediction against the actual patient outcome, the prediction is correct for 79% of the patients, which is quite an improvement on the previous model.

The formula for estimating the probability of success is:

$$e^{(-2.07+D*(-0.17)+Hyp*(2.33)+He*(-0.79))} \Big/ (1 + e^{(-2.07+D*(-0.17)+Hyp*(2.33)+He*(-0.79))})$$

If the probability is less than .5, we predict a failure, and if greater than or equal to .5, we predict a success.

In my case, the model predicts a probability of success of 60%. You can also do this for yourself with the (shared) online calculator here.

Section 7: Discussion

Study deficiencies

In this study our sample size is very small and in addition we have no control group. Statisticians would call this a small investigational study. These types of studies are used to determine if there is likely to be any effect of the treatment and to provide justification for a larger randomized controlled trial.

The fact that we have no control group makes it difficult to draw conclusions and the sample size is so small that one additional patient can make a significant change in results. The vendor of the device has performed more extensive trials; however, the official results of these trials are not available at the time of writing.

In addition to the above, our study was conducted over the Internet. We did not meet or talk to a single person and all communications was via email or forum messaging. To help mitigate the possibility of some patients not being genuine, we derived a measure to assess the authenticity of patients. In the study results, we included all patients, but we also present results where we have eliminate patients with particularly low scores (refer Appendix 7).

Does it Work?

That's what we all want to know. But it's not that simple. We can see a summary of results of the study in Section 1, Executive Summary and on the surface, it looks like there is a clear-cut answer. There are large statistically significant reductions in TFI (average of -13.86) and about 40% of patients reporting results experienced clinically significant reductions (with 17% reporting adverse outcomes and the remainder no significant change). Furthermore, there are patient characteristics (Hyperacusis, No Hearing Loss) which have statistically significant correlations with TFI reduction.

However, because we have no control group, it's not possible to determine if the Lenire works or not. The effects we are seeing could entirely be to the placebo effect. That is, if we had another arm which delivered tones and electrical pulses to patients in a random way, it is entirely possible that a similar level of reduction in TFI could have occurred. The correlations we are seeing could also be due to placebo as these are reasonably well known and there was no blinding during the study. There is no way of knowing without conducting the trial. We do have unofficial relevant information from Neuromod[3] which we will consider later.

Do our results relating to factors align with other studies?

In the interview between Neuromod and Tinnitus Talk, it was noted by Dr Ross O'Neil that there was a strong relationship between the extent of a patient's response to treatment and the extent to which the patients suffered from Hyperacusis.

[3] Neuromod conference presentation collateral was leaked several months ago. It contains unofficial information on the results of the trials that have been conducted by Neuromod.

This relationship was also replicated in our study, although our sample size is very small (but surprisingly our hyperacusis sample size is larger than the Neuromod TENT-A1 ARM1 hyperacusis sample size). The average reduction in THI for patients with hyperacusis in TENT-A1 ARM1 was 26.8 (12 patients), whereas in our study the average reduction in TFI for patients with hyperacusis was 17.7 (20 patients).

In addition to the above, there is anecdotal evidence that the extent of hearing loss is also an important factor relating to the successful outcomes when using the Lenire as it is known from the Tinnitus Talk forum that some patients have been rejected as candidates by Neuromod on the basis of their hearing. This aligns with the findings in our study.

Why didn't Neuromod perform a trial with a control arm?

In the Tinnitus Hub Podcast with the Dr Ross O'Neil, the founder and CEO of Neuromod Devices, was asked this question. Dr Ross's response was:

"The traditional placebo design is designed for drugs. It is very easy to give someone a sugar pill. With other technologies it's proving more and more difficult. I think that model, the placebo trial has served well for regulators up to now but as we develop new technologies like neuromodulation we're going to have to look at other ways of proving the efficacy. Our challenge is that the nature of the Lenire treatment is that patients hear sounds through the ears and feel stimulation through the tongue, If we turn off either of those to make it a placebo treatment, the patient will notice and what happens then you get unblinding and the patients who don't get the treatment know they're not getting the treatment and then the integrity of that placebo controlled trial is compromised. So what you do then, you look at other ways to do it. Our approach is to look at the varying types of stimulation parameters and showing there are differences between those, so what we saw in TENT-A1 was that there were differences between high frequency synchronous stimulation and low frequency asynchronous stimulation over the long run. Over 12 months we saw the two groups diverged. So we're seeing differential effects from different parameters.".

If it's not possible to mock-up a device that is obviously placebo but not obviously so to patients (as it would be for a pill), then this position sounds reasonable to me. In this circumstance, if I were going to design an arm to contrast against the treatment arm, I would design the treatment to be in accordance with patient's broad expectations (sound and electrical stimulation), but make it lack the treatment features which I believed to be responsible for a successful outcome. For example, taking into account the research of others (e.g. [5]) I might change the timing of the signals so that they are not coordinated with the sounds, and make the frequency quite a bit different than normal tinnitus frequencies (which are typically quite high).

If we look at reference [1], there were three arms in the trial's protocol. Arm 3 has the properties I mentioned above. To me, this arm appears to have been created because the designers of the protocol believed that it would be likely the results in this arm would indeed contrast with the other arms and thereby lend support to the effectiveness of either or both of Arms 1 and 2.

Table 1	Stimulation parameter set for the three parallel arms	
	Auditory stimulation	**Temporal relationship with somatosensory stimulation**
Arm 1	Sequence of tones mixed with a broadband noise that is spectrally modified to compensate for any hearing loss	Somatosensory pulses are synchronised with the tones
Arm 2	Sequence of tones mixed with a broadband noise that is spectrally modified to compensate for any hearing loss	Somatosensory pulses are temporally aligned with the tones with varying short delays
Arm 3	Sequence of tones mixed with a broadband noise with the spectral range outside the regions normally associated with sensorineural hearing loss	Somatosensory pulses are temporally aligned with the tones with varying long delays

Table 21 - Neuromod Arm Definition

There is further support for this idea in unofficial Neuromod conference collateral. In this material Arm 1 is compared with Arm 3 at 64 weeks showing a significant THI improvement for Arm 1 (8 points, p=0.042), and Arm1 is again compared with Arm 3 for Hyperacusis-only patients, again showing a significant improvement (13.7 points, p=0.01).

This material also shows, however, that after 12 weeks Arms 1 and Arm 3 have very similar results (Arm 1 had a 14.6 average THI reduction, p<.001 and Arm 3 a 13.7 point THI reduction, p<0.001).

So, the results appear to be showing:

- At 12 weeks, the average reduction in THI from this type of treatment is remarkably resilient to the timing of signals and the frequency of sounds
- The average THI reduction for patients with hyperacusis DOES show a statistical (and clinically) significant improvement between Arms. This is quite encouraging.
- The average THI reduction at 64 weeks DOES show a statistically significant difference.

If the ARM1 and ARM3 means are approximately equal, yet the ARM1 hyperacusis patients have large drops in THI, we might expect the non-hyperacusis patients in ARM3 do exceptionally well. If we do the maths, the non-hyperacusis patients in ARM1 averaged a drop of -12.6 and the non-hyperacusis patients in ARM3 averaged a drop of -14.1. Not quite a significant as we might expect due to the relatively small number of hyperacusis patients.

Would I use the Lenire?

This is a difficult question to answer and our study only provides hints as to the effectiveness. We really need a peer-reviewed article appearing in the medical literature to answer this question using a large sample. This is pending from Neuromod.

Looking at the unofficial Neuromod results, to me, this point is the most encouraging result:

- The average THI reduction for patients with hyperacusis DOES show a statistical (and clinically) significant improvement between Arms.

It appears that for most people with good hearing and hyperacusis there is a good chance of success (although we saw 5 of 7 patients with these characteristics in our study have a successful outcome, our study is too small to reach this conclusion and there is no control; we need to rely on the Neuromod leaked report which had 12 patients in Arm1 with Hyperacusis and 21 in Arm 3 and which

showed a statistically significant difference in results in favour of Arm1). We should also note, however, that some people in our study with good hearing and hyperacusis experienced no benefit and some experienced adverse outcomes. In addition, the evidence for reductions is appearing in leaked reports rather than peer reviewed journals.

Taking into account the above, if I had good hearing and hyperacusis, Tinnitus was having a big impact on my life and the cost was not significant when considering my income/assets, I think the decision to use it would be reasonable. Others may wish for more research to become available. This is my opinion only and not an endorsement by Tinnitus Talk.

Other studies

Susan Shore and her team from the University of Michigan are conducting trials on a similar device [5]. It's interesting to contrast her results and approach against those of Neuromod:

- Susan Shore's team used animal experiments prior to using their treatment in humans. The team found that the treatment effectiveness was heavily dependent on the timings between the auditory and electrical stimulus, with the optimal timing being between -5ms and -10 ms. In the animal experiments, treatment was for 25 days with 20-minute daily sessions. In addition to the treatment arm, there were arms with no treatment, audio only, and electrical only. The treatment arm showed significantly reduced tinnitus at the treatment frequency (as measured by "acoustic startle response").
- On the basis of the animal studies, a similar treatment was then used in a human study. Twenty patients were subjected to treatment. Ten started with 4 weeks of sham (auditory only), followed by 4 weeks of "washout", followed by 4 weeks of treatment, followed by 4 weeks of washout. Another ten used the treatment in the reverse direction.

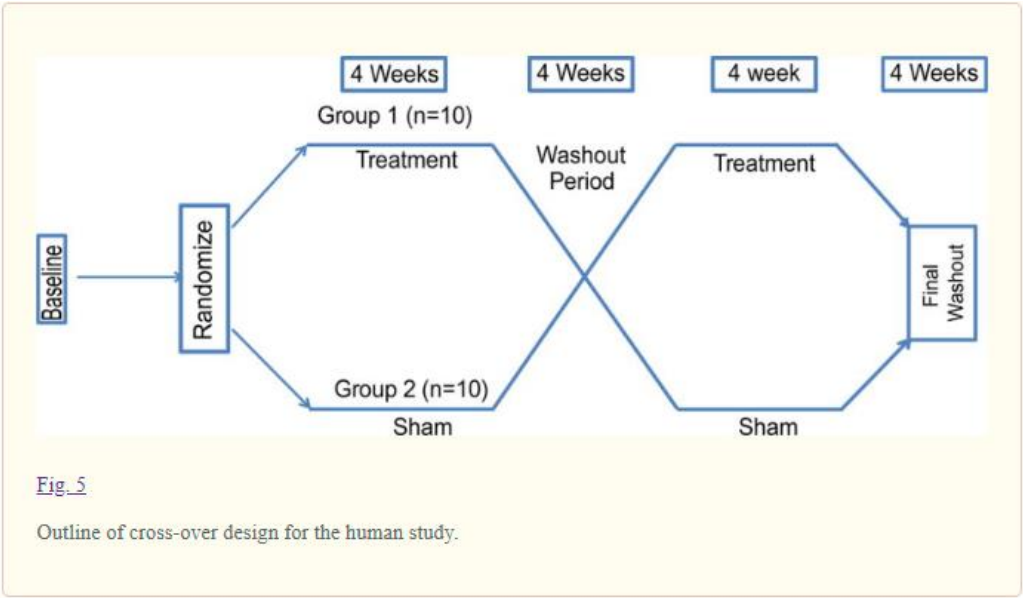


Fig. 5

Outline of cross-over design for the human study.

Table 22 - UoM Treatment cross-over design

Auditory stimulus was customised for the patient and the auditory/electrical stimulus interval was -5ms. Patients received the treatment for 30 minutes once a day. It's not clear from the paper if patients were aware that they were not receiving electrical stimulus during the sham treatment[4] (i.e. if the electrical stimulus could be detected). If they were aware, there is a possibility of a placebo effect. The team found that during the 4 weeks of treatment, tinnitus loudness reduced by an average of 12.2 dB, and TFI by 6.3 (with 10 of 20 patients having a TFI reduction of more than 13; more than 13 is clinically significant). The TFI reduction at the end of the treatment was about 13. They also found the TFI reductions (but not the Loudness reductions) persisted during the washout period.

A summary of the results of the UoM study is shown below:

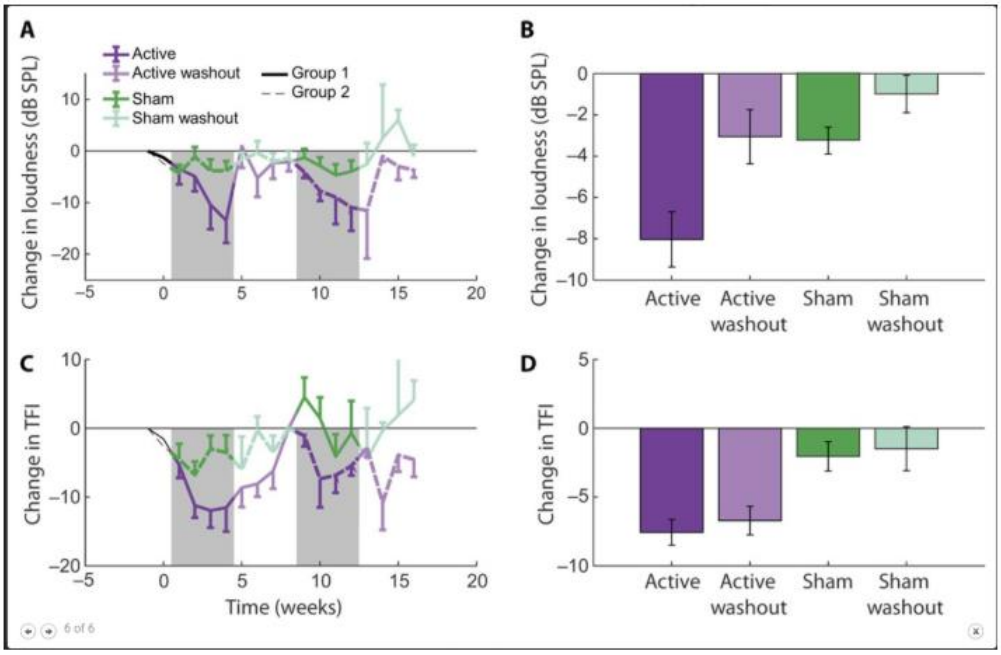


Table 23 - UoM Treatment Outcomes

When comparing the University of Michigan (UoM) approach and results with the Neuromod results, we can note:

- The UoM approach is based on animal studies, whereas the Neuromod studies are not. Some people have questioned the validity of animal studies [6]. In addition, some treatments have been shown to work in animals, with the same treatment not working in humans. (refer to Animal Models of Tinnitus section here).
- In the UoM study, significant effects are apparent at 4 weeks. In our study of the Neuromod treatment, and unofficial information from Neuromod, significant effects are apparent at 6 weeks.

[4] According to a forum member who participated in the study, "the devices were calibrated such that you would tell them when you were aware of the stimulation, and then it would be reduced from there. They said that the stimulation did not have to be at a level that was perceivable as tingling for the principle to work, and that more or less aligned with my experience."

- The UoM team have presented their results in a peer reviewed publication, whereas this has not been done by Neuromod.
- In the UoM study, there were only 20 patients. Neuromod have used significantly larger sample sizes (260 in TENT-A1 according to unofficial information).
- In the UoM study, the audio stimulus was derived from each individual's tinnitus spectrum and audiogram (although it isn't clear how this was done). In the Neuromod study the audio stimulus was not related to the patient's tinnitus frequency.
- In the UoM study, the treatment was for 30 minutes a day, while Neuromod recommend 2 x 30 minute sessions a day.
- In the UoM study, animal studies showed that the timing of auditory and electrical stimulation and the frequency of the auditory signal was extremely important to the success of the treatment at 4 weeks, whereas in the Neuromod studies it appears (from unofficial sources) that significant variation of the timing of the signals and the frequency has not impacted on the treatment success in the short term (although it does impact the success in the longer term of 64 weeks and also in the effectiveness of the treatment in the short term for patients with hyperacusis).
- In the UoM study, both TFI and Loudness were used to assess the effectiveness of the treatment (with Loudness being arguably more objective). In the Neuromod study, we only have THI results available (albeit from unofficial sources). Note that TFI and THI have a very close correlation.
- In the UoM study, the control treatment was a treatment with auditory only stimulus. Refer to footnote 4 on the previous page for information the possibility of a placebo effect.. In the Neuromod study, there was no explicit control. There were three arms, each with different frequencies and timings. Arm 3 was quite a bit different than other arms and used asynchronous extended timings and low frequencies atypical of tinnitus frequencies.
- In the UoM study the electrical shock was delivered via electrodes on the cervical spine or cheek (depending on which manoeuvres induced the strongest change in tinnitus), while in the Neuromod study the shock was delivered to the tongue via a tongue tip.
- In the UoM study, the average TFI reduction during the 4 weeks of treatment was 7.3 (sample size 20) and approx. -13 at the 4 week mark, whereas the unofficial Neuromod collateral indicates that the average THI reduction (not directly comparable to TFI) was 14.6 (in Arm1 of TENT-A1). In the UoM study, 50% of patients had a clinically significant change in their tinnitus at 4 weeks, while in the Neuromod study, 65.9% had clinically significant improvements (in Arm1 of TENT-A1).
- Neuromod have commercialized their device, whereas commercialization of the UoM device may be 1-2 years away.

The UoM team are now engaged in a second study and the results should be very interesting.

In this presentation, Susan Shore emphasizes the role of basic science and the importance of a control especially for tinnitus patients:

"Well we had a very promising result that we published in 'Science Translational Medicine' last year, and the exciting part of that research was that it came directly out of the studies with animals. And

also that we were very careful to do a well-controlled clinical trial in which we were double-blinded and we had a crossover so that every subject received a sham treatment and also the active treatment so that each subject was their own control. And I think it's very important to do a clinical trial like that, especially with tinnitus because the placebo effect is very strong in people with tinnitus. So people can often try something and just the fact they've tried something will initially help the tinnitus patient. But that's not doing a treatment a service because you want to very carefully control your trial so that you really know whether it is working or not and it's not just a chance effect or a placebo effect. So in our second trial we're being even more rigorous than we were in our first trial, and we hope that we'll have some results by the middle of next year."

(posted 8 October, 2019.)

Hopefully the next study will eliminate any potential source of placebo effect.

Moving Forwards

It's early days in the world of bimodal stimulation. I am certainly looking forwards to Neuromod's published results and the results of the next UoM trial.

References

[1] Bi-modal stimulation in the treatment of tinnitus: a study protocol for an exploratory trial to optimise stimulation parameters and patient subtyping,, BMJ, D'Arcy Et al, 25th October, 2017.

[2] Noninvasive Bimodal Neuromodulation for the Treatment of Tinnitus: Protocol for a Second Large-Scale Double-Blind Randomized Clinical Trial to Optimize Stimulation Parameters, Conlon et al, JIMR Prptoc 2019; 8(9)

[3] Lenire User Experience Group Study – Report 1, Cohort Analysis, January 2020, Tinnitus Hub, @PeterPan.

[4]. Significant p-values in small samples, 25th Jan, 2012, Allen Fleishman.

[5] Auditory-somatosensory bimodal stimulation desynchronizes brain circuitry to reduce tinnitus in guinea pigs and humans, Marks et Al, Sci Transl Med, 2018, Jan 3.

[6] Hearing loss, hyperacusis, or tinnitus: what is modeled in animal research, Eggermont, 2012, Feb 7.

[7] Why is there no cure for Tinnitus, Don McFerran et al, Frontiers in Neurosceince, 6 August 2019

Appendix 1 - Summary of Factors Studied

Factor	Option 1	Option 2	Option 3	Option 4	Option 5	Option 6	Option 7	Option 8	Option 9
Age									
Gender	Male	Female							
Duration	< 3 months	4-6 months	6-12 months	1-2 years	2-3 years	3-5 years	5-10 years	10-20 years	> 20 years
Severity Rating	Borderline	Mild	Moderate	Substantial	Severe	Catastrophic			
Loudness	Very Quiet	Quiet	Moderate	Loud	Very Loud				
Intermittency	Occasional	50%	Mostly	All the time					
Hyperacusis	None	Mild	Moderate	Severe					
Hearing Loss (R)	None	Mild	Moderate	Severe					
Hearing Loss (L)	None	Mild	Moderate	Severe					
Somatic	Somatic	Non Somatic							
Source	Left Ear	Right Ear	Both Ears	Inside Head	Inside + ears	Other			
Reactivity to Noise	Lot Worse	Little worse	No effect	Little Better	Lot Better				
Variation within a Day	No change	Less in AM	Less in PM	No pattern	Other				
Variation between Days	Constant	Some	Significant						
Pitch	Very High	High	Medium	Low					
Compliance	< 50%	> 50%	> 90%	100%					
Additional Derived Factors									
Engagement	Low	Med-Low	Medium	High					
Min Hearing Loss	None	Mild	Moderate	Severe					
Max Hearing Loss	None	Mild	Moderate	Severe					
Hearing Loss (B)	No HL	Some HL							
Hyperacusis (B)	No Hyper	Hyperacusis							
HLHY	NoHL, NoHY	NoHL, HY	HL, No Hy	HL, HY					
TFI at Baseline	<25	<50, >=25	<75, >=50	>=75					

Table 24 - Summary of Factors Studied

Appendix 2 - Statistical Techniques

One Way Anova

ANOVA is a statistical technique that compares variation between and amongst groups to analyse the differences in group means in a sample. It tells us if we should reject the null hypothesis that group means are identical, at a given level of confidence. It's important to note that ANOVA only tells us if there is a difference between groups, and to find out which groups are different, we need to execute another test (we chose the Tukey HSD for this). An example of using ANOVA may be found here.

⚠ We should point out that the sample size we are using in this study is very small, and the sample is not randomized but self-selected. As such, any conclusions we come to regarding differences in means between groups **should be approached with caution.** For an introduction to the subject of small sample sizes and statistical significance refer to [4].

Linear Regression

Linear regression is a statistical technique that used to model a dependent variable on one or more independent (or explanatory) variables. When more than one independent variables are used, the technique is described as Multiple Linear Regression, which is described further below.

The linear regression process involves fitting a straight line to data plots of a dependent variable against an independent variable. The straight line which minimizes the sum of the squares of the differences to the line is the linear regression plot. The slope of the line is an indicator of the linear nature of the relationship. For example, a slope of 2 would indicate that, using the fitted line, the dependent variable changes by twice the value of the change in the independent variable. We are often interested in determining if the slope of the line is different than zero (a zero slope indicates no relationship). We can use statistical tests to determine if the slope is zero or not and the result is a "p" value. A "p" value less than 0.05 indicates that we can reject the null hypothesis that the slope is zero with a 95% level of confidence. More information here.

The other statistic that is often mentioned in relation to linear regression is R^2. R^2 represents the percentage of the dependent variable that is explained by a linear model. In general, the higher the R^2, the better the model fits the data. More information here. R is also known as the Pearson Correlation Coefficient.

⚠ Normally the independent and dependent variables used in linear regressions should be continuous (e.g. Age, Duration or similar), however it is common practice to also use linear regression when the independent variable has a Likert type scale outcome (e.g. Borderline, Mild, Moderate, Substantial, Severe) and we do this here. More information, for example, may be found here. Alternative tests ("non-parametric tests") which do not require these variables to be continuous are available (e.g. Spearman's Rank Correlation, or Kendall's Tau). These test for a monotone relationship rather than a linear one. These tests often result in very similar results to the Pearson test.

⚠ There are many rules of thumb for the minimal sample size required for multiple linear regression. For example (Green 1991) indicated a sample size N > 50 + 8m, where m is the number of independent variables (1 in linear regression), and N > 104 + m for individual predictors. Harris (1985) states the number of participants should be at least 50, Van Voothis & Morgan states that for 6 predictors, the absolute minimum number of participants should be 10, but it is better to have 30 per variable. We have 43 participants here for m = 1, so the results should be treated with caution.

Pair-wise t tests

Pairwise t-tests are used to compare the means of two samples where the population standard deviation is not known and where the two different samples can be paired in some way (in our case the same patient at each of the stages of treatment).

Fisher Exact test

Fisher's exact test is used to examine the significance of an association using two kinds of classification. In our case, for example we can look at a distribution of patients across groups before treatment and after treatment. The null hypothesis is that the treatment does not affect outcomes and the distribution of patients across groups after treatment is likely to occur by chance. We reject the null hypothesis (there is a dependence on the treatment) when the p value is sufficiently small.

The fisher exact test can be used when the sample size is small. When the number of groups is large, the p-value is difficult to calculate and the Chi-square test is used instead, which is a good approximation.

Chi Square test

The Chi-Squared test is similar to the fisher exact test, but used when the number of groups is larger.

Multiple Linear Regression

Multiple Linear Regression is a special case of linear regression. In this case the dependent variable is now modelled as a linear sum of several independent variable rather than just one.

Logistic Regression

In logistic regression the dependent variable is a binary value (in our case, a successful treatment or an unsuccessful treatment, as measured by the change in TFI – 13 points or more is regarded as successful). In this technique the model uses the independent variables to estimate the probability of success. It assumes a linear relationship between the independent variables and the log-odds of success (where log odds is the log of (P(success)/(1-P(success))).

Wilcoxon Rank Test

The Wilcoxon Signed Rank test is a similar test to the paired t-test, but we make no assumptions about the distribution of differences between the samples.

Appendix 3 – Report Caveats

It's important that we point out the caveats that apply to this study.

- We are trying to estimate statistics for the general population of people who are eligible for use of the Lenire and likely to purchase it. The sample we are using is self-selected from Tinnitus Talk forum members who have purchased the device and volunteered to provide their experiences. This may not be a representative sample of the population mentioned above (For example, participants from the TT forum may have more severe tinnitus, especially early adopters). As such, the conclusions of this report may not be valid for the population who are likely to use the Lenire in the future.
- Survey responses such as the extent of hearing loss are self-reported and not measured independently. One person's moderate hearing loss may be another person's mild hearing loss.
- The sample size is not large (43). It is difficult to make conclusions about the significance of statistics with small sample sizes. In small samples, statistically significant results tend to be fragile and subject to change as a result of a small change in the sample. In addition, smaller samples may fail to reject null hypotheses that would be rejected by larger samples.
- This is an observational study. There is no control group. We can't be sure that the effects we are observing in the treatment stage would not have been experienced in part or full by a control group undertaking a placebo treatment. **That is, we cannot say that the Lenire is the cause of any observed improvements or changes.**
- It is known that tinnitus is more likely to spontaneously resolve for people who have been afflicted for a short duration than those who have been afflicted for a longer period. As there is no control, we can't be sure that improvements for people with short duration tinnitus is related to the use of the Lenire.
- Correlation does not imply causation. If an independent variable is correlated with a tinnitus change, it does not mean it is the cause of the change.
- The staff performing the data collection and analysis are not professional researchers. While we are trying to minimise errors by leveraging the experience of the members of the forum, performing reviews of the results by experts, and also making use of university researchers who have agreed to collaborate, a more ideal scenario would involve the use of professional researchers.
- Patients are providing information anonymously over the Internet. While some patients are well known on the Tinnitus Talk forum and have been contributing for years, others are relatively new and have no previous history of contributing. While we have asked contributors to provide photos of the device to establish their bona-fides, this has not always been done.
- Communication with patients is with email and the forum messaging only. The native language of some patients is not English. In a small number of cases this has led to communication problems and ambiguities and to an overall reduction in quality of the data.
- In a small number of cases, we have accepted surveys from people who, due to unexpected issues, have already started using the device.

Appendix 4 – Suggested Viewing - Statistics

Understanding p-values

Understanding the p-value – Statistics Help

Anova

Introduction to One-way Anova

Linear Regression

Introduction to Simple Linear Regression

Fisher Exact Test

Fisher's exact test

Chi Square Test

Simple Explanation of Chi-squared

Paired t-tests

Matched or Paired Samples T-Test - Hypothesis Testing

Wilcoxon Rank Test

Introduction to the Wilcoxon Signed-Rank Test

Logistic Regression

Statistics 101: Logistic Regression, An Introduction

Appendix 5 – Free Text Patient Responses

Has the nature of your tinnitus changed since the device fitting appointment? If it has changed, describe how it is changed.

At 6 weeks:

It's less loud. Though this has happened about two weeks after stopping usage of the device so I have no idea if it had to do anything with it.. I will not be going to the follow up appointment, Male 27.

Less crickets and crackles, Male 49

It has somewhat lessened since my last appointment. There are generally more "better" days than before. However, when it is severe during the course of a day, the level is not any less than it was prior to my appointment, Male 61

It's gotten more intrusive and loud, Female 21.

I feel the sound has softened also not having as many loud fluctuations in afternoon or evening time. Mine tends to fluctuate for no reason I do not have hyperacusis I might add, Female 50

Sounds have changed and become thinner and lower. Still have quite loud nights and mornings, Male 39

its worst, intrusive as before the treatment, Male 51

I now have 2 frequency's in the left ear. Right ear is the same, Male 50

Initially, lenire recalled old sounds that have already disappeared. Now it rings sometimes, but I usually have a standard hum stand, but quieter, Female 23

Turned into more of a high pitch hiss than a high pitched tone, Male 24

Is a bit louder. It fluctuates much more now. Before Lenire it was fairly constant with very little change, Male 36

i feel i'm starting to notice it less. Its still there, but i only seem to have had say two bad days in the last 10. Still early days. For the first 5weeks i'd say it was worse. Really only started getting better recently, Male 47

The "bothersome sound" is now mostly on the left side. The sound on the right side is not completely gone but it doesn't bother me. The "sound" on the left didn't change much in pitch and intensity but had variations that seem subdued. It is more stable now, Male 57

No spikes, less intense, generally better, Male 45

My tinnitus is much less bothersome (see my response to question 60 below regarding feedback on my tinnitus in the last week). At my initial consultation with Neuromod my MML (Minimum Masking Level) was measured at 26db. At my 4 week fitting appointment it had dropped to 22db and then at my 6 week treatment appointment it had dropped further to 16db. At my 6 week appointment my

THI score had also dropped down into a Stage 3 rather than a Stage 4 (it was Stage 4 at my initial consultation). At my initial consultation I would have rated the severity of my tinnitus as an 8/10 however there were times during weeks 4/5/6 of the treatment plan were I would have rated it a 3/10. The treatment also seemed to reduce the pure high tone I was hearing and left me with just my lesser low, soft twinkling, buzzing, static sound., Female 26

The volume has reduced. The frequency of how often I hear tinnitus has listed. The 'buzziness' has gone, mostly, Male 38

Some rings are now quieter but have a higher pitched hiss which as development in place. Strongest ringing is still present, Male 29

Not so reactive as before lenire, Female 37

At 12 Weeks

Worst days sank from a 6 to a 3 of 10. Many more days with a 0, Male 44

My left ear used to be more prominent. Especially with more moving sounds. This is no longer the case, Male 49

Some reduction but react badly to stress although Lenire does calm these spikes, Male 49

On the whole, it has decreased. Generally two days in a row of relative silence then it might ramp up a little, Male 61

Less aggressive at times, my left ear hiss has turn into a rolling sound. But I have a new (faint) sound in my right ear. Not sure if it connected to Lenire as it appeared after a lot of noise exposure, Male 44.

Old sounds have dissapeared, new sounds have come. The changed setting on 6weeks was bad and aggravated tinnitus PS4 (second setting as they also call it), Male 39

Has gone from a high pitch tone to a less higher pitch hiss, with bad days a high pitched tone/hiss, Male 24

Tone has become less harsh. From higher pitch to lower pitch, Male 36

It sometimes changes position. From my head further out towards my ears, Female, 63

My tinnitus didn't lower the loudness significantly, but the mix of sounds is more stabilised, sounding more like a stable hiss/cicada than anything else. It is now mostly only the left side. The right side is becoming very mild, it doesn't bother me as much as the left, Male 57

Doesn't spike randomly like bfore, Male 45

During weeks 1-6 (on device setting 1) my tinnitus was much reduced (in volume and annoyance) towards weeks 5-6. Once I was placed on device setting 4 at week 6 I then began experiencing increased volume in my tinnitus. It became very intrusive and bothersome during my work and sleep.

I rand Neuromod after being no this new setting for 3-4 weeks and I was told to reduce my usage to just 1 half hour a day as I was being overly stimulated. This perhaps helped slightly but not a lot. I then had my final appointment with Neuromod a couple of weeks later (in the run up to my appointment I just did that one half hour). At my final appointment they put me back onto Setting 1. I would like to note that since being back onto setting 1 my tinnitus has greatly reduced. I have had 4 very very quiet days in a row, followed by a loud day, followed by a quiet day, followed by a medium day. So its all very much looking up! And Neuromod are confident it will continue to improve., Female 26

The buzzing has largely stopped and the volume has decreased. I experience long spells of silence, Male 38

Tinnitus is audibly louder than the weeks proceeding treatment. This has been proven by a 6db increase in the masking tests carried out at Neuromod, Male 29

Not louder than tv's or radio anymore, Female 37

Please provide some feedback about your experience of tinnitus during the last week and how it is affecting your life.

At 6 Weeks

Daily fluctuations, sleep changes the "natyre" of tt. Does affect some days, but not as bad before Lenire, Male 44

Experiencing more good days than usual but still unsure if it's not just a good period anyway, Male 33

It has certainly been less loud and I've been bearing it much less in the car and in the rain (I used to hear it through the rain unless it was pouring), Male 27

It seems to be about half a step down in total impact. Before I varied between low level severe to low libel moderate now I vary from moderate to upper mild. I have had a few, maybe 7 mild days since starting as opposed to 2 mild days over the past 9 months. I still have the occasional intense day but now that is more like a 1 in 10 event rather than a 1 in 3 day event. Please note I can't got back for 6 week appointment due to covid, Male 49

Still bothers me at times but also getting times when it is reduced, Male 49

As a musician, my routine is sporadic so it is difficult to pinpoint a consistent behaviour of my tinnitus. What I went through in the previous week is not necessarily the norm. During the past week, it has been better compared to other weeks, Male 61

I've been experiencing a massive spike in my tinnitus for the past two weeks coupled with severe sound distortion, which has triggered panic attacks and anxiety that I didn't have prior to Lenire., Female 21

I am having much quieter periods during day hours and some days where there are no increase in volume, Female 50

My tinnitus is still very much disrupting my life. It fluctuates a lot but the "bad phases" are much more tolerable and not si intrusive, Male 44

It fluctuates, there are better days and worse days. Tinnitus does impact me mainly emotionally causing anxiety and distraction, Male 40

Much less reactive. Noticeably and measurably quieter (MML went from 10 to 6 dB), Male 31

Has become even more intrusive., Male 50

If I hear that, sometimes I would like it to disappear completely, but sometimes I am ready to accept such a level of sound (on the basis of a mature party that complete recovery may be unreal). That's a lot, because before the idea of lack of silence for the rest of my life I could only panic / cry. I am much more interested in other areas of my life. For example, I think a lot about the exam session, while for the previous semesters with tinnitus it was only hostile "why do I need it, since I don't have silence, I don't care if I pass or fail." I even think about losing weight (again, I'm somewhat interested in my appearance) although I don't think I feel ready yet;) It must be quieter, it just has to be. I have never responded positively to the concepts of acceptance, diversion of attention etc. - I have OCD. The correlation is simple: it's quieter - I feel safer - I'm interested in other aspects of life., Female 23

Is more Better and more Happy, Male 22

As the tone has become less harsh, I am able to concentrate on other things and watch the tv without hearing it, Male 24

My tinnitus remains a bother in my life. I am copying with it and it doesn't necessarily affect my day to day. I probably think about it more now that I am doing my treatments., Male 36

Tinnitus still impacts my life on a constant basis. It affects my concentration, sleep and ability to socialise and work, Female 63

i think this device is actually starting to work. The Tinnitus is still there, but i am noticing it less and less. I do still have a bad day here or there. So not counting all my lucky stars yet. Its certainly not a cure, but i do finally feel after a few weeks of saying to myself this probably isn't going to work, to somewhat hopefull. The last two weeks, i've had mostly good days., Male 47

My tinnitus is now mostly affecting only my sleep. During the day, with ambient sound and focus on activities I mostly either not hear it or forget about it. At night I still need relaxation medication and white noise on the left side to have a good night sleep., Male 57

My tinnitus continues to fluctuate and I still find it bothersome but I've definitely experienced some improvement. My sleep has improved and I've even been able to watch TV at times without it being overly intrusive, Male 45

tinnitus temporarily becomes worse for 30-60 minutes after each treatment, Male 68

The first 2-3 weeks into the Lenire treatment my tinnitus got a lot worse. I experienced very bad spikes and a pureness of tone (when usually I would just experience a buzzing and not a very loud apparent clear tone). It was particularly bad at night making it hard to fall asleep and causing me to wake during the night and be restless. Around week 4-5 I started to experience some benefits from the treatment. The volume of my tinnitus decreased and I started to only notice it if I thought about it, otherwise I wasn't noticing it – this was during my day to day activities like work, shopping, talking to people etc. The only time I noticed when I wasn't thinking about it (so it was involuntarily intrusive) was at night time going to sleep – but it was more minimal than before the treatment. Waking up n the mornings the volume was realty low also – there were about 3-4 mornings where in a row where I could barely hear it as I was waking up and this was bliss. It did get progressively a little louder as the day went on but it would return back to a low volume the next morning. My emotional response when I heard my tinnitus was also much reduced. I didn't get upset (often in the past I would cry and get anxious). When I heard it I didn't hear it as a foreign sound to be frightened of – I heard it more as a familiar sounds that was 'part of me' – it's hard to explain – I feel like I'm just getting used to the sound and tolerating it more. It is obviously more tolerable because I hear it less often now too thanks to Lenire!, Female 26

Less intrusive day to day, easier to sleep at night, Male 36

Last week was able to work everyday . when waking up the morning T is very high for the first 30 min ...then become quieter...evening much louder, Male 48

My Tinnitus has become significantly easier to manage and ignore. I mostly hear it now in quiet spaces when I have no distractions., Male 38

The Tinnitus is always there but I'm noticing it slightly less. It doesn't seem to be as overbearing as it was prior to the treatment. I've had some very quiet nights but also some extremely loud nights which balances everything out., Male 29

My T has just been much the same as it ever was - I have good days, where I can hear it all the time but it doesn't upset me, and then bad days, where the loudness and intensity of it increase and it becomes extremely distressing, Male 46

At 12 Weeks

The worst days are seldom now. Last week none. Worst days much better, much less bothersome., Male 44

Hard to say. In general I have been doing better. I notice it less and have more frequent days on the low end of my range. This last week has been bad because I've had an ear infection which has ramped up the T, Male 44

Stressful period due to CV19 and work so tinnitus has been worse as a result., Male 44

It has been quite good. Since I have noticed the improvement, I have been easing off the treatment regime. I generally experience a spike at after I have a treatment but it subsides within an hour., Male 61

It's difficult to say with my tinnitus because it fluctuates so much. I do not think the device has made a difference however, Female 21

I can hear it very little ina quiet room it varies tho evening time I can hear it more buts no where as loud when I do hear it. My t varies during day with evening time most bothersome I'm hoping evenings will improve more as I am seeing improvements, Female 50

Tinnitus is still bothering me a lot but I appreciate the quiet moments., Male 44

About 1-2 days a week I feel the tinnitus reaches almost a mildstate. Not only the sound but how much energy it seems to be taking from my brain. Some days it feels one can´t think straight cause of T and some days are just pure bliss., Male 39

The stimulus used from Week 6 to Week 12 didn't work very well and it caused a spike. Neuromod says this'll go away once I get beck on the original stimulus, Male 31

The impact is small. Of course, I'm afraid that it may get worse again (this is a kind of trauma) especially since settings number two worked badly for me but I live almost like before the disease., Female 23

My tinnitus has changed to more of a high pitched hiss and due to this, my T is easier masked. For example my T is now masked (most of the time) by the TV, which it was not prior to using Lenire. I also find that since using/completing the treatment program my T is not as harsh and allot easier to deal with. This is likely due to the sound changing somewhat to a hiss rather than a pure tone. I would like to add that my head T has overall improved, although the lower pitch drone in my right ear has not changed throughout the treatment., Male 24

Tinnitus remains since starting treatment, although I feel it has improved. Overall it bothers me less. I still have issues if I am in a busy room or there are many conversations or noises, Male 36

I still hear it above everything. I still have poor sleep although occasionally sleep for a longer period without waking up. It still dominates my life., Female 63

I have good days and bad days, as i've always had. I had a string of good days after about 5weeks of use.. About 5, and that had me excited, but in all honesty i don't think this device is doing much. My T is around the same vol, pitch on the bad days as it was prior to treatment., Male 47

Nowadays my tinnitus does not affect me much during the day, there are long periods in which I don't even think about it. It does bother me at night and I have adopted a few "strategies" to cope with it, which include: adhering to more disciplined sleep schedule (even on weekends), taking a few sleep helping supplements and medication (magnesium, valerian root and sometimes low dosage bromazepam) and using a white noise speaker on my left ear., Male 57

Tinnitus negatively affects my entire life. relationships, work, well being, health etc, Male 45

During the last week my tinnitus has affected my concentration and particularly my sleep. I have a lower mood when my tinnitus is high (I believe it causes me anxiety) and I tend to comfort eat during these periods which isn't great!, Female 26

Easier to sleep and less intrusive during the day., Male 36

bad days are more manageable, Male 48

I am only bothered by my tinnitus now at night or in silent rooms., Male 38

Difficulty getting to sleep. Cannot stand in a completely silent room as the Tinnitus becomes somewhat overwhelming. It is much more noticeable during day to day activities which is unnerving., Male 29

Just the same as normal - I have good days, where I hear it all the time but it doesn't upset me, and bad days where I hear it, it seems to be louder and more intense and it upsets me greatly, Male 46

Not as bothersome, feeling like I'm getting back to my old self again., Female 37

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Appendix 6 – Lessons Learned

The following lessons were learned during the project to develop this report and could be taken into consideration if a similar undertaking was made in the future:

- We made reporting of TFI optional and responders could instead provide a high level descriptor of the status of their tinnitus. The reason is that we felt that a long survey may cause a high drop out rate. In fact almost all responders chose the TFI, with a small number of exceptions. The exceptions meant that we lost some valuable data which could have been used for analysis. Next time it might be better to make TFI mandatory.
- We made use of TFI rather than THI. Some researchers have recommended the use of THI rather than TFI as a scale when the objective is to compare patient changes in tinnitus severity. Next time it may be better to use THI.
- The use of an automated tool for sending out surveys and reminders would be of value as this process is time consuming. It might be worthwhile performing some research into the availability of such a tool.
- To encourage fully completed responses, it might be worthwhile providing a raffled prize for patients who complete all their surveys. Care would need to be taken to ensure this does not encourage bogus responders. The use of photos of the device could be used to establish bonafides.
- In order to improve analysis, it may have been better to ask when tinnitus started (rather than asking to choose amongst a number of high level duration options). This would have allowed linear regression which may have been more meaningful.
- We asked patients to provide the baseline response around the time of the device fitting. Around this time the patient may be experiencing placebo effects or adverse effects due to travel. It might have been better to ask them to do the survey several weeks in advance.
- The amount of work required to complete the report was substantial. It might have been sensible to build a larger team for the completion of the work (e.g. some persons could be responsible for data collection etc).
- We used email and TT handles to communicate with patients. It was easy to lose contact with patients. It might have been better to get a mobile number as well.

Appendix 7 – Statistical results removing low engagement patients

This survey was completed by email and forum messaging only. We did not meet the patients or even call them. In order to mitigate the risk that reported results were not genuine, we made an estimate of the extent of patient engagement and used this when considering statistical results. Patients were awarded points as per the below:

- Duration of membership of the forum (if a member at all), up until Aug 1, 2019:
  - 100 points for membership of more than 36 months
  - 60 points for more than 12 months membership and less than 36
  - 40 points for more than 4 months membership and less than 60
- 40 points for posting in the user experience forum
- An additional 20 points for multiple posts in the user experience forum.
- 100 points for familiarity of the patient to the Tinnitus Hub directors
- 100 points for providing a personalised photo of the device
- 100 points for posting Neuromod related collateral in the Tinnitus Hub forum.

A score was then derived from the number of points:

Points	Score	Rating
Less than 40	1	Low
40, more than 40 and less than 60	2	Low-Med
60, more than 60 and less than 80	3	Med
80 or more than 80	4	High

Table 25 - Engagement Score Table

When the points would otherwise be less than 100, we asked each patient to provide a personalised photo and followed up at least 3 times. The distribution of the score is shown below. It's gratifying that for most patients, there was a high level of engagement.

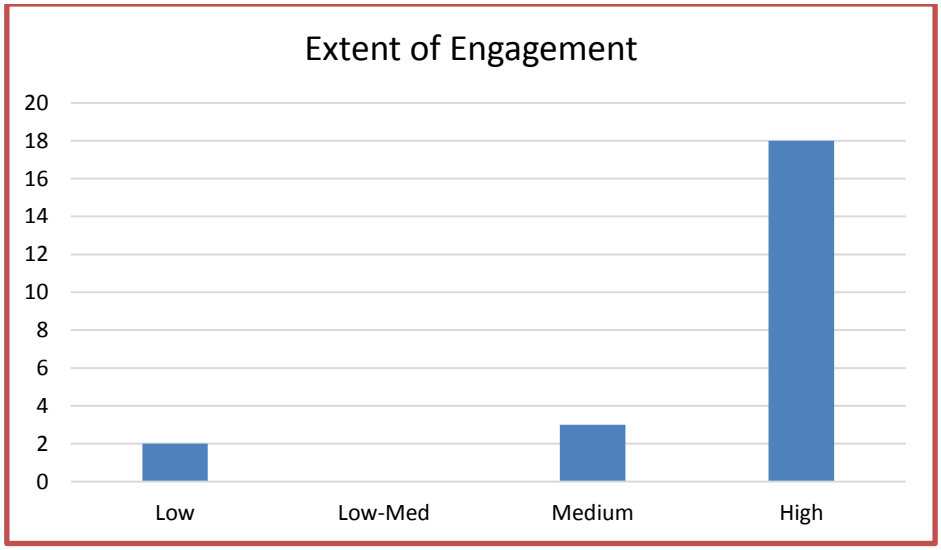
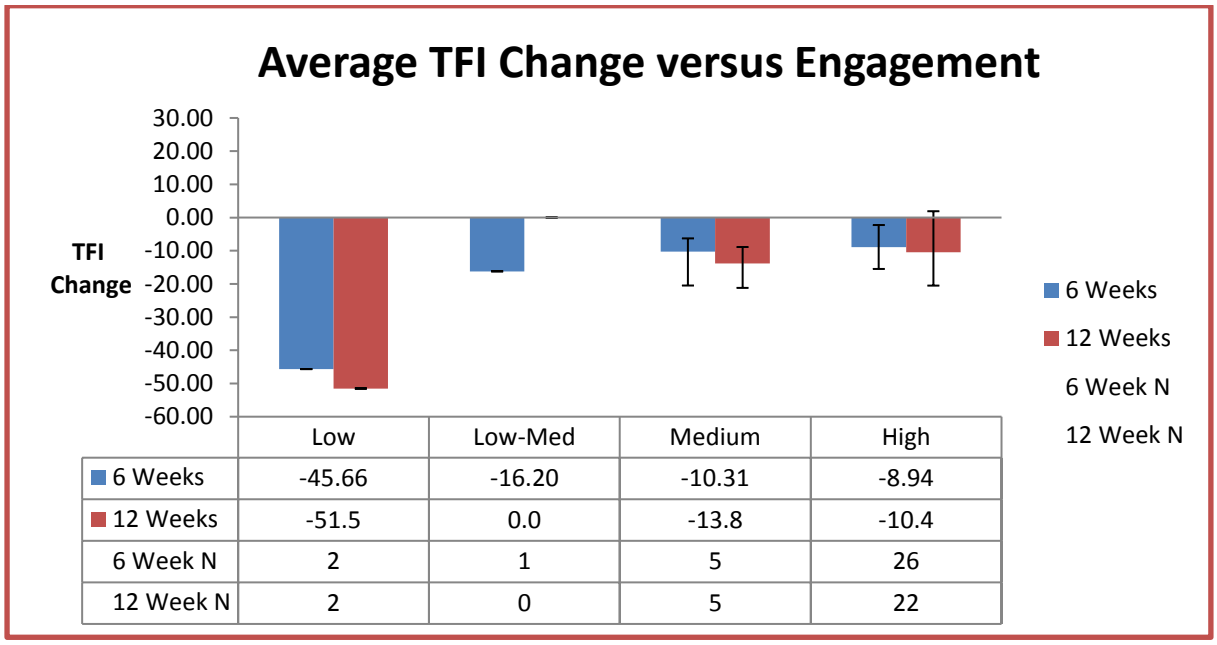


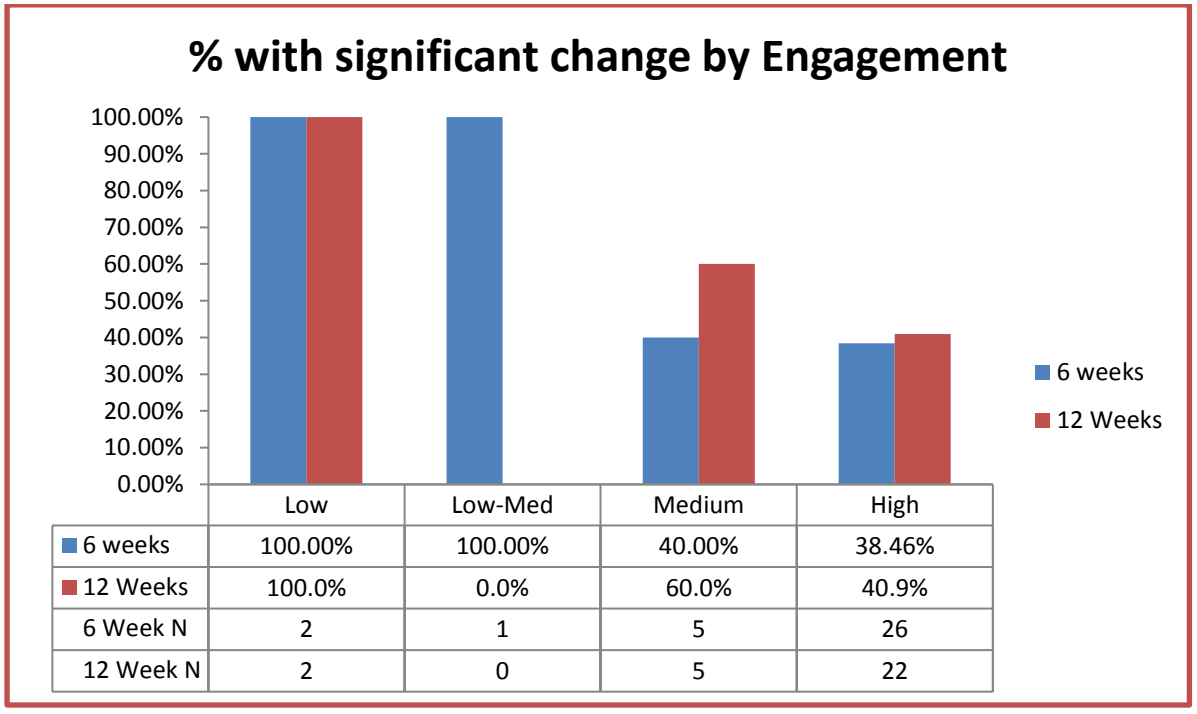
Figure 27 - Distribution of Scores - Extent of Engagement

Here are some charts showing the relationship between engagement and TFI reduction:



	Low	Low-Med	Medium	High
6 Weeks	-45.66	-16.20	-10.31	-8.94
12 Weeks	-51.5	0.0	-13.8	-10.4
6 Week N	2	1	5	26
12 Week N	2	0	5	22

Figure 28 - Average TFI Change by Engagement



	Low	Low-Med	Medium	High
6 weeks	100.00%	100.00%	40.00%	38.46%
12 Weeks	100.0%	0.0%	60.0%	40.9%
6 Week N	2	1	5	26
12 Week N	2	0	5	22

Figure 29 - Percentage with significant change by engagement

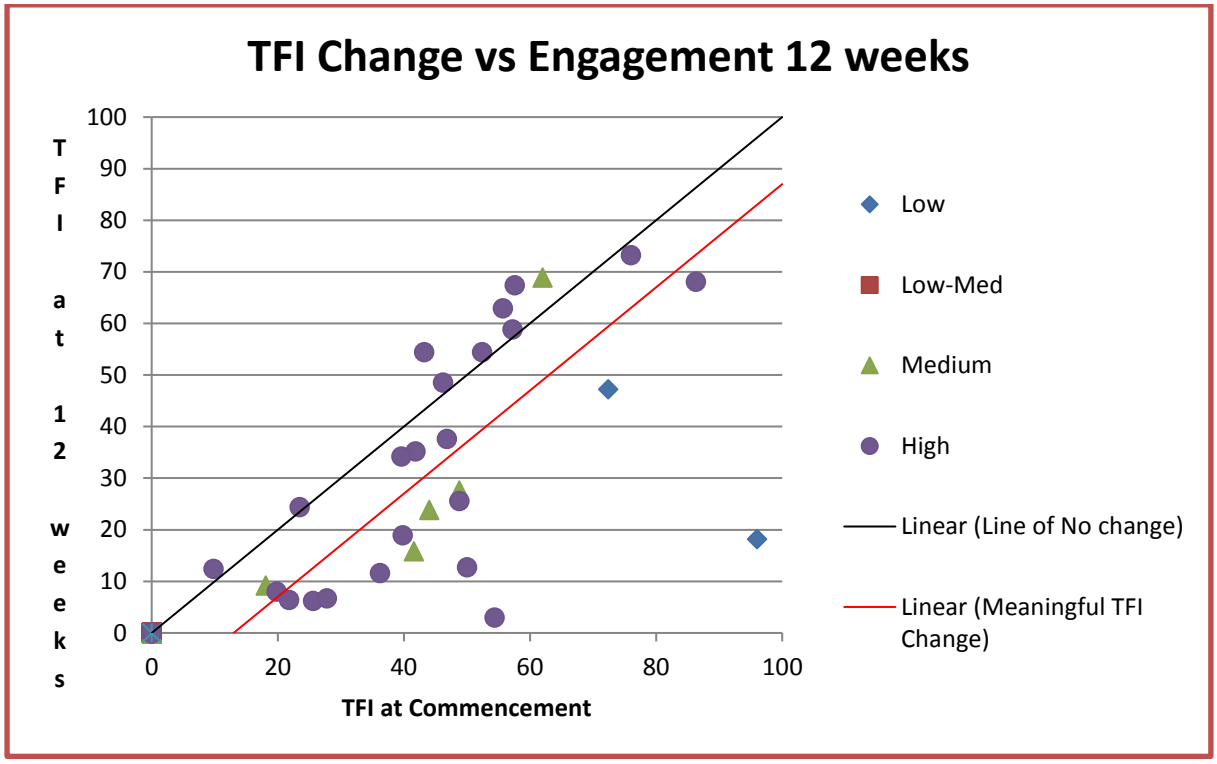


Figure 30 - TFI Change versus Engagement at 12 weeks

You can see that:

- Those with low engagement scores also tend to have high reductions in TFI. This is further reinforced by the statistics (Linear regression p=0.005, Adjusted R^2 0.234).
- While the number of patients with high engagement is quite high (78%), the average TFI change at 12 weeks for these patients was only -10.4, and the percentage with a clinically significant change was only 40.9%.

If we redo the statistics, but this time remove the patients with low engagement, we get quite different results. Some of these are shown below.

Pairwise t-test

	Average Change	Paired t test p score (One Tailed)	Paired t test p score (Two Tailed)	Lower 95% confidence interval	Upper 95% confidence interval
0 to 6 weeks	-9.38	0.000	0.001	-4.13	-14.63
0 to 12 weeks	-11.07	0.001	0.002	-5.09	-17.05
6 to 12 weeks	0.40	0.84			

Table 26 - Pairwise t-test removing Low engagement patients

One-Way ANOVA

	One Way Anova p score	
Factor	6 Weeks	12 Weeks
Hyperacusis	0.981	0.440
Duration	0.169	0.133
Age	0.521	0.792
Hearing Loss (Average)	0.357	0.224
Hearing Loss (Worst Ear)	0.189	0.080
Hearing Loss (Best Ear)	0.151	0.095
Pitch	0.116	0.089
Loudness	0.881	0.865
Intermittency	0.646	0.518
Engagement	0.884	0.659
Source	0.514	0.790
Reactivity to Noise	0.621	0.471
Variation within a Day	0.726	0.761
Variation between Days	0.681	0.514
Compliance	0.434	0.812
Gender	0.712	0.454
Somatic Modulation	0.631	0.596
Hearing Loss Binary	0.151	0.095
Hyperacusis Binary	0.974	0.171
HL and Hy Binary	0.489	0.047
TFI	0.541	0.781
Severity	0.556	0.096

Table 27- One Way ANOVA removing low engagement patients

Fisher Exact p-test

	Fisher Test p score	
Factor	6 Weeks	12 Weeks
Hyperacusis	0.557	0.112
Duration	0.389	0.207
Age	0.922	0.107
Hearing Loss (Average)	0.310	0.283
Hearing Loss (Worst Ear)	0.688	0.204
Hearing Loss (Best Ear)	0.427	0.398
Pitch	0.085	0.357
Intermittency	0.593	0.336
Engagement	0.778	0.628
Reactivity to Noise	0.431	0.713
Variation within a day	1.000	0.556
Variation between days	0.795	0.568
Compliance	0.644	1.000
Gender	1.000	0.628
Somatic Modulation	0.420	0.408
Loudness	0.377	0.663
Hyperacusis Binary	1.000	0.217
Hearing Loss Binary	0.427	0.398
Hearing Loss and Hyp Binary	0.488	0.050
TFI	0.215	0.382
Severity	0.663	0.242

Table 28 - Fisher Exact p-test removing low engagement patients

Chi Square Severity

	Chi Square Severity	
Factor	6 Weeks	12 Weeks
Severity	0.271	0.033

Table 29 - Chi Square Severity removing low engagement patients

Appendix 8 – Cohort Characteristics – Summary

Lenire User Experience Group Cohort Analysis Summary

- A total of 43 patients signed-up for the study and provided baseline tinnitus data. The average age of the patients was 41.6 and the standard deviation[1] was 11.5. The youngest was 21 and the oldest 68. The average duration of tinnitus was approximately 6.3 years, and the duration standard deviation was approximately 7.6. 58% of patients originated from either the UK, the US or Ireland.
- The sample size is quite small and may make it difficult to arrive at reliable statistical conclusions relating to changes as a result of treatment.
- Of the 43 patients, 40 provided a TFI score at baseline. TFI is a popular method of capturing tinnitus severity and was optional in this survey.
- The average TFI rating for the patients who provided it was 45.9, and the standard deviation 19.0. The lowest was 9.8 and the highest 96. Patients reported a variety of causes for their tinnitus, with the most common being related to sudden acoustic trauma or noise-induced hearing loss.
- We had many more males (34) respond to the questionnaire than females (9). Female tinnitus severity showed a much higher average value and a much higher variability than male responses.
- The questionnaire we used to capture patient information was well designed in the sense that in most cases there was a reasonably even distribution of question responses across the possible questionnaire options.
- Patients' experience with Neuromod during their initial appointments was positive, with an overall experience rating of 4.4/5.
- When comparing the TFI group (e.g Male, Female) means within a factor (e.g. Gender) these means were statistically significantly different within the "Gender", "Loudness" and "Severity" factors and no others.
- When comparing the patient characteristics (factors) with each other and with their TFI score, there were some statistically significant correlations:
    - Reduced intermittency was correlated with a higher TFI, increased duration, increased age, higher pitch, increased perceived loudness and increased perceived severity.
    - Hearing Loss was correlated with age.
    - Higher pitch was correlated with increased loudness and severity.
    - Increased loudness and severity were correlated with higher TFI and with each other.

[1] The Standard Deviation of a sample is a measure of the sample spread. If the sample is from a normal distribution, 68% of the values will typically fall within the mean +/- one standard deviation and 95% within 2 standard deviations either side of the mean. A normal distribution is bell shaped and used to model a wide variety of phenomena.

Appendix 9 – Analysis with "Last Value Carried Forwards"

In this section, we use the data from patients who dropped out at 6 weeks and use this as their 12-week data as well. We get an additional 5 patients this way in the 12-week analysis. It was noted earlier that most of the average benefits accrue at 6 weeks, but we have also noticed that there can sometimes be a big change from 6 weeks to 12 weeks for individual patients. With this in mind, here are the results:

Change in TFI

	Average Change	Paired t test p score (One Tailed)	Paired t test p score (Two Tailed)	Lower 95% confidence interval	Upper 95% confidence interval
0 to 6 weeks	-11.5	0.000	0.000	-5.7	-17.4
0 to 12 weeks	-11.5	0.002	0.005	-4.4	-18.6
6 to 12 weeks	0.0	0.99			

Table 30 – Change in TFI using Last Value Carried Forwards Technique

The reduction in TFI is now lower at 12 weeks, which we might expect as people dropping out at 6 weeks probably have lower TFI reductions. But, the change is still statistically highly significant.

One Way Anova

	One Way Anova p score	
Factor	6 Weeks	12 Weeks
Hyperacusis	0.255	0.044
Duration	0.090	0.076
Age	0.467	0.516
Hearing Loss (Average)	0.076	0.031
Hearing Loss (Worst Ear)	0.035	0.009
Hearing Loss (Best Ear)	0.022	0.010
Pitch	0.029	0.018
Loudness	0.558	0.101
Intermittency	0.628	0.734
Engagement	0.021	0.011
Source	0.611	0.847
Reactivity to Noise	0.459	0.328
Variation within a Day	0.989	0.827
Variation between Days	0.364	0.719
Compliance	0.302	0.722
Gender	0.081	0.033
Somatic Modulation	0.790	0.650
Hearing Loss Binary	0.022	0.010
Hyperacusis Binary	0.612	0.190
HL and Hy Binary	0.145	0.032
TFI	0.269	0.295
Severity	0.311	0.008

Table 31 - One Way Anova using Last Value Carried Forwards Technique

Fisher Exact Test

	Fisher Test p score	
Factor	6 Weeks	12 Weeks
Hyperacusis	0.880	0.032
Duration	0.212	0.066
Age	0.932	0.226
Hearing Loss (Average)	0.187	0.042
Hearing Loss (Worst Ear)	0.273	0.031
Hearing Loss (Best Ear)	0.151	0.066
Pitch	0.028	0.061
Intermittency	0.490	0.308
Engagement	0.321	0.238
Reactivity to Noise	0.570	0.469
Variation within a day	0.888	0.624
Variation between days	0.908	0.730
Compliance	0.416	0.832
Gender	0.672	0.214
Somatic Modulation	0.697	0.448
Loudness	0.215	0.236
Hyperacusis Binary	1.000	0.080
Hearing Loss Binary	0.151	0.066
Hearing Loss and Hyp Binary	0.399	0.007
TFI	0.155	0.301
Severity	0.710	0.277

Table 32 - Fisher Exact Test using Last Value Carried Forwards Technique

Hearing loss is now showing as significant and Hearing Loss/Hyp Binary is now much more significant.

Wilcoxon Signed Rank for Severity

	Delta Median	p-value
0-6 Weeks	-1	0.013
0-12 Weeks	-1	0.004
6-12 weeks	0	0.146

Table 33 - Wilcoxon Signed Rank for Severity using Last Value Carried Forwards Technique

Multiple Linear Regression

Combination	1	2	3	4	5	6
	Age					
	Duration			Duration	Duration	
	Intermittency	Duration	Duration	Intermittency	Hearing Loss	
	Hearing Loss	Intermittency	Hearing Loss (Best)	Hearing Loss	Hyperacusis	Hearing Loss
	Hyperacusis	Hyperacusis	Hyperacusis	Hyperacusis	TFI	Hyperacusis
R^2 Adjusted	0.44	0.35	0.48	0.45	0.47	0.10
p- values	0.001	0.001	0.000	0.000	0.000	0.123
PeterPan Prediction	12.5	16.8	12.0	10.4	9.3	12.8

Table 34 - Multiple Linear Regression using the Last Value Carried Forwards Technique

The R^2 values are now quite a bit better.

Logistic Regression

Combination	1	2	3	4	5
				Age	TFI
		Duration	Age	Duration	Duration
	Hyperacusis	Hyperacusis	Duration	Hyperacusis	Hyperacusis
	Hearing Loss	Hearing Loss (Best Ear)	Hyperacusis	Hearing Loss	Hearing Loss
R^2 (CS)	0.26	0.43	0.36	0.42	0.40
p- values	0.006	0.000	0.002	0.001	0.005
% Correct Predictions	68%	65%	76%	76%	76%
PeterPan prediction	50%	6%	70%	78%	64%

Table 35 - Logistic Regression using the Last Value Carried Forwards Technique