Rev Laryngol Otol Rhinol.
2017;138,3:79-85.

OTOLOGY
MAIN ARTICLE

Etude observationnelle évaluant l'effet d'Audistim® sur la qualité de vie de patients présentant des acouphènes chroniques

Observational study to assess the effect of Audistim® on the quality of life of patients presenting with chronic tinnitus

Frachet B. [1]
Portmann D. [2]
Allaert F. A. [3]
(Paris, Bordeaux, Dijon)

Résumé

Objectifs *: évaluer l'amélioration des symptômes, de la qualité de vie, du stress psychologique et de la qualité du sommeil des personnes souffrant d'acouphènes chroniques après 3 mois de prise d'Audistim®.* ***Méthodes*** *: étude observationnelle d'Audistim® par des médecins ORL chez des personnes venant les consulter pour des acouphènes chroniques. Critère d'évaluation : score de qualité de vie THI, score de sommeil PSQI, score de Stress MSP-9. Les patients étaient vus à l'inclusion et au 3ème mois.* ***Résultats*** *: 314 patients âgés de 54,1 ± 13,0 ans et souffrant d'acouphènes depuis 5,8 ± 7,3 ans ont été inclus dans l'étude. Au terme des 3 mois, la qualité de vie des patients est passée de 44,6 ± 23,4 à 26,7 ± 18,7 soit une amélioration de 40,1 % (< 0,0001), le stress des sujets de 38,5 ± 13,3 à 30,1 ± 10,8 à 3 mois soit une amélioration de 21,8 % (< 0,0001) et la qualité du sommeil de 8,4 ± 4,5 à 5,4 ± 3,2 soit une amélioration de 35,7 %. L'amélioration de la qualité de vie est significativement corrélée à l'amélioration du stress (r : 0,77 (p < 0,0001) et du sommeil (r : 0,70 (p < 0,0001). Les acouphènes sont améliorés chez 70,0 % des sujets selon les médecins, et chez 69 % d'entre eux de l'avis des patients eux-mêmes. 2,8 % des patients ont éprouvé un événement indésirable essentiellement digestif dont aucun n'a été jugé attribuable à la prise d'Audistim® par les médecins.* ***Conclusion*** *: la composition originale d'Audistim® associant plusieurs ingrédients actifs utilisés pour lutter contre les acouphènes induit des améliorations nettes de la qualité de vie, du stress et du sommeil des patients éprouvant des acouphènes et suscite leur satisfaction et cela sans risque d'événements indésirables.*

Mots-clés : Acouphènes, traitement, THI, PSQI, MSP-9, stress, sommeil.

Summary

Objectives*: To evaluate the improvement of symptoms, quality of life, psychological stress and sleep quality of patients suffering from chronic tinnitus after a 3 months intake of Audistim®.* ***Methods****: Observational study of Audistim® by ENT doctors in patients consulting them for chronic tinnitus. Evaluation criterion: THI quality of life score, PSQI sleep score, MSP-9 Stress score. Patients were examined at baseline and at 3 months.* ***Results****: 314 patients aged 54.1 ± 13.0 years and suffering from tinnitus since 5.8 ± 7.3 years were included in the study. At the end of the 3 months, patients' quality of life changed from 44.6 ± 23.4 to 26.7 ± 18.7 corresponding to an improvement of 40.1% (< 0.0001), subjects' stress from 38.5 ± 13.3 to 30.1 ± 10.8 to 3 months corresponding to an improvement of 21.8% (<0.0001) and sleep quality of 8.4 ± 4.5 to 5.4 ± 3.2 corresponding to an improvement of 35.7%. Quality of life improvement was significantly correlated with stress improvement (r: 0.77 (p< 0.0001) and sleep (r: 0.70 (p< 0.0001). Tinnitus were improved in 70.0% of patients according to doctors, and in 69% of them according to the patients themselves. 2.8% of patients experienced adverse events, essentially digestive, none of which was judged by doctors as imputable to the intake of Audistim®.* ***Conclusion****: The original composition of Audistim® combining several active ingredients used to control tinnitus gives rise to clear improvements in the quality of life, stress and sleep of the patients experiencing tinnitus and provides them satisfaction without the risk of adverse events.*

Key-words: Tinnitus, treatment, THI, PSQI, MSP-9, stress, sleep.

INTRODUCTION

An Ipsos survey conducted for France's 17th National Hearing Day reports that one in four adults nationwide, i.e. 16 million people, suffer from ringing or buzzing in their ears [1]. These symptoms are increasingly complained of by all age groups in the population. They

1. Hôpital Rothschild, 5 rue Santerre, 75012 Paris, France.
2. Institut G. Portmann, 114 avenue d'Arès, 33074 Bordeaux cedex, France. E-mail: institut.portmann@wanadoo.fr
3. Chaire d'Evaluation des Allégations de Santé BSB & Cen Nutriment, Dijon, France.

Article received: 08/08/17 accepted: 08/26/17

may have varied and sometimes substantial repercussions on sufferers' work, family life, psychological state and ability to concentrate.

Tinnitus is characterized by more or less constant noise or ringing in the ears. It is evidence of neuronal hyperactivity in some location along the auditory pathways. In the majority of cases, the hyperactivity is certainly generated by impairment of the hair cells of the cochlea.

A survey of its members by the association France Acouphènes [2] shows that tinnitus sufferers are unhappy with their current standard of care. The study shows in particular that 82% of patients state they are not satisfied with their initial consultation for tinnitus, that nearly 9 out of 10 people go for a repeat consultation, and that after a first consultation with an ear, nose and throat doctor 92% of patients see another one. Moreover, after consulting the ENT specialist about half of the patients consult other practitioners in acupuncture (55%), general practice (51%), osteopathy (46%) and homeopathy (38%).

To try to relieve patients, AUDISTIM Pharma has developed the eponymous Audistim® in accordance with an original formula combining hawthorn, Ginkgo biloba, melatonin, lemon balm and California poppy [3-5]. Audistim® has been on sale in France since September 2015. To document the product, AUDISTIM Pharma has first sought to conduct an observational study to identify the most relevant evaluation criterion and to quantify the sample size for observing the expected effect in preparation for a double-blind, randomized, controlled clinical trial. This observational study conducted in real life by ENT physicians among patients suffering from chronic tinnitus has thus evaluated in particular changes in the quality of life, stress, and sleep when taking Audistim® as a dietary supplement. These results give a first indication of the benefits that the subsequent clinical trial might be able to demonstrate.

MATERIAL AND METHODS

Nature of the study

An observational study of Audistim® by ENT physicians among people consulting for chronic tinnitus.

Objectives

This prospective observational study by ENT physicians in everyday community or hospital practice was designed to evaluate the benefits on quality of life, psychological stress and quality of sleep after three months of taking Audistim® as a food supplement. Its secondary objectives were to evaluate the overall improvement as perceived by both the clinician and patients, relief from suffering, satisfaction, adherence to supplement intake and tolerance of the product.

Patient selection and adherence criteria

The ENT physicians were to enrol in the study the first five subjects aged 18 to 75 years suffering from chronic tinnitus for whom they decided freely to begin supplementation with Audistim®. Each patient was to have been duly informed of the aims of the study, the anonymous character of the information collected and of their right to decline to participate in the study or to interrupt their participation without that harming their relations with the physician or their medical care. The form handed to the patient was not to show either their refusal to participate in the study or their prohibition on information concerning the patient being used anonymously (non-objection principle). Lastly, to reflect observational conditions, no exclusion criterion was defined except for presenting with major or evolving illnesses, participating in another observational study or clinical trial or presenting a known hypersensitivity to the constituents of the product under study. Patients were informed they would have to purchase the product themselves for the three months of the study.

Evaluation criteria

The criteria for evaluating efficacy were:

- Quality of life evaluated by the Tinnitus Handicap Inventory (THI score) [8].
- Psychological stress evaluated by the Psychological Stress Measure (MSP-9) scale [9].
- Quality of sleep evaluated by the Pittsburgh Sleep Quality Index (PSQI) [10].
- Clinical Global Impression of Improvement (CGI-I) [11].
- Patient Global Impression of Improvement (PGII) [11].
- Satisfaction on a 5-point Likert scale.
- Compliance with taking the supplement was quantified using the Morisky Medication Adherence Scale (MMAS-4) [12].
- Tolerance was evaluated from reports of adverse events.

Survey process and data collection

The study involved an enrolment visit (M0) and a three-month follow-up visit (M3). At the enrolment visit (M0), the physician described the subject's sociodemographic characteristics (age, weight, height, sex, occupation), history and characteristics of tinnitus (time since onset, location, causes, associated disorders or symptoms, any previous treatment for tinnitus) and asked the subject to complete the THI, MSP-9 and PSQI self-questionnaires.

At the follow-up visit (M3), the physician described his opinion about the global improvement of the patient's tinnitus (CGI-I), recorded any adverse events that had occurred and asked the subject to complete the THI, MSP-9 and PSQI self-questionnaires anew. The physician also asked the patient's opinion about any change in their tinnitus (PGI-I), to quantify their satisfaction on the Likert scale and to complete the MMAS adherence questionnaire.

Nutrivigilance

As the product investigated was a nutritional supplement, the declaration of adverse events was the responsibility of the prescribers in the context of nurtivigiliance obligations. The participating physicians reported any adverse events under the National Nutrivigilance Scheme in the manner described on the website of the French Agency for Food, Environmental and Occupational Health & Safety (Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail, ANSES).

The study product, Audistim®

The Audistim® supplement under study consists of one "day" capsule in the morning and one "night" capsule in the evening, 30–60 minutes before going to bed, for three months. The composition is given below:

❒ Day capsule ingredients:

Marine magnesium oxide, maltodextrin, hawthorn leaf and flower extract (Crataegus monogyna and Crataegus laevigata), L-Theanine, Ginkgo biloba leaf extract, Quercetin, nicotinamide (vit B3), anti-caking agents: magnesium salts of fatty acids, cyanocobalamine (vit B12), Pyridoxine hydrochloride (vit B6), Thiamin hydrochloride (vit B1). Capsule: gelatine, colouring agents: E171, E172, E122* *E122.

❒ Night capsule ingredients:

Maltodextrin, Tryptocetine® (L-Tryptophan, Quercetin complex), marine magnesium oxide, lemon balm leaf extract (Melissa officinalis), California poppy extract (Eschscholzia californica) aerial parts, zinc citrate, Ginkgo biloba leaf extract, anti-caking agents: magnesium salts of fatty acids, silica, melatonin. Capsule: gelatine, colouring agents: E171, E132.

STATISTICAL ANALYSIS PLAN

Populations studied

The analysis was performed for the enrolled patients whose records could be evaluated at the end of the data review. The study population corresponds to all subjects meeting the inclusion and non-exclusion criteria having taken Audistim® and having gone through evaluation for the main inclusion criterion and at the follow-up visit.

The tolerance population consists of all subjects having taken at least one dose of Audistim®.

Description of the statistical analysis

Description of the subjects at enrolment

The socio-demographic and clinical characteristics of subjects at enrolment were conducted using means and standard deviations for quantitative variables and using frequencies and percentages for qualitative variables.

Efficacy study

The quantitative change in the THI quality of life score between M0 and M3 was computed using a Student's t-test on paired series and its change in classes by a Wilcoxon signed rank test. The clinical characteristics of subjects and especially tinnitus liable to influence this change were sought by comparing the mean values of these changes as a function of these characteristics by analysis of variance. The variables tested were age, sex, BMI, time since onset of tinnitus, location and severity of tinnitus, probable causes, complaints/symptoms associated with tinnitus, PSQI and MSP-9 scores upon enrolment.

The MSP-9 stress and PSQI scores were also compared using Student's t-tests on paired series. Global improvements perceived by the patient and clinician (PGII and CGII), the Morisky adherence to treatment score (MMAS-4) and satisfaction were described by frequencies and percentages as were adverse events.

In addition, so as to confirm the results, correlation analyses were performed between improvement in quality of life (THI score), sleep (PSQI) and stress by calculating the Pearson coefficient and between improvement in quality of life, physicians' opinions and subjects' impressions by analyses of variance.

Justification of the number of patients/centres

Sample size was calculated on the basis of the change in quality of life evaluated on the THI scale. It was grounded on the assumption of a mean reduction of 5 points of the THI score after three months of taking Audistim® [13]. Under these circumstances, by the computation performed with Nquery software, with alpha risk = 0.05, power of 90% and a standard deviation of difference of 30 [13], the number of patients to be included came out at 310.

Analysis software and statistical level of significance

The data were recorded in Capture System and processed with SAS software version 9.3. The level of statistical significance was set at $p < 0.05$.

Regulatory framework

This was a "non-interventional study" as defined by Directive 2001/20/EC [6] and complied with existing good practice [7]. In particular, prescription of the product was not to be decided on in advance by the study protocol but to be part of the physician's usual practice

and their decision alone; no additional diagnostic or supervision procedure was to be used with the patients. Prescription did not entail any modification in patient care and under these circumstances it did not come within the scope of article L.1121-1 ff of the French Public Health Code. Lastly, because it began before publication of the enforcing decree of the Jardé Act in November 2016 now requiring an ethics committee examination of observation studies, that provision was not applicable to the study.

RESULTS

Study outcome

Three hundred and sixteen (316) subjects were enrolled in the study by 93 centres in France in community or hospital consultations. Two subjects were not seen again and excluded from the analysis. The analysis of efficacy and tolerance concerned the 314 subjects.

Subjects' socio-demographic and clinical characteristics

The 314 patients in the study were aged 54.1 ± 13.0 years with equivalent proportions of men and women (48.7%/51.3%) and they lived throughout France. Of their number 57.2% were in work, 33.5% retired and 9.2% were inactive or unemployed. The occupations of those in work globally reflected those of the French population (table I).

TABLE I : Patient characteristics at enrolment.

	Mean ± SD or N/%
Age (years)	54.1 ± 13.0
Sex, Male	153 (48.7)
BMI	24.9 ± 4.0
Occupational status, in work	179 (57.2)
Time since onset of tinnitus (years)	5.8 ± 7.3
Severity of tinnitus, Permanent	239 (76.1)
THI score at enrolment	44.6 ± 23.4
MSP-9 score at enrolment	38.5 ± 13.3
PSQI score at enrolment	8.4 ± 4.5

In terms of ENT complaints, 91.4% of them had had an audiogram, 21.0% MRI and 8.9% a CT scan that had shown no notable anomaly. Their tinnitus had first appeared 5.8 ± 7.3 years previously and was bilateral for half of the subjects (52.5%) (table I). It was permanent for three out of four of them (76.1%). Among the likely causes, the most commonly cited were acoustic traumas (29.0%), presbyacusis (29.0%), vascular and circulatory disorders (14.0%), damage to the auditory nerve and inner ear (8.8%), Menière's disease (7.8%) and high blood pressure (7.2%).

Numerous disorders were associated with tinnitus including in particular 49.0% auditory loss, 21.7% migraine, 21.7% vertigo, 17.2% cervical pain, 13.5% hyperacusis, 11.5% balance disorders.

More than one in three patients (35.0%) had already been treated for their tinnitus by very varied medications. The reasons for discontinuing treatment were ineffectiveness in 94.0% of cases and the occurrence of adverse events in 2.0% of cases.

Impact of tinnitus

The THI score measuring the impact of tinnitus on quality of life was 44.6 ± 23.4 out of a maximum of 100 and according to the classification of the tinnitus the impact was "slight" for 12.4% of subjects, "mild" for 30.6%, "moderate" for 27.1%, "severe" for 19.4% and "catastrophic" for 10.5%. The mean MSP-9 score was 38.5 ± 13.3 out of 72 for maximum stress and was higher when the THI score was high. Study of their correlation showed a Pearson coefficient of 0.67 ($p < 0.0001$) and mean stress values ranging from 28.1 ± 10.4 in subjects reporting slight impact to 58.4 ± 11.5 among subjects reporting catastrophic impact ($p < 0.0001$). Sleep quality evaluated by PSQI was "very good" for 3.8% of subjects, "fairly good" for 47.1%, "fairly poor" for 39.2% and "very poor" for 9.9%.

Change in efficacy criteria with Audistim®

The Morisky adherence score shows 76.5% of subjects had high adherence, 19.3% medium adherence and 4.2% low adherence.

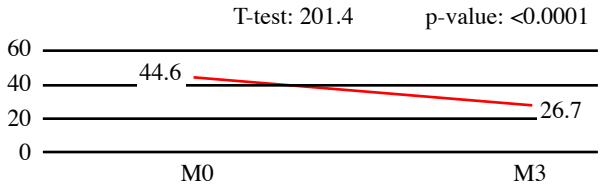


Fig. 1A : Global improvement of THI score between M0 and M3.

After taking Audistim® for three months, the impact of tinnitus on quality of life was 26.7 ± 18.7 that is an improvement of 40.1% (< 0.0001) (fig. 1A), whereas the percentage of patients whose tinnitus was "severe or catastrophic" fell from 29.9% to 8.0%. Figure 1B illustra-

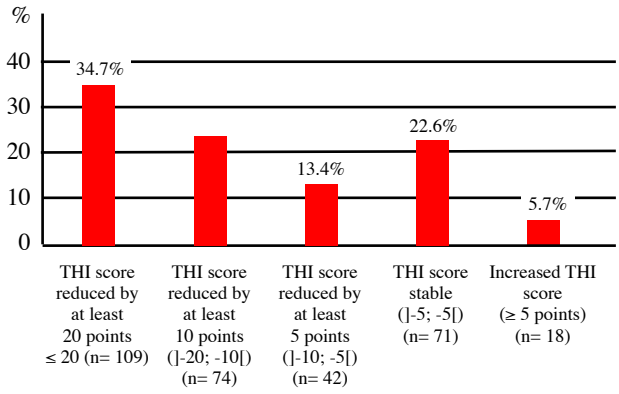


Fig. 1B: Percentage change in THI score.

tes the size of THI improvements and reductions of 10 points or more are found for 58.3% of patients.

Subjects stress was evaluated at 30.1 ± 10.8 after three months, that is an improvement of 21.8% (< 0.0001) and sleep quality at 5.4 ± 3.2, that is a 35.7% improvement (fig. 2).

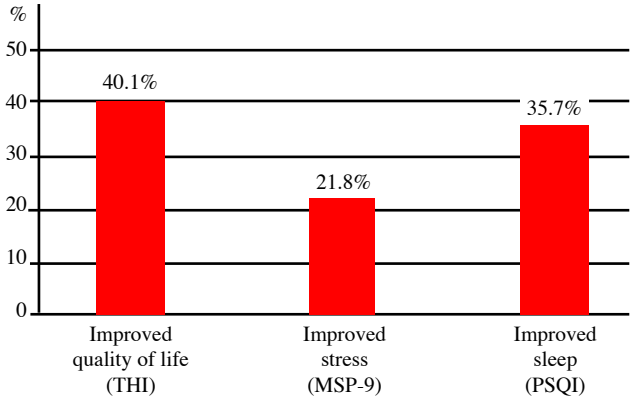


Fig. 2: Improvement in quality of life, stress and sleep between M0 and M3.

Improved quality of life is significantly correlated with improvement of stress evaluated by the MSP-9 scale with a Pearson cœfficient of 0.77 (p< 0.0001) (Figure 3) and improvement of sleep with a Pearson cœfficient of 0.70 (p< 0.0001) (Figure 4).

It is also observed that improved quality of life is significantly greater when the tinnitus is associated with migraines (-31.8 ± 31.3 vs -14.0 ± 17.4; p(< 0.0001) or vertigo (-24.5 ± 27.0 vs -16.1 ± 20.6; p(< 0.01). However, improved quality of life is comparable regardless of age, sex, time since onset of tinnitus, whether one- or two-sided, permanent or intermittent.

Physicians' and patients' opinions on changes in tinnitus

Tinnitus is improved in 70.0% of subjects (very much or much improved 31.0%, minimally improved 39.0%) according to physicians and in 69% of subjects (very much or much improved 33.1%, minimally improved 35.9%) according to patients themselves. Physicians' opinions on the improvement of tinnitus is closely correlated with improved quality of life with variations of THI of -49.8 when they judge it much improved versus -5.2 when they judge the condition unchanged. Similar results are found for patients' opinions with very similar decreases of -42.3 versus -6.6. Nearly two in three patients (61.8%) are satisfied with the treatment including 35.9% whose satisfaction is high or very high. There is also close correlation between the level of satisfaction and the improvement in quality of life with improvements of 49.4 points in subjects reporting they are very satisfied versus 13.2 among those moderately satisfied and 6.2 among subjects not at all satisfied.

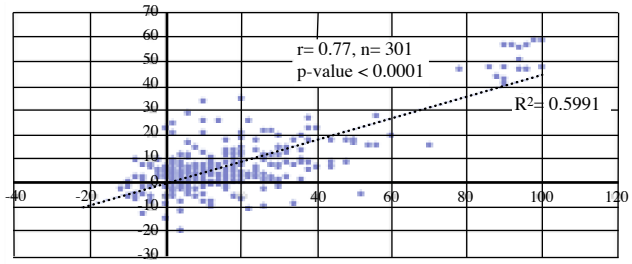
Tolerance of the product

Nine subjects, that is 2.8% of all those who took Audistim® at least once reported a total of 11 adverse events including five of a digestive nature. None of the undesirable events reported was thought by the physicians to be attributable to the intake of Audistim®.

DISCUSSION

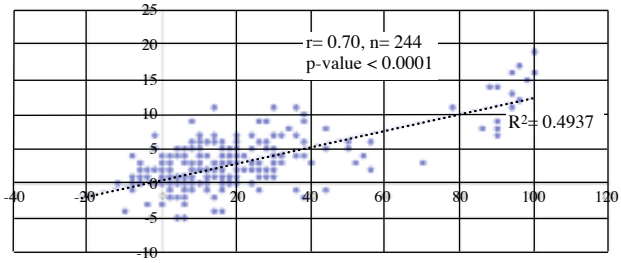
Tinnitus is a frequent, very mundane, but sometimes impairing symptom either because of its impact or because of its cause. This is the first difficulty with it; determining how severe it is. The second difficulty lies in proposing suitable treatment, ranging from so-called "mental" care for it (information, behavioural and cognitive therapy, sophrology, etc...) to a surgical solution by way of psychotropic medication. Weighing the benefits and risks, it is useful to have a food supplement such as Audistim® among proposed therapies.

The situation of people suffering from tinnitus is still particularly difficult to live with for some. Current studies and recommendations agree that these complaints are particularly frequent, considerably impair quality of life and have substantial economic repercussions. Epidemiological studies for Europe and the USA [15] show that as in the Ipsos survey [1] cited in the introduction



X= Improved THI score between D0 and M3
Y= Improved MSP-9 score between D0 and M3

Fig. 3: Correlation between improved quality of life (THI score) and improved stress (MSP-9 score).



X= Improved THI score between D0 and M3
Y= Improved MSP-9 score between D0 and M3

Fig. 4: Correlation between improved quality of life (THI score) and improved sleep (PSQI score).

about a quarter of the total population has experienced tinnitus at least once and that 10 to 15% suffer from it chronically. Economically tinnitus costs a lot not just in health insurance for care and medical services but in days off work. Businesses incur loss of productivity at work because of patients' difficulties in concentrating and because of fatigue resulting from sleep disorders [1].

In terms of evidence-based medicine, none of the very many treatments used for this indication whether medication, surgery, physical or psychotherapy techniques or nutritional supplements have been proved to be effective. This can be explained probably both by the lack of efficacy of some of the treatments but also because most treatments in this area are not conducive to double-blind, randomized, placebo-controlled clinical trials that are the gold standard of evaluation [1, 16]. The recommendations from the US otolaryngology academy [16] include a detailed analysis of the main products used in this domain, namely Ginkgo biloba, lemon balm and zinc, and although these recommendations conclude these products cannot be officially recommended as of present – as is the case for all of the medications used for that matter – they do cite the existence of many positive studies for each of them. These recommendations also emphasize the poor tolerance of medication.

Confronted with this situation, nutritional supplements and plant therapy remain a therapeutic option. As for efficacy, the combination of several natural active principles rather than a single one is an interesting approach and may potentialize the effect of the product. For this reason Audistim® contains hawthorn which has a protective action on capillaries for circulation in the inner ear and Ginkgo biloba for peripheral microcirculation. Recently an article by Von Boetticher examined and evaluated 19 clinical studies on the effects of a Ginkgo biloba extract on tinnitus [3]. The results of eight of these controlled studies of tinnitus with cerebrovascular insufficiency or other disorders largely showed the superiority of treatment with Ginkgo biloba over placebo or other medications over a period of one to three months [3]. Melatonin before going to bed shortens the time taken to fall asleep [4] while lemon balm acts on the quality of sleep. California poppy acts on psychological stress and zinc contributes to normal cognitive function as the European Food Safety Agency indicates in health claims it officially recognizes [5]. The results of this observation study by ENT physicians are quantitatively significant with the improvement in quality of life, stress and sleep providing satisfaction for more than two in three patients. It is of course legitimate and standard practice to emphasize the limitations of conclusions from observational studies but the study of the very positive correlations between improved quality of life, sleep and stress level make them more valuable. The same applies for analyses showing significant improvements in quality of life as a function of subjects' impressions and degree of satisfaction. Likewise, it should be emphasized that quality of life is more improved when the tinnitus is associated with migraines or vertigo, which is consistent with the possible modes of action of several of the components of Audistim® [3-5, 16]. It shall also be emphasized that these evaluations in terms of quality of life and stress via duly validated questionnaires are a more global approach to tinnitus than attempting to make specific measurements of it, particularly because, for reasons of habituation phenomena, there is not necessarily a linear correlation between the intensity of the tinnitus and the disturbance caused. It would be desirable, of course, for this study to be supplemented by a double-blind, randomized, placebo-controlled trial. Thanks to this large-scale observational study such a trial will not be conducted, as is often the case, on the basis of a priori assumptions but on the basis of tangible results that attest to the expected efficacy of Audistim® and indicating the criteria and size effect that might be used in a clinical trial. Another element in favour of the ingredients of the product is that they are well tolerated.

CONCLUSION

The original composition of Audistim® combining several active ingredients traditionally used to combat tinnitus induces marked improvements in quality of life, stress and quality of sleep of subjects experiencing tinnitus and meets their satisfaction without the risk of adverse events that medication (such as psychotropic drugs) regularly used for this indication may cause.

References

1. IPSOS. Enquête auprès de la population française sur le phénomène des acouphènes. *Communication. 17ème édition de la Journée Nationale de l'Audition.* 2014 Mars.
2. ASSOCIATION FRANCE ACOUPHENES. *Unpublished data.* 2013.
3. VON BOETTICHER A. Ginkgo biloba extract in the treatment of tinnitus: A systematic review. Neuropsychiatr Dis Treat. 2011;7: 441-447.
4. EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA); Scientific Opinion on the substantiation of health claims related to melatonin and alleviation of subjective feelings of jet lag (ID 1953), and reduction of sleep onset latency, and improvement of sleep quality (ID 1953) pursuant to Article 13 (1) of Regulation (EC) No 1924/2006. EFSA Journal. 2010;8(2):1467.
5. EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA); Scientific Opinion on the substantiation of health claims related to zinc and function of the immune system (ID 291, 1757), DNA synthesis and cell division (ID 292, 1759), protection of DNA, proteins and lipids from oxidative damage (ID 294, 1758), maintenance of bone (ID 295, 1756), cognitive function (ID 296), fertility and reproduction (ID 297, 300), reproductive development (ID 298), muscle function (ID 299), metabolism of fatty acids (ID 302), maintenance of joints (ID 305), function of the heart and blood vessels (ID 306), prostate function (ID 307), thyroid function (ID 308), acid-base metabolism (ID 360), vitamin A metabolism (ID 361) and maintenance of vision (ID 361) pursuant to Article 13 of Regulation (EC) No 1924/2006 on request from European Commission. EFSA Journal. 2009;7(9):1229.
6. Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. Official Journal of the European Communities. 2001;L/21/34.

7. EPSTEIN M on behalf of ISPE. *Guidelines for Good Pharmacoepidemiology Practices (GPP). Pharmacoepidemiology and Drug Safety*. 2005;14:589-95.
8. NEWMAN CW, JACOBSON GP, SPITZER JB. Development of the Tinnitus Handicap Inventory. Arch Otolaryngol Head Neck Surg. 1996;122:143-8.
9. LEMYRE L, TESSIER R, FILLION L. Mesure du stress psychologique (M.S.P.) : manuel d'utilisation. *Québec, Qué : Éditions Behaviora Inc*. 1990.
10. BACKHAUS J, JUNGHANNS K, BROOCKS A, RIEMANN D, HOHAGEN F. Test-retest reliability and validity of the Pittsburgh Sleep Quality Index in primary insomnia. J Psychosom Res. 2002 Sep;53(3):737-40.
11. GUY W. Clinical Global Impression. *In: ECDEU Assessment Manual for Psychopharmacology, revised National Institute of Mental Health, Rockville, MD*. 1976.
12. MORISKY DE, GREEN LW, LEVINE DM. Concurrent and predictive validity of a self-reported measure of medication adherence. Med Care. 1986;24:67-74.
13. NERI G, DE STEFANO A, BAFFA C, KULAMARVA G, DI GIOVANNI P, PETRUCCI G, POLIANDRI A, DISPENZA F, CITRARO L, CROCE A. Treatment of central and sensorineural tinnitus with orally administered Melatonin and Sulodexide: Personal experience from a randomized controlled study. Acta Otorhinolaryngol Ital. 2009 Apr;29(2):86-91.
14. Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the Protection of Individuals with Regard to the Processing of Personal Data and on the Free Movement of Such Data. Official Journal of the European Communities. 1995: L281/31.
15. HESSE G. Evidence and evidence gaps in tinnitus therapy. GMS Current Topics in Otorhinolaryngology Head and Neck Surgery. 2016;15.
16. TUNKEL DE, BAUER CA, SUN GH, ROSENFELD RM, CHANDRASEKHAR SS, CUNNINGHAM ER JR, ARCHER SM, BLAKLEY BW, CARTER JM, GRANIERI EC, HENRY JA, HOLLINGSWORTH D, KHAN FA, MITCHELL S, MONFARED A, NEWMAN CW, OMOLE FS, PHILLIPS CD, ROBINSON SK, TAW MB, TYLER RS, WAGUESPACK R, WHAMOND EJ. Clinical practice guideline: Tinnitus. Otolaryngol Head Neck Surg. 2014 Oct;151(2 Suppl):S1-S40.