

Original Article

Patient Perceptions of Effectiveness in Treatments for Menière's Disease: a National Survey in Italy

Bryan Ward , Vincent Wettstein , John Golding , Giulia Corallo , Daniele Nuti ,
Franco Trabalzini , Marco Mandalà 

Department of Otolaryngology-Head and Neck Surgery, Johns Hopkins University School of Medicine, Baltimore, USA (BW)

Department of Otorhinolaryngology-Head and Neck Surgery, University Hospital Zurich, Zurich, Switzerland (VW)

Department of Psychology, University of Westminster, School for Social Sciences, London, United Kingdom (JG)

Department of Otolaryngology and Skull Base Surgery, University of Siena, Siena, Italy (GC, DN, MM)

Department of Otolaryngology, University Hospital Meyer, Firenze, Italy (FT)

ORCID IDs of the authors: B.W. 0000-0001-5201-6117; V.W. 0000-0003-4444-0211; J.G. 0000-0003-0971-9508; G.C. 0000-0003-2366-681X; D.N. 0000-0002-1525-7218; F.T. 0000-0003-3207-1535; M.M. 0000-0001-6743-7491.

Cite this article as: Ward BK, Wettstein VG, Golding JF, Corallo G, Nuti D, Trabalzini F, et al. Patient Perceptions of Effectiveness in Treatments for Menière's Disease: a National Survey in Italy. J Int Adv Otol 2019; 15(1): 112-7.

OBJECTIVES: The aim of the present study was to investigate current treatment practices and self-reported effectiveness in Ménière's disease.

MATERIALS and METHODS: Members of two Italian Ménière's disease support (n=170) with ≥6-month history of Ménière's disease were administered an online survey about recent treatments. Vertigo episode count, work absenteeism, and limitations in family life, social life, work, or travel as included in the Social Life and Work Impact of Dizziness Questionnaire before and after recent treatments were queried.

RESULTS: Twenty-four different treatments were reported for Ménière's disease, with dietary modifications (55%), diuretics (47%), and betahistine (41%) being the most common. The majority (71%) received multiple simultaneous treatments. Prior to the most recent treatments, 78%-89% of respondents indicated limitations in family or social life, work, or traveling. After their most recent treatment, respondents reported improvements in mean vertigo episode counts (5.7±7.6 vs. 2.6±4.6, p<0.001), days off work per month (10.1±9.2 vs. 4.2±6.7, p<0.001), and proportions indicating limitations in any functional measure assessed (p<0.05). These findings were consistent regardless of treatment approach (p<0.05 for all). Intratympanic gentamicin provided the greatest reductions in vertigo count, functional limitations, and work absenteeism (p<0.01 for all), as well as the fewest respondents reporting post-treatment functional limitations (16%-37%).

CONCLUSION: Despite many treatment approaches targeting different proposed pathophysiology for Ménière's disease in this cross-sectional survey, all treatments are reported as effective by patients. These findings support a prominent placebo effect in Ménière's disease and highlight challenges in studying treatment outcomes; there is a critical need to better understand Ménière's disease.

KEYWORDS: Dizziness, social impact, sensorineural hearing loss

INTRODUCTION

Ménière's disease is a clinical syndrome of recurrent episodes of vertigo, low- to mid-frequency sensorineural hearing loss, and fluctuating aural fullness, tinnitus, and hearing levels that are associated with vertigo episodes^[1,2]. The reported prevalence has varied widely across studies ranging from 3.5 to 513 per 100,000 individuals^[3-5]. Affected individuals suffer impaired overall quality of life^[6] and disease-specific quality of life^[7,8].

The pathophysiology of Ménière's disease is unknown, although dilation of the membranous labyrinth (i.e., endolymphatic hydrops) is a closely associated finding on post-mortem studies^[9] and, increasingly, on in vivo imaging as well^[10,11]. Owing to the unclear pathophysiology of Ménière's disease, the optimal treatment is also unknown^[12]. However, many treatment options are offered by clinicians; some of which include dietary modifications, medical management with diuretics, steroids or betahistine, and surgeries,

This study was presented at the 7th International Symposium on Meniere's Disease and Inner Ear Disorders, October 18, 2015, Rome, Italy.

Corresponding Author: Marco Mandalà E-mail: marcomand@hotmail.com

Submitted: 25.06.2018 • **Revision Received:** 04.11.2018 • **Accepted:** 26.02.2019

©Copyright 2019 by The European Academy of Otolaryngology and Neurotology and The Politzer Society - Available online at www.advancedotology.org

such as decompression of the endolymphatic sac^[13]. Famously, in a vast review of literature, Torok reported in 1977 that the authors consistently identify improvements in 60%-80% of patients regardless of the intervention used^[14]. Few studies have observed the natural history of the disease^[15], but among placebo-controlled studies, the authors have reported over a 50% reduction in attack frequency at 9 months^[16] and improvements in Ménière's disease symptoms more broadly at 1 year^[17]. In some patients with medically refractory recurrent vertigo, ablative therapies that destroy labyrinthine function, such as intratympanic gentamicin, vestibular neurectomy, and surgical labyrinthectomy, are effective at reducing episodes of vertigo, but with either sacrifice or risk to residual hearing and any remaining vestibular function in the treated ear.

With many treatment options available and without consensus on optimal care, patients with Ménière's disease are likely to be offered therapy dependent on the preferences of providers at the clinics to which they present. We had hypothesized that a national survey of patients with Ménière's disease would identify which of the many available treatments patients report as being more or less effective. The aim of the present study was to assess the cross-sectional prevalence of different treatment approaches to Ménière's disease, as well as the patient-reported effectiveness of their most recent intervention in a nationally representative sample of Italian patients.

MATERIALS AND METHODS

Participants completed an online Italian language questionnaire (www.surveymonkey.com) about the treatment of their Ménière's disease and its impact on their quality of life. Recruitment occurred over 6 months between July 2015 and January 2016. The questionnaire was distributed by two Italian non-profit support organizations for patients with Ménière's disease (Associazione Malati Ménière Insieme and Associazione Italiana Malati di Ménière ONLUS). Inclusion criteria for the study were: (a) diagnosis of definite Ménière's disease according to either the American Academy of Otolaryngology-Head and Neck Surgery guidelines or the 2015 Barany Society guidelines as determined by the patient's otolaryngologist and (b) disease duration of at least 6 months. Prior to joining the organizations, prospective members undergo an interview to confirm a clinician diagnosis of Ménière's disease. A link to the survey was electronically distributed by the organizations to members. Approximately 400 members received the link to a questionnaire. Anonymous data were stored electronically by the hosting survey website and downloaded for analysis at the completion of recruitment.

An English language translation of the complete questionnaire is included in Appendix A. The questionnaire was translated and agreed upon by bilingual members of the research team.

The questionnaire consisted of 17 items. Demographic data including age, gender, and date of initial diagnosis were collected in Questions 1-3. Question 4 asked respondents to report the most recent treatments received for their Ménière's disease. Major therapeutic categories included "betahistine," "diuretics," "oral steroids," "dietary modifications," "cinnarizine," "tympanostomy tube," "surgery of the nerve or inner ear," "intratympanic gentamicin," or "others." Selecting "others" prompted respondents to specify the treatment provided. Multiple selections were permitted. Questions 5 and 6 requested

the estimated number of vertigo episodes per month prior to and following the most recent treatment. Items from the Social Life and Work Impact of Dizziness (SWID)-4 Questionnaire were included in the subsequent questions^[18]. The SWID-4 short form questionnaire is a series of four questions that assess the effects of dizziness on social life, family life, work, and abilities to travel. This instrument was chosen due to its simplicity and the authors' prior use of these items in a validation study of the SWID-4^[18]. Available responses are binary (yes/no). Participants were asked to provide responses indicating their limitations prior to and following their most recent therapies for Ménière's disease. For questions about work limitations, respondents could also indicate "unemployed or retired." If participants did not select "unemployed or retired," they were then asked to estimate the number of days off work per month attributable to Ménière's disease before and after their most recent treatment. The final question requested respondents to evaluate, based on their experience, which treatment they would recommend to a patient suffering from Ménière's disease.

A total SWID-4 score was calculated for each respondent by defining "yes" responses as 1 and "no" responses as 0 and summing the responses. Higher values indicate greater functional limitations.

Statistical Analysis

Statistical analysis was conducted by paired Student's t-test for pre- and post-treatment responses of continuous variables, and Fisher's exact test for binary variables. Between-group comparisons of continuous variables were performed using ANOVA with post-hoc pairwise comparisons performed if statistically significant. A $p < 0.05$ was considered statistically significant. All data were analyzed using GraphPad Prism 6 (GraphPad Software, Inc., La Jolla, CA, USA). Ethical approval was obtained from the ethics committee of University of Siena. Informed consent was included as part of the online survey.

RESULTS

A total of 176 respondents participated in the study. Six respondents submitted incomplete questionnaires, and their data were excluded in the analysis. Demographic and clinical data are shown in Table 1. There were no significant differences between men and women in mean number of vertigo episodes per month, mean days off work due to Ménière's disease per month, or SWID-4 scores ($p > 0.05$). Respondents most commonly indicated that their last treatments included: dietary modifications, followed by diuretics, betahistine, oral steroids, and intratympanic gentamicin. They selected "others" as frequently as betahistine (41%). When specifying further, respondents selecting "others" reported having received any of 19 additional different therapies for their Ménière's disease. These included medical therapies, such as cinnarizine or cinnarizine/dimenhydrinate, citicoline, thiethylperazine, delorazepam or clonazepam, sulodexide, nimodipine, lipoflavonoid cereals, and levosulpiride, as well as hospital admission for intravenous mannitol or glycerol. Procedures described under "others" included intratympanic steroids, tympanostomy tube placement, acupuncture, "surgery of the nerve or inner ear," endolymphatic sac decompression and shunt, and percutaneous transluminal angioplasty for chronic cerebrospinal venous insufficiency.

A large proportion (121/170, 71%) of respondents reported having received at least two treatments simultaneously. Betahistine (58/69,

84%), diuretics (77/80, 96%), steroids (47/48, 98%), and dietary modifications (81/93, 87%) were the most common treatments prescribed in combination, whereas intratympanic gentamicin was uncommonly provided as part of combination therapy (6/19, 32%).

Among all respondents, both the mean number of days per month off work due to Ménière's disease and the mean count of vertigo episodes per month significantly improved after their most recent treatment ($p < 0.0001$; Table 1). When separating the study population by treatment type—understanding the high rate of combination therapy—each group had a similar mean number of vertigo episodes per month before treatment ($p > 0.05$); however, each of the most frequently reported therapeutic options was effective in reducing vertigo episode count ($p < 0.005$, t-test; Figure 1). Of the treatments, intratympanic gentamicin had the greatest absolute reduction (8.3 ± 7.3 vs. 1.5 ± 1.9 episodes, $p = 0.0004$, t-test). Owing to the small sample of respondents indicating having received one of the many treatments in the category “others,” these treatments were not analyzed separately. However, given the reported effectiveness of all the most

commonly used treatments at reducing vertigo episode count, we hypothesized that combining the other treatments into a single category would also demonstrate effectiveness. Respondents who selected “others” also reported significantly fewer vertigo episodes per month (4.7 ± 6.7 vs. 1.8 ± 3.4 , $p = 0.0026$). After treatment, each group had a similar mean number of vertigo episodes per month ($p > 0.05$).

Similarly, before treatment, each group had a similar mean number of days off work per month due to Ménière's disease ($p > 0.05$). Following treatment, there was a reduction in days per month off work due to Ménière's disease for each of the most frequently reported therapeutic options ($p < 0.05$, t-test; Figure 2), except for the oral steroids group ($p = 0.122$, t-test). There were also no differences across the treatment groups in the mean number of days off work per month due to Ménière's disease after treatment ($p > 0.05$).

The four SWID questions assessing lifestyle limitations were also compared before and after treatment among all respondents and separated by the treatment groups. Among all respondents, the

Table 1. Demographic and clinical data of all respondents

N=170 respondents		Statistic	
Age, years	50.3±12.3	-	
Male/female ratio	41/129	-	
Duration of MD, years	7.8±7.9	-	
Mean number of vertigo episodes per month (before last treatment)	5.7±7.6	$p < 0.0001$	
Mean number of vertigo episodes per month (after last treatment)	2.6±4.6		
No. of subjects retired/unemployed (%)	32 (19%)	-	
Days off work due to MD per month (before last treatment)*	10.1±9.2	$p < 0.0001$	
Days off work due to MD per month (after last treatment)*	4.2±6.7		
SWID-4 total score before treatment	3.3±1.0	$p < 0.0001$	
SWID-4 total score after treatment	1.9±1.5		
No. of treatments (%)	1	49 (29%)	-
	2	64 (38%)	
	3	29 (17%)	
	>3	28 (16%)	
	No. of subjects in each treatment group (%) #	Diuretics	80 (47%)
Betahistine		69 (41%)	
Oral steroids		48 (28%)	
Dietary		93 (55%)	
IT gentamicin		19 (11%)	
Others		69 (41%)	

MD: Ménière's disease; IT: intratympanic; SWID: Social Life and Work Impact of Dizziness
 *This value does not include respondents who indicated “retired/unemployed.”
 #Percentages do not add to 100% as many respondents received at least two treatments simultaneously.

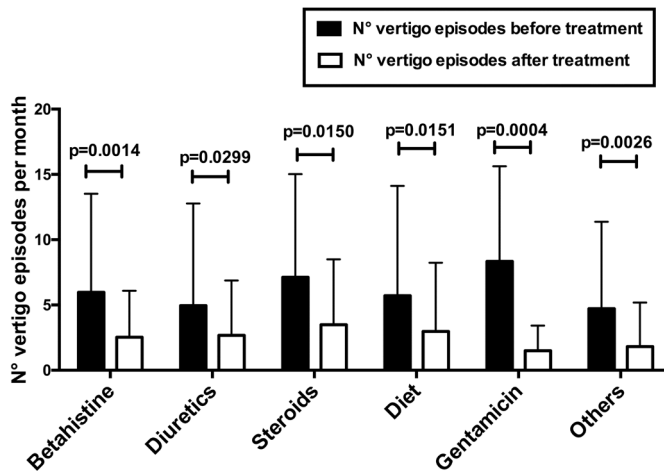


Figure 1. Mean (SD) episodes of vertigo per month before and after treatment, by treatment group.

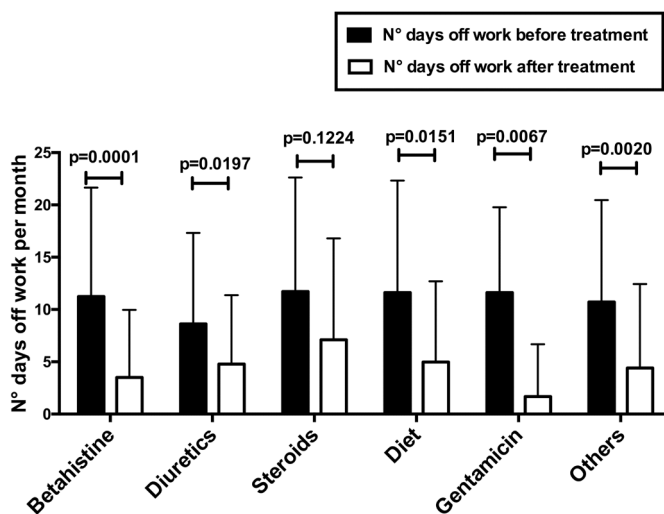


Figure 2. Mean (SD) number of days off work per month due to Ménière's disease before and after treatment, by treatment group.

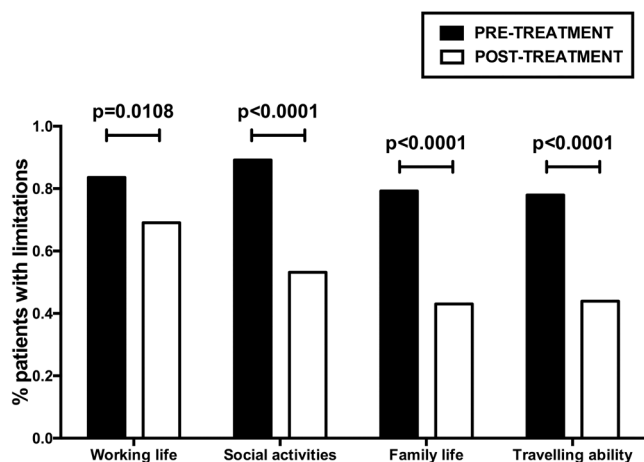


Figure 3. Proportion of all respondents reporting limitations in each SWID-4 question before and after treatment.

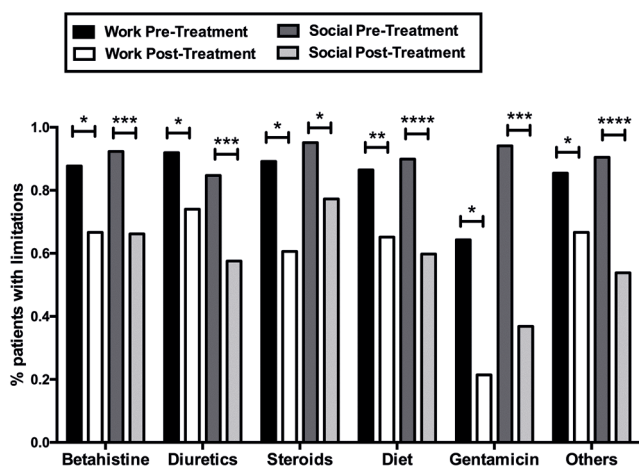


Figure 4. Proportion of respondents reporting limitations in working life and social activities before and after treatment, by treatment group. * $p<0.05$, ** $p<0.01$, *** $p<0.001$, **** $p<0.0001$.

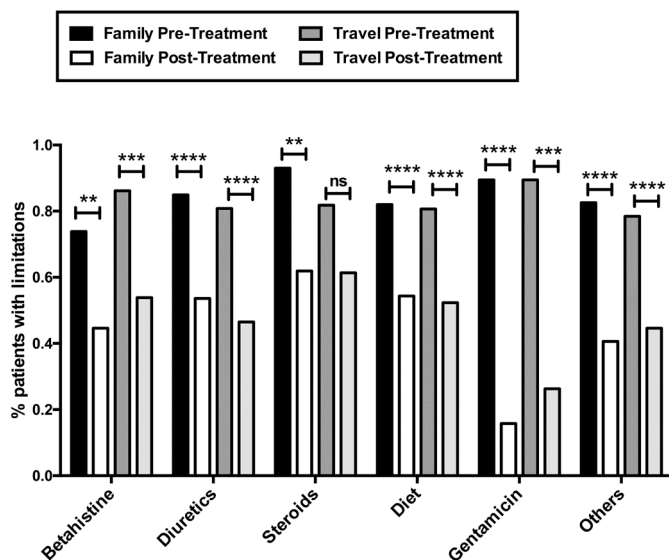


Figure 5. Proportion of respondents reporting limitations in family life and traveling ability before and after treatment, by treatment group. ns, not significant, * $p<0.05$, ** $p<0.01$, *** $p<0.001$, **** $p<0.0001$.

SWID-4 total score significantly decreased after the most recent treatment ($p<0.0001$; Table 1). For each of the SWID-4 questions, after treatment, respondents reported fewer limitations in working life (84% vs. 69%, $p=0.0108$, Fisher's exact test), social activities (89% vs. 53%, $p<0.0001$, Fisher's exact test), family life (79% vs. 43%, $p<0.0001$, Fisher's exact test), and ability to travel (78% vs. 44%, $p<0.0001$, Fisher's exact test; Figure 3). Most respondents experienced working limitations before treatment and reported a significant improvement after any of the therapeutic options (Figure 4). An even greater treatment effect was observed for limitations in social life (Figure 4), family life, and ability to travel (Figure 5). However, among the treatment groups, those respondents receiving intratympanic gentamicin reported the greatest absolute reductions in limitations at work (64% vs. 21%), social life (94% vs. 37%), family life (89% vs. 16%), and ability to travel (89 vs. 26%, $p<0.05$ for each, Fisher's exact test). In addition, those receiving intratympanic gentamicin had the lowest proportion of respondents reporting limitations after treatment for each of the SWID questions.

The final question asked which treatment the respondent would recommend to a patient diagnosed with Ménière's disease. The most recommended treatments were dietary modifications (45%), diuretics (31%), betahistine (29%), gentamicin (16%), and steroids (14%). One-quarter (25%) of respondents were unable to suggest any treatment based on their experience. When comparing these results to the percentages of most recent treatments received by respondents, only gentamicin showed a favorable recommendation (+5%), whereas all other treatment options demonstrated a decrease in willingness to recommend a received treatment, ranging from -24% (dietary modifications) to -12% (betahistine).

DISCUSSION

The present study identified a broad range of treatments used in a large nationally representative Italian population of patients with Ménière's disease. The most frequently reported treatments included conservative therapies, such as dietary modifications, or the medications betahistine and oral diuretics. Other common treatments included oral steroids and vestibular suppressants, such as benzodiazepines or the antihistamine and calcium-channel blocker cinnarizine. These therapies were often used in combination.

Approximately 12% of patients reported that their last treatment was destructive therapy, such as chemical labyrinthectomy with intratympanic gentamicin or vestibular neurectomy. Many other treatments with varying side effect profiles were also listed by patients ranging from the relatively benign, such as lipoflavonoid cereals and acupuncture, to the more invasive, including tympanostomy tubes, hospital admission for intravenous glycerol or mannitol, endolymphatic shunt placement, and endovascular dilations of the cervical venous drainage, a procedure reported as being used by 10 patients in the present study. Overall, 24 different treatments were reported by patients as therapy for their Ménière's disease.

Similarly, in other studies, patients reported significant disability associated with their disease, with the majority indicating limitations at work, social or family life, and traveling. Nineteen percent reported being unemployed, with several adding comments that they lost their job as a result of Ménière's disease. Ménière's disease is known to be

impairing to the overall health-related quality of life, with one study showing over 40% reduction compared with a healthy adult population^[6]. Patients often report vertigo as the most debilitating symptom^[19], and the accompanying anxiety related to the unpredictable nature of attacks leads to limitations in social activities and work^[20,21]. Fortunately, vertigo is also the symptom most likely to improve following treatment^[22], and vertigo episode counts have been the most commonly used outcome measure in studies of Ménière's disease.

Perhaps unsurprising given the history of treatments for Ménière's disease, all of the many treatments in the present study were reported by patients as effective, with respondents reporting fewer episodes of vertigo, regardless of treatment type, as well as reduced numbers of absentee days from work. This observation occurred despite the treatments targeting several different proposed disease mechanisms (e.g., hydrops, inflammatory, allergic, vascular, and channelopathy). However, this is consistent with the report by Torok, who noted a treatment effect in Ménière's disease regardless of the chosen management approach^[14].

This finding supports a strong placebo effect in the treatment of Ménière's disease and also highlights one of the challenging aspects of studying this condition: it is a disabling condition, but spontaneous remissions are common. As a result of the unclear pathophysiology, a myriad of treatments has been proposed, the majority of which has not been subject to randomized placebo-controlled studies of adequate duration. Sam Crowe, former chairman of Otolaryngology—Head and Neck Surgery at Johns Hopkins Hospital, described in 1938 the available treatments for Ménière's disease, prior to Walter Dandy's popularizing of the vestibular nerve section: "the attacks were extremely severe and disabling, so much so that, having already tried one or more of the commonly employed therapeutic measures, such as dietary treatment and drugs, removal of teeth, tonsils, appendix or gall bladder, and in some cases extensive nasal sinus or pelvic operations, [patients] came to the hospital to have their vestibular nerve divided"^[23]. Since 1861 when Prosper Ménière localized recurrent episodes of vertigo to the inner ear, physicians have been seeking novel approaches to relieve suffering from his eponymous syndrome.

Fortunately for patients, recovery is common regardless of the therapeutic approach. However, physicians should consider carefully the risk of each proposed therapy and counsel patients about the likelihood of recovery with various treatments.

However, as also described in Torok's report, not all patients recover. In the present study, although after treatment a smaller proportion of respondents indicated limitations in the quality of life, over 40% continued to report impairments at work, in social or family activities, and in travel capabilities. This also contributes to why the majority of patients were treated with multiple therapies. While it may be presumed that at least some of the therapies are not addressing the true underlying pathophysiology of Ménière's disease, it is unknown whether this ongoing disability is due to recurrent episodes, hearing loss, unilateral vestibular impairment, or persistent postural-perceptual dizziness. Other studies, for example, have shown impaired health-related quality of life in some patients with Ménière's disease many years even after ablative treatment^[24]. We included a limited number of demographic variables in our survey. Hearing loss or tinnitus, for instance, were not

assessed and may differ among the treatment groups or could be accounting for long-term impairments in the quality of life. The reasons for these lasting effects on the quality of life in patients with treated Ménière's disease deserve additional study.

This was a retrospective study so causation cannot be determined. However, it was noteworthy that of the treatments identified by the survey, intratympanic gentamicin showed the greatest treatment effect, as represented by larger reductions in both self-reported vertigo episodes and work absenteeism. Patients who received gentamicin also had greater reductions in the proportion that indicated limitations in work, social activities, family activities, or travel compared with other treatments. Although one might expect similar beneficial effects after surgical labyrinthectomy or vestibular neurectomy, there were too few patients reporting these treatments in the present study to allow a separate analysis. Longitudinal studies have also shown improved quality of life measures after both surgical and chemical labyrinthectomy^[25, 26]. However, patients receiving destructive therapies in the present study had more frequent episodes of vertigo prior to the intervention, likely prompting their providers to offer more aggressive treatment. This higher pre-treatment value contributed to the greater treatment effect observed for gentamicin compared with the other treatments. However, in addition to this greater reduction in vertigo episodes and work absenteeism, the proportion of patients reporting limitations in the quality of life was substantially smaller than post-treatment values for other therapies. These findings suggest greater effectiveness of intratympanic gentamicin for reducing vertigo episodes and improving the quality of life in Ménière's disease. Furthermore, respondents were likely to recommend this treatment for another patient with Ménière's disease.

In the present study, the outcome measure "lost days of work per month due to disease" showed a greater treatment effect compared with episodes of vertigo, suggesting that this measure might be useful for future studies. While other cross-sectional studies have noted substantial impairment in work-related productivity in patients with vestibular disease^[18, 24], to our knowledge, none has used this as an outcome measure for a treatment effect. Work-related absenteeism—while a secondary effect of disease symptoms—may better reflect functional impairment due to disease than vertigo episode counts. However, a clear limitation of this outcome is that when questioned about work absenteeism, approximately 19% of participants reported retirement from work or current unemployment and were excluded from this part of the analysis.

Response biases may have contributed to a greater likelihood of participants attributing an improvement in functional limitations to recent treatment. However, it is worth noting that the mean numbers of vertigo episodes reported per month in the present study before (5.7, standard deviation (SD) 7.6) and after (2.6, SD 4.6) the most recent treatments were comparable to a recent well-designed placebo-controlled study^[16]. Adrion et al.^[16] reported that at study enrollment, participants in the placebo group experience 6.2 (SD 6.9) mean vertigo episodes per month that decreased to 2.7 (95% confidence interval 1.3-6.3) episodes per month over 7-9 months of placebo treatment. It appears that patients with Ménière's disease start new medications or enroll in clinical trials when their symptoms are most severe and then improve over the subsequent months, regard-

less of treatment approach. All participants in the present study were recruited from two national organizations for patients with Ménière's disease and had been evaluated and treated by local physicians. While a diagnosis of definite Ménière's disease was inclusion criteria for the study, this could not be confirmed. However, the present study reflects current diagnostic and therapeutic patterns of Italian physicians seeing patients with recurrent vertigo and symptoms consistent with Ménière's disease. Furthermore, the majority of patients received multiple treatments, and close follow-up of each patient was not possible, impairing any assessment of treatment efficacy. Nevertheless, the study design provides a unique opportunity to assess how patients receive and experience the effects of their therapies in an unobserved setting.

CONCLUSION

This nationally representative cross-sectional survey of Italian patients with Ménière's disease revealed a high prevalence of functional disability that persists in many patients despite treatment. However, regardless of the many treatment approaches, all therapies are associated with fewer reported mean vertigo episodes and fewer patients reporting impairments in the quality of life. Compared with other treatments, chemical labyrinthectomy with intratympanic gentamicin was associated with the greatest treatment effect, providing the greatest reduction in both reported vertigo episodes and workplace absenteeism, as well as the smallest proportion of patients reporting functional limitations after treatment. The findings in the present study support a prominent placebo effect in treatments for Ménière's disease and highlight not only the challenges of studying outcomes in treatment for Ménière's disease but also the critical need to better understand its pathophysiology.

Ethics Committee Approval: Ethics Committee approval was received for this study from Ethical Committee of University Hospital of Siena.

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – M.M., D.N.; Design – M.M., D.N., J.F.G.; Supervision – F.T., D.N.; Resource – M.M.; Materials – M.M.; Data Collection and/or Processing – M.M., V.G.W.; Analysis and/or Interpretation – B.W., M.M., V.G.W.; Literature Search – B.W., M.M.; Writing – B.W., M.M., G.C.; Critical Reviews – All authors.

Acknowledgements: We would like to thank the members and staff of Associazione Malati Ménière Insieme and Associazione Italiana Malati di Ménière ONLUS (AIMM) for their generosity and participation in this study.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Committee on Hearing and Equilibrium guidelines for the diagnosis and evaluation of therapy in Ménière's disease. American Academy of Otolaryngology-Head and Neck Foundation, Inc. *Otolaryngol Head Neck Surg* 1995; 113: 181-5. [\[CrossRef\]](#)
2. Lopez-Escamez J, Carey J. Diagnostic criteria for Ménière's disease. *J Vestib Res* 363 2015; 25: 1-7.
3. Alexander TH, Harris JP. Current epidemiology of Meniere's syndrome. *Otolaryngol Clin North Am* 2010; 43: 965-70. [\[CrossRef\]](#)
4. Wladislavosky-Waserman P, Facer GW, Mokri B, Kurland LT. Meniere's disease: A 30-Year epidemiologic and clinical study in rochester, mn, 1951-1980. *Laryngoscope* 1984; 94: 1098-102. [\[CrossRef\]](#)
5. Havia M, Kentala E, Pyykkö I. Prevalence of Meniere's disease in general population of Southern Finland. *Otolaryngol Neck Surg* 2005; 133: 762-8. [\[CrossRef\]](#)
6. Anderson JP, Harris JP. Impact of Ménière's disease on quality of life. *Otol Neurotol* 2001; 22: 888-94. [\[CrossRef\]](#)
7. Söderman AC, Bergenius J, Bagger-Sjöbäck D, Tjell C, Langius A. Patients subjective evaluations of quality of life related to disease-specific symptoms, sense of coherence, and treatment in Ménière's disease. *Otol Neurotol* 2001; 22: 526-33. [\[CrossRef\]](#)
8. Green J, Verrall A, Gates G. Quality of life instruments in Meniere's disease. *Laryngoscope* 2007; 117: 1622-8. [\[CrossRef\]](#)
9. Rauch SD, Merchant SN, Thedinger BA. Meniere's syndrome and endolymphatic hydrops. Double-blind temporal bone study. *Ann Otol Rhinol Laryngol* 1989; 98: 873-83. [\[CrossRef\]](#)
10. Nakashima T1, Naganawa S, Sugiura M, Teranishi M, Sone M, Hayashi H, et al. Visualization of endolymphatic hydrops in patients with Meniere's disease. *Laryngoscope* 2007; 117: 415-20. [\[CrossRef\]](#)
11. Gürkov R, Flatz W, Louza J, Strupp M, Ertl-Wagner B, Krause E. Herniation of the membranous labyrinth into the horizontal semicircular canal is correlated with impaired caloric response in Ménière's disease. *Otol Neurotol* 2012; 33: 1375-9. [\[CrossRef\]](#)
12. Agrawal Y, Ward BK, Minor LB. Vestibular dysfunction: prevalence, impact and need for targeted treatment. *J Vestib Res Equilib Orientat* 2013; 23: 113-7.
13. Sharon J, Trevino C. Treatment of Meniere's Disease. *Curr Treat Options Neurol* 2015; 17: 1-16. [\[CrossRef\]](#)
14. Torok N. Old and new in Ménière disease. *Laryngoscope* 1977; 87: 1870-7. [\[CrossRef\]](#)
15. Silverstein H, Smouha E, Jones R. Natural history vs. surgery for Meniere's disease. *Otolaryngol Head Neck Surg* 1989; 100: 6-16. [\[CrossRef\]](#)
16. Adrion C, Fischer CS, Wagner J, Gürkov R, Mansmann U, Strupp M, et al. Efficacy and safety of betahistine treatment in patients with Meniere's disease: primary results of a long term, multicentre, double blind, randomised, placebo controlled, dose defining trial 393 (BEMED trial). *BMJ* 2016; 352: h6816. [\[CrossRef\]](#)
17. Thomsen J, Bretlau P, Tos M, Johnsen NJ. Placebo effect in surgery for Ménière's disease. A double-blind, placebo-controlled study on endolymphatic sac shunt surgery. *Arch Otolaryngol* 1981; 107: 271-7. [\[CrossRef\]](#)
18. Bronstein AM, Golding JF, Gresty MA, Mandalà M, Nuti D, Shetye A, et al. The social impact of dizziness in London and Siena. *J Neurol* 2010; 257: 183-90. [\[CrossRef\]](#)
19. Yardley L, Dibb B, Osborne G. Factors associated with quality of life in Meniere's disease. *Clin Otolaryngol Allied Sci* 2003; 28: 436-41. [\[CrossRef\]](#)
20. Cohen H, Ewell LR, Jenkins HA. Disability in Ménière's disease. *Arch Otolaryngol Head Neck Surg* 1995; 121: 29-33. [\[CrossRef\]](#)
21. Hagnebo C, Melin L, Larsen HC, Lindberg P, Lyttkens L, Scott B. The influence of vertigo, hearing impairment and tinnitus on the daily life of Ménière patients. *Scand Audiol* 1997; 26: 69-76. [\[CrossRef\]](#)
22. Rauch SD. Clinical hints and precipitating factors in patients suffering from Meniere's disease. *Otolaryngol Clin North Am* 2010; 43: 1011-7. [\[CrossRef\]](#)
23. Crowe S. Meniere's Disease: A Study Based on Examinations Made Before and After an Intracranial Division of the Vestibular Nerve. *Medicine (Baltimore)* 1938; 17: 1-36. [\[CrossRef\]](#)
24. Sun DQ, Ward BK, Semenov YR, Carey JP, Della Santina CC. Bilateral Vestibular Deficiency: Quality of Life and Economic Implications. *JAMA Otolaryngol Head Neck Surg* 2014; 140: 527-34. [\[CrossRef\]](#)
25. Diaz R, LaRouere M, Bojrab D. Quality-of-life assessment of Ménière's disease patients after surgical labyrinthectomy. *Otol Neurotol* 2007; 28: 74-86. [\[CrossRef\]](#)
26. Perez N, Martín E, García-Tapia R. Intratympanic gentamicin for intractable Meniere's disease. *Laryngoscope* 2003; 113: 456-64. [\[CrossRef\]](#)