

Meniett Clinical Trial: Long-term Follow-up

George A. Gates, MD; Aimee Verrall, CCRP; J. Douglas Green, Jr, MD; Debara L. Tucci, MD; Steven A. Telian, MD

Objective: To delineate 2-year efficacy of Meniett device therapy in people with classic, unilateral, Ménière's disease unresponsive to traditional medical treatment.

Design: A 2-year long-term unblinded follow-up after a prior randomized, placebo-controlled, multicenter clinical trial of the Meniett device for Ménière's disease.

Setting: Follow-up was performed remotely by using diaries and questionnaires mailed to the data coordinating center by the participants. Those who failed to mail their diaries were interviewed by telephone.

Participants: Sixty-one study participants agreed to use the Meniett device and report their symptoms for 2 years. All had active, unilateral cochleovestibular disease. Outcomes are available for 58 participants; 2 were unavailable for follow-up and 1 was excluded because of a concurrent condition that precluded Meniett device use.

Interventions: Participants were advised to adhere to a low-sodium diet, use the Meniett device 3 times daily, and maintain a patent tympanostomy tube in the affected ear. Diuretic and vestibular suppressant medications were used as needed.

Main Outcome Measures: Outcomes were based on the participants' daily diary, questionnaires, and telephone interviews. Three different analyses were pre-

pared: tracking of vertigo frequency throughout the study, comparison of vertigo frequency before and at the end of Meniett device use (American Academy of Otolaryngology-Head and Neck Surgery Foundation reporting guideline), and Kaplan-Meier estimates of vertigo remission and recurrence.

Results: Vertigo levels gradually improved for most but not all participants. American Academy of Otolaryngology-Head and Neck Surgery Foundation class A (remission) or class B (greatly improved) results occurred in 67% (39/58) of participants, and class F (dropped out to receive surgical therapy) results occurred in 24%. Of the 44 nondropout participants, 39 (89%) had American Academy of Otolaryngology-Head and Neck Surgery Foundation group A or B outcomes. People who went into remission were highly likely (80%) to remain in remission long term; participants who achieved remission (20/43; 47%) did so within the first year of follow-up.

Conclusions: Use of the Meniett device was associated with a significant reduction in vertigo frequency in about two thirds of the participants, and this improvement was maintained long term. Therapy with the Meniett device is a safe and effective option for people with substantial vertigo uncontrolled by medical therapy.

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Author Affiliations: Virginia Merrill Bloedel Hearing Research Center (Dr Gates and Ms Verrall), Department of Otolaryngology-Head and Neck Surgery (Dr Gates), University of Washington School of Medicine, Seattle; Jacksonville Hearing and Balance Institute, Jacksonville, Fla (Dr Green); Division of Otolaryngology-Head and Neck Surgery, Duke University, Durham, NC (Dr Tucci); and Department of Otolaryngology-Head and Neck Surgery, University of Michigan Medical Center, Ann Arbor (Dr Telian).

THE IDEAL TREATMENT FOR Ménière's disease remains uncertain. There is general agreement that a conservative regimen consisting of reduced dietary sodium intake, education about the disorder, and use of a diuretic (as appropriate) should be used initially. There is little agreement as to which therapy to recommend next should the initial treatment fail, as it does in about 30% of cases.¹ Before the introduction of the Meniett device, surgical intervention or intratympanic gentamicin sulfate administration was usually the next treatment recommendation.

Now that results from 3 randomized, double-blind, placebo-controlled clinical trials have demonstrated that the Meniett device is safe and effective in the short

term,²⁻⁴ it is being used as an intermediate treatment. However, without evidence of long-term effectiveness, there has been reluctance to designate the device formally as an established treatment method. To date, results of 2 long-term 2-year follow-up studies showing effectiveness in non-US populations have been published.^{5,6}

This article describes the 2-year long-term results of the participants in our previously reported US clinical trial² in which significant reduction in vertigo frequency and severity occurred in the treated group compared with the control group. The control group used a placebo device, whereas the treated group used an active device. All participants had tympanostomy tubes inserted before use of either device. Both the control and active treatment groups from that trial were treated openly with the Me-

Table 1. American Academy of Otolaryngology–Head and Neck Surgery Foundation Classification Description

Numerical Value*	Class
0	A†
1-40	B
41-80	C
81-120	D
>120	E
Secondary treatment initiated because of disability from vertigo	F

*The numerical value is the ratio of the average number of vertigo spells during the pretreatment period divided by the average number of vertigo spells for the same number of months at the end of the reporting period.

†Complete control of definitive spells.

niett device for 2 years after the conclusion of the prior clinical trial. Several methods for assessing long-term outcome are used to provide as full a picture of the results as possible.

METHODS

PARTICIPANTS

At the end of the 4-month clinical trial reported earlier,² 61 of the 62 participants volunteered to participate in a 2-year long-term follow-up and agreed to record their vertigo symptoms each day on a diary card and to complete a questionnaire every 3 months. All participants were provided with a new, fully functioning Meniett device. No other incentives were offered. Informed consent was collected by the site coordinators for each participant, and institutional review board approval was maintained throughout the 2-year project. Participants were instructed to verify tube patency by means of a Valsalva maneuver before each use of the Meniett device and be seen by their otolaryngologist to replace the blocked tube as well as monitor the tympanostomy tube and replace it as necessary. All participants had clinical evidence of unilateral cochleovestibular Ménière's disease at the time of random assignment in the clinical trial.

SYMPTOM DIARIES

The chief outcome measure was vertigo, rated daily on the symptom diary by using a Likert scale from 0 (no vertigo) to 4 (worst vertigo attack ever). Vertigo rated 2 or greater represents an attack lasting more than 20 minutes, which is considered a definitive vertigo attack day. If there were 2 attacks in a day, only the worst one was scored. In addition to vertigo, participants recorded activity (where 0 indicates no limitation of daily activities and 4, confined to bed) and stress (where 0 indicates no stress and 4, maximum stress) levels using a 5-point Likert scale, as well as the number of Meniett device applications per day. The cards were prestamped and mailed to the data coordination center monthly. Two consecutive months of missing diaries warranted the mailing of a reminder postcard notifying the participant which monthly cards were missing. Reminder telephone calls were initiated if the postcards failed to bring compliance. Nineteen participants provided little or no follow-up data; they were contacted at the end of the 2 years, and 17 responded to a structured telephone interview regarding their current Ménière's status.

STRUCTURED QUESTIONNAIRE

The questionnaire was to be completed every 3 months for a total of 8 questionnaires during the entire follow-up. The questionnaire contained a global Ménière's question and incorporated questions from the first page of the Ménière's Disease Patient-Oriented Symptom-Severity Index,^{7,8} as well as 4 questions asking the participants specifically about the Meniett device.

STATISTICAL ANALYSIS

Vertigo data were summarized in 3 ways: (1) the average monthly number of days with definitive vertigo were compared before and after Meniett device use, (2) the change in number of definitive vertigo attacks per month before treatment and at the end of follow-up were assessed according to the American Academy of Otolaryngology-Head and Neck Surgery Foundation (AAO-HNSF) guideline, and (3) Kaplan-Meier estimates were used to examine the time course of relapse and remission as separate end points.

DAYS WITH DEFINITIVE VERTIGO

This statistic was computed by counting the number of days with definitive vertigo (level 2 rating or greater per the diaries) for each person, for each month, which allows the time course of the disorder and its therapy to be evaluated. For the control participants, the 4 months of blinded placebo use were included in the baseline period.

AAO-HNSF GUIDELINE

This guideline has been used as a standard for publication of the unblinded results of surgical therapy for Ménière's disease. It is based on a comparison of the frequency of vertigo averaged across 2 periods of 6 months—at baseline before surgery and 18 to 24 months after surgery—and is reported as a percentage. For the present study, the AAO-HNSF guideline required modification because none of the treatment group members had undergone 6 months of observation before using the Meniett device, although the control participants had. Therefore, for the treatment group, we compared the average frequency of vertigo during the baseline period (typically 2 months) with the same time period at the end of their active follow-up and calculated the percentage of improvement according to the guideline formula. For the control group, the average frequency before using the Meniett device was determined by averaging the number of definitive attacks across the baseline period and the 4-month trial period of blinded use of the nonfunctional placebo device and comparing this average to the average number of spells across the same number of months at the end of the open-label follow-up.

The AAO-HNSF formula calculates percentage reduction as $(X/Y) \times 100$, rounded to the nearest whole number, where Y is the average number of definitive spells per month for the number of observed months before treatment and X is the average number of definitive spells per month for the last number of months of the follow-up. The results are grouped according to the categories illustrated in **Table 1**.

KAPLAN-MEIER ESTIMATES

The statistic was based on the number of vertigo attacks (vertigo rated level 2 and greater) per month. Remissions were defined as 6 consecutive months with no definitive vertigo attacks. For participants who reached remission or entered in remission, we evaluated the chance of relapse. A relapse was

Table 2. Demographic Characteristics

Characteristic	Value
No. of participants	58
Age, mean±SD (range) y	48.9 ± 9.3 (33-71)
Female sex, %	66
Placebo, %	50
Affected ear, % left	60
Median No. of completed diaries (25th-75th percentile)*	24.5 (12-29)

*Four-month and 2-year follow-up combined.

defined as 2 consecutive months with at least 1 or more definitive vertigo attacks.

RESULTS

Of the 61 participants who agreed to participate in the 2-year follow-up, 1 was excluded because of a concurrent health problem that precluded Meniett device use and 2 were unavailable for follow-up, leaving 58 participants for analysis. Three participants reported bilateral Ménière's diagnosis during follow-up: 2 received bilateral tubes and continued Meniett therapy in both ears; the third did not. No adverse events were reported during the 2-year follow-up. The demographic characteristics of the participants are shown in **Table 2**.

DROPOUT PARTICIPANTS

Fourteen participants dropped out to seek alternative surgical treatment during the 2-year follow-up. These treatments were labyrinthectomy (n=5), endolymphatic sac surgery (n=5), gentamicin injections (n=2), and unknown surgical procedures (n=2).

LOST TO FOLLOW-UP (MISSING DATA)

Nineteen participants were lost to follow-up. They were contacted via telephone and administered a quick structured interview. Seventeen interviews were obtained: 12 participants reported being in remission; the conditions of 4 were improved and the condition of 1 had not improved.

VERTIGO EXPERIENCE

Figure 1 shows the box plots of the median number of definitive vertigo attacks per month grouped according to response group (remission, improved, relapse, no improvement). Note the marked variation in number of attacks, as indicated by the height of the box (interquartile range) in many cases. In general, the responders had consistent results, whereas the remainder had a wide range of vertigo experience. These data reinforce the difficulty in characterizing intermittent and recurrent symptoms.

AAO-HNSF GUIDELINE

Table 3 illustrates the long-term change in vertigo experience on the basis of the guideline promulgated by the AAO-

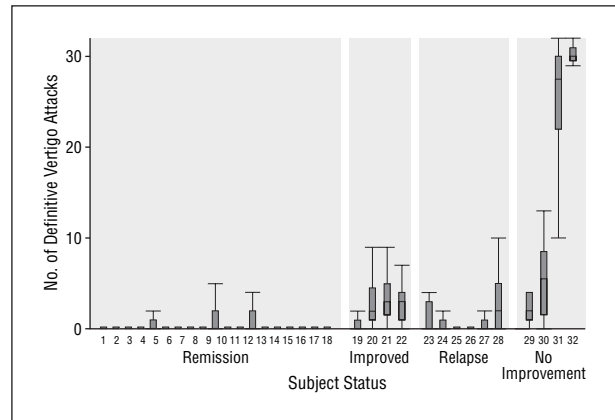


Figure 1. Box plots of the total number of definitive vertigo attacks across the entire 2-year follow-up for each participant displays the range of vertigo experience of the cohort. The box portion of a box plot represents the interquartile range (25th-75th percentile) of the number of definitive vertigo attacks, and the horizontal line in the middle of the box plot is the median. The wider the box plot, the more variation a participant had across the 2 years, whereas the narrower the box plot, the less variation. Participants are displayed in order of their status: remission, improved (vertigo less than before the study), relapsed, and no improvement (vertigo same or worse than before the study). Participants who were unavailable for follow-up are not included on this graph, and those with fewer than 6 diaries are excluded.

Table 3. American Academy of Otolaryngology–Head and Neck Surgery Foundation Classification Summary

Numerical Value*	Class	No. (%) (n = 58)	Classification Score, Mean ± SD
0	A	26 (45)†	...
1-40	B	13 (22)†	14.7 ± 11.1
41-80	C	4 (7)	49.7 ± 7.6
81-120	D	0	...
>120	E	1 (2)	251.0 ± 0
Dropped out‡	F	14 (24)	‡

*The numerical value is the ratio of the average number of vertigo spells during the pretreatment period divided by the average number of vertigo spells for the same number of months at the end of the reporting period.

†Dropouts were those who underwent surgical therapy during follow-up.

‡The participants dropped out of the study.

HNSF,⁹ as modified for the reduced observation periods in this study. For the entire group, 67% (39/58) had class A (remission) or B (greatly improved) results; 14 (24%) of the 58 had class F results (dropped out to receive alternative surgical treatment). Eighty-nine percent (39/44) of the non-dropout cases were classified as group A or B. Robust logistic regression with group A as the independent variable and sex, age, treatment group, canal weakness on electronystagmography, baseline vertigo, and stage of Ménière's disease as the dependent variables showed no statistically significant associations ($P > .05$).

2-YEAR STRUCTURED QUESTIONNAIRE

Forty-four participants complied with the questionnaire data collection: 25 were participants who completed 75% or better of the symptom diaries (average of 7.6 questionnaires), 14 were incomplete (average of 4.5

Table 4. Ratings of the Responses to the Meniett-Oriented Questions From the 8 Structured Questionnaires Completed Every 3 Months of the 2-Year Follow-up*

Statement	2-Year End Status†		
	Remission (n = 27)	Improved (n = 10)	No Change or Worsened (n = 8)
I think my symptoms are in remission after being on the Meniett device	4 (3-5)	4 (3-4)	3 (2-4)
I continue to have vertigo attacks, but I feel better overall—ear pressure, hearing, etc	2 (1-4)	4 (2-4)	3 (2-3)
I feel only somewhat better after using the Meniett device (50% improved)	2 (1-3)	2 (1-3)	3 (1.5-4)
I continue to have severe attacks; I do not think the Meniett device is working for me	1 (1-1)	1 (1-1.5)	2.5 (1-3)

*Data are given as median (25th-75th percentile). Participants rated their agreement to the statements where 1 is "strongly disagree," 2 is "disagree," 3 is "I don't know (or does not apply)," 4 is "agree," and 5 is "strongly agree."
†As determined by means of Kaplan-Meier estimates.

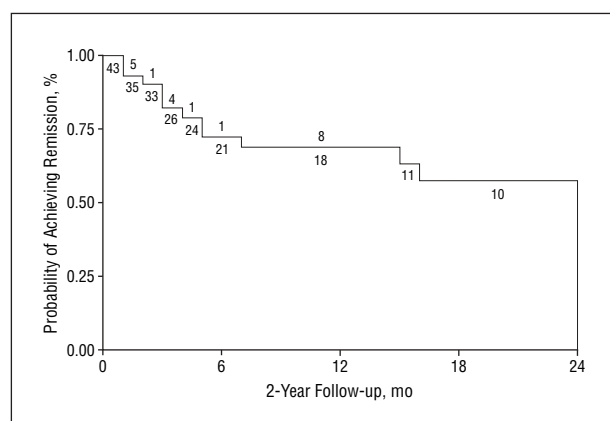


Figure 2. Kaplan-Meier estimates for the probability of achieving remission of vertigo during the 2-year follow-up. The numbers above the plotted line indicate participants who achieved remission (n=20). The numbers below the plotted line indicate the number of participants waiting to reach remission (43 participants entered with active vertigo; 10 remained in the follow-up who never had a remission [the conditions of 8 improved and 1 the conditions of 2 worsened or had no change]). Achieving remission (6 consecutive months with absolutely no definitive vertigo attacks) occurred quickly, within the first 5 months (72%) and at 1 year (69%) of using the Meniett device.

questionnaires), and 5 were dropouts (average of 4.4 questionnaires). The first item on the questionnaire asked participants to rate the frequency of definitive vertigo attacks for the last 3 months on a scale of 0 (none) to 5 (very often [≥ 10 attacks]). The median rating across 2 years was 0, with the 25th to 75th percentiles being 0 to 2.

The open-ended comment sections of the questionnaires were evaluated for tube issues: 3 participants reported tube replacement in this section. Otherwise, no comments regarding tube infection or other adverse events were noted. **Table 4** shows the median responses to the 4 specific questions regarding Meniett treatment according to vertigo control status (remission, improved, no change or worsened).

KAPLAN-MEIER REMISSION/RELAPSE ANALYSIS

Forty-three participants entered the 2-year follow-up with active Ménière's disease, whereas 15 were in remission at the time of entry.

TIME TO REMISSION

Of the 43 participants with active vertigo at the time of entry, 20 went into remission during the 2-year follow-up. On average, participants achieved remission of vertigo in 2.8 ± 3.7 (mean \pm SD) months. In **Figure 2**, the Kaplan-Meier estimates show the probability of achieving remission was more likely in the first 5 months (72%), whereas by the first year it decreases to 69%. Of the 23 participants who did not reach remission, 13 dropped out and sought alternative surgical options. The conditions of 8 improved and the conditions of 2 worsened or the participants saw no improvement yet continued to participate in the 2-year follow-up. We found no differences in age, sex, study site, or treatment group between those who went into late remission and those who did not. Robust logistic regression with the remission status as the independent variable and sex, age, treatment group, canal weakness on electronystagmography, baseline vertigo, and stage of Ménière's disease as the dependent variables revealed a statistically significant difference only for baseline vertigo (odds ratio, 0.80; 95% confidence interval, 0.67-0.96; $P = .02$) but not for any of the other dependent variables ($P > .05$).

TIME TO RELAPSE

As shown in **Figure 3**, among the 35 participants who achieved remission, the Kaplan-Meier estimates for the probability of being relapse free during the 2-year follow-up is high; once in remission, the estimated probability of staying in remission was greater than 80%. Only 7 (20%) of 35 had a relapse of active Ménière's attacks. Of these 7, only 2 dropped out to pursue surgical therapy, whereas the other 5 chose to continue Meniett therapy and complete the 2-year follow-up.

COMMENT

The present study is based on an unblinded protocol and, as such, may reflect the effects of therapy, placebo, and the natural history of the disorder. The data confirm the long-term remission of vertigo in people who respond

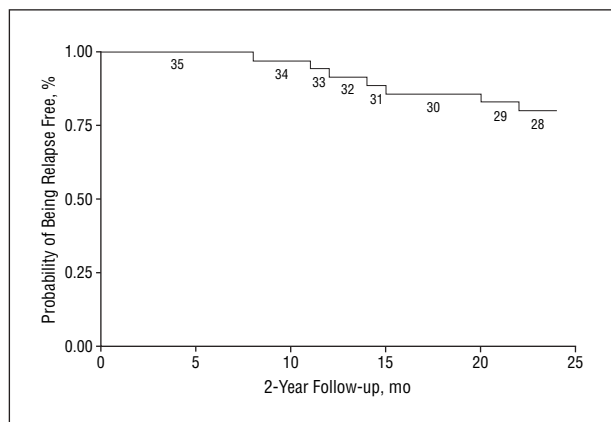


Figure 3. Kaplan-Meier estimates for the probability of remaining in remission without relapses during the 2-year follow-up. The numbers below the plotted line represent the number of participants in remission who did not have a relapse. Thirty-five participants achieved remission during follow-up, and 28 (80%) remained in remission at the end of 2 years. Seven participants had a relapse (at least 1 definitive attack a month for 2 consecutive months). Only 2 of these 7 participants dropped out to have surgery, whereas the other 5 who remained in the follow-up study chose to continue Meniett therapy.

to use of the Meniett device. These data provide insight into the time course of the disorder. Most people who responded to the Meniett device did so relatively promptly, although the conditions of some continued to improve across many months. On the basis of results from the 4-month report² and the present study, it seems that use of the Meniett device accelerates the resolution of vertigo symptoms in people who are likely to respond to therapy. Most good responses occur with treatment periods of a year or less, and the diseases of few people go into remission after that time. Once remission of vertigo occurs, participants tended to gradually use the Meniett device less often.

Questions asking specifically about Meniett treatment on the questionnaires allowed us insight into the participants' view of the Meniett device. Eight participants who showed no change in vertigo or whose vertigo worsened disagreed with the statement "I continue to have severe attacks, I don't think the Meniett device is working for me." In addition, the Kaplan-Meier analysis revealed 10 of the 23 participants who never reached remission (6 months without significant vertigo) chose to continue using the Meniett device as did 5 of the 7 participants who had relapses. We interpret these findings to be indicators of a partial response to Meniett therapy and consider such a response to be of value to patients.

The present study is concerned primarily with the symptom of episodic vertigo. Activity data closely paralleled the vertigo data and thus were not reported. No objective measurement of hearing was obtained, and most participants indicated that their hearing did not improve with either short-term or long-term use of the Meniett device.

Compliance in the long-term study was a problem. People who were doing well used the device less often or simply stopped using it and stopped reporting their symptoms. Although we regularly reminded the participants that continued reporting of symptoms was a condition of their entry into the study, no other measures to motivate compliance, such as monetary compensation, were

used. Most noncompliant participants reported to the telephone interviewer that they stopped participating because they no longer had vertigo and did not see the need for continued reporting of symptoms. Thus, the long-term data display a paradox: those who used the device the most had the most symptoms, and those who used the device the least across the long term had the fewest symptoms.

The primary problem associated with Meniett device use was infection of the middle ear associated with tympanostomy tube use. Tubes plugged from time to time and required cleaning or removal. Experience suggests that, for individuals responding to the Meniett device, it may be advisable to consider intubation with a long-stemmed T-type tube. Use of the Meniett device without a patent tube is contraindicated because the pressure increase due to middle ear mechanics may exacerbate symptoms.¹⁰

The AAO-HNSF guideline has been used widely to report the results of treating Ménière's disease. It was originally designed to allow sufficient time after endolymphatic sac surgery to be reasonably certain that short-term placebo effects did not account for the outcome. We had to modify the guideline to account for the shorter pretreatment observation period (≤ 2 vs 6 months) because our protocol allowed for only 2 months of observation before treatment began. We then compared equal periods before treatment and at the end of follow-up for each person.

We believe this modification fulfills the intent of the guideline because most participants had stable vertigo levels at the end of follow-up, and it would have made little difference whether 2 months or 6 months of data collection had been used. In clinical practice, an arbitrary requirement for 6 months of observation before treatment could be at odds with good patient care. Although the intent of the guideline—to have an adequate period of observation—is not unreasonable, flexibility must be ensured to meet patients' needs in a timely manner. We point out the discrepancy between people who reached remission (6 months' absence of clinically significant vertigo) and later relapsed vs those who had class A outcome according to the AAO-HNSF guideline but had had significant vertigo at 1 year, for example, but freedom of vertigo during the final reporting period. We suggest that the entire 2-year period should be included in the accounting, not just the last 6 months, while acknowledging that episodic symptoms, such as vertigo, are difficult to characterize with a simple yardstick.

Long-term evaluation of the Meniett device shows the pressure therapy to be a safe and effective treatment to control the acute vertigo attacks associated with Ménière's disease.

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Correspondence: George A. Gates, MD, Virginia Merrill Bloedel Hearing Research Center, University of Washington, Campus Box 357923, Seattle, WA 98195-7923 (ggates@u.washington.edu).

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Gates, Tucci, and Telian. *Acquisition of data*: Gates, Verrall, Green, Tucci, and Telian. *Analysis and interpretation of data*: Gates, Verrall, Green, Tucci, and Telian. *Drafting of the manuscript*: Gates and Verrall. *Critical revision of the manuscript for important intellectual content*: Verrall, Green, Tucci, and Telian. *Statistical analysis*: Gates, Verrall, and Telian. *Obtained funding*: Gates and Green. *Administrative, technical, and material support*: Verrall, Green, and Tucci. *Study supervision*: Gates, Tucci, and Telian.

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