Assessing the Efficacy of a Serotonin and Norepinephrine Reuptake Inhibitor for Improving Meniere's Disease Outcomes

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SUMMARY

Meniere's disease (MD) affects 2 to 4 people per 10,000 and represents up to 15% of new patients with vertigo in a tertiary neurotology clinic.[1] As of yet, its pathophysiology is uncertain and there is no gold-standard treatment.[2] Given the lack of level I evidence for MD therapies, we seek to perform a randomized, placebo-controlled, double-blind, crossover, pilot trial of venlafaxine extended-release (ER) 37.5 mg daily for the prophylactic treatment of MD. Venlafaxine is a safe and well-tolerated medication,[3-5] and it will be trialed at the lower end of the dosage spectrum typically used for depression.[6] No literature exists for the use of venlafaxine in MD, but there is evidence that it could be effective through both central and peripheral vestibular-modulating mechanisms.

Venlafaxine is a serotonin and norepinephrine reuptake inhibitor (SNRI) typically used in the treatment of depression.[7] There is evidence to suggest that selective serotonin reuptake inhibitors (SSRIs) can be effective in the treatment of MD through serotonin's ability to modulate vestibular function in vestibular nuclei, the inferior olive, and the cerebellum.[8,9] Norepinephrine has also been shown to inhibit activity in vestibular nuclei.[10] Lamotrigine, a serotonin, norepinephrine, and dopamine reuptake inhibitor, has been shown to be effective in treating MD and is currently in a clinical trial.[11] Venlafaxine can reduce vasopressin receptor activation.[12] This may reduce endolymphatic hydrops, because the endolymphatic sac expresses vasopressin receptors which may be important in fluid and ion homeostasis in the inner ear.[13-16]

Venlafaxine is well-known in the treatment of anxiety and depression,[17,18] which are common comorbidities in MD[19] that may ultimately contribute to a cycle of somatic and psychological symptoms synergistically aggravating disease perception.[19,20] Furthermore, migraine is quite common in MD.[21,22] Venlafaxine has been shown to be effective in the

treatment of migraine[6] and vestibular migraine,[23,24] which highlights its potential in treating MD given that vestibular migraine may share with MD many aspects of presentation and pathophysiology.[25,26]

This trial will take place in a tertiary, multidisciplinary, vestibular-focused, neurotology clinic at the Medical University of South Carolina (MUSC), led by Dr. Habib Rizk. Dr. Yuan Liu will assist with patient recruitment in clinic and project coordination. Dr. Shaun Nguyen will also help with project coordination, as well as data analysis given his expertise in conducting clinical trials. Forty subjects will be recruited to achieve 80% power in detecting at least a 30% difference in vertigo frequency control. The study will require about 14.5 months to complete: an 8-month recruitment period to obtain 40 subjects; and for each subject a 1-month lead-in screening period, a 2-month first treatment phase, a 1.5-month washout phase, and a 2-month second treatment phase. The subjects will be randomized to treatment and the investigators will be blinded to outcomes until after the data have been collected and analyzed. Using patient-reported symptoms and various validated instruments, the outcomes measured will include change in vertiginous symptoms, functional level, cognitive function, anxiety and depression severity, and quality of life (QOL).

If the results demonstrate that venlafaxine is effective in the prophylactic treatment of patients with MD, the path will be paved for larger parallel-treatment design studies. Serotonin and norepinephrine reuptake inhibitors have not been trialed in MD, but they hold promise as a non-invasive medical treatment option.

63 **TABLE OF CONTENTS**

80

BUDGET

- Number of venlafaxine ER capsules needed: 3048
    - 60 capsules for 40 subject for 2 months of treatment: 2400
    - 7 capsules for 20 subjects for weaning over 2 weeks after the 1st treatment phase: 140
    - 20% drop-out rate (e.g., side effects, loss to follow-up): additional 508 capsules
- Number of placebo capsules needed: 3048
    - 60 capsules for 40 subject for 2 months of treatment: 2400
    - 7 capsules for 20 subjects for weaning over 2 weeks after the 1st treatment phase: 140
    - 20% drop-out rate: 508 capsules
- Total capsules needed: 6092
- Items 1-5 were reviewed and approved by the Investigational Drug Services (IDS) pharmacy at the Medical University of South Carolina (MUSC).
- Item 6 cost estimate was obtained from the MUSC drug distribution center.
- Item 7 cost estimate was obtained from the South Carolina Clinical and Translational Research Institute for hiring trained research personnel.
- Item 8 cost estimate was obtained from the MUSC outpatient laboratory.
- This budget was approved by the MUSC Office of Research and Sponsored Programs.

Number	Item	Cost ($)
1	IDS pharmacy randomization fee (one time)	50.00
2	IDS compounding fee ($1.25 per capsule)	7620.00
3	IDS pharmacy setup and initiation cost	3250.00
4	IDS pharmacy annual renewal fee	525.00
5	IDS dose dispensing fee ($25 per dose, 2 dispenses per subject, 20% drop-out rate)	2400.00
6	Venlafaxine extended-release cost ($3.01 per 30 capsules, plus 9% sales tax)	333.34
7	Research coordinator ($55 per hour, estimate 1 hour per subject per data collection time point for 4 time points)	8800.00
8	Comprehensive metabolic panel ($27.90 per subject, 20% drop-out rate)	1339.20
	Total	**$24317.54**

BIOGRAPHICAL SKETCH

Principal Investigator

Contact Information

- Address: 135 Rutledge Avenue, MSC 550, Charleston, SC 29425
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- Fax: 843-792-0546

NAME: Rizk, Habib Georges

eRA COMMONS USER NAME: rizkhabib

POSITION TITLE: Assistant Professor of Otolaryngology Head & Neck Surgery

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE (if applicable)	START DATE MM/YYYY	END DATE MM/YYYY	FIELD OF STUDY
Saint-Joseph University, Beirut	MD	09/2000	06/2007	Medicine
Saint-Joseph University, Beirut	MS	07/2007	10/2010	Biomedical Sciences
Saint-Joseph University, Beirut	MS	09/2009	06/2010	Microvascular Surgery
Medical University of South Carolina, Charleston, SC	MS	07/2015	06/2017	Master of Science in Clinical Research
Saint-Joseph University/University of the Mediterranean-Aix Marseille III, Beirut/Marseille	Resident	07/2009	06/2011	Interuniversity Diploma in Endoscopy and Surgery in Otorhinolaryngology and Skull Base
Hôtel-Dieu de France Hospital, Beirut	Resident	07/2007	06/2012	Otolaryngology-Head & Neck Surgery Resident
Christiana Care Health System, Newark, DE	Fellow	07/2012	06/2013	Otology Medicine and Surgery Fellowship
Medical University of South Carolina, Charleston, SC	Fellow	07/2013	06/2015	Neurotology Fellowship

A. Personal Statement

I am a neurotologist committed to a research career aiming to develop a better understanding of undertreated/underdiagnosed or poorly investigated vestibular disorders such as vestibular migraine, Meniere's disease and superior semicircular canal dehiscence, their impact on patients, as well as determining the best treatment course for these entities. My long-term goal is to develop metrics that would allow us to improve patients' quality of life, reduce their fall risk, and minimize their loss of productivity. I am a fellowship-trained neurotologist and have participated in multiple clinical outcomes-related research trials for various neurotologic pathologies during my postdoctoral training, resulting in 30 publications. Upon completing my clinical training, I was recruited to establish and direct a multidisciplinary vestibular program at the Medical University of South Carolina. Our team is comprised of neurologists, physical therapists, dieticians, and audiologists who collaborate to provide the best care for patients with vestibular disorders. We see approximately 2000 patients a year with various causes of dizziness and gait disturbances. Since 2015, I have served on educational panels in the American Academy of Otolaryngology, notably the Equilibrium Committee, as well as the joint task force with the American Academy of Neurology to develop measures aiming to improve the clinical evaluation of vestibular patients. I have also served as a physician expert on the American Balance Society (ABS) multidisciplinary meetings. I am also an ABS board member and I chair the program and the nomination committees. I am the co-director of the biennial Charleston Vestibular Update Course. I have completed a Master of Science in Clinical Research to get more formal training in epidemiology, study design and analysis, biostatistics and regression analysis, community engagement research, grant application development, and team science, in order to better accomplish my research goals. To date, we have quantified the impact of vestibular disorders on cognitive function (a). We have also defined the skull base thickness in patients with superior semicircular canal dehiscence (b). These works led to a collaboration with the Otolaryngology and Neurosurgery departments of the University of Cincinnati on a contemporary review on idiopathic intracranial hypertension (c), as well as to a collaboration with the Neurotology Division at the University of California San Francisco on the epidemiology of vestibular migraine (d). I currently have an intramural grant to foster interprofessional/interdisciplinary training in the clinical care setting at the Medical University of South Carolina. I am currently mentoring two vestibular audiologists (Christine Strange and Cortney Van Ausdal) as well as one of our vestibular therapists (Rebecca English) to help with their career development. They have presented data from our vestibular clinic in national meetings over the past three years as well as participated in expert panels at the American Academy of Otolaryngology National Meeting. I have mentored a predoctoral student (Taylor Locklear) funded by a T32 institutional grant for the summer of 2018. In the past 9 months, he has already had two oral presentations at national meetings, one manuscript published, and one manuscript submitted and undergoing the peer-review process at the Journal of Vestibular Research concerning the association of vitamin D and BPPV.

a. Liu YF, Locklear TD, Sharon JD, Lacroix E, Nguyen SA, Rizk HG. Quantification of Cognitive Dysfunction in Dizzy Patients Using the Neuropsychological Vertigo Inventory. Otol Neurotol, 2019;40(7):e723-e731. PMID: 31295206

b. Rizk HG, Hatch J, Stevens SM, Lambert PR and Meyer TA, Lateral Skull Base Attenuation in Patients with Superior Semicircular Canal Dehiscence, Otolaryngol H Neck Surg, 2016, 155:641-648. PMID: 27221578

c. Stevens SM, Rizk HG, Golnik K, Andaluz N, Samy RN, Meyer TA, Lambert PR, Idiopathic intracranial Hypertension: Contemporary review and implications for the Otolaryngologist, Laryngoscope. 2018, 128: 248-256, doi:10.1002/lary26581. PMID: 28349571.

d. Formeister EJ, Rizk HG, Kohn MA and Sharon JD, The Epidemiology of Vestibular Migraine: A Population-based Survey Study, Otol Neurotol, 2018, 39:1037-1044. doi:10.1097/MAO0000000000001900. PMID 30020261

B. Positions and Honors

Positions and Employment

2015 -	Assistant Professor of Otolaryngology Head & Neck Surgery, Medical University of South Carolina, Charleston, SC
2015 -	Director Vestibular Program, Medical University of South Carolina, Charleston, SC

Other Experience and Professional Memberships

2008 -	Member, Lebanese Order of Physicians
2012 -	Member, American Academy of Otolaryngology- Head & Neck Surgery
2015 -	Member, Vestibular Disorders Association
2016 -	Member, Equilibrium Committee-American Academy of Otolaryngology-Head &Neck Surgery
2016 -	Member, History and Archives Committee-American Academy of Otolaryngology-Head &Neck Surgery
2017 -	Programs Committee Member, American Balance Society
2017 -	American Academy of Otolaryngology-Head &Neck Surgery and American Academy of Neurology, Neurotology Measures workgroup
2017 -	Editorial Board, Frontiers in Neurology-Neurotology Subsection
2018 - 2020	Board of Directors, American Balance Society

Honors

2000	Summa Cum Laude, French Baccalaureate-Academie d'Aix-Marseille
2000	Cum Laude, Lebanese Baccalaureate
2000	USJ's 125th Anniversary Academic Achievement Award, Saint Joseph University
2010	Resident Research Award (3rd prize of the jury), International Francophone Society of Otolaryngology
2016	Board of Directors Nominee, American Balance Society

2017	Board of Directors Nominee, American Balance Society
2017	AAOHNS representative for Neurotology Measures Group, American Academy of Otolaryngology-Head & Neck Surgery
2018-2020	Board of Directors, American Balance Society
2018-2020	Chairman, Program Committee American Balance Society (2019). Member, Program Committee (2018,2020)

C. Contribution to Science

1. Quality of life measures and cognitive dysfunction in vestibular pathologies:

   This project started with the advent of our multidisciplinary vestibular clinic. A large portion of our patients with dizziness complained of cognitive difficulties. Our current dizziness-related QOL questionnaires usually assess the physical, functional and emotional dimensions of a pathology's impact, with few or non-existent inquiries into the cognitive dysfunction of those patients. It is the latter that usually affects QOL and productivity the most. With the lack of a standardized tool to measure this impairment, we administered the well-established general Cognitive Failure Questionnaire (CFQ) on all our dizzy patients to quantify that dimension of the QOL that is affected. We found major disparities of cognitive dysfunction that are driven by the etiology, in conjunction with other factors. Vestibular migraine and Meniere's disease drove the CFQ scale very high (a). We then proceeded to test the English version of the newly-developed Neuropsychological Vertigo Inventory (NVI). We have started the project and are collaborating with the Neurotology Division at UCSF. We will be studying the NVI as well to assess its usability in clinic as an outcome tool and clinical tool and have already obtained pilot results (b). In collaboration with UCSF we have also participated in a project to describe the epidemiology of vestibular migraine (c). During the course of these projects, we collected a vast amount of information about vestibular function tests, in patients with various diagnoses, especially in regard to vestibular evoked myogenic potentials, to look at their role in non-traditional indications such as Meniere's disease and vestibular migraine (d). This is the subject of a submitted manuscript to Audiology and Neurotology that is currently under peer-review.

   a. Rizk HG, Thomas C and Meyer TA, Self-Perceived cognitive dysfunction in patients with various diagnoses of dizziness, AAO-HNS Meeting, Chicago, IL, September 2017
   b. Liu YF, Locklear TD, Sharon JD, Lacroix E, Nguyen SA, Rizk HG. Quantification of Cognitive Dysfunction in Dizzy Patients Using the Neuropsychological Vertigo Inventory. Otol Neurotol, 2019;40(7):e723-e731. PMID: 31295206
   c. Formeister EJ, Rizk HG, Kohn MA and Sharon JD, The Epidemiology of Vestibular Migraine: A Population-based Survey Study, Otol Neurotol, 2018, 39:1037-1044. doi:10.1097/MAO0000000000001900 PubMed PMID 30020261
   d. Rizk H, Strange C, Van Ausdal C, English R, McRackan TM and Meyer TA, Are VEMPs useful for the differential diagnosis of Ménière's Disease and Vestibular Migraine, American Academy Otolaryngology-Head&Neck Surgery, Atlanta, October 2018

2. Radiographic characteristics and clinical outcomes in patients with vestibular and neurotological pathologies:

My neurotology fellowship was focused on chronic ear disease, cochlear implantation, and spontaneous cerebrospinal fluid leaks research. Over the course of two years, I was involved in a protocol for measuring skull base thickness in our CSF leak patients, providing quantifying metrics about the pathology. This initial project was expanded to look at outcomes of surgery correlated to the skull base thickness and body mass index (BMI). Once our vestibular clinic was established, I translated this protocol into our superior semicircular canal dehiscence (SSCD) patients. We found, interestingly, that despite having on average a lower BMI than our spontaneous leak patients, the SSCD subjects had a generalized thinner skull base. This reinforces the possibility of multiple mechanisms, probably autocrine, independent of increased intracranial pressure, which participate in some of those neurotologic pathologies. Other teams corroborated these findings in subsequent studies.

a. Stevens SM, Rizk HG, Golnik K, Andaluz N, Samy RN, Meyer TA, Lambert PR, Idiopathic intracranial Hypertension: Contemporary review and implications for the Otolaryngologist, Laryngoscope. 2018, 128: 248-256, doi:10.1002/lary2658. PubMed PMID: 28349571.
b. Rizk HG, Hatch JL, Stevens SM, Lambert PR, Meyer TA. Lateral Skull Base Attenuation in Superior Semicircular Canal Dehiscence and Spontaneous Cerebrospinal Fluid Otorrhea. Otolaryngol Head Neck Surg. 2016 Oct;155(4):641-8. PubMed PMID: 27221578.
c. Stevens SM, Rizk HG, McIlwain WR, Lambert PR, Meyer TA. Association between Lateral Skull Base Thickness and Surgical Outcomes in Spontaneous CSF Otorrhea. Otolaryngol Head Neck Surg. 2016 Apr;154(4):707-14. PubMed PMID: 26908549.
d. Hatch JL, Schopper H, Boersma IM, Rizk HG, Nguyen SA et al, The Bone Mineral Density of the Lateral Skull Base and its Relation to Obesity and Spontaneous Cerebrospinal Fluid Leaks, Otol Neurotol, 2018, doi: 10.1097/MAO.0000000000001969 PubMed PMID: 30124620

Complete List of Published Work in MyBibliography

https://www.ncbi.nlm.nih.gov/myncbi/1VM4mAsHw2qQq/bibliography/public/

D. Additional Information: Research Support and/or Scholastic Performance

- MUSC 2018-2020 Interprofessional Team-Based Clinical Experience Development Grant program: Development of new Interprofessional, Team-Based, Patient-Care Experiences for MUSC Interdisciplinary/Interprofessional Management of Patients at the MUSC Dizziness and Vestibular Disorders Clinic

Co-Investigator

Contact Information
- Address: 135 Rutledge Avenue, MSC 550, Charleston, SC 29425
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- Phone: 843-876-0112
- Fax: 843-792-0546

NAME: Liu, Yuan Fang

eRA COMMONS USER NAME: liuyua

POSITION TITLE: Neurotology and Skull Base Surgery Fellow

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE (if applicable)	START DATE MM/YYYY	END DATE MM/YYYY	FIELD OF STUDY
David Geffen School of Medicine at University of California, Los Angeles; Los Angeles, CA	MD	08/2009	06/2013	Medicine
Loma Linda University Health, Department of Otolaryngology – Head and Neck Surgery; Loma Linda, CA		07/2013	06/2018	Otolaryngology (Residency)
Medical University of South Carolina, Department of Otolaryngology – Head and Neck Surgery; Charleston, SC		07/2018	06/2020	Neurotology and skull base surgery (Fellowship)

A. Personal Statement

I am in my final year of training in neurotology and skull base surgery. I have been developing over these past years the foundational knowledge in medicine and medical research needed to successfully complete this prospective study. I have broad training in otolaryngology, but throughout my residency and into fellowship, I have delved deeper into the study of neurotologic diseases, especially vestibular disorders such as Meniere's disease and vestibular migraine. I have won awards from the American Otological Society and Triological Society for quality of research submitted to national meetings as a resident. I have also won the Research Resident Award repeatedly during residency. In my final year of residency, I served on the Otology and Neurotology Education Committee of the American Academy of Otolaryngology – Head and Neck Surgery. I also co-authored a chapter on dizziness in the book *ENT Essentials*. As a fellow, I have increased my research workload due to a growing interest in many fields of otology and neurotology, and in anticipation of a future as an academic neurotologist, with the career goal of advancing knowledge in hearing and vestibular sciences. I have successfully collaborated with

colleagues, residents, and medical students on numerous publications, and I am currently mentoring several residents and medical students in otologic research. I have worked closely with Dr. Rizk, who is one of my current mentors, since the start of fellowship. I hope to build the neurotology and skull base program at Loma Linda University, where I will likely return to work after completing fellowship; and I will strive to establish a partnership with the Medical University of South Carolina to tackle challenges in research which require a multi-institutional approach. This current proposal builds on my previous work in Meniere's disease and vestibular migraine. If successful, it will be a significant advance in the study of Meniere's disease treatment and has the potential to spur on new investigative pathways in understanding the disorder.

a. Liu YF, Locklear TD, Sharon JD, Lacroix E, Nguyen SA, Rizk HG. Quantification of Cognitive Dysfunction in Dizzy Patients Using the Neuropsychological Vertigo Inventory. Otol Neurotol, 2019;40(7):e723-e731.
b. Liu YF, Renk E, Rauch SD, Xu HX. Efficacy of intratympanic gentamicin in Menière's disease with and without migraine. Otol Neurotol. 2017 Aug;38(7):1005-1009.
c. Liu YF, Xu H. The intimate relationship between vestibular migraine and Meniere's disease: a review of pathogenesis and presentation. Behav Neurol. 2016;2016:3182735.
d. Liu YF, Hu J, Streelman M. The Epworth Sleepiness Scale in the assessment of sleep disturbance in veterans with tinnitus. Int J Otolaryngol. 2015;2015:429469.

B. Positions and Honors

Positions and Employment

2018 -	Clinical Instructor of Otolaryngology – Head and Neck Surgery, Medical University of South Carolina; Charleston, SC

Other Experience and Professional Memberships

2013 -	American Academy of Otolaryngology – Head and Neck Surgery
2017 - 2018	Member, Otology and Neurotology Education Committee, American Academy of Otolaryngology- Head & Neck Surgery

Honors

2006, 2007	Harvard College Research Grant
2007	Harvard College Scholar
2009	Cum laude in biochemical sciences, Harvard University
2009	California Regents Scholarship
2009	Donald, Jason, and Stefan Wong Memorial Scholarship, David Geffen School of Medicine at UCLA
2000	Chief's Research Fellowship, UCLA Department of Internal Medicine

2011	Subspecialty Award, 39th Annual Western Student Medical Research Forum Regional Meeting
2011	Community Service Award, David Geffen School of Medicine at UCLA
2016	Travel Award, Triological Society
2016, 2018	Resident Research Award, Loma Linda University Department of Otolarygnology – Head and Neck Surgery
2017	Resident Research Travel Award, American Otological Society
2017	Resident In-Service Exam Award, Loma Linda University Department of Otolarygnology – Head and Neck Surgery
2017	Dr. George Chonkich Resident of the Year Award, Loma Linda University Department of Otolarygnology – Head and Neck Surgery
2018	Chief Resident of the Year Award, Loma Linda University Department of Otolarygnology – Head and Neck Surgery

C. Contribution to Science

1. My initial research interests were broadly distributed in various disciplines of otolaryngology. Specially pertaining to head and neck surgery, I uncovered the benefits of early swallowing exercises for patients undergoing chemoradiation, performed a pilot study of a novel free flap monitoring system, revealed mechanical properties of the nasal septal cartilage and the effects of surgery on its integrity, explored the efficacy of various maxillomandibular procedures in improving sleep apnea, reported on the efficacy of a treatment protocol for burning mouth syndrome, systematically reviewed the utility of preoperative imaging for parathyroid disease in patients with concurrent thyroid disease, and discovered the need for reduced prescription of postoperative opioids in a prospective, randomized trial.

    a. Liu YF, Vuong C, Walker PC, Peterson NR, Inman JC, Andrade Filho PA, Lee SC. Noninvasive free flap monitoring using Eulerian video magnification. Case Rep Otolaryngol. 2016;2016:9471696.
    b. Liu YF, Messinger K, Inman JC. Yield strength testing in human cadaver nasal septal cartilage and L-strut constructs. JAMA Facial Plast Surg. 2017;19(1):40-45.
    c. Han P, Liu YF, Messinger K, Ardeshirpour F, Inman J. Redefining the nasal septal L-strut: a quantitative analysis of septal arcs and angles. Laryngoscope. 2018;128(8):1806-1810.
    d. Nguyen KS, Liu YF, Chang C, Park J, Kim C, Hondorp B, Vuong C, Xu H, Crawley B, Simental A, Church C, Inman J. A randomized single-blinded trial of ibuprofen versus opioid-based primary analgesic therapy in outpatient otolaryngology surgery. Otolaryngol Head Neck Surg. 2019 Mar 5:194599819832528.

2. When I decided on a career in otology and neurotology, I began to focus my research efforts in hearing and vestibular sciences. I revealed that intratympanic gentamicin was less effective in treating functional deficit of those suffering from Meniere's disease when vestibular migraine was a comorbidity. In recent collaborations with Dr. Rizk, I described

ways that different characteristics of vestibular evoked myogenic potentials can be useful in differentiating Meniere's disease and vestibular migraine (submitted for publication). Concurrently, I worked with Dr. Rizk to describe cognitive function in patients with various vestibular diseases, such as Meniere's disease, vestibular migraine, and benign paroxysmal positional vertigo (BPPV). We used a novel instrument developed specifically for patients with dizziness, and found that Meniere's disease had similar cognitive impairment to vestibular migraine, both worse than BPPV. We are starting a new prospective phase of the study to recruit healthy subjects in order to compare cognitive function among those with dizziness with those without.

a. Liu YF, Renk E, Rauch SD, Xu HX. Efficacy of intratympanic gentamicin in Meniere's disease with and without migraine. Otol Neurotol. 2017;38(7):1005-1009.
b. Liu YF, Locklear TD, Sharon JD, Lacroix E, Nguyen SA, Rizk HG. Quantification of Cognitive Dysfunction in Dizzy Patients Using the Neuropsychological Vertigo Inventory. Otol Neurotol, 2019;40(7):e723-e731.

Complete List of Published Work in MyBibliography

https://www.ncbi.nlm.nih.gov/myncbi/1NU3b9rUboo5a/bibliography/public/

D. Additional Information: Research Support and/or Scholastic Performance

None

Co-Investigator

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- Phone: 843-876-0112
- Fax: 843-792-0546

NAME: Nguyen, Shaun A.

eRA COMMONS USER NAME: nguyensa

POSITION TITLE: Professor and Director of Clinical Research

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE (if applicable)	START DATE MM/YYYY	END DATE MM/YYYY	FIELD OF STUDY
University of South Carolina; Columbia, SC	BS	08/1985	05/1989	Biology
East Carolina University; Greenville, NC	MA	07/1989	05/1993	Applied Sociology and Biostatistics Radiological Science
SHSU with University College London; London, United Kingdom	MD	06/1993	06/1999	Medicine
North Middlesex Hospital, University College London; London, United Kingdom		07/1999	06/2000	House Officer Medicine/Surgery
North Middlesex Hospital, University College London; London, United Kingdom		07/2000	06/2001	Senior House Officer in Surgery
Medical University of South Carolina; Charleston, SC		07/2001	12/2005	NIAAA Fellow in Addiction and Substance Abuse Psychiatry
Medical University of South Carolina; Charleston, SC		01/2005	12/2006	Radiology Fellowship

A. Personal Statement

I have the expertise, leadership, and motivation necessary to successfully carry out the proposed work in Meniere's disease research. I have a broad background in otolaryngology, radiology, and clinical trials research, with specific training and expertise in key research areas (research methodology, biostatistics, outcomes research, cost-effective analysis, and clinical trials) for this application. As a resident/fellow, I carried out translational research in alcohol addiction models, clinical research involving investigational new drugs, and outcomes research in substance abuse where I won seven national/international research awards. As one of the first certified principal investigators (CPI) by the American Academy of Physician Investigators, I am directing one of the most robust clinical trials programs in otolaryngology – head and neck surgery in the world, where I have served as principal investigator/co-investigator on over 200 clinical trials (Phases 1, 2, and 3) investigating the treatment of hearing loss, Meniere's disease, tinnitus, chronic sinusitis, obstructive sleep apnea, and head and neck cancer. I will work with Dr. Rizk and Dr. Liu in identifying and enrolling potential patients with Meniere's disease. In summary, I have a demonstrated record of accomplished and productive research projects with over 165 publications in an area of high relevance in otolaryngology, and my expertise and experience have prepared me to become an important member in the proposed project.

B. Positions and Honors

Positions and Employment

2005 - 2008	Assistant Professor, Department of Radiology and Radiological Science, Medical University of South Carolina (MUSC), Charleston, SC
2006 - 2008	Assistant Professor, Clinical Services, MUSC
2008 - 2009	Assistant Professor, College of Health Professions, MUSC
2008 - 2011	Assistant Professor, Department of Otolaryngology - Head and Neck Surgery, MUSC
2008 -	Director of Clinical Research Fellowship Program, Department of Otolaryngology- Head and Neck Surgery, MUSC.
2009 - 2010	Assistant Professor, Division of Physician Assistant Studies, College of Health Professions, MUSC
2010 -	Associate Member, College of Graduate Studies, MUSC
2011 - 2012	Assistant Professor, Department of Otolaryngology - Head and Neck Surgery, MUSC
2012 - 2015	Associate Professor, Department of Otolaryngology - Head and Neck Surgery, MUSC
2015 -	Professor, Department of Otolaryngology – Head and Neck Surgery, MUSC

Other Experience and Professional Memberships

2005	Judge- Medical University of South Carolina Student Research Day
2006 - 2018	Judge- Perry Halushka Student Research Day at MUSC.

2019	Chair Judge- Perry Halushka Student Research Day at MUSC.

Academic Committee Activities (past 5 years):

University

Year	Name of Committee	Role	Institution
2008 -	Faculty Senate	Senator	MUSC
2008 -	Institutional Advancement Committee	Member	MUSC

College of Medicine

Year	Name of Committee	Role	Institution
2013 -	Admissions Committee	Interviewer	MUSC
2013 -	Diversity Committee	Member	MUSC

College of Health Professions

Year	Name of Committee	Role	Program
2007 – 2010	Thesis Committee	Director	M.S. in Nurse Anesthesia
2007 – 2010	Thesis Committee	Director	M.S. in Physician Assistant Studies

College of Graduate Studies

Year	Name of Committee	Role	Program
2009 -	Thesis Committee	Mentor	M.S. in Clinical Research

Honors

1989	Phi Delta Kappa National Honor Society
1989	Gamma Beta Phi National Honor Society
1989	Golden Key National Honor Society
1992	Eta Sigma Gamma National Honor Society
1992	Kappa Delta Pi National Honor Society
2002	Junior Investigator Award- Research Society on Alcoholism
2002	Resident/Fellow Research Award- MUSC Annual Research Day
2003	Junior Investigator Award- Research Society on Alcoholism
2003	Enoch Gordis Award Finalist- Research Society on Alcoholism
2004	Resident/Fellow Research Award- MUSC Annual Research Day
2004	Junior Investigator Award- Research Society on Alcoholism
2004	Junior Investigator Award- Guze Symposium on Alcoholism
2006	Cum Laude Award- Outstanding Scientific Paper- Society of Computed Body Tomography and Magnetic Resonance.

C. Contribution to Science

My bibliography on NCBI: https://www.ncbi.nlm.nih.gov/pubmed/?term=nguyen+sa

382 **Funding**

383 - Current funding: none

384 - Overlapping funding: none

385 - Pending funding: none

386

MUSC
MEDICAL UNIVERSITY
of SOUTH CAROLINA
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Paul R. Lambert, M.D., *Department Chair*

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Otologic Research
Judy R. Dubno, Ph.D., Director

Rhinology Research
Jennifer K. Mulligan, Ph.D.

July 15, 2019

Dear American Hearing Research Foundation Research Committee,

I am writing on behalf of the Neurotology Division of the Medical University of South Carolina (MUSC) Department of Otolaryngology – Head and Neck Surgery in support of Dr. Rizk's proposal to conduct a trial of the efficacy of venlafaxine in the treatment of Meniere's disease. As you all are aware, a cure for Meniere's disease has eluded the scientific community for over a century. Given the intimate relationship between vestibular migraine and Meniere's disease, the knowledge foundation upon which Dr. Rizk's proposal was built appears robust. There has not been a new approach for Meniere's disease for some time, and using venlafaxine, a migraine medication, holds promise.

I have known Dr. Rizk since the beginning of his fellowship at MUSC in 2013, during which time I served as his mentor. He has been an outstanding physician in every sense. As part of our Otology – Neurotology Division, he has pursued the mission to advance knowledge in vestibular diseases through numerous clinical projects dedication to this vexing population of patients. To this end, he has established a multidisciplinary vestibular and balance disorders program at MUSC.

I am confident of Dr. Rizk's ability to conduct and complete this project. He has previously been involved in recruiting patients for several clinical trials in Meniere's disease and has recently completed a pilot study examining cognitive dysfunction in patients with dizziness. During the course of the trial he proposes, I and the neurotology team will support him with all available resources, including our expertise in running clinical trials, the help of a full-time research physician who can also assist with statistical analyses, and a team of research fellows who can help with administrative tasks. Furthermore, the culture of MUSC is very supportive of innovative research, and MUSC has established different venues with advisors who can help troubleshoot any issues that arise.

The results of Dr. Rizk's proposal will hopefully prove beneficial for patients afflicted with Meniere's disease, In addition, the data he will gather on the psychological, cognitive, and quality-of-life aspects of Meniere's disease, which have not been well-studied, should add significantly to our current body of knowledge. I give Dr. Rizk my unqualified support and will do all that is necessary from our Department and my resources to ensure the completion of this research project.

Sincerely,

Paul Lambert

Paul Lambert, M.D.
Chair, Department of Otolaryngology – Head & Neck Surgery, MUSC

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HEARING RESEARCH PROGRAM

17 July 2019

To the Research Committee of the American Hearing Research Foundation:

I am writing this letter in strong support of the proposal submitted to the American Hearing Research Foundation, "Assessing the Efficacy of a Serotonin and Norepinephrine Reuptake Inhibitor for Improving Meniere's Disease Outcomes," with Habib Rizk, MD as Principal Investigator and Yuan Liu, MD as Co-Investigator. The project aims to compare the efficacy of the drug venlafaxine in decreasing the number and severity of dizziness episodes, improving functional outcomes, and improving self-perceived cognitive, psychological, and quality of life outcomes in patients with Meniere's disease. There has not been a new treatment for Meniere's disease for some time, and this novel approach to using venlafaxine, a migraine medication, holds promise, especially given the similarities between the two pathologies. Dr. Rizk also plans to expand methods to evaluate cognitive dysfunction associated with Meniere's disease and its response to treatment using a novel instrument, the Neuropsychological Vertigo Inventory. The data collected will help validate this instrument into a new patient-reported outcome measure addressing a dimension of disability often missed by other instruments.

I have known Dr. Rizk since he began his otology fellowship at MUSC in 2013. After completing his fellowship, he was appointed to the MUSC faculty and charged with building a multidisciplinary vestibular program, which he has done with great success. He sees ~1,000 new dizzy patients a year, including a large volume of referrals, of which about 15% are Meniere's disease patients.

I am confident in Dr. Rizk's ability to conduct and complete this project, with the assistance of Dr. Liu, the current otology fellow. Dr. Rizk previously has been involved in recruiting patients for clinical trials in Meniere's disease, and he has recently completed a pilot study examining cognitive dysfunction in patients with dizziness. The research coordinator on the project will be recruited from the South Carolina Translational Research Center, which is housed in MUSC. The culture of MUSC, and our department in particular, is highly supportive of research. Indeed, the department's faculty includes multiple NIH-funded physician-scientists with K awards and R01s. During the course of the trial he proposes, Dr. Rizk has the full support of his division and the department (see letter of support from the department chair, Dr. Lambert), which includes the help of a full-time research physician with expertise in conducting clinical trials who can also assist with statistical analyses, and a team of research fellows who are available to help with administrative tasks.

Thank you for your consideration of this exciting proposal, which has the potential to identify a promising treatment for this debilitating and understudied auditory disorder.

Sincerely,

Judy R. Dubno

Judy R. Dubno, PhD
Professor and Director, Hearing Research Program
Department of Otolaryngology-Head and Neck Surgery

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MUSC Health
PHARMACY SERVICES

Investigational Drug Services
169 Ashley Ave, MH Room 161
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843-792-9643 (p)
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Dear American Hearing Research Foundation Research Committee,

The Investigational Drug Services (IDS) Pharmacy of the Medical University of South Carolina (MUSC) has reviewed the proposal titled "Assessing the Efficacy of a Serotonin and Norepinephrine Reuptake Inhibitor for Improving Meniere's Disease Outcomes" through the Services, Pricing, and Application for Research Centers (SPARC) request ID 13398. The study proposes a double-blind, crossover, placebo-controlled trial of venlafaxine (extended-release) for the treatment of Meniere's disease. Our involvement will entail randomization of the 40 subjects, keeping confidential records of subject identity, compounding venlafaxine and placebo to ensure patient blinding, and dispensing the medications to patients at the appropriate time points.

The proposed budget for the pharmacy set-up and initiation, subject randomization, compounding of matching capsules for venlafaxine and placebo, dose dispensation, and annual renewal, totaling $13,445 has been approved by MUSC IDS. We will adhere to the protocol discussed in the proposal and support the investigator team to complete the clinical trial.

Investigational Drug Services
Medical University of South Carolina

Melinda J Lange, CPhT
12 Aug 2019

Joseph Cerenzia, PharmD
12 AUG 2019

SPECIFIC AIMS

MD is a frequent cause of episodic vertigo, but evidence-based therapies for MD are limited. The goal of the proposed project is to identify evidence-based treatments for MD that will improve disease-specific outcomes as well as cognitive, psychological, and quality of life outcomes. Our overall objective for this proposal is to determine the efficacy of venlafaxine ER at a dose of 37.5 mg per day in the treatment of MD, with specific attention to change in dizziness episode frequency and severity, along with the other above mentioned outcomes. Our central hypothesis is that venlafaxine in the prophylactic treatment of MD reduces the severity and the frequency of the vertigo spells and improves functional, cognitive, psychological, and quality of life outcomes in these patients.

The specific aims of this project are the following:

- **Aim 1** is to compare the efficacy of venlafaxine to placebo in decreasing the number and severity of dizziness episodes, and in improving functional outcomes in patients with definite MD.
- **Aim 2** is to compare the efficacy of venlafaxine to placebo in improving self-perceived cognitive, psychological, and QOL outcomes in definite MD.
- Our **exploratory aim** is to validate the English version of the newly developed Neuropsychological Vertigo Inventory as an appropriate tool to measure cognitive dysfunction in patients with MD and to measure response to treatment.

BACKGROUND AND SIGNIFICANCE

Meniere's disease (MD) is a major cause of episodic vertigo, affecting around 190 people per 100,000 in the US.[27] It represents up to 15% of new patient consultations for vertigo in a tertiary neurotology clinic.[1] MD was first described in the 19th century and is one of the most studied topics in otology.[28] But despite its prominent historical role in research, its etiology is uncertain and a cure remains absent.[29,30]

Many therapies have been tried to curtail the symptoms of MD, including lifestyle modifications with reduction of salt intake and increase in water intake; medications such as diuretics, betahistine, transtympanic steroids, transtympanic gentamicin; and surgical treatments such as endolymphatic sac decompression, vestibular neurectomy, and labyrinthectomy.[2] However, no gold-standard treatment or treatment protocol exists, and existing therapies for MD rely heavily on lower levels of evidence.[2,31] Furthermore, although some therapies have proven to reduce episodic vertigo, such as transtympanic gentamicin, they carry significant side effects including hearing loss and tinnitus, which are already consequences of the disease itself.[32]

Venlafaxine is a serotonin and norepinephrine reuptake inhibitor (SNRI) typically used in the treatment of depression.[7] It has been shown to be effective for depression at doses between 75 mg and 375 mg, 2 to 3 times daily.[7] We aim to use a 37.5 mg daily dose, as has been used in successful treatment of vestibular migraine.[23,24] There are several reasons why we seek to conduct a trial to evaluate the efficacy of venlafaxine in the treatment of MD, as detailed below.

There is evidence to suggest that selective serotonin reuptake inhibitors (SSRIs) can be effective in the treatment of MD through central mechanisms.[33-35] It has been shown in rats that serotonin can modify responsiveness to glutamate and N-methyl-d-aspartate (NMDA) in

vestibular nuclei, leading to depression of excitatory activity.[8] In addition, microinjection of serotonin into the rat inferior olive has been shown to increase firing rate of neurons while slowing oscillation frequency and increasing oscillation coherence, suggesting a role for serotonin in enhancing motor timing in the olivocerebellar system.[9] These studies suggest that serotonin plays an important role in regulating vestibular function, as SSRIs have been shown to be effective in treating vertigo, and SSRI withdrawal has been associated with acute dizziness, vertigo, and incoordination.[36-39] Norepinephrine has been shown to have inhibitory activity in the medial vestibular nuclei and excitatory activity in the lateral vestibular nuclei of rats.[10] In one study, 85% of neurons in all vestibular nuclei experienced change in basal firing rate with norepinephrine application, with inhibition in 86% of those tested, acting mainly through alpha2-adrenergic receptors.[40] Lamotrigine, a serotonin, norepinephrine, and dopamine reuptake inhibitor, has been shown to be effective in treating MD and is currently in a clinical trial.[11] Venlafaxine, through its activity in increasing serotonin and norepinephrine concentrations, could therefore mitigate the vestibular symptoms of MD through central mechanisms.

Venlafaxine has been shown to reduce vasopressin receptor activation in mice.[12] This potential action of venlafaxine is important in that plasma vasopressin has been found to be increased in MD and implicated in endolymphatic hydrops.[41,42] The endolymphatic sac is important in regulating ion and fluid homeostasis in the inner ear,[43,44] and is therefore important to consider in the development of MD, as MD has been shown to be a disease of endolymphatic hydrops.[45] Notably, vasopressin type 2 receptors have been found to be expressed in the luminal epithelium of the endolymphatic sac,[13] and vasopressin is thought to be a potential regulator of endolymphatic ion and fluid homeostasis.[14,15] It has been proposed that similar to how vasopressin induces translocation of aquaporins into luminal cell membranes in the kidney, it

may play a role in fluid dysregulation in the endolymphatic sac in MD.[13,46] Specifically, Claudin 4, a tight junction molecule expressed in the endolymphatic duct and sac, was recently shown to be a target of vasopressin.[47] Systemic administration of vasopressin in guinea pigs has been demonstrated to cause bilateral inner ear hydrops with hearing loss.[16] Furthermore, interventions aimed to decrease systemic vasopressin such as stress reduction have been shown to be better than traditional medications alone in controlling vertigo in MD after a 2-year follow up.[41] One study found that long term decreased vasopressin after endolymphatic sac surgery was associated with better vertigo control.[48] These data suggest that venlafaxine may be useful in treating MD through its vasopressin modulating activity.

A large number of patients with MD suffer from comorbid anxiety and depression.[19] One study found that 70-80% of patients with active MD could be diagnosed with depression while the same was true in 32-39% of those with inactive MD.[49] It is unclear whether psychological factors such as anxiety and depression could take part in causing MD, but it is feasible that once these factors are present, a positive feedback loop may set in where the somatic symptoms of MD could worsen the psychological symptoms, which could then in turn worsen the perception of somatic symptoms, and so on.[19,20] This is the basis for the potential development of persistent postural-perceptual dizziness, a disease that is exceptionally difficult to manage, in patients with MD.[50] Furthermore, vasopressin, as a stress hormone related to anxiety and depression,[51] could alter inner ear fluid mechanics as earlier mentioned.[14] We have found through a prospective study of cognitive function in dizzy patients that MD presents with cognitive dysfunction greater than that of benign paroxysmal positional vertigo, and comparable to that of vestibular migraine; and a great deal of this cognitive decline was mediated through depression.[52] Venlafaxine is a

well-known and effective treatment for anxiety and depression,[17,18] and as such, may prove useful in treating both the psychological and somatic repercussions of MD.

Migraine is comorbid in 22-56% of MD patients, twice as high as the general population.[21,22] It has come to be increasingly recognized that MD and vestibular migraine are closely related in that they have great overlap in presentation,[53] diagnostic criteria,[54,55] and potentially pathophysiology.[25,26] For instance, the trigeminovascular system, which is widely thought to be the pathway for activation of migraine,[25] can directly affect inner ear blood flow through the trigeminal nerve.[56] It has been hypothesized that chronic under-perfusion may lead to ischemic injury and incite MD.[57] Venlafaxine has shown efficacy in the treatment of migraine**Error! Bookmark not defined.** and vestibular migraine,[23,24] but it has never been trialed for MD.

Venlafaxine has a well-established safety profile.[3] It is well-tolerated in the treatment of depression.[4,5] In addition, it will be used in the proposed trial at the lower end of the depression treatment dosage spectrum (typically >75 mg daily). In a trial of venlafaxine 75 mg daily vs. placebo for migraine prophylaxis, excellent or good tolerance was reported in 86.7% of patients, with common side effects of nausea, vomiting, drowsiness, fatigue, and insomnia.[6] It does not bind significantly to adrenergic, muscarinic cholinergic, or histamine H1 receptors.[7] Thus, it has a low risk of causing significant anticholinergic side effects.[4]

High quality evidence is needed when examining MD treatments, especially when introducing a potential new class of therapy. A 2018 international consensus article provided an algorithm for MD treatment, which found a lack of level I evidence for any specific modality.[30] Thus, given the evidence discussed suggesting the potential of venlafaxine as a non-invasive therapy to alter the natural course of MD through both central and peripheral vestibular mechanisms, we believe a high-quality pilot study seeking to examine changes to multiple

aspects of disease burden (i.e., vestibular, functional, psychiatric, cognitive, quality of life) would be worthwhile to prove or disprove the efficacy of this class of medication.

SUBJECTS AND METHODS

Institutional Review Board (IRB) approval for this prospective study will be requested prior to enrollment of subjects.

Subject Selection

Study subjects will be prospectively recruited from patients presenting with dizziness to our tertiary, multidisciplinary, vestibular-focused, neurotology clinic. Subjects must meet the following inclusion criteria: be 18 years of age or older; have definite MD as defined by the Barany Society 2015 international consensus statement[54] (**Table 1**); have active MD with at least 2 vertigo episodes in the month prior to enrollment; and score at least 36 on the Dizziness Handicap Inventory (DHI),[58] representing at least moderate handicap. Patients with the following will be excluded: other concurrent vestibular or balance disorder (especially those with vestibular migraine-related vertigo episodes despite not meeting diagnostic criteria for vestibular migraine); prior treatment with venlafaxine; history of medical (e.g., gentamicin) or surgical (e.g., labyrinthectomy) vestibular ablative treatment; history of otologic, lateral skull base, or brain surgery; history of radiation to the head or neck; known neurologic disorder affecting cognition; currently taking another serotonin modulating medication; seizures; stroke; myocardial infarction; hepatic or renal impairment; hyperlipidemia; coagulopathy; psychiatric disorder other than anxiety or depression; glaucoma; uncontrolled hypertension; and pregnancy or intention of pregnancy.

Sample Size

This is a randomized, double-blind, crossover trial which will required a treatment group and a placebo group. Based on a power of 80%, we calculated possible sample sizes using: 1) expected proportion of subjects achieving treatment success, and 2) difference in DHI score needed for clinical significance.

We estimate 20% of the placebo group will develop a good response to treatment (>50% reduction in vertigo frequency).[59-62] To detect a difference of 30% in success rate, such that at least 50% of patients in the venlafaxine arm will develop a similar response, 36 subjects would be needed per treatment arm. Given the crossover design this would results in 18 subjects per treatment arm before crossing over, and 36 total subjects.

The original publication detailing the development of the DHI found a standard deviation in score of 21.9 among dizzy patients, and a minimum difference of 18 points after treatment to signify a significant change in self-perceived dizziness handicap.[58] Using these values, we calculate a per treatment arm sample size of 24, which results in 24 total patients needed for the crossover design.

Using the proportions sample size calculation (because it has a greater number of subjects), and factoring in a 10% drop-out rate (e.g., improper medication use, inadequate data), a total of 40 patients would need to be enrolled.

Study Protocol

A timeline summary of the study protocol is presented in **Figure 1** and **Table 2.** Based on our high clinical volume of new dizzy patients (around 80 per month), and that approximately 10% of patients will have a diagnosis of definite MD, we estimate that 8 patients can be screened per

month. Because around 40% of our referrals are outside the Tri-county area of Charleston, which may present a problem for follow-up, a conservative estimate of enrollment is 5 subjects per month. In order to enroll 40 patients, our total study period will be approximately 14.5 months (last patient screened will require 6.5 months to provide all data).

Screening Period

New patients diagnosed with definite MD will undergo a 1-month screening period during which they will keep a diary of each vertigo episode, including duration, severity on a visual-analog scale of 1 to 10 from least to most severe, and associated symptoms (aural fullness/pressure, hearing loss, tinnitus, and/or headache). They will receive an audiogram from our clinic audiologist at their initial visit to make the diagnosis of definite MD, which will be staged based on hearing loss according to the 1995 American Academy of Otolaryngology Head and Neck Surgery (AAOHNS) guidelines[63] (**Table 3**). The frequency of their vertigo episodes in the 2 months prior will be documented, along with all prior medical treatments for MD.

Before the end of their initial clinic visit, they will receive conservative treatment typically recommended for patients diagnosed with MD in our clinic. This treatment will consist of dietary and lifestyle modifications, including salt restriction to 1500 mg a day; increased water intake to a minimum of 35 ml/kg per day; and caffeine, alcohol, tobacco, and stress avoidance.[30,64-66] Subjects who are considering enrollment in the trial will be instructed to stop all medications used for MD, such as diuretics and betahistine. Patients who require oral or transtympanic steroids for acute hearing loss will not be eligible for enrollment.

We suspect many patients will have comorbid migraine as has been seen in our clinic.

These patients will be counseled about trigger identification (e.g., dietary, environments, workplace, lifestyle). Our migraine treatment strategies are outlined in **Appendix A.**

Enrollment and Randomization

Patients who document 2 or more MD-related vertigo episodes in their diary during the screening period will be offered enrollment in the study. Patients who document fewer episodes will continue to receive standard of care treatment in clinic. If a patient is interested in participating, the study coordinator will describe the study protocol, assess the patient's eligibility based on the inclusion and exclusion criteria, and have the patient sign necessary paperwork per standard IRB procedures. Patients will be required to receive comprehensive metabolic panel testing to rule out metabolic disturbances and renal and liver dysfunction. Vitals will also be screened for uncontrolled hypertension. Female patients who have not undergone menopause will be given urine pregnancy tests and advised against pregnancy during the trial period. Once enrolled, the patient will complete the following surveys: 1) Dizziness Handicap Inventory (DHI),[58] 2) Neuropsychological Vertigo Inventory (NVI),[67] 3) Cognitive Failure Questionnaire (CFQ),[68] 4) Patient Health Questionnaire-9 (PHQ9),[69] 5) Penn State Worry Questionnaire (PSWQ),[70] 6) Meniere's Disease Patient-Oriented Symptom Index (MDPOSI),[71] and 7) 20-Item Short Form Health Survey (SF20).[72] Descriptions of these tools are provided below in the Outcome Measures section.

Enrolled subjects will be randomly assigned to 2 groups, one taking a daily venlafaxine ER 37.5 mg tablet, and the other taking a daily placebo replica of venlafaxine manufactured by our university investigational drug services pharmacy. Randomization of subjects will take place

before enrollment of any subjects. The pharmacy staff will not have access to patient data beside patient identifiers. The pharmacy will be instructed to use the Excel random number generator function to generate a list of 40 numbers between 1 and 1000, representing patients 1 through 40, in order of enrollment. The 20 lowest numbers will be assigned to the venlafaxine group, and the rest to the placebo group. The pharmacy staff will then distribute the medication or placebo accordingly to the blinded clinicians to give to subjects in order of enrollment. When the groups cross over, the pharmacy staff will perform a switch in the medication without revealing subject group identities to the clinician. For patients who drop out, the subsequent enrolled patients will take on their treatment group assignment. After all data have been collected, the pharmacy staff will reveal to the statistician whether a patient belongs in group "1" or "2", without revealing which group received the placebo first. After all data have been analyzed, the pharmacy staff will give the identifier key (revealing identity of groups 1 and 2) to the investigators to interpret the results.

Subjects will be given a 2-month supply of medication or placebo plus 7 capsules for the 2-week weaning period by the pharmacy. They will be advised on how to take the medication and the side effects of venlafaxine by the investigator. They will be instructed to call the principal (HR) or co-investigator (YL) at the clinic number or page either of them (instructions will be provided) afterhours, if any side effects are affecting their ability to take the medication. Subjects will again be instructed to keep a diary of every vertigo episode.

Treatment and Washout Phases

Each treatment phase will last 2 months. Details of patient diaries will also be documented and patients will be instructed to maintain their diaries. Diaries will also be checked for adequacy to make sure subjects are documenting their symptoms appropriately. Between the first and second 2-month treatment phases there will be a 1.5-month washout period, during the first 2 weeks of which, subjects will wean off the first medication by taking the capsules every other day, and during the last 4 weeks of which, no trial medication or any other new medication will be taken but diaries will be maintained. If at any point in the trial acute hearing loss develops, a new audiogram will be obtained and transtympanic and oral steroid treatments will be offered. If a patient chooses to receive steroid treatment after being counseled about the risks and benefits, he or she will be disqualified from the trial.

Outcome Measures

Symptoms and Functional Level

The main symptoms of MD to be examined are number of vertigo episodes and severity of episodes. Symptom reduction will be calculated based on the 1995 AAOHNS guidelines[63] for assessing MD improvement after treatment (**Table 4)** and previous studies on treatment outcomes of episodic vestibular disorders such as vestibular migraines.[73,74] We will use a modified version of vertigo control classification because our treatment phases are 2 months long and we will not be able to wait 18-24 months after treatment to assess efficacy per AAOHNS guidelines.[63] Previous studies have defined four categories of response to treatment: 1) very good response if more than 75% reduction in vertigo spells frequency and/or intensity, 2) good response if 50-75% reduction, 3) fair response if 25-50% reduction, and 4) poor response if less

than 25% reduction. Combining the 2 approaches, our numerical value calculation (**Table 4**) will be the mean number of vertigo episodes in the 2 months after starting a treatment (either 1st or 2nd treatment phase) divided by the mean number of vertigo episodes in the 3 months prior to the 1st treatment phase multiplied by 100 and round to the nearest whole number. Our vertigo control classes will be defined as follows:

- Class A: numerical value 0 (complete control of vertigo)
- Class B: numerical value 0-40 or >60% reduction in mean vertigo episode severity (good control of vertigo)
- Class C: numerical value 41-80 or 20-60% reduction in severity (fair control of vertigo)
- Class D: numerical value 81-120 or -20-20% reduction in severity (no change in vertigo)
- Class E: numerical value >120 or >20% worsening in severity (worse vertigo)
- Class F: secondary treatment initiated due to disability from vertigo (e.g. steroid injection, gentamicin injection, endolymphatic sac decompression, labyrinthectomy)

We will document duration of episodes and associated symptoms (aural fullness/pressure, hearing loss, tinnitus, and/or headache) as well, but will simply conduct direct numerical comparisons or provide descriptive analyses given their likely subjectivity and variability. Functional level will be assessed according to the 1995 AAOHNS guidelines[63] (**Table 5**) at every visit.

Questionnaires

The Dizziness Handicap Inventory (DHI, **Appendix B**) is a 25-item questionnaire of self-perceived handicap from dizziness.[58] There are 7 questions in the physical domain, 9 in the

emotional domain, and 8 in the functional domain. The DHI has been shown to be valid and reliable, has been translated into 14 languages, and is the most widely-used survey of self-reported impairment from dizziness.[58,75] It has also been shown to correlate well with balance testing.[76] The DHI will be used to assess the overall severity of vestibular symptoms in our MD subjects.

The English version of the Neuropsychological Vertigo Inventory (NVI, **Appendix C**) consists of 28-items with a 5-point Likert scale for each question.[67**Error! Bookmark not defined.**] It was recently developed as a cognitive assessment specific to patients with dizziness. The NVI assesses 7 domains of cognition: space perception, attention, time perception, memory, emotional, visual/oculomotor, and motor. We recently conducted a prospective study showing that the NVI can detect a difference in cognitive dysfunction among different vestibular disorders; including MD, vestibular migraine, and benign paroxysmal positional vertigo; and that it is more sensitive than the DHI in revealing these differences.[52] We will use the NVI to gauge vestibular-specific changes in cognitive impairment after treatment.

The Cognitive Failure Questionnaire (CFQ, **Appendix D**) is a 25-item survey which assesses cognitive and executive function not tied to any specific disease state.[68] It aims to assess perception, memory, and motor function in everyday tasks. The CFQ is valid and well-established,[77,78] and will be used as a reference for cognitive dysfunction to gauge the results of the NVI, since the NVI is a newer survey.

The Patient Health Questionnaire (PHQ9, **Appendix E**) is a 9-item survey that assesses the severity of depression.[69] It is a validated tool that has been shown to be reliable in assessing outcomes of depression treatment.[79] The Penn State Worry Questionnaire (PSWQ, **Appendix F**) is a 16-item survey for assessment of anxiety which has been used to identify generalized anxiety

disorder.[70,80] Psychological disturbances have been recognized in MD and it is important to assess their severity along with that of vestibular symptoms.[19,81] Therefore, the PHQ9 and PSWQ will be used to assess the extent of depression and anxiety effects on quality of life in MD subjects.

The Meniere's Disease Patient-Oriented Symptom Index (MDPOSI, **Appendix G**) is a 23-item survey developed as a MD-specific tool to assess the impact of MD symptoms on patients' lives.[82] It is valid and reliable, and we aim to use it as a more specific measure of disease-related quality of life than the DHI.[71]

The Medical Outcomes Study 20-item Short Form Health Survey (SF20, available at https://www.rand.org/health-care/surveys_tools/mos/20-item-short-form/survey-instrument.html) is a 20-item general health questionnaire originally developed for the Medical Outcomes Study to assess quality of life in chronic diseases.[72] It assesses 6 areas of health: physical functioning, role functioning, social functioning, mental health, health perceptions, and pain. We will use this survey to gauge in a broad sense the general quality of life of MD patients given MD is a chronic disease.

Adverse Effects

Side effects experienced by subjects at any point, whether it affects their ability to continue treatment or not, will be tabulated during visits and from patient phone calls. Specifically, we will monitor for minor side effects of nausea, insomnia, somnolence, constipation, sweating, dry mouth, nervousness and asthenia; and major side effects of rash, increase in blood pressure, weight change, seizures, and serotonin syndrome.[4] A comprehensive metabolic panel will be

required prior to taking any medication to rule out any gross renal or hepatic abnormalities. Urine pregnancy tests will be administered for female patients who have not undergone menopause. No other laboratory tests will be performed unless other abnormalities are suspected.

Data Analysis

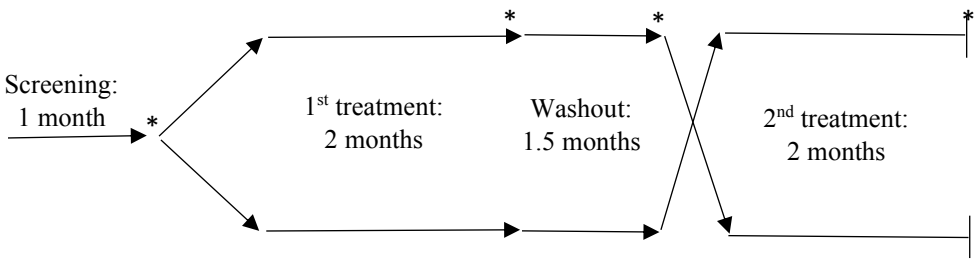
The benefit of a crossover study over a traditional clinical trial design is that it relies on elimination of carryover effects after the 1st treatment phase.[83] A confirmatory pre-test to check the adequacy of the washout period and the assumption of negligible carryover effects will be performed by using unpaired Student *t*-tests comparing all outcome measure means at the end of the 2nd treatment phase with that of the end of the 1st treatment phase for both the venlafaxine and placebo groups. For outcome measures that pass the confirmatory test, paired *t*-tests will be used to gauge within-subject differences per the crossover study design. For outcome measures that do not pass the confirmatory test, only the 1st treatment phase data will be used for analysis as if it were a parallel-treatment clinical trial.

Descriptive statistics will be performed on demographics and all other variables. In general, Student *t*-tests will be used to compare means of 2 groups and Pearson chi-square tests will be used to compare proportions where appropriate. The Kolmogorov-Smirnov test will be used to assess normality of variables and the Mann-Whitney U test will be used in lieu of the Student *t*- test for variables with non-normal distributions. Pearson correlations will be calculated to assess associations among questionnaire results. Linear regression will be performed to weigh the effect of venlafaxine or placebo against that of other variables such as depression and anxiety, which may confound results. $P<0.05$ will be used to establish statistical significance.

Potential Limitations

Vestibular symptoms may wax and wane over time in MD, potentially biasing results of the treatment phases due to underlying natural progression of the disease. However, this difference should be minimal given the short interval of 3 months between start of the first and second treatment. Another problem may be inadequate washout time for the effects of the 1st treatment phase to wear off. We will assess for significant carryover effects as described above. There may, however, be permanent carryover effects after 1 course of treatment which we cannot control.

Figure 1. Study timeline summary. During the 1st and 2nd treatment phases, patients could receive either venlafaxine or placebo according to randomization performed by the pharmacy to ensure that the physician and patient are blinded. Asterisks indicate data collection time points by study coordinator.



743 **Table 1.** Definite Meniere's disease diagnostic criteria from Barany Society international

744 consensus statement.[54]

A	Two or more spontaneous episodes of vertigo, each lasting 20 minutes to 12 hours.
B	Audiometrically documented low- to medium-frequency sensorineural hearing loss in one ear, defining the affected ear on at least one occasion before, during or after one of the episodes of vertigo.
C	Fluctuating aural symptoms (hearing, tinnitus or fullness) in the affected ear.
D	Not better accounted for by another vestibular diagnosis.

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747 **Table 2.** Study protocol summary. Bolded actions signify data collection time points.

Phase	Timing	Actions
Screening	1 month before enrollment (1st clinic visit)	Diagnose definite MD
		Audiogram
		Document vertigo frequency during prior 2 months
		Assess symptoms and function
		Recommend dietary and lifestyle modifications
		Instruct patient to keep diary of vertigo episodes and associated symptoms
	1 month period	Patient keeps diary
Round 1	Enrollment and treatment round 1 begins (2nd visit)	**Assess symptoms and function**
		Patient completes DHI, NVI, CFQ, PHQ9, PSWQ, MDPOSI, and SF20
		Patient starts venlafaxine or placebo based on randomized, blind assignment prior to enrollment, comprehensive metabolic panel prior to starting medication, urine pregnancy test if appropriate
		Instruct patient to keep diary of vertigo episodes and associated symptoms
	2 month period	Patient takes medication and keeps diary
	Treatment round 1 ends (3rd visit)	**Assess symptoms and function**
		Repeat same questionnaires from enrollment
Washout	1.5 month period	Wean off 1st medication by taking it every other day for 2 weeks, then no medications for 4 weeks
		Patient keeps diary
Round 2	Treatment round 2 begins (4th visit)	**Assess symptoms and function**
		Repeat same questionnaires from enrollment
		Patient crosses over to venlafaxine or placebo with clinician still blinded
	2 month period	Patient takes medication and keeps diary
	Treatment round 2 ends (5th visit)	**Assess symptoms and function**
		Repeat same questionnaires from enrollment

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Table 3. Meniere's disease staging. The table and footnotes below are from the guideline publication verbatim.[63]

Stage	Four-tone average (dB)
1	<25
2	26-40
3	41-70
4	>70

"Staging is based on the four-tone average (arithmetic mean rounded to the nearest whole number) of the pure-tone thresholds at 0.5, 1,2, and 3 kHz of the worst audiogram during the interval 6 months before treatment. This is the same audiogram that is used as the baseline evaluation to determine hearing outcome from treatment. Staging should be applied only to cases of definite or certain Meniere's disease."

Table 4. Vertigo control classification. The table and footnotes below are from the guideline publication verbatim.[63]

Quantifying control of vertigo spells in response to treatment	
Numerical Value	**Class**
0	A (complete control of definitive spells)
1-40	B
41-80	C
81-120	D
>120	E
Secondary treatment initiated due to disability from vertigo	F

"Numerical Value=(X/Y)x100, rounded to the nearest whole number, where X is the average number of definitive spells per months for one year after initiating therapy and Y is the average number of definitive spells in the 6 months preceding therapy (including the lead-in screening month)."

764 **Table 5.** Functional level assessment. The table below is from the guideline publication
765 verbatim.[63]

Regarding your current state of overall functioning, not just during attacks, check the ONE that best applies:
1. My dizziness has no effect on my activities at all.
2. When I am dizzy, I have to stop what I am doing for a while, but it soon passes and I can resume activities. I continue to work, drive and engage in any activity I choose without restriction. I have not changed any plans or activities to accommodate my dizziness.
3. When I am dizzy, I have to stop what I am doing for a while, but it does pass and I can resume activities. I continue to work, drive and engage in most activities I choose, but I have had to change some plans and make some allowance for my dizziness.
4. I am able to work, drive, travel, take care of a family or engage in most essential activities, but I must exert a great deal of effort to do so. I must constantly make adjustments in my activities and budget my energies. I am barely making it.
5. I am unable to work, drive or take care of a family. I am unable to do most of the active things that I used to. Even essential activities must be limited. I am disabled.
6. I have been disabled for one year or longer and/or I receive compensation (money) because of my dizziness or balance problem.

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Appendix A. Outline of headache treatment protocol. Adapted from Robbins et al.[84]

Education

- Diary
- Trigger identification and avoidance
- Lifestyle hygiene- sleep, diet, exercise

First-line migraine abortive medications

- Sumatriptan (Imitrex): gold standard; given as 50 mg x 2, 100 mg x 1, 20 mg nasal spray, 6 mg IM, or Treximet (sumatriptan and naproxen) x1
- Rizatriptan (Maxalt): fast (oral disintegrating tablets: Maxalt MLT); given as 5 mg or 10 mg, max 20 mg/day
- Naratriptan (Amerge): longer duration, lower side effects, decreased efficacy, can be used for menstrual migraine; given as 1 mg or 2.5 mg
- Zolmitriptan (Zolmig): fastest, long half-life; given as 2.5 mg or 5 mg tab, or 5 mg nasal spray
- Eletriptan (Relpax): given as 40 mg or 80 mg
- Almotriptan (Axert): low adverse effects; given as 6.25 mg or 12.5 mg
- Aspirin, caffeine, and acetaminophen (Excedrin Migraine): can have rebound headache; max 2 cap/day
- Naproxen (Aleve): good for young patients, can cause GI upset; given at onset with food, repeat in 2 hours, max 6 tab/day
- Ibuprofen: 400 mg to 800 mg Q3H, maximum 2,400 mg/day
- Isometheptene mucate, dichloralphenazone, and acetaminophen (Amidrine): safe in children
- Dihydroergotamine (Migranal): good for morning headaches, menstrual migraine; do not use with antifungals, protease inhibitors, triptans, in cardiovascular disease, uncontrolled hypertension; max 8 nasal sprays/day

Second-line abortive medications

- Ergotamine (Ergomar)
- Caffeine and ergotamine (Cafergot)
- Dihydroergotamine
- Ketorolac (Toradol)
- Compounded suppositories: see Robbins
- Compounded lozenges: see Robbins

First-line preventive medications

- Amitriptyline (Elavil): best efficacy, more side effects than nortriptyline; 10 mg QHS and titrate up
- Nortriptyline (Pamelor): 10 mg QHS and titrate up; EKG if 50 mg reached, (20 mg often sufficient)
- Propranolol (Inderal): 60 mg slow release to start, can increase to 120 mg
- Naproxen: 500 mg daily, can be BID

- Verapamil: 120 mg to start then double
- Clonazepam (Klonopin): 0.25 mg or 0.5mg, titrate up to 0.5 mg BID
- Sodium valproate (Depakote): 250 mg, titrate up to 500 mg BID
- Topiramate (Topamax): 25 mg BID, increase 25 mg/week up to 50 mg BID
- Magnesium gluconate: safe except in renal failure, good add-on; 1000 mg TID

Second-line preventive medications

- Combination therapy:
    - Amitriptyline and propranolol
    - First-line preventative and Mg gluconate
    - First-line preventative and NSAID
- Gabapentin (Neurontin): 300 mg BID
- Pregabalin (Lyrica): 50 mg or 100 mg, titrate up to 200 mg BID
- Tanacetum parthenium (Feverfew): 2-4 tabs/day

Third-line preventive medications

- Phenelzine (Nardil):
- Repetitive dihydroergotamine cycle breaking

Menstrual migraines preventive medications

- NSAID
- Ergotamine
- Triptans (naratriptan 2.5 mg daily or BID for 3 days)
- Hormonal therapy (estrogen patch, long cycle contraceptives)
- Tamoxifen – see Robbins

Alternative medications

- Butterbur extract (Petadolex)
- Vitamin B2: 400 mg/day
- CoEnzyme Q: 100 mg TID

Migraine hypothesis testing

- Steroids (prednisone): 50 mg, repeat x3 days

Antiemetic

- Promethazine (Phenergan): very effective; given as 25 mg or 50 mg pill or suppositories Q6H as needed

Notes on medications we rarely use

- Isometheptene mucate, dichloralphenazone, and acetaminophen
- Caffeine only if too much sedation
- Butalbital (Fiorinal)
- Butalbital, caffeine, and acetaminophen (Esgic, Fioricet)
- Narcotics

Appendix B. Dizziness Handicap Inventory (DHI). Used with permission from GP Jacobson.[58]

The patient is asked to answer each question as it pertains to dizziness or unsteadiness problems, specifically considering their condition during the last month. Questions are designed to incorporate functional (F), physical (P), and emotional (E) impacts on disability.

To each item, the following scores can be assigned: No=0 Sometimes=2 Yes=4

Scoring:

- Scores greater than 10 points should be referred to balance specialists for further evaluation.
- 16-34 Points (mild handicap)
- 36-52 Points (moderate handicap)
- 54+ Points (severe handicap)

P1. Does looking up increase your problem?	○ Yes ○ Sometimes ○ No
E2. Because of your problem, do you feel frustrated?	○ Yes ○ Sometimes ○ No
F3. Because of your problem, do you restrict your travel for business or recreation?	○ Yes ○ Sometimes ○ No
P4. Does walking down the aisle of a supermarket increase your problems?	○ Yes ○ Sometimes ○ No
F5. Because of your problem, do you have difficulty getting into or out of bed?	○ Yes ○ Sometimes ○ No
F6. Does your problem significantly restrict your participation in social activities, such as going out to dinner, going to the movies, dancing, or going to parties?	○ Yes ○ Sometimes ○ No
F7. Because of your problem, do you have difficulty reading?	○ Yes ○ Sometimes ○ No
P8. Does performing more ambitious activities such as sports, dancing, household chores (sweeping or putting dishes away) increase your problems?	○ Yes ○ Sometimes ○ No
E9. Because of your problem, are you afraid to leave your home without having someone accompany you?	○ Yes ○ Sometimes ○ No
E10. Because of your problem have you been embarrassed in front of others?	○ Yes ○ Sometimes ○ No
P11. Do quick movements of your head increase your problem?	○ Yes ○ Sometimes ○ No
F12. Because of your problem, do you avoid heights?	○ Yes ○ Sometimes ○ No
P13. Does turning over in bed increase your problem?	○ Yes ○ Sometimes ○ No

F14. Because of your problem, is it difficult for you to do strenuous homework or yard work?	○ Yes ○ Sometimes ○ No
E15. Because of your problem, are you afraid people may think you are intoxicated?	○ Yes ○ Sometimes ○ No
F16. Because of your problem, is it difficult for you to go for a walk by yourself?	○ Yes ○ Sometimes ○ No
P17. Does walking down a sidewalk increase your problem?	○ Yes ○ Sometimes ○ No
E18.Because of your problem, is it difficult for you to concentrate	○ Yes ○ Sometimes ○ No
F19. Because of your problem, is it difficult for you to walk around your house in the dark?	○ Yes ○ Sometimes ○ No
E20. Because of your problem, are you afraid to stay home alone?	○ Yes ○ Sometimes ○ No
E21. Because of your problem, do you feel handicapped?	○ Yes ○ Sometimes ○ No
E22. Has the problem placed stress on your relationships with members of your family or friends?	○ Yes ○ Sometimes ○ No
E23. Because of your problem, are you depressed?	○ Yes ○ Sometimes ○ No
F24. Does your problem interfere with your job or household responsibilities?	○ Yes ○ Sometimes ○ No
P25. Does bending over increase your problem?	○ Yes ○ Sometimes ○ No

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Appendix C. Neuropsychological Vertigo Inventory (NVI).[67] Used with permission from authors of the original study and use of the English version with permission from Dr. R. Srinivasa Raghavan of The Royal Surrey County Hospital.

Please choose an appropriate response to the statements based on your most recent experience of everyday life:

1. Never **2.** Rarely **3.** Sometimes **4.** Very often **5.** All the time (or)

1. Strongly disagree **2.** Disagree **3.** Not sure / Not applicable **4.** Agree **5.** Strongly agree

Q1 I have a poor sense of direction	
Q2 I find it difficult to locate myself on a map	
Q3 I tend to go the wrong way when I set off to go somewhere	
Q4 When I go out I have trouble finding my way back	
Q5 I can't place major historical events in the right chronological order	
Q6 I get confused about what day of the week it is	
Q7 I don't always know what year we are in	
Q8 I don't know which season we are in	
Q9 I find it difficult to concentrate	
Q10I am absent minded	
Q11I find it difficult to organize myself	
Q12I am easily distracted	
Q13I forget my appointments	
Q14I have problems with my memory	
Q15I find it hard to remember names of people	
Q16I forget birthdays and anniversaries	
Q17My mood changes each day	
Q18I find it hard to get up in the morning	
Q19I feel depressed	

Q20I feel tired	
Q21My eyes feel tired when I use the computer or watch television	
Q22I tend to lose track of what I am reading and have to start all over again	
Q23I am a slow reader	
Q24For me table entries and newspaper columns appear jumbled	
Q25I am clumsy	
Q26I don't think my handwriting is neat	
Q27 I am not very good using my hands when it comes to DIY, drawing or sculpture	
Q28My balance is poor	
Total score	

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Appendix D. Cognitive Failure Questionnaire (CFQ).[68]

The following questions are about minor mistakes which everyone makes from time to time, but some of which happen more often than others. We want to know how often these things have happened to you in the past 6 months. Please circle the appropriate number.

		Very often	Quite often	Occasion-ally	Very rarely	Never
1.	Do you read something and find you haven't been thinking about it and must read it again?	4	3	2	1	0
2.	Do you find you forget why you went from one part of the house to the other?	4	3	2	1	0
3.	Do you fail to notice signposts on the road?	4	3	2	1	0
4.	Do you find you confuse right and left when giving directions?	4	3	2	1	0
5.	Do you bump into people?	4	3	2	1	0
6.	Do you find you forget whether you've turned off a light or a fire or locked the door?	4	3	2	1	0
7.	Do you fail to listen to people's names when you are meeting them?	4	3	2	1	0
8.	Do you say something and realize afterwards that it might be taken as insulting?	4	3	2	1	0
9.	Do you fail to hear people speaking to you when you are doing something else?	4	3	2	1	0
10.	Do you lose your temper and regret it?	4	3	2	1	0
11.	Do you leave important letters unanswered for days?	4	3	2	1	0
12.	Do you find you forget which way to turn on a road you know well but rarely use?	4	3	2	1	0
13.	Do you fail to see what you want in a supermarket (although it's there)?	4	3	2	1	0
14.	Do you find yourself suddenly wondering whether you've used a word correctly?	4	3	2	1	0

15.	Do you have trouble making up your mind?	4	3	2	1	0
16.	Do you find you forget appointments?	4	3	2	1	0
17.	Do you forget where you put something like a newspaper or a book?	4	3	2	1	0
18.	Do you find you accidentally throw away the thing you want and keep what you meant to throw away – as in the example of throwing away the matchbox and putting the used match in your pocket?	4	3	2	1	0
19.	Do you daydream when you ought to be listening to something?	4	3	2	1	0
20.	Do you find you forget people's names?	4	3	2	1	0
21.	Do you start doing one thing at home and get distracted into doing something else (unintentionally)?	4	3	2	1	0
22.	Do you find you can't quite remember something although it's "on the tip of your tongue"?	4	3	2	1	0
23.	Do you find you forget what you came to the shops to buy?	4	3	2	1	0
24.	Do you drop things?	4	3	2	1	0
25.	Do you find you can't think of anything to say?	4	3	2	1	0

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Appendix E. Patient Health Questionnaire (PHQ9).[69]

Use of the PHQ-9 to Make a Tentative Depression Diagnosis:

The clinician should rule out physical causes of depression, normal bereavement and a history of a manic/hypomanic episode

Step 1: Questions 1 and 2

Need one or both of the first two questions endorsed as a "2" or a "3" (2 = "More than half the days" or 3 = "Nearly every day")

Step 2: Questions 1 through 9

Need a total of five or more boxes endorsed within the shaded area of the form to arrive at the total symptom count. (Questions 1-8 must be endorsed as a "2" or a "3"; Question 9 must be endorsed as "1" a "2' or a "3")

Step 3: Question 10

This question must be endorsed as ''Somewhat difficult'' or ''Very difficult'' or ''Extremely difficult''

Use of the PHQ-9 for Treatment Selection and Monitoring
Step 1

A depression diagnosis that warrants treatment or a treatment change, needs at least one of the first two questions endorsed as positive ("more than half the days" or "nearly every day") in the past two weeks. In addition, the tenth question, about difficulty at work or home or getting along with others should be answered at least "somewhat difficult"

Step 2

Add the total points for each of the columns 2-4 separately

(Column 1 = Several days; Column 2 = More than half the days; Column 3 = Nearly every day. Add the totals for each of the three columns together. This is the Total Score

The Total Score = the Severity Score

Step 3

Review the Severity Score using the following TABLE.

PHQ9 Score	**Provisional Diagnosis**	**Treatment Recommendation** ***Patient Preferences should be***

		considered
5-9	Minimal Symptoms*	Support, educate to call if worse, return in one month
10-14	Minor depression ++ Dysthymia* Major Depression, mild	Support, watchful waiting Antidepressant or psychotherapy Antidepressant or psychotherapy
15-19	Major depression, moderately severe	Antidepressant or psychotherapy
>20	Major Depression, severe	Antidepressant and psychotherapy (especially if not improved on monotherapy)

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908 * If symptoms present ≥ two years, then probable chronic depression which warrants
909 antidepressants or psychotherapy (ask "In the past 2 years have you felt depressed or sad
910 most days, even if you felt okay sometimes?")

911 ++ If symptoms present ≥ one month or severe functional impairment, consider active treatment

912

913

Over the past 2 weeks, how often have you been bothered by any of the following problems?	**Not At all**	**Several Days**	**More Than Half the Days**	**Nearly Every Day**
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed or hopeless	0	1	2	3
Trouble falling asleep, staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
Feeling bad about yourself - or that you're a failure or have let yourself or your family down	0	1	2	3
Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3

Moving or speaking so slowly that other people could have noticed. Or, the opposite - being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

914

915 10. If you checked off any problems, how difficult have those problems made it for you to Do
916 your work, take care of things at home, or get along with other people?

917 Not difficult at all

918 Somewhat difficult

919 Very difficult

920 Extremely difficult

921

Appendix F. Penn State Worry Questionnaire (PSWQ).[70]

Each item is scored 1-5, as indicated below. Items 1, 3, 8, 10, and 11 are reversed scored. Total is sum of all 16 items. Possible range of scores is 16-80.

Algorithm

Total = 16-39 Low Worry

Total = 40-59 Moderate Worry

Total = 60-80 High Worry

Instructions: Rate each of the following statements on a scale of 1 ("not at all typical of me") to 5 ("very typical of me"). Please do not leave any items blank.

1 2 3 4 5

Not at all typical of me Very typical of me

1. If I do not have enough time to do everything, I do not worry about it.
2. My worries overwhelm me.
3. I do not tend to worry about things.
4. Many situations make me worry.
5. I know I should not worry about things, but I just cannot help it.
6. When I am under pressure I worry a lot.
7. I am always worrying about something.
8. I find it easy to dismiss worrisome thoughts.
9. As soon as I finish one task, I start to worry about everything else I have to do.
10. I never worry about anything.
11. When there is nothing more I can do about a concern, I do not worry about it anymore.
12. I have been a worrier all my life.
13. I notice that I have been worrying about things.
14. Once I start worrying, I cannot stop.
15. I worry all the time.

951 **Appendix G.** Meniere's Disease Patient-Oriented Symptom Index (MDPOSI).[71,82]

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MENIERE'S DISEASE PATIENT-ORIENTED SYMPTOM INDEX (MD POSI)

To indicate how much your inner ear problem is affecting your health and well-being, your answers to the following questions are very important. There are no right or wrong answers: only YOU can determine how much your life has changed because of your Meniere's disease.

For each of the following statements, fill the circles over the number that best indicates how much that area of your life has been changed. If you do not have a problem in that area or the statement does not apply to you, fill the circle over 0 and go to the next item.

As you know, Meniere's disease may affect people very differently and even in the same person, the symptoms vary from attack to attack. Please rate the following problems as they apply to you, on average, over the past three months. Knowing how bad the problems are now and how they affect your life will help in judging the effectiveness of treatment in your specific case.

It is important that you answer ALL questions. Please use black ink to fill the circles.

Meniere's Problems List
(Over the past 3 months)

Problem Scale (Fill the circle over the best answer)

A. During my most recent typical Meniere's attacks I had trouble with:	None	Slight	Mild	Moderate	Severe	Worse Ever
1. Hearing	○ 0	○ 1	○ 2	○ 3	○ 4	○ 5
2. Balance	○ 0	○ 1	○ 2	○ 3	○ 4	○ 5
3. Ears, Noise, & Pressure	○ 0	○ 1	○ 2	○ 3	○ 4	○ 5
4. Performing daily activities	○ 0	○ 1	○ 2	○ 3	○ 4	○ 5

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B. In-between attacks, I have trouble with:

	0	1	2	3	4	5
5. Hearing	○	○	○	○	○	○
6. Balance	○	○	○	○	○	○
7. Mental Concentration (reading etc.)	○	○	○	○	○	○
8. Performing daily activities						
9. Fear of travel	○	○	○	○	○	○
10. Memory Loss	○	○	○	○	○	○

C. Meniere's disease has affected my:

	0	1	2	3	4	5
11. Social life	○	○	○	○	○	○
12. Being close to others	○	○	○	○	○	○
13. General mood	○	○	○	○	○	○
14. Outlook for the future	○	○	○	○	○	○

Problem Scale (Fill the circle over the best answer)

D. In regard to my employment, my Meniere's disease has resulted in:	None 0	Slight 1	Mild 2	Moderate 3	Severe 4	Worse Ever 5
15. Questions about my reliability	○	○	○	○	○	○
16. Job modification/reassignment	○	○	○	○	○	○
E. 17. Overall, my Meniere's disease is	○	○	○	○	○	○

	Little 1	Minor degree 2	Moderate 3	A Lot 4	Extremely 5
18. Overall, my Meniere's disease has changed my life	○	○	○	○	○

	Excellent 1	Very Good 2	Good 3	Fair 4	Poor 5
19. Compared to others my age, my health is	○	○	○	○	○
20. I expect my health in 5 years to be	○	○	○	○	○

21. Please add any comments here. Thank you for completing this questionnaire.

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