A Prospective Randomized Cross-over Trial of Nortryptyline and Topiramate in the Initial Treatment of Vestibular Migraine.

NCT02169830

10 October 2019

Protocol Title: A Prospective randomized cross-over trial of nortriptyline and topiramate in the initial treatment of vestibular migraine

Protocol Status: CLOSED

Date Submitted: 02/11/2019

Approval Period: Draft

Important Note: This Print View may not reflect all comments and contingencies for approval. Please check the comments section of the online protocol. Questions that appear to not have been answered may not have been required for this submission. Please see the system application for more details.

* * * Personnel Information * * *

Study Personnel Roles:
-Principal Investigator: accepts responsibility for study, must sign obligations, can edit protocol and submit to IRB
-Administrative Contact: additional study contact, may or may not also be member of research team, can edit/prepare protocol and submit to IRB
-Key Personnel (Research Team): SLU member of research team, can view protocol (not edit)
-Non-SLU Collaborator: member of research team from another institution or organization outside of SLU, has no access to system, must be provided with PDF of protocol. NOTE: SLUH/SSM employees who collaborate regularly may obtain a guest SLU account if access to system is needed.
-Department Chair: Official Department Chair, may or may not also be a member of research team, can view the protocol (not edit). NOTE: a proxy may be listed if the Chair is the PI.

IMPORTANT NOTE: Human Subjects Protection Training is mandatory for all research team personnel.

Principal Investigator (PI) Mandatory

PI must be SLU affiliate.

Name of Principal Investigator (Faculty, Staff or Student)	Degree (MD/PhD)	Title
Mikulec, Anthony	MD	Associate Professor

Email	Phone	Fax
mikuleca@slu.edu	(314) 577-8885	

Department Name
Otolaryngology

Human Subjects Training Completed? Y
WARNING: Proof of training must show below or the application will be returned. If your training information isn't showing, upload a copy in the Attachments section.

Research Experience *?HELP?*
Dr. Mikulec has many years of clinical trial experience

Research Team Member Duties Picklist

1.	X	Recruitment	2.	X	Obtains consent
3.	X	Determine Subject Eligibility for Accrual	4a.	X	Subject Physical Examinations
4b.	X	Follow-up Visits including physical assessments	5.	X	Perform study procedures or Specimen Collection
6a.		Administer and/or Dispense Study Drugs, Biologics or Devices (must be licensed)	6b.		Receive, Store, Manipulate or Account for Study Drugs, Biologics or Devices
7.	X	Subject Randomization or Registry	8.	X	Collection of Subject Data
9.	X	Report Data (CRFs, e-CRFs, Spreadsheets)	10.	X	Data Analysis

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11a. X Review Adverse Events

11b. X Treat and Classify Adverse Events

12. Other (Please insert explanation below.)

UserID	CourseCompletionDate	Course
mikuleca	07-15-2005	CITI Biomedical Research Basic Training
mikuleca	03-01-2016	Good Clinical Practice (GCP)
mikuleca	01-21-2019	Good Clinical Practice (GCP) Refresher

Administrative Contact

Name of Administrative Contact	Degree	Title
Webb, Deniece	BA	Administrative Assistant I

Key Personnel (Research Team)

Name of Key Personnel (Research Team)	Degree	Title	Department Name
Hentzelman, Joshua	MD	Assistant Professor	Otolaryngology
Keenan, Sarah		Nurse Practitioner	Otolaryngology
Armbrecht, Eric		Assistant Professor	SLUCOR

Department Chair Mandatory

The official Department Chair should be listed here. If the Department Chair is the PI, a proxy may be listed.

Name of Department Chair
Antisdel, Jastin

Degree
MD

Title
Associate Professor

Email
antisdel@slu.edu

Phone
(314) 577-8885

Fax

Department Name
Otolaryngology

Is this individual also a member of the research team? N

Human Subjects Training Completed?
WARNING: Proof of training must show below or the application will be

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returned. If your training information isn't showing, upload a copy in the Attachments section.

Research Experience *?HELP?*

Research Team Member Duties Picklist

1.	Recruitment	2.	Obtains consent
3.	Determine Subject Eligibility for Accrual	4a.	Subject Physical Examinations
4b.	Follow-up Visits including physical assessments	5.	Perform study procedures or Specimen Collection
6a.	Administer and/or Dispense Study Drugs, Biologics or Devices (must be licensed)	6b.	Receive, Store, Manipulate or Account for Study Drugs, Biologics or Devices
7.	Subject Randomization or Registry	8.	Collection of Subject Data
9.	Report Data (CRFs, e-CRFs, Spreadsheets)	10.	Data Analysis
11a.	Review Adverse Events	11b.	Treat and Classify Adverse Events
12.	Other (Please insert explanation below.)		

UserID	CourseCompletionDate	Course
antisdel	03-08-2017	Good Clinical Practice (GCP)
antisdel	02-19-2007	CITI Biomedical Research Basic Training

Research Team Roles

Name(s), Degree	Department	Experience	Duties
Mikulec, Anthony, MD	Otolaryngology	Dr. Mikulec has many years of clinical trial experience	Recruitment, Obtains consent, Determine Subject Eligibility for Accrual, Subject Physical Examinations, Follow-up Visits including physical assessments, Perform study procedures or Specimen Collection, Subject Randomization or Registry, Collection of Subject Data, Report Data (CRFs, e-CRFs, Spreadsheets), Data Analysis, Review Adverse Events, Treat and Classify Adverse Events
Hentzelman, Joshua, MD	Otolaryngology	Dr. Hentzelman has participated in multiple clinical research projects during his education and training and will work closely with Dr. Mikulec	Recruitment, Obtains consent, Determine Subject Eligibility for Accrual, Subject Physical Examinations , Follow-up Visits including physical assessments, Perform study procedures or

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			Specimen Collection, Subject Randomization or Registry, Collection of Subject Data, Report Data (CRFs, e-CRFs, Spreadsheets), Data Analysis, Review Adverse Events, Treat and Classify Adverse Events
Keenan, Sarah	Otolaryngology	Sarah will be supervised by Dr. Mikulec, as she is new to research	Recruitment, Obtains consent, Determine Subject Eligibility for Accrual, Subject Physical Examinations , Follow-up Visits including physical assessments, Perform study procedures or Specimen Collection, Subject Randomization or Registry, Collection of Subject Data, Report Data (CRFs, e-CRFs, Spreadsheets), Review Adverse Events, Treat and Classify Adverse Events
Armbrecht, Eric	SLUCOR	Dr. Armbrecht has extensive data analysis experience, he will work closely with Dr. Mikulec	Data Analysis

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* * * Subject Population * * *

Subject Population(s) Checklist

Select All That Apply :

X Adults
Cognitively Impaired Subjects
Employees (specifically targeted)
Fetuses
Minors (under 18)
Neonates
Non English Speaking Subjects
Pregnant Women
Prisoners
Students (specifically targeted)
Terminally Ill Subjects
Wards of the State
Other (any population that is not specified above)

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* * * Study Location * * *

Study Location(s) Checklist

Indicate where the study will be conducted. Select all that apply:

X Saint Louis University, Medical Center Campus

Saint Louis University, Frost Campus

Saint Louis University, Madrid Campus

X Saint Louis University, SLUCare Practice Locations

SSM STL (DePaul Hospital, St. Mary's Health Center, St. Joseph (St. Charles, Wentzville, Lake Saint Louis), St. Clare)

Cardinal Glennon Children's Medical Center

Saint Louis University Hospital (SSM Health- SLU Hospital)

SLU-SSM Cancer Center Research Alliance Sites

Other (In the box below, list any off-campus institutions or locations and describe the activities being conducted there. Please provide letters of cooperation and/or IRB approvals from each location to document support/approval of the study. You may provide such documentation as it becomes available, but you may not begin work at those sites until documentation of support is provided to the IRB.) Please refer to the Guidance for involving non-SLU institutions in human subject research.

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* * * General Checklist * * *

General Checklist

Select All That Apply :

Collection of Specimens

Data collection via e-mail or the Internet

Deception/Incomplete Disclosure

Dietary Supplements, Vitamins, and Other Food Agents

FDA Approved Device

X FDA approved drugs, reagents, other chemicals administered to subjects (even if they are not being studied), or biologic products

Genetic Testing

HIV Testing

Human blood, cells, tissues, or body fluids

International Research or Research on International Populations

Investigational drugs, reagents, chemicals, or biologic products

Investigational Device

X Investigator Initiated Study *?HELP?*

X Medical Records

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Photography, Video, or Voice-Recording Subjects
X Questionnaires and/or tests
Radioisotopes/radiation-producing machines, even if standard of care
rDNA/Gene Transfer Therapy
Registry(ies)
Specimens to be stored for future research projects (must be in consent form)
Study of existing data or specimens
X University Indemnified Study (SLU is responsible for liability coverage) *?HELP?*
Other (clarify in text box to the right)

Single Use. Provide a brief summary and justification for the Single Use Therapy. Note: This application will refer to research. For Single Use applications it is understood that 'research' will mean 'therapy'.

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* * * Funding * * *

Funding Checklist

NONE

Funding - Grants/Contracts

Funding Type	Funded By
Private Agency/Foundation	Association of Migraine Disorders

NOTE: Applicable grant application, contract or subcontract, investigator's brochure, and sponsor's protocol (for all industry sponsored clinical trials) must be attached. You will be prompted for these in section #16 (Attachments).

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* * * Expedited Paragraphs * * *

To request an Expedited Review, check the appropriate category(ies) below. Provide justification for your request for Expedited Review.

To qualify for expedited review, research activities must (1) present no more than minimal risk to human subjects,

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and (2) involve only procedures listed in one or more of the categories below.

1. Clinical studies of drugs and medical devices only when condition (a) or (b) is met.

a) Research on drugs for which an investigational new drug application (21 CFR Part 31, 32) is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)

b) Research on medical devices for which

(i) An investigational device exemption application (21 CFR Part 812) is not required; or

(ii) The medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.

2. Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:

a) From healthy, nonpregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8-week period and collection may not occur more frequently than 2 times per week; or

From other adults and children, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8-week period and collection may not occur more frequently than 2 times per week.

Children are "persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted."

3. Prospective collection of biological specimens for research purposes by non-invasive means.

EXAMPLES: (a) hair and nail clippings in a nondisfiguring manner; (b) deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction; (c) permanent teeth if routine patient care indicates a need for extraction; (d) excreta and external secretions (including sweat); (e) uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or by applying a dilute citric solution to the tongue; (f) placenta removed at delivery; (g) amniotic fluid obtained at the time of rupture of the membrane prior to or during labor; (h) supra-and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques; (i) mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings; (j) sputum collected after saline mist nebulization.

4. Collection of data through non-invasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving X-rays or microwaves. Where

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routinely employed in clinical practice, excluding procedures involving X-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.)

EXAMPLES: (a) physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subjects' privacy; (b) weighing or testing sensory acuity; (c) magnetic resonance imaging; (d) electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiology; (e) moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight and health of the individual.

5. Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis). (NOTE: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. 45CFR 46.101(b)(4). This listing refers only to research that is not exempt.)

6. Collection of data from voice, video, digital, or image recordings made for research purposes.

7. Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. (NOTE: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. 45 CFR 46.101(b)(2) and (b)(3). This listing refers only to research that is not exempt.)

8. [FOR IRB use only]. Continuing review of research previously approved by a convened IRB only when condition (a), (b), or (c) is met.

   a) Previously approved research where
      (i) The research is permanently closed to the enrollment of new subjects;
      (ii) All subjects have completed all research-related interventions; and
      (iii) The research remains active only for the long term follow-up of subjects.

   b) Previously approved research where no subjects have been enrolled and no additional risks have been identified.

   c) Previously approved research where the remaining research activities are limited to data analysis.

9. [FOR IRB use only]. Continuing review or research not conducted under an investigational new drug application or investigational drug exemption where expedited categories two (2) through eight (8) do not apply but the IRB has determined and documented at a convened meeting that the research

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involves no greater than minimal risk and no additional risks have been identified.

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* * * Background, Purpose, Study Procedures * * *

Title

A Prospective randomized cross-over trial of nortriptyline and topiramate in the initial treatment of vestibular migraine

Complete Sections 1 - 16. In sections that allow reference to sponsor protocol or grant, clearly state section and page numbers. Any information that is different or specific to the local site should be in the SLU application. Specify N/A as appropriate.

1. Background

Page numbers from a sponsor's protocol/grant may be referenced in 1a and 1b.

a) **Provide an introduction and background information. Describe past experimental and/or clinical findings leading to the formulation of the study, if applicable. Investigator Initiated studies must cite references in the response provided or attach a bibliography. *?HELP?***

As vestibular migraine, also known as migraine associated dizziness, is not recognized as a variant of migraine by the International Headache Society (IHS) (Headache Classificiation Subcommittee, 2004), diagnostic and treatment guidelines remain to be determined. Neuhauser and collaborators have attempted to define criteria for definite (dVM) and probable vestibular migraine (pVM) (Neuhauser, 2009), but consensus on what constitutes vestibular migraine is lacking. We feel that the Neuhauser criteria may be too restrictive. The treatment of vestibular migraine involves trial of various medications such as nortriptyline, topiramate, clonidine, beta blockers, and calcium channel blockers (Reploeg, 2002). Comparative effectiveness of these medications in the treatment of vestibular migraine is unknown.

Our study plans to treat all patients initially with a one month trial of migraine diet and then randomize treatment naive patients with vestibular migraine to an 8 week trial of an escalating dose of either nortriptyline or topiramate followed by an 8 week crossover to the other drug. Response to therapy will be quantified by the Migraine Specific Quality of Life (MSQ),(Renas-Baum, 2013) Dizziness Handicap Inventory (DHI) (Jacobson, 1990; Vereeck, 2006) and Motion Sensitivity Questionaire (MoSQ) (Dannenbaum, 2011) administered at multiple time points during the study. Three groups of patients eligible for the study will include 1) patients with Neuhauser dVM; 2) patients with pVM; and 3) patients with dizziness that falls outside the Neuhauser criteria (non-Neuhauser vestibular migraine or nNVM) but is still felt by the investigators to be most likely due to a migraine variant.

Meniere's syndrome is a completely different entity from vestibular migraine. Meniere's involves episodic vertigo associated with a fluctuating hearing loss, ear fullness and tinnitus. In contrast, vestibular migraine, also known as migraine associated dizziness involves episodic dizziness and imbalance at times associated with headache, but without hearing change. Meniere's is a disorder of the inner ear, while vestibular migraine is a migraine that affects the part of the brain dealing with balance.

Please save frequently

b) **Describe any animal experimentation and findings leading to the formulation of the study, if**

there is no supporting human data.

n/a

2. Purpose of the study

a) **Provide a brief lay summary of the project in <200 words. The lay summary should be readily understandable to the general public.**

Our study plans to randomize treatment naive patients with vestibular migraine to an 8 week trial of an escalating dose of either nortriptyline or topiramate followed by an 8 week crossover to the other drug if patient is willing, if patient wants to stay on first medication we will just continue to follow. During the first 8 weeks if there is an intolerance to the first drug they can be switched to the other drug at any point and then followed on that medication for the remainder of the study. Response to therapy will be quantified by the Migraine Specific Quality of Life (MSQ) and Dizziness Handicap Inventory (DHI) administered at multiple time points during the study. Three groups of patients that will be eligible for the study will include 1)Patients with Neuhauser dVM; 2)Patients with pVM; and 3) Patients with dizziness that falls outside the Neuhauser criteria (non-Neuhauser vestibular migraine or nNVM).

Our hypothesis is that even patients with dizziness outside of the Neuhauser dVM and pVM spectrum will respond to treatment for vestibular migraine, and thus likely have migraine as a cause of their dizziness. Previous research by our group has suggested that such patients do in fact respond to migraine therapy1. A second goal of the study is to evaluate the comparative efficacy of nortriptyline and topiramate in the treatment of these three subgroups of patients with vestibular migraine.

Page numbers from a sponsor's protocol/grant may be referenced in 2b and 2c.

b) **List your research objectives (specific aims & hypotheses of the study).**

The primary goal of the study is to evaluate the comparative effectiveness of migraine diet, nortriptyline and topiramate in the treatment of these three subgroups of patients with vestibular migraine. A secondary hypothesis is that even patients with dizziness outside of the Neuhauser dVM and pVM spectrum will respond to treatment for vestibular migraine, and thus likely have migraine as a cause of their dizziness. Previous research by our group has suggested that such patients do in fact respond to migraine therapy (Mikulec, 2012).

Our hypothesis is that even patients with dizziness outside of the Neuhauser dVM and pVM spectrum will respond to treatment for vestibular migraine, and thus likely have migraine as a cause of their dizziness. Previous research by our group has suggested that such patients do in fact respond to migraine therapy1. A second goal of the study is to evaluate the comparative efficacy of nortriptyline and topiramate in the treatment of these three subgroups of patients with vestibular migraine.

Please save frequently

c) **Describe the study design (e.g., single/double blind, parallel, crossover, control, experimental, observational, etc.). If the study is investigator-initiated, a timeline for individual subject recruitment, follow-up, and analysis for the study is required. Also, indicate if the subjects will be randomized.**

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Randomized cross over trial

Subject recruitment will commence once IRB approval is obtained and progress for one year. Individual patients will be in the study as indicated on the timeline. At the end of one year, data will be analyzed, a process which will likely take 3 to 6 months.

d) If subjects will be given placebo, please justify placebo use. *?HELP?*

n/a

3. Study Procedures

a) N Is this project a multicenter study (i.e., same project is conducted elsewhere by a different investigator) OR does this study involve conduct of research at multiple sites?

Is SLU acting as a coordinating center for other sites OR is the SLU PI a direct recipient of a federal grant for this research? If yes, complete and attach the Supplemental Application for Coordinating Center Activities.

Will the SLU site be participating in all parts/procedures/arms of the study?

If No, explain what SLU will NOT participate in:

Please save frequently

Page numbers from a sponsor's protocol/grant may be referenced in 3b, 3c, and 3d.

b) Describe all the procedures, from screening through end-of-study, that the human subject must undergo in the research project, including study visits, drug treatments, randomization and the procedures that are part of standard of care. Specify which procedures are for research and which are standard of care. Please note: The box below is for text only. If you would like to add tables, charts, etc., attach those files in the Attachment section (#16).

The attached flow chart illustrates the study design (Figure 1). After identification and trial entry, we will complete intake questionnaire to determine what type of vestibular migraine category the patients qualify for, a standard of care office visit with history and physical (Standard of Care) to review symptoms and previous treatment, patients height and weight (standard of care) will be obtained. Patients will complete a standard of care audiology assessment, and the following questionnaires: MSQ (Migraine Symptom Questionnaire) Version 2.1, DHI (Dizziness Questionnaire) , C-SSRS (Columbia Suicide Severity Rating Scale) and the MoSQ (Motion Sensitivity Questionnaire). All drug naive patients will undergo a one month lead in of treatment involving dietary and behavioral control of migraine. Emphasis will be given to cessation of known migraine triggers such as caffeine, sodas, chocolates, alcohol (especially red wine) and aged cheeses. Patients who have complete control of their symptoms with diet and behavior modification alone will be followed for a total of 4 months to determine the durability of symptom relief. Patients who fail behavior modification during the 2 to 4 month time point can chose to enter the drug treatment portion of the study, as defined below.

At the one month point, patients will be brought into the clinic for a office visit or contacted by phone and will complete medical history, MSQ V2.1, DHI, C-SSRS and the MoSQ, then will be randomization to either nortriptyline or topiramate will occur. Randomization will occur by opening the lowest numbered of a stack of envelopes which will contain a randomly preselected

opening the lowest numbered of a stack of envelopes which will contain a randomly preselected card indicating which drug is to be used. The nortriptyline will be given in an escalating fashion, starting at 25 mg PO qhs for 2 weeks, followed by 50 mg PO qhs for 2 weeks, and finally 75 mg PO qhs. Patients will be encouraged to use the lowest effective dose and to self-titrate their medication. Topiramate dosing will be 25 mg PO qhs for 1 week, followed by 25 mg BID for 1 week, followed by 25 mg in the morning and 50 mg qhs for 1 week, and finally 50 mg BID. Patients will be allowed considerable leeway in adjusting their dosage and will be encouraged to stay on the lowest effective dose. Medication will be provided open label to the patient and paid for through the patients' insurance, as this intervention falls within current standard practice, and is not investigational.

After two, three and four months on drug patients will be brought into the clinic for a office visit or contacted by phone with history, and will complete MSQ V2.1, DHI, C-SSRS and the MoSQ, then patients will be offered the opportunity to switch to the other drug. Those patients who wish to switch drugs will first be weaned off their current drug over a one week time period. Patients who elect to stay on their initial drug will be followed for a total of four months. Patients who opt for trial of a second drug will then be started on the second drug via a self-titrating protocol as described above and followed on that drug for up to 4 months.

Our clinical experience has shown that on occasion patients will refuse to take more than a few doses of nortriptyline or topiramate due to intolerable side effects. Such patients will be allowed to immediately initiate therapy with the other drug. The medication change can be done with a phone call to their pharmacy without an office visit, as is done in standard of care. Also, patients who already follow a rigorous migraine diet will be allowed to enter the drug treatment phase immediately. In our experience, such patient make up less than 5% of the population that presents for treatment of vestibular migraine.

The response to therapy will be assessed during monthly visits with the use of the MSQ, DHI and MoSQ questionnaires. Patients will be provided compensation for participating in the study. $60 dollars will be paid to each patient for each month that they participate in the study. Our goal is to recruit 100 patients over the span of one year.

Data which will be collected include age, sex, height, weight, body mass index (BMI), prior head MRI or CT, results of vestibular testing, family history of migraine. A careful history will focus on vestibular migraine comorbidities such as visual scotoma, ability to ride in the back seat of a car, and history of "sinus pain".

Patients will be identified as having one of three subtypes of vestibular migraine, based on their symptoms and history as obtained during their initial visit.

Criteria for Neuhauser definite vestibular migraine (dVM): (Neuhauser, 2009):
1. Episodic vestibular symptoms of at least moderate severity.
2. Current of previous history of migraine according to the 2004 criteria of the International Headache Society (IHS)
3. One of the following migrainous symptoms during 2 or more attacks of vertigo: migrainous headache, photophobia, phonophobia, visual aura, or other aura
4. Other causes ruled out by appropriate investigations

Criteria for probable vestibular migraine (pVM):
1. Episodic vestibular symptoms of at least moderate severity
2. One of the following
A. current or previous history of migraine according to the 2004 criteria of the IHS
B. migrainous symptoms during vestibular symptoms
C. migraine precipitants of vertigo in > 50% of attacks: food triggers, sleep irregularities, or hormonal change
D. Response to migraine medications in more than 50% of attacks
3. Other causes ruled out by appropriate investigations

Criteria for (non-Neuhauser vestibular migraine or nNVM) will include those patients who do not fit the criteria for dVM and pVM but are felt by the investigator to have underlying migraine as a possible cause of their dizziness. This includes patients with a remote history of migraines, those with visual auras without headache, those with recurring self-described "sinus pain" and those with significant motion intolerance, either to their own head motion or motion in their surroundings.

Due to know drug interactions, patients taking the following medications will be excluded.
Nortriptyline: monoamine oxidase inhibitors (MAO) such as phenelzine. Patients on oral contraceptives will be asked to use a secondary method as nortriptyline can reduce the effectiveness of oral contraceptives.
Topiramate: acetazolamide (kidney stones), digoxin

An electronic health record (EPIC) will be used for secure collection of all patient data. Questionnaires filled out by patients will be scanned into EPIC.

A sample size of 100, which nets 90 subjects into the randomized medication trial (two equal groups of 45 subjects each), yields a power of 82% to detect a difference in patient-reported effectiveness/acceptability between the nortriptyline and topiramate groups after two months of medication use. This sample size estimate assumes 60% of subjects using nortriptyline report it as effective/acceptable, in contrast to half as many subjects (or 30%) using topiramate. The power calculation is based on a two-sized Z-test with pooled variance and targeted significance level (alpha) of 0.05. The expected difference in outcome between the two groups is based on our prior research (Mikulec, 2012).

Adverse effects of the two drugs will be assessed. Specifically, the following known side effects will be asked about and recorded.
Nortriptyline: somnolence, weight gain, dry mouth, blurred vision
Topiramate: Weight loss, parasthesias, forgetfulness, nausea, diarrhea, fatigue

The subjects will be allowed to maintain therapy or taper off the drugs. It is anticipated that those that derive benefit from the drugs will choose to stay on them. All patients will have the option of remaining under our care outside of the study.

c) If the proposed study is a clinical trial where a drug, vaccine, device or other treatment is compared to a placebo group or comparison treatment group, what are the guidelines or endpoints by which early decisions regarding efficacy or lack of efficacy can be made? For example, it may be reasonable to stop enrollment on a study when efficacy has already been clearly demonstrated, to avoid unnecessary enrollments of additional subjects. Alternatively, it may be reasonable to stop enrollment when it is clear that efficacy will never be demonstrated, given the statistical power of the study as designed. Describe the guidelines that are in place to assist in making these determinations, if relevant to the proposed study.

Our clinical experience has shown that on occasion patients will refuse to take more than a few doses of nortiptyline or topiramate due to intolerable side effects. Such patients will be allowed to immediately initiate therapy with the other drug. Otherwise the physician will be in close contact with the patients and if there are any concerns or problems patients will be given the option to stop or switch treatment methods and if the PI feels necessary will recommend alternative treatment.

d) Describe how data analysis will be performed (statistical tests, methods of evaluating data) and indicate the smallest group/unit for which separate reporting will occur. For studies involving a questionnaire, if data and reliability information are available, please describe or provide

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references. For full board, unfunded studies describe sample size determination and power analysis. If none, please justify.

The core of the analysis plan includes two components: (1) nortriptyline versus topiramate comparison at two-months and (2) cross-over. In addition to measuring differences in patient-reported effectiveness/acceptability between nortriptyline versus topiramate for the first component, repeated measures ANOVA will be employed to assess change in Migraine Specific Quality of Life (MSQ) and Dizziness Handicap Inventory (DHI) between the groups. A subgroup analysis for the three subtypes of vestibular migraine will be also conducted. Descriptive statistics for subject attributes will be reported by group and assessed for potential confounding. In the second component, data from subjects who choose to try the alternate medication will be used for the cross-over analysis. This plan calls for comparing change in each subject's DHI score for their experience using nortriptyline versus topiramate. With this approach each subject serves as its own control, which helps to minimize selection bias in this component of the study. Significance will be set at the alpha level of 0.05 for both components of the analysis plan. All analyses will be coordinated by Dr. Eric Armbrecht and staff at the Saint Louis University Center for Outcomes Research, an academic unit that specializes in statistical analysis for clinical studies.

Please save frequently

e) **State if deception (including incomplete disclosure of study purpose/procedures) will be used. If so, describe the nature of the deception and provide a rationale for its use. Also, describe debriefing procedures or justify a waiver of the requirement to debrief. NOTE: for studies using deception, an alteration of consent must be justified in the Informed Consent section of the protocol (#13) and the debriefing script/statement must be uploaded in the Attachments section (#16). See IRB Deception Guidelines.**

f) **Is there an accepted standard of care and/or standard practice at SLU for the condition/disease/situation being studied? This information will assist in comparing the risk/benefit ratio of study procedures relevant to usual care that would be received outside of the research context. *?HELP?*** Y

If yes, please describe the standard of care and standard practice at SLU for the condition/disease/situation being studied.

Nortriptyline and topiramate are standard of care for vestibular migraine. We are trying to assess comparative efficacy.

g) **Does this study involve any diagnostic imaging, labwork or genetic testing that could result in clinical discovery (diagnoses, genetic mutations, etc.)? Note that this could include discovery that is expected (related to the research) or incidental (not related to research aims, but possible, like a mass/shadow found in imaging despite not looking for it).** N

If yes, please describe and include whether there are plans to share findings with study participants.

h) **Is this study subject to the NIH Genomic Data Sharing Policy?** N

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The NIH GDS policy applies to all NIH-funded research that generates large-scale human genomic data as well as the use of these data for subsequent research and includes: genome-wide association studies (GWAS), single nucleotide polymorphisms (SNP) arrays, and genome sequence, transcriptomic, metagenomics, epigenomic and gene expression data, irrespective of NIH funding mechanism. Click here for more specific examples.

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* * * Radioisotopes or Radiation Machines * * *

You have not selected the Radioisotopes option in the General Checklist. If you would like to add Radioisotopes information, please select the option to enable this section.

4. Radioisotopes or Radiation Machines

In this section, investigators must enter all radiation usage associated with the protocol.

Important: Protocols that involve non-standard of care radioactive materials (which includes the terms "radioisotopes", "radionuclides", "radiopharmaceuticals", and "nuclear medicine studies", e.g., "PET", "MUGA", "Zevalin", and/or specific radionuclides such as "F-18", "Tc-99m", "Th-201", "I-131", "Ra-233", "Y-90", etc.) will receive review by the Radiation Safety Officer (RSO) and/or Radiation Safety Committee (RSC). In these cases, submission to the RSO/RSC should occur first, even before submission to IRB. For more information on how to submit for radiation safety review, see RSC instructions or contact the Radiation Safety Officer at 977-6895.

(1) It is the responsibility of the PI to assure the accuracy and completeness of the data submitted in this section, consistent with guidelines provided below. (2) For projects requiring radiation procedures, please refer to this guidance.

a) **If applicable, list and quantify the radiographic diagnostic and therapeutic procedures associated with this protocol by clicking "Add" and adding to Table 1 below. (Includes X-ray, fluoroscopy, CT, radioactive materials, nuclear medicine, PET-CT, radiation oncology, accelerator, Cyber Knife procedures, etc.)**

b) **Total estimated research radiation dose * :** _____

* Calculate from the table above by adding the Effective Dose Subtotals for all procedures.

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NOTE: Informed Consent Radiation Exposure Risk Statement- The applicant must insert the appropriate Informed Consent Radiation Exposure Risk Statement template language into the SLU IRB Informed Consent, inclusive of applying the total estimated research radiation dose specified in item b) from the table above, as instructed in the SLU IRB Informed Consent Template. Contact the IRB Office at 977-7744 or irb@slu.edu with any questions.

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* * * Devices * * *

5. Devices

a) Please list in the space below all investigational devices to be used on subjects during this study.

b) Please list in the space below all FDA approved devices to be used on subjects during this study.

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* * * Drugs, Reagents, Chemicals, or Biologic Products * * *

6. Drugs, Reagents, Chemicals, Biologic Products, or Dietary Supplements, Vitamins, and Other Food Agents

Pilot	Phase I	Phase II
Phase III	Phase IV	X Not Phased

List placebo if it is considered a drug (contains more than inactive ingredients). For example, normal saline is considered a drug that should be listed, whereas placebo tablets are usually inert ingredients that do not need to be listed.

b) Please list in the space below all investigational drugs, reagents or chemicals to be administered to subjects during this study. Attach all applicable Investigator Brochures in section #16 (Attachments).

c) Please list in the space below all FDA approved drugs, reagents, chemicals to be administered to subjects during this study. Attach all applicable package inserts in section #16 (Attachments).

FDA Approved Drugs, Reagents, Chemicals, Biologic Product

Drug Name	Manufacturer	Source (e.g., Pharmacy, Sponsor, etc.)	Dosage
topiramate	Janssen Pharmaceuticals, Inc	Pharmacy	25-100 mg per day
Nortriptyline	Teva Pharmaceuticals USA Inc	pharmacy	25 - 75 mg in escalating dose to self titrate

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d) **Please list in the space below all dietary supplements, vitamins, minerals, or foods to be administered to subjects during this study.**

Please read the IND Statements.

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* * * Other Levels Of Review * * *

7. Other Levels Of Review

1. University Radiation Safety

Protocols that involve non-standard of care radioactive materials (which includes the terms "radioisotopes", "radionuclides", "radiopharmaceuticals", and "nuclear medicine studies", e.g., "PET", "MUGA", "Zevalin", and/or specific radionuclides such as "F-18", "Tc-99m", "Th-201", "I-131", "Ra-223", "Y-90", etc.) will receive review by the Radiation Safety Officer (RSO) and/or Radiation Safety Committee (RSC). For information on how to submit for radiation safety review, see RSC instructions or contact the Radiation Safety Officer at 977-6895.

X **Not Applicable**

Yes, study involves radioactive materials (per instructions, submit to RSC before IRB)

2. Institutional Biosafety

Experiments involving the deliberate transfer of Recombinant or Synthetic Nucleic Acid Molecules (e.g., Gene Transfer), or DNA or RNA derived from Recombinant or Synthetic Nucleic Acid Molecules, or Microorganisms containing Recombinant or Synthetic Nucleic Acid Molecules and/or infectious agents (including select agents and toxins as defined by CDC and/or Animal and Plant Health Inspection Service (APHIS)) into one or more human research participants must be reviewed by the SLU Biological Safety Officer. Most of these protocols also require review and approval by the SLU Institutional Biosafety Committee (IBC). Please contact the SLU Biological Safety Officer at 977-6888 for more information.

X **Not Applicable**

Yes, study requires Institutional Biosafety review

3. Pharmacy, Therapeutics, Nutrition, and Transfusion (PTNT) Committee

Saint Louis University Hospital requires that all research involving the administration of medications within the hospital (including outpatient areas such as the Emergency Department, Outpatient Center, Saint Louis University Hospital-South Campus, etc.) be reviewed and approved by the Pharmacy, Therapeutics, Nutrition, and Transfusion (PTNT) Committee and that study drugs are received, stored, prepared, and dispensed by the Hospital's Department of Pharmacy Services. Please contact the

Investigational Drug Services Clinical Pharmacist at 268-7156 or SLUH-IDS@ssmsluh.com for more information.

X **Not Applicable**

Yes, study requires PTNT review

4. Saint Louis University Hospital

All research involving Saint Louis University Hospital, including the Emergency Department, inpatient or outpatient services (including outpatient surgery at ABI and the infusion center at DOB) and medical record access, requires approval from the Saint Louis University Hospital Research Review Committee prior to study initiation. This process is designed to facilitate compliance with state and federal regulations as they pertain to research in hospitals and clinical research billing. Documents should be submitted as soon as possible, or at the latest, concurrently with IRB submission. Please contact the Research Compliance Office at 577-8113 or sluh-research@ssmhealth.com of the SLU Clinical Trials Office (CTO) at 977-6335 or clinical-trials-office@health.slu.edu for more information.

X **Not Applicable**

Yes, study requires Saint Louis University Hospital review

5. SSMSL

All research involving SSMSL locations (including Cardinal Glennon), including inpatient or outpatient services and medical record access, requires approval from the SSM STL or SSM Cardinal Glennon Research Business Review (RBR) prior to study initiation. This process is designed to facilitate compliance with state and federal regulations as they pertain to research in hospitals and clinical research billing. While researchers can begin to complete the SSM RBR form at any time, the form should not be submitted until the IRB and the CTO have approved the study. Please contact the SSMSL Office at 989-2058 or Marcy.Young@ssmhealth.com for more information.

X **Not Applicable**

Yes, study requires RBR review

6. Does this project require registration on ClinicalTrials.gov, and/or is this project subject to the NIH GCP Training Requirement? (Select "Yes" if either apply) Y

Registration may be required if any of the following apply: 1) The project meets the FDAAA definition of an "Applicable Clinical Trial", which requires registration on ClinicalTrials.gov. 2) As of January 1, 2017, a new NIH policy mandated biomedical and behavioral "Clinical Trials" to be registered on ClinicalTrials.gov. In addition, NIH policies require personnel on NIH "Clinical Trials" to take GCP training every three years. 3) Registering may be required for Journal Publication (ICMJE). Please review relevant definitions here. Contact the CTO at clinical-trials-office@slu.edu with questions about registering on ClinicalTrials.gov and refer to the training page of the IRB website for information on NIH GCP Training requirements.

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* * * Subject Population * * *

8. Subject Population - In the space below, please detail the participants that you are requesting to recruit (include description of each group requested)

a) **Expected age range of subjects. (For example ≥ 18 yrs to 90 yrs).**

18-70 years of age inclusive

b) **Number of evaluable subjects to be accrued at SLU or SLU site (this includes all sites under the direction of the SLU PI).** 100

Exceeding the number listed here is a protocol violation. Prior IRB approval is required if additional participants are to be accrued. If applicable, this number should be consistent with your power analysis described in 3d.

c) **Number of evaluable subjects to be accrued study wide. *?HELP?*** 100

d) **If including vulnerable populations (minors, pregnant women and fetuses, neonates, non-English speaking, economically or educationally disadvantaged, prisoners, adults temporarily or permanently unable to consent for themselves): 1) provide the rationale for the importance of including this population in the research, and 2) specify the measures being taken to minimize risks to potentially vulnerable subjects. Click on hyperlinks to access SLU Guidelines containing additional considerations and strategies for mitigating risks.**

n/a

e) **If women, minorities, or minors are not included, a clear compelling rationale must be provided unless not applicable. Examples for not including minors: disease does not occur in children; drug or device would interfere with normal growth and development; etc. If federally funded reference appropriate section of the sponsors protocol/grant. *?HELP?***

minors are not included in this protocol because patients will be recruited from an adult clinic and the problem is not common in children

f) **If any specifically targeted subjects are students, employees, or laboratory personnel, specify the measures being taken to minimize the risks and the chance of harm to these potentially vulnerable subjects. See SLU Guidelines for additional considerations and strategies for mitigating risks.**

g) **Describe (labeled a-c): a) who you are recruiting for this study (e.g., your patients/students/colleagues, those in existing database or registry, the general public), and b) how you are recruiting (flyers, advertisements, direct call/mailing, membership networks, in-person recruitment in clinic, classroom, public locations, etc.). For secondary data analysis or specimen studies, state how you have access to materials. Importantly: do not contact participants prior to obtaining IRB approval for your study.**

c) Also indicate whether or not you plan to obtain personal/private information or biospecimens for the purpose of screening, recruiting, or determining eligibility of prospective subjects prior to obtaining informed consent and how (obtained by communicating with prospective subjects or obtained by accessing records

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or stored biospecimens). Note: if you are accessing medical records other than those of your own patients or those in your immediate department, you will need to submit a <a href= https://www.slu.edu/research/faculty-resources/research-integrity-safety/institutional-review-board-irb/irb_assets/prep_to_research_form.doc target=_blank>HIPAA Preparatory to Research form and submit to the SLU Privacy Officer PRIOR to accessing records.

Please refer to the <a href=https://www.slu.edu/research/faculty-resources/research-integrity-safety/institutional-review-board-irb/irb_assets/guidelines_subject_recruitment.doc target=_blank>SLU IRB Recruitment Guidelines when designing recruitment strategies and upload recruitment materials to the Attachments page for IRB review. You are expected to obtain permission for individuals/organizations that assist with recruitment, and whenever possible, those assisting should share your materials with potential participants on your behalf rather than providing you with private contact information.

Patients will be selected from the busy clinical practices of Drs. Mikulec and other reserach team members. Combined, they currently see approximately five new patients with vestibular migraine per week. In addition, print advertisements in a local newspaper will be used to advertise the study. The study coordinator Melissa McConnell will screen by phone patients responding to the advertisements.

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* * * Subject Population * * *

8. Subject Population (continued)

Page numbers from a sponsor's protocol/grant may be referenced in 8h.

h) Inclusion and Exclusion Criteria.

Identify inclusion criteria.

Men and women aged 18 to 70 with untreated vestibular migraine variant as diagnosed by history.

Identify exclusion criteria.

Patients with allergies to nortriptyline or topiramate and their analogs or medication interactions that preclude their use. Patients under the care of a psychiatrist. Patients who are pregnant or trying to become pregnant. Patients taking more than 5 prescription medications. Patients with cancer. Patient has a history of immunodeficiency. Patient has a history of substance abuse within the preceding 6 months prior to screening. Patient has used an investigational drug or device in the the 3 months prior to screening. Patient is using marijuana for medical or other uses. Patient has any other clinically significant illness or medical condition that, in the investigator's opinion, would prohibit the subject from participating in the study. Patient with traumatic brain injury.

Due to know drug interactions, patients taking the following medications will be excluded.
Nortriptyline: monoamine oxidase inhibitors (MAO) such as phenelzine. Patients on oral contraceptives will be asked to use a secondary method as nortriptyline can reduce the effectiveness of oral contraceptives.
Topiramate: acetazolamide (kidney stones), digoxin

Exclude subjects with liver dysfunction, kidney dysfunction and glaucoma (per the risks associated with topiramate).

i) Compensation. Explain the amount and schedule of compensation, if any, that will be paid for participation in the study. Include provisions for prorating payment.

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$60 will be paid to each patient per visit that they participate in the research study. Checks will be sent monthly after each visit. Costs of the medication is standard of care. The subject will be responsible for picking up and paying for the medication at their preferred pharmacy.

j) **Describe who will cover study related costs. Explain any costs that will be charged to the subject.**

Association for Migraine Disorders has funded the study and will cover all costs.

k) **Estimate the probable duration of the entire study including data analysis and publication. This estimate should include the total time each subject is to be involved and the duration the data about the subject is to be collected. If the study is Investigator-initiated, a timeline for individual subject recruitment, follow-up, total time for subject accrual, and data analysis for the study is required.**

Patients are expected to participate for a maximum of 5 months, the study will be active with recruitement and follow-up to meet enrollment criteria for approximately 2 years.

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* * * Risks * * *

9. Risks

There is no research that can be considered totally risk free (e.g., a potential risk of breach of confidentiality). Therefore, when describing the risk, the lowest level of risk is "no more than minimal risk".

Page numbers from a sponsor's protocol/grant may be referenced in 9.1, 9.2, 9.3, and 9.4.

1. **Use of investigational devices. Please include the clinical adverse events (AEs) associated with each of the devices with an indication of frequency, severity and reversibility. This information can often be found in the Investigator(s) brochure. NOTE: Include any likely adverse effects associated with procedures that subjects may experience while in the study.**

2. **Use of investigational drugs. Please include the clinical AEs associated with each of the drugs with an indication of frequency, severity and reversibility. This information can often be found in the Investigator(s) brochure. NOTE: Include any likely adverse effects associated with placebos or washout periods that subjects may experience while in the study.**

3. **Use of FDA approved drugs, reagents, chemicals, or biologic products. Please include the clinical AEs associated with each of the drugs with an indication of frequency, severity and reversibility. This information can often be found in the package insert provided by the manufacturer. NOTE: Include any likely adverse effects associated with placebos or washout periods that subjects may experience while in the study.**

Nortriptyline: Possible adverse reactions

Cardiovascular - Hypotension, hypertension, tachycardia, palpitation, myocardial infarction,

arrhythmias,
heart block, stroke.
Psychiatric - Confusional states (especially in the elderly) with hallucinations, disorientation, delusions; anxiety, restlessness, agitation; insomnia, panic, nightmares; hypomania; exacerbation of psychosis.
Neurologic - Numbness, tingling, paresthesias of extremities; incoordination, ataxia, tremors; peripheral neuropathy; extrapyramidal symptoms; seizures, alteration in EEG patterns; tinnitus.
Anticholinergic - Dry mouth and, rarely, associated sublingual adenitis; blurred vision, disturbance of accommodation, mydriasis; constipation, paralytic ileus; urinary retention, delayed micturition, dilation of the urinary tract.
Allergic - Skin rash, petechiae, urticaria, itching, photosensitization (avoid excessive exposure to sunlight); edema (general or of face and tongue), drug fever, cross-sensitivity with other tricyclic drugs.
Hematologic - Bone marrow depression, including agranulocytosis; eosinophilia; purpura; thrombocytopenia.
Gastrointestinal - Nausea and vomiting, anorexia, epigastric distress, diarrhea, peculiar taste, stomatitis,
abdominal cramps, black-tongue.
Endocrine - Gynecomastia in the male, breast enlargement and galactorrhea in the female; increased or decreased libido, impotence; testicular swelling; elevation or depression of blood sugar levels; syndrome of inappropriate ADH (antidiuretic hormone) secretion.
Other - Jaundice (simulating obstructive), altered liver function; weight gain or loss; perspiration; Suicide
Serotonin Syndrome (>>>>>>)

Topiramate: Possible adverse reactions

oral contraceptive pills may have reduced efficacy when used with topiramate

paresthesia (35-50%) and taste perversion (10-15%)

Acute Myopia and Secondary Angle Closure Glaucoma, Visual Field Defects, Oligohidrosis and Hyperthermia, Metabolic Acidosis, Suicidal Behavior and Ideation, Cognitive/Neuropsychiatric Adverse Reactions (including cognitive dysfunction, psychiatric/behavioral disturbances and somnolence/fatigue), Hyperammonemia and Encephalopathy, Kidney Stones. Additionally, the adverse effects section in the package insert Table 10 (incidence of 2-5%) includes fatigue, hypoesthesia, language problems, nausea, diarrhea, decreased weight, arthralgia anorexia, somnolence, difficulty with memory, difficulty with concentration/attention.

Patients will be asked to wean off of drug over the course of one week if they have been on the drug more than a week. Specific issues we will watch for include:
Nortriptyline: At the low dosages used in this study, abrupt withdrawal has not been shown to be harmful.
Topiramate: Acute myopia due to secondary angle closure glaucoma has been rarely reported in acute withdrawal.

4. **Use of FDA approved devices. Please include the clinical adverse events (AEs) associated with each of the devices with an indication of frequency, severity and reversibility. This information can often be found in the Investigator(s) brochure. NOTE: Include any likely adverse effects associated with procedures that subjects may experience while in the study.**

5. **Describe any risks related to performing study procedures. Please include all investigational, non-**

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investigational, and non-invasive procedures (e.g., surgery, blood draws, treadmill tests).

n/a

6. **Describe any risks related to the use of radioisotopes/radiation-producing machines (e.g., X-rays, CT scans, fluoroscopy).**

7. **Describe why this investigational compound/drug/device/procedure's risks/benefits are potentially better than standard of care or other common alternatives. Any standard treatment that is being withheld must be disclosed and the information must be included in the consent form. *?HELP?***

This drug is standard of care so the risks/benefits are identical to that of standard of care.

8. **Describe any psychological, social, or legal risks the subject may experience. *?HELP?***

Risk of Questionnaires:

Some questions on the questionnaires may make patients feel uncomfortable, they may not answer any question they do not feel comfortable answering

Loss of Confidentiality

Page numbers from a sponsor's protocol/grant may be referenced in 9.9 and 9.10.

9. **Special Precautions. Describe the planned procedures for protecting against or minimizing potential risks. If appropriate, include the standards for termination of the participation of the individual subject. Discuss plans for ensuring necessary medical or professional intervention in the event of adverse effects to the subjects.**

Patients will be closely followed while they are on study and can stop or change medications if they do not like the medications effects that they are on. You will be given the Columbia Suicide Severity Rating Scale at each appointment to evaluate any changes in mood and behavior related to suicidal thoughts. Dr. Mikulec will be available to evaluate and treat or refer to a specialist for any adverse reactions.

10. **Reproductive Risks.**

a. **Please list the pregnancy category of any drugs or N/A.**

D

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b. **Please describe any reproductive risk associated with any part of the research study. Include any data from other studies (animal or human).**

If patients are pregnant, or become pregnant, they cannot take part in this research study. It is important that they let the research study doctor know if they are breast-feeding. If patients are pregnant or think they are pregnant, it is important for them to let the investigator know immediately.

If patients are sexually active during their participation in the research, they will use effective measures (chosen in consultation with their health care provider) to avoid becoming pregnant.

TOPAMAX (topiramate) can cause fetal harm when administered to a pregnant woman. Data from pregnancy registries indicate that infants exposed to topiramate in utero have an increased risk for cleft lip and/or cleft palate (oral clefts).

Nortriptyline is category D (from Pregnancy and Lactation text book - there is not a manufacturer designation). Information from the PI states "Safe use of nortriptyline hydrochloride during pregnancy and lactation has not been established; therefore, when the drug is administered to pregnant patients, nursing mothers, or women of childbearing potential, the potential benefits must be weighed against the possible hazards. Animal reproduction studies have yielded inconclusive results. Information from the above cited text states possible cardiovascular anomalies.

11. Data Safety Monitoring

Federal regulations require that when appropriate, the research protocol makes adequate provisions for monitoring the data to ensure the safety of participants. Monitoring should be commensurate with risks and with the size and complexity of the research, and could range from no plan needed to an independent data safety monitoring board. Please refer to SLU Guidelines for Data and Safety Monitoring as you complete the questions below.

a. Is there a Data Monitoring Committee (DMC) or Board (DSMB)? N

If yes, please provide the following information (labeled a-g): a) the composition of the board (degrees/qualifications of members), b) whether the board is independent from the sponsor and research team or not, c) frequency of meetings and issuance of reports to sites, d) assurance that the board is reviewing aggregate safety data and making recommendations regarding study continuance, e) provisions for ad hoc meetings if needed, f) who is reviewing SAEs in real time (MD or DO), and g) stopping/halting rules (if any exist).
A DSM charter can be referenced for all items except for "f) who is reviewing SAEs in real time."

If no, please justify why not.

Treatment is standard of care

b. Is there a Data Safety Monitoring Plan (DSMP)? N

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Note, if all relevant plan information is included in DSMB question above, select 'Yes' and state "see above" in the answer box.

If yes, provide details (labeled a-e) including: a) what types of data or events are captured and how are they documented, b) who is monitoring data, their independence/affiliation with the research and their degrees/qualifications, c) frequency of aggregate data review, d) who is reviewing SAEs in real time (MD or DO), and e) stopping/halting rules (if any exist).

If no, please justify why not.

Treatment is standard of care.

12. In case of international research (research outside of the U.S. or research on international populations (non-U.S.)), describe qualifications/preparations that enable you to evaluate cultural appropriateness and estimate/minimize risks to subjects. Include whether research is sensitive given cultural norms.

a. State any local laws/regulations governing Human Subjects Research in the country(ies) you will conduct the research and attach any relevant approvals. If none, state N/A.

b. Will there be language barriers and if so, how will they be addressed?

Note: If materials are to be distributed to subjects in their native language, please follow SLU's Guidance For Studies Involving Non-English Speaking Subjects.

NOTE: Export control laws include the transfer of technical information and data, as well as information and technology to foreign nationals. If this study has international components, contact the SLU Export Control Officer for direction on whether export control policies apply.

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* * * Benefits/Alternatives, Procedures to Maintain Confidentiality and Privacy * * *

10. Benefits/Alternatives

a) Benefits. Describe the potential benefit(s) to be gained by the subjects and how the results of the study may benefit future subjects and/or society in general. Indicate if there is no direct benefit to the participants.

Patients may or may not benefit from this study. Future patients with vestibular migraines may benefit from the knowledge obtained from this study.

b) Alternatives. Describe any alternative treatments and procedures available to the subjects should they choose not to participate in the study. If no such alternatives exist, please state that the alternative is nonparticipation. For some studies, such as record reviews, a description of alternatives would not be applicable.

The alternative is not participating.

both topiramate and nortriptyline are available and readily prescribed outside of this protocol.

11. Procedures to Maintain Confidentiality and Privacy

Federal regulations require that research materials be kept for a minimum of three (3) years and HIPAA documents be kept for a minimum of six (6) years after the closure of the study. For FDA-regulated or sponsored projects, the PI may be required to keep the data and documents for a longer time period.

Confidentiality

To determine whether adequate provisions for confidentiality of data are in place, the IRB must ensure that research materials are stored in appropriate locations throughout the study (during collection, transport/transmission, analysis and long term storage). Research information must be protected using appropriate safeguards based on identifiability of the data and risk associated with the study (See SLU IRB Confidentiality Guidelines).

For the questions below, please use the following definitions:

Anonymous/De-identified: data contain no identifiers, including code numbers that investigators can link to individual identities;

Coded: data in which (1) identifying information, such as name or social security number, has been replaced with a number, letter, symbol, or combination thereof (i.e., the code), and (2) a key to decipher the code exists enabling linkage of data to identifying information (e.g., a master list), and (3) the key (master list) is kept separately from coded data; AND/OR

Identifiable: data that includes personal identifiers (e.g., name, social security number), such that information could be readily connected to respective individuals.

a) Electronic (Computer) Data

Click "Add" to enter data security information for each type of electronic data that will be created in the study: anonymous/de-identified, coded, and/or identifiable (see definitions above).

To properly address this question, there should only be one listing of each type of data in the table. Depending on your project, you could have up to three types of data. See the SLU ITS Sensitive Data Guide for acceptable data security methods.

Not Applicable, No Electronic (Computer) Data

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X Study IRB-approved Prior to New Question (Question N/A- Grandfathered)

b) Hardcopy (Paper) Data

Click "Add" to enter information for each type of hardcopy (paper) data that will be created in the study: anonymous/de-identified, coded, and/or identifiable (see definitions above).

To properly address this question, there should only be one listing of each type of data in the table. Depending on your project, you could have up to three types of data.

Not Applicable, No Hardcopy (Paper) Data

X Study IRB-approved Prior to New Question (Question N/A- Grandfathered)

c) If a master list is used in this study (linking study codes to subject identifiers), explain: a) how and where you will secure the master list, b) how long it will be kept/when it will be destroyed, and c) provide a sample of the code.

All data will be coded data stored for research purposes will be coded with a master list kept separately on a secure network, all hard copy data will be kept in a locked file cabinet in a locked office and coded, with a master list kept separately.

The coded master list will be destroyed as soon as data collection is complete.

d) If data or specimens are being shared outside of the research team, indicate who will receive the material, specifically what they will receive (data or specimens), and if an agreement has been signed to cover the transfer. Note: unless covered under a Clinical Trial or other agreement, the transfer of data or specimens to an external entity will require an agreement. For the transfer of materials (specimens), a Materials Transfer Agreement (MTA) is used; for the transfer of data, a Data Use or Data Transfer Agreement is used. Please contact the Research Innovation Group at 314-925-3027 for assistance.

Association of Migraine Disorders is a recipient of data, but this organization will only have access to aggregate data.

e) If samples or data will be provided to SLU from an outside source, indicate whether you will have access to identifiers, and if so, how identifiable information is protected. Note: unless covered under another agreement (e.g., Clinical Trial Agreement or subcontract), the transfer of data or specimens from an external entity to SLU may require an agreement. For the transfer of materials (specimens), a Materials Transfer Agreement (MTA) may be required; for the transfer of data, a Data Use or Data Transfer Agreement may be required. Please contact the Research Innovation Group at 314-925-3027 for assistance.

n/a

f) If data will be collected via e-mail or the Internet, how will anonymity or confidentiality be affected? Describe how data will be recorded (i.e., will internet protocol (IP) addresses and/or e-mail addresses be removed from data?).

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g) If you will be audio/video recording or photographing subjects, provide a rationale as voiceprints and images of faces/unique body markings are considered identifiers. Describe confidentiality procedures, including any restricted access to images and/or the final disposition of the recordings/photos (destruction, archiving, etc.).

h) Describe any study-specific (non standard of care) information or documentation that will be put in the participants' medical records for this research (e.g., study visit notes, lab results, etc.). If none, state "not applicable". NOTE: documentation of research in Epic should be done in accordance with the SLUCare Epic Research Charting Policy and Clinical Workflow: Documenting Research Encounters in Epic.

not applicable

i) Are there any information security requirements identified in the project's RFP/Award Notice/Contract? This could include data security, technical safeguards, security controls, NIST, FISMA, CFR, etc. N

If yes, SLU ITS approval is required. Contact InfoSecurityTeam@slu.edu to start the approval process.

Privacy

Privacy refers to persons having control over the sharing of oneself with others.

j) Please indicate how participant privacy will be protected in this study (select all that apply):

X Discussion of health related and/or personal information in a private room/area

X Research interactions/interventions are conducted in a private room/area

Use of drapes or other privacy measures

Collection of sensitive/identifiable information is limited to the minimum necessary to achieve the aims of the research

X Access to study information is limited to the minimum amount of persons necessary to achieve the aims of the research (e.g., access restricted to research team members only)

Consideration of parental inclusion/absence for studies involving minors

Other (please explain):

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* * * Potential Conflict of Interest * * *

12. Potential Conflict of Interest

Indicate whether you, your spouse or dependent children, have, or anticipate having, any income from or financial interest in a sponsor, device or drug manufacturer of this protocol, or a company that owns/licenses the technology being studied. Please remember that you are responding for you and any other investigator participating in the study. Financial Interest includes but is not limited to: consulting; speaking or other fees; honoraria; gifts; licensing revenues; equity interests (including stock, stock options, warrants, partnership and other equitable ownership interests). For questions regarding Conflict of Interest consult the Conflict of Interest in Research Policy.

Check one of the following (please remember that you are responding for yourself, your spouse, dependent children and any investigator, investigator's spouse and dependent children participating in the study):

1) X No equity interest and/or Financial Interest less than or equal to $5K
2) Any equity interest and/or Financial Interest exceeding $5K but not exceeding $25K in the past year or expected in the current year
3) Financial Interest exceeding $25K in the past year or expected in the current year

Check all those that apply:

Consulting
Speaking Fees or Honoraria
Gifts
Licensing agreement or royalty income
Equity interests, (including stock, stock options, warrants, partnership or equitable ownership interests), or serving on a scientific advisory board or board of directors
Other fees/compensation

If you have marked #2 or #3, please contact coi@slu.edu to initiate review of this study and provide the following information:

1. A Conflict of Interest Management Plan.
   has been approved for all investigators for this study
   is pending
   has not been initiated

2. Describe who has, and briefly explain, the conflict of interest and indicate specific amounts for each subcategory checked:

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Note to Investigator(s) Reporting a Potential Conflict of Interest

Investigator(s) must have:

1. Current, up-to-date Conflict of Interest Disclosure Form on file with the SLU Conflict of Interest in Research Committee (COIRC) that describes any financial relationship indicated above.

   . This information must be disclosed on the SLU confidential Conflict of Interest Disclosure Form and reviewed by the COIRC before accruing research subjects in this study. If your current Disclosure Form does not contain this information, you are required to submit an updated Disclosure Form to the COIRC.

2. You may not begin your study until your disclosure form has been reviewed and any required management plan has been approved by the COIRC for this study. To initiate COIRC review of your study, please contact coi@slu.edu.

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* * * Informed Consent * * *

13. Informed Consent

Federal regulations require that informed consent be obtained from individuals prior to their participation in research unless the IRB grants a waiver of consent. Answer the questions, below, then click Add to provide the necessary consent documents and information regarding subject consent. Multiple consents/waivers may be added, but they must be uploaded one at a time.

NOTE: You may refer to the SLU IRB Guidance for Obtaining Informed Consent for considerations regarding the consent/assent process.

State N/A if not applicable.

1) **How is consent being obtained? When and where will the discussion take place? If the study involves a Non-English Speaking participant/population, please include details about plans for translated consent materials and interpreters to be used (see SLU Guidelines for Involving Non-English Speaking Subjects for more details).**

patients will be consented at a regular standard of care office visit prior to be placed on a medication for vestibular migraines. Patients will be consented prior to enrollment in the study which may be before or after they have tried diet modifications

2) **If the study involves adults unable to consent for themselves (whether diminished capacity to consent is temporary, permanent, progressive or fluctuating), please address the following: a) how is capacity to provide consent being assessed (initially and throughout study, if applicable); b) if unable to provide consent, how is LAR being determined (See SLU LAR Guidelines); c) if unable to provide consent, will assent be obtained and if not, why not?; d) if unable to provide assent, will dissent be honored and if not, why not? Note: participants initially unable to provide consent for themselves are**

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expected to be given an opportunity to provide consent once capacity is gained. See SLU Guidelines for Adults Unable to Provide Consent for additional detail.

n/a

Note: Any assent documents which will be used per the Adults Unable to Provide Consent guidance, should be appropriately named and uploaded using the Add button and the Consent drop down menu selection.

Informed Consent

Title	Consent Type	Attached Date
Approved_CR2019_Consent Version 5	Consent	03/11/2019

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* * * Assent * * *

14. Assent

Complete this section if your study includes minors. The Assent Form Template provides guidelines for writing assent documents.

1. Will minors be asked to give assent, then consent once they reach adulthood? If not, please justify. If not capable to provide assent initially, please address whether assent will be obtained as the minor gains capacity. Note: children who reach the age of adulthood during participation should be given the opportunity to provide consent as parent/guardian consent no longer applies. If obtaining consent would be impracticable (e.g., this is a registry with data/specimen obtained long ago), a waiver of consent should be added for IRB review. See SLU Guidelines for Research Involving Minors for additional detail.

2. If minors are asked to assent and do not wish to participate, will they still be accrued in the study? If yes, justify.

3. How will the minor's ability to give assent be assessed? (Consider the age and maturity of the minors as well as their physical or mental condition). If capacity is fluctuating, please explain how capacity will be assessed throughout the study.

Note: For studies that require a discussion about reproductive risks, note that the conversation with the minor should take place separately from the parents. Also, if a minor will reach adulthood (18 in Missouri) during the course of the study, they will need to be asked to consent as an adult at that time to continue in the study.

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* * * HIPAA * * *

15. HIPAA

Studies that access, receive or collect protected health information (PHI) are subject to HIPAA regulations. PHI is health information with one or more personal identifiers. For more information visit the IRB HIPAA page or refer to the SLU IRB HIPAA Guidance.

1. Will health information be accessed, received or collected?

No health information. HIPAA does not apply.

X Yes (continue to question 2).

2. Which personal identifiers will be received or collected/recorded?

No identifiers. I certify that no identifiers from the list below will be received or collected and linked to health information. (Skip remainder of page).

Limited identifiers will be received or collected/recorded (study will likely require a data use agreement). Select Data Use Agreement- INTERNAL or Data Use Agreement- EXTERNAL as appropriate, below.

City/State/Zip codes

Person-specific dates (e.g., date of birth, dates of service, admission/discharge dates, etc.)

Age (if subjects are 90+ years)

At least one direct identifier will be received or collected/recorded.

X Names

X Social Security numbers

X Telephone numbers

X Linkable code or any other unique identifying number (note this does not mean the unique code assigned by the Investigator(s) to code the research data)

X All geographic subdivisions smaller than a State, including street address, city, county, precinct, zip code, and their equivalent geocodes, except for the initial three digits of a zip code, if, according to the current publicly available data from the Bureau of the Census: (1) The geographic unit formed by combining all zip codes with the same three initial digits contains more than 20,000 people; and (2) The initial three digits of a zip code for all such geographic units containing 20,000 or fewer people is changed to 000

X All elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death; and all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older

Fax numbers

Electronic mail addresses

X Medical record numbers

Health plan beneficiary numbers

Account numbers

Certificate/license numbers

Vehicle identifiers and serial numbers, including license plate numbers

Device identifiers and serial numbers

Web Universal Resource Locations (URLs)
Internet Protocol (IP) address numbers
Biometric identifiers, including finger and voice prints
Full face photographic images and any comparable images

If you are receiving or collecting/recording health information and at least one personal identifier, please continue to complete the sections, below.

3. Sources of Protected Health Information:

X Hospital/medical records for in or out patients
X Physician/clinic records
Laboratory, pathology and/or radiology results
Biological samples
X Interviews or questionnaires/health histories
Mental health records
Data previously collected for research purposes
Billing records
Other
Please describe:

4. If data will be shared outside the research team and the study involves PHI indicate how the research team will share the information.

X Not applicable (continue to question 5).
Only linkable code that can link data to the identity of the subject. A code access agreement or business associate agreement may be needed when data are shared with other non-SLU entities. If necessary, the agreement can be added and uploaded in item #5, below.
Limited identifiers: Zip codes, dates of birth, or other dates only. The study qualifies as a Limited Data Set. A data use agreement may be needed when data are shared with other non-SLU entities. If necessary, the agreement can be added and uploaded in item #5, below, using DUA-external option.
With unlimited identifiers. The consent document and HIPAA Authorization form must describe how the information will be disclosed.

5. HIPAA Documentation is required for this study. Use the table below to add HIPAA Documents for your study.

HIPAA Documents

HIPAA Documents	Title	Attached Date
HIPAA Authorization	Approved_HIPAA Version 3	05/13/2014

Protocol Title: A Prospective randomized cross-over trial of nortriptyline and topiramate in the initial treatment of vestibular migraine

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* * * Attachments * * *

16. Attachments

In this section, please upload additional documents associated with your protocol. Failure to attach files associated with the protocol may result in the protocol being returned to you.

Possible documents for this protocol could include:

- **Bibliography**
- **Cooperating Institution's IRB Approval**
- **Data Collection Sheet**
- **Debriefing Script**
- **Device Information/Documentation**
- **Grant Proposal/Sub-Contract**
- **Human Subjects Training Certificate/Proof of Training**
- **Information Sheet/Brochure**
- **Interview/Focus Group Questions**
- **Investigator's Brochure**
- **Letter of Agreement/Cooperation**
- **IND Application Letter**
- **Package Insert**
- **Patient Diary Form**
- **Questionnaire/Survey**
- **Recruitment Material (e.g., flyers, ads, e-mail text)**
- **Safety Information (DSM Information)**
- **Scientific/PPC Review or Department Chair Review**
- **Sponsor's Protocol**
- **Sponsor's Protocol Amendment**
- **Study Design Chart/Table**
- **Other files associated with the protocol (most standard formats accepted: pdf, jpg, tiff, mp3, wmv, etc.)**

To update or revise any attachments, please delete the existing attachment and upload the revised document to replace it.

Document Type	Document Name	Attached Date	Submitted Date
Package Insert	topamax insert	03/13/2014	03/16/2014
Package Insert	nortriptyline insert	03/13/2014	03/16/2014

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Grant Proposal/Sub-Contract	Mikulec Grant Application	03/20/2014	04/29/2014
Study Design Chart/Table	flow chart	04/29/2014	04/29/2014
Questionnaire/Survey	Approved_C-SSRS_1_14_09_Baseline (1)	04/29/2014	04/29/2014
Questionnaire/Survey	Approved_C-SSRS_1-14-09-Since_Last_Visit_Clinical (3)	04/29/2014	04/29/2014
Other	Approved_Diet handout	05/13/2014	05/13/2014
Questionnaire/Survey	Approved_Dizziness Questionnaire	05/13/2014	05/13/2014
Questionnaire/Survey	Approved_Intake questionnaire	05/13/2014	05/13/2014
Questionnaire/Survey	Approved_Migraine Symptom Questionnaire V 2.1	05/13/2014	05/13/2014
Questionnaire/Survey	Approved_DHI	05/13/2014	05/13/2014
Questionnaire/Survey	Approved_C-SSRS_1_14_09_Baseline (1)_	05/13/2014	05/13/2014
Questionnaire/Survey	Approved_C-SSRS_1-14-09-Since_Last_Visit_Clinical (3)_	05/13/2014	05/13/2014
Recruitment Material (e.g., flyers, ads, e-mail text)	Approved_5-7-14 Dizzy ad Final	05/13/2014	05/13/2014
Phone Script	Approved_Phone script for migraine follow-up	12/23/2015	12/23/2015
Grant Proposal/Sub-Contract	No-Cost_Extension__APPROVAL_8.01.16-7.31.18	02/06/2017	02/08/2017
