## I. OVERVIEW

About 20% of adults faint recurrently. These patients are often highly symptomatic, have problems with employment and driving, and have reduced quality of life. There are no therapies that have withstood the test of adequately designed and conducted randomized clinical trials. We will conduct a prospective, randomized, parallel, double-blind, proof-of-concept study to test the hypothesis that norepinephrine transporter inhibition (with atomoxetine) prevents tilt-induced vasovagal syncope (VVS)/pre-syncope in patients with clinical VVS. A total of 64 patients with quantitative clinical diagnostic criteria for VVS and at least 1 syncopal spell in the preceding year will be randomized in a double blind acute phase 2 study to atomoxetine 40mg PO BID x 2 doses or matching placebo. The endpoint will be the onset of presyncope or syncope on tilt testing associated with diagnostic hemodynamic changes. These data should provide useful preliminary data as a foundation on which to conduct a subsequent randomized clinical trial.

## II. BACKGROUND

**2.1. Syncope Natural History:** VVS is a common and frequently distressing problem. About 40% of people faint at least once in their life, and at least 20% of adults faint more than once[1, 2]. It usually first presents in adolescence and early adulthood, and the predilection to fainting is lifelong. [1-4] Most patients seen in referral clinics have fainted repeatedly; in the University of Calgary Syncope Clinic, the median number of faints is 10-15, over a median duration of 15-20 years. In the 1st and 2nd Prevention of Syncope Trials (POST [5] and POST2 [6]) the median number of syncopal spells in the preceding year was 4. Many patients have frequent presyncopal spells. ***Although most syncope patients do not require lifetime therapy, some do merit treatment that lasts from months to years***.

**2.2. Syncope Severity and Quality of Life***:* VVS carries a surprisingly high clinical burden. About 18% of syncope patients have trauma associated with syncope ranging from bruises through fractures to head injuries. Patients with frequent syncope have a markedly reduced quality of life, similar to that of patients with severe rheumatoid arthritis or chronic low back pain[7-9]. Patients with syncope have a reduced quality of life that is related to the frequency of syncope. Quality of life is substantially impaired in all dimensions of health, and particularly in terms of mobility, usual activities, and self care[7-9].

**2.3. Impact on Health Care System:** Most patients with syncope with otherwise unknown cause in the community, and about 43% of syncope patients who present to emergency rooms in North American and Europe have VVS. In the United States about $2.4 billion is spent yearly in hospitals caring for patients with syncope[10]. In the Netherlands population 0-65 years old there are 3.8 and 8.5 visits for syncope per 1000 person years to family doctors for males and females, respectively[3]. In Canada we estimate about 418,000 visits yearly to family physicians for syncope, and about 39,000 to 100,000 visits yearly to the emergency room, for a total of at least 457,000 visits for care of syncope annually.

**2.4. Current Treatments:** VVS is characterized by paroxysmal, reflex-mediated hypotension and bradycardia. Serotonin, opiate, and beta-adrenergic receptors might mediate integration of this reflex response. Bradycardia is caused by increased vagal tone and hypotension is caused by withdrawal of alpha-adrenergic tone to venous and resistance vessels.

*2.4.1. Diet and physical manoeuvres:* Many syncope patients are encouraged to increase their salt and fluid intake, although the evidence is weak and comes mainly from tilt test studies[11]. The usual reported dose of salt tablets is 6-9 gm (100-150 mmol) per day. There is limited evidence supporting the use of exercise training to prevent syncope [12], but a very underpowered randomized study did not detect a reduction in the likelihood of syncope in exercised patients[13]. Considerable evidence supports the use of physical counterpressure manoeuvres (PCM), which are squats or isometric contractions of the legs. The Physical Counterpressure Manoeuvres Trial (PC Trial) was a randomized controlled trial that showed some benefit compared to conventional therapy [14]. However, fully 35% of patients had insufficient prodrome to perform the techniques, and the effect size in the PC Trial is about the same as the placebo effect size in general.

*2.4.2. Beta blockers:* There have been 5 randomized clinical trials of the efficacy or effectiveness of β-adrenergic blockers for the prevention of syncope[15]. On the whole they were negative. We reported the results of POST in 2006[5]. It was the pivotal randomized, placebo-controlled, double-blind trial, and assessed the effects of metoprolol in VVS over a 1 year treatment period. A total of 208 patients were randomized to metoprolol or placebo. Metoprolol provided no benefit, with nearly identical outcome rates in both study arms. More recently, we reported a small meta-analysis that showed a 50% risk reduction with beta blockers in patients >42 years old.

*2.4.3. Fludrocortisone:* Fludrocortisone is a corticosteroid with mainly mineralocorticoid activity resulting in sodium and water retention and potassium excretion, which should increase blood volume. To assess its effectiveness in adults we conducted POST2), a multinational, randomized, placebo-controlled clinical trial[6]. A total of 209 patients with recurrent VVS received either fludrocortisone or placebo for 1 year; the primary outcome is the proportion of patients with at least one syncope recurrence. There was only a trend to benefit, with a 30% relative risk reduction (p=0.07)

*2.4.4. Serotonin reuptake inhibitors:* Central serotonin levels might contribute to VVS. A randomized, double blind, placebo-controlled study of 68 consecutive patients who had not responded to other treatments was reported to be positive[16] but this could not be reproduced in two further studies [17]. [18]

*2.4.5. Permanent pacemakers:* Permanent pacemakers do not benefit the majority of patients with VVS, although those over 40 years of age with documented asystolic pauses during syncope do benefit from pacing. The strategy of first screening with an implanted loop recorder, then inserting a permanent pacemaker if indicated, will only benefit 3-10% of older patients.

*2.4.6. Midodrine* is a pro-drug whose active metabolite is effective in preventing orthostatic hypotension secondary to autonomic failure. Midodrine prevents orthostatic hypotension in patients with autonomic failure[19, 20]. Whether it is effective in VVS is not established conclusively. It was beneficial in 4 small and inadequately designed clinical trials[21] [22] [23], and is now the subject of the POST 4: Assessment of Midodrine in the Prevention of Vasovagal Syncope [24].

**2.5. Norepinephrine and VVS:** Numerous early studies suggested that the hypotension accompanying VVS is due to an abrupt withdrawal of sympathetic traffic, resulting in vasodilatation and a reduction in peripheral resistance[25-27]. However this has been challenged repeatedly [28-30]. We reported a failure of venoconstriction during mental stress in syncope patients but not control subjects [31], and two groups have recently

reported that the principle hemodynamic change leading up to presyncope on tilt tests is peripheral venous pooling and a reduction in cardiac output in the face of unchanged peripheral resistance, implying a reduction in venous return[32, 33]. Therefore the hypotension of VVS might be due to a failure of venoconstriction, vasoconstriction, or both. We will address this as a substudy of this proposed phase 2 trial.

***2.6.1. Norepinephrine Transporter Dysregulation in VVS:*** Norepinephrine released at central and peripheral synapses is inactivated through active transport into terminals by the presynaptically-localized norepinephrine transporter (NET).[35] NET immunoreactivity is present in sympathetic nerves and central nervous system noradrenergic neurons near NE release sites[34, 35]. NET recaptures as much as 90% of released norepinephrine in the heart, making it a critical mediator of NE inactivation and presynaptic catecholamine homeostasis[36]. NET is also a target for tricyclic antidepressants, NET-selective reuptake inhibitors (NRIs; common antidepressants), and psychostimulants[37, 38]. The importance of NET to norepinephrine homeostasis suggests that NET dysfunction may contribute to the autonomic reflexes causing VVS.

***Central to this proposal is the growing evidence that NET dysregulation is present in VVS*.** Vaddadi et al. [30] have recently reported on their study of sympathetic nervous system responses to head up tilt test in VVS compared to healthy controls. Healthy subjects increased both their muscle sympathetic nerve activity (MSNA) and their norepinephrine spillover to plasma with tilt. The VVS patients also increased their MSNA to a similar or greater degree, but the NE spillover response was subnormal. Thus, ***VVS patients exhibited disconnect between nerve firing and norepinephrine release***, lowering norepinephrine availability, and impairing the circulatory response with resultant syncope. These data suggest that there are some VVS patients with excessive norepinephrine reuptake (and thus excessive norepinephrine clearance) from the sympathetic nerve terminal, which in turn results in inadequate vasoconstriction and clinical syncope in response to orthostatic stress. ***These VVS patients may benefit from a reduction in their NET activity with pharmacological NET inhibitors***.

**2.6.2.** ***NET Inhibition with Atomoxetine Raises Blood Pressure in Patients with Central Autonomic Failure:*** Atomoxetine 18mg (pediatric dose) and placebo, in a crossover fashion, to 10 patients with central autonomic failure and clinical orthostatic hypotension with syncope[39]. At 1 hour, atomoxetine acutely increased seated and standing systolic BP in patients with central autonomic failure by 54±26 mmHg (mean±SD; P=0.004) and 45±23 mmHg (P=0.016), respectively, as compared with placebo. This increase in BP is likely due to an increase in vasoconstriction and venoconstriction. While one might not expect such a striking increase in BP in VVS patients (given their intact autonomic reflexes), ***these data provide "proof of concept" that NET inhibition can support BP and HR in patients with syncope disorders***.

***2.6.3. NET Inhibition to Prevent Tilt-Induced Syncope in Healthy Volunteers:*** Reboxetine is a highly specific norepinephrine transporter inhibitor approved as a clinical antidepressant in Europe, but not in the North America. Its high specificity as a NET inhibitor led Schroeder et al[40] to question whether high doses might transiently induce a clinical state resembling postural tachycardia syndrome (POTS). They gave 18 *healthy volunteers* reboxetine 8 mg orally 12 hours and 1 hour before observations, and compared their responses to reboxetine vs. placebo. As part of the study the subjects underwent prolonged head-up tilt table testing, a major diagnostic modality for VVS. Of the 18 subjects,

9 fainted while taking placebo and only 1 fainted while taking reboxetine (P<0.01). This was reproduced in further studies using reboxetine and another NET inhibitor, sibutramine[41]. The mechanism of benefit of NET inhibition in VVS is unclear: it might be simply acting indirectly as a peripheral arterial vasoconstrictor, a peripheral venoconstrictor, or through another novel mechanism. NET inhibitors are the only drug class in credible, placebo-controlled studies to show efficacy in preventing syncope induced by tilt table testing.

***2.6.4. NET Inhibition to Decrease Faints in Malignant VVS:*** Sibutramine was an anorexigenic agent that was widely available in North America and Europe before the results of the SCOUT trial were released[42]. While it was available we performed an observational, compassionate use, off-label, prospective dose-ranging study of sibutramine in the suppression of VVS in extremely symptomatic patients[43]. Seven patients with very frequent and medically-refractory syncope were treated with 10 mg/day, 15 mg/day and 20 mg/day sibutramine for 1 month each. All doses were tolerated by 6 patients (83%). The median spell frequency (per 28 days) decreased from 8 (no sibutramine) to 4 (10mg/day), to 3 (15mg/day) and to 1 (20 mg/day). Five patients were "responders" to sibutramine, pre-specified as >50% reduction in spells at the maximal tolerated dose. These data suggest that NET inhibition can be effective in preventing VVS in highly symptomatic patients.

***2.6.5. Drug availability.*** Sibutramine was withdrawn from the market after the SCOUT study results were released, and reboxetine, although available in Europe, did not have a successful pivotal study for depression in North America. Pfizer refused to make it available for further study. Atomoxetine[39] is clinically approved in Canada and the United States of America for treatment of attention deficit disorder[44].

## III. PROPOSED STUDY

**3.1. Hypothesis:** We will test the hypothesis that pharmacological NET inhibition will increase tilt test tolerance prior to syncope in patients with recurrent VVS.

**3.3. Inclusion criteria:** Patients will be eligible if they have: (A) ≥1 syncopal spells in the year preceding enrolment, and (B) ≥-2 points on the Calgary Syncope Symptom Score, and (C) Age ≥18 years with informed consent. The Calgary Syncope Symptom Score is used to diagnose VVS in patients with structurally normal hearts[45]. It has an overall 90% accuracy in distinguishing VVS from other causes of syncope in this population. It provided the diagnostic inclusion criteria for POST2 (a randomized clinical trial of fludrocortisone[6], and for a study of the impact of a parental history of fainting on the likelihood of fainting in offspring[2] and is used in POST4 and POST5. It will provide inclusion criteria for this study

**3.4. Exclusion criteria:** Patients will be excluded if they have: (1) other causes of syncope, such as ventricular tachycardia, complete heart block, orthostatic hypotension or hypersensitive carotid sinus syndrome, (2) an inability to give informed consent, (3) important valvular, coronary, myocardial or conduction abnormality or significant arrhythmia, (4) hypertrophic cardiomyopathy, (5) a permanent pacemaker, (6) a seizure disorder, (7) hypertension defined as >150/90 mm Hg (8) pregnancy, (9) lactating women, (10) glaucoma, (11) medications with known effects on blood pressure, (12) Known

hypersensitivity to atomoxetine and derivatives, and (13) other factors which, in the investigator's opinion, would prevent the subject from completing the protocol.

**3.5. Enrollment/recruitment:** Patients will be recruited locally from referrals to the University of Calgary Syncope Clinic. Patients will also be recruited at Vanderbilt University and McMaster University. Studies in Calgary will take place in the Libin Cardiovascular Institute of Alberta.

**3.6. Screening:** Each subject will have undergone a complete history and physical examination with an electrocardiogram (ECG) has not been performed in the previous 5 years, one will be done as part of routine practice.

**3.7. Study Diet and Co-Medications:** Subjects will be asked to avoid or discontinue all non-prescription medications and supplements that might contain stimulants on the day before the study.

**3.8. Study Design:** This will be a randomized, double-blind, parallel-arm study in which the subjects will undergo a tilt table test following 2 doses of atomoxetine 40mg PO (evening before and morning of study) or after 2 doses of matching placebo (on separate days). On the morning of the study, the fasting subject (except for medications) will be instrumented, on an empty bladder. ECG electrodes will be applied to monitor continuous heart rhythm. Blood pressure will be monitored continuously using a finger volume clamp method using one or more of several extant devices, and calibrated with intermittent brachial cuff measurements. One intravenous cannula will be placed in the contralateral arm (to the blood pressure cuff) for blood sampling.

**3.9. Tilt Table Protocol:** Following the insertion of the venous cannulae, a period of at least 20 minutes will be allowed to elapse before a 10-minute basal control (baseline) period. Baseline data will be digitally recorded in this time. In the last 5 minutes of this period, blood will be drawn for fractionated plasma catecholamines. The table will be rapidly raised to 80 degrees for up to 60 minutes. We are deliberately avoiding tilt test methods with provocative medications to avoid the issue of multiple causal factors. At 10 minutes and 30 minutes following onset of tilt (or at the onset of severe presyncope or hypotension [systolic blood pressure <70 mmHg]), venous fractionated catecholamines will be sampled. The study will be terminated if the subject develops syncope, at the completion of the protocol, or if the subject requests termination.

**3.10 Questionnaires:** A brief online questionnaire will be administered to the patients to get a metric of their health-related quality of life (RAND-36), anxiety and depression symptoms (HADS), orthostatic symptom burden (OGS) and global ratings of fatigue and well-being. This will be administered through RedCap Survey through the University of Calgary.

**3.11. Trial Team:** The Principal Investigators will be Drs RS Sheldon (Calgary), Dr C Morillo (McMaster) and Dr SR Raj (Calgary). Coordination, data management, and analysis will be performed in Calgary.

## IV. STATISTICAL CONSIDERATIONS

**4.1. Primary Analysis:** The primary statistical analysis will assess whether atomoxetine, compared to placebo, reduces the proportion of subjects who become presyncopal or syncopal associated with diagnostic criteria of hypotension and bradycardia. A Chi Square test will assess the statistical significance of the difference in

outcome proportions. The results will be displayed in a Kaplan-Meier analysis and the significance of differences between the two arms of the study tested with the log-rank test.

**4.2. Secondary Analyses:** Secondary non-clinical endpoints will include plasma catecholamine levels, changes in estimated stroke volume (from the continuous BP monitor), cardiac output, and systematic vascular resistance. These will all be compared between the two interventions.

**4.3. General Statistical Considerations:** Parametric data will be presented as mean±SD, and non-parametric data with median and interquartile range. Paired data will be analysed using an unpaired t-test for parametric data, or a Wilcoxon signed-rank test used for non-parametric analysis. Confidence intervals (95%) will be reported when appropriate. All analytical techniques will be two-sided. Exact P values will be reported. Data will be entered into a Microsoft Excel spreadsheet or a REDCap database and SPSS for Windows (version 21.0) or similar statistical software package will be used for data analysis.

**4.4. Sample Size Calculation:** Sample size was calculated based upon the primary clinical endpoint. In a review of 4 studies comprising 304 patients utilizing this tilt test protocol (at 60 degree head-up tilt) the likelihood of a positive test was 69%. Locally we conducted a randomized trial of the tilt angles 60 degrees versus 80 degrees [46]. The likelihood of a positive tilt test outcome was 0.6% and 1.1% per minute at 60 and 80 degrees. Therefore after 60 minutes of 80 degree head-up tilt we expect a positivity rate of 65%. The effect of NET inhibitors used a slightly different tilt test protocol, and the positive outcome rate was 49% in the placebo arms. In the NET intervention arms the positive outcome rate was 18%, of which 4% was due to diagnostic presyncope and 14% was due to orthostatic intolerance without bradycardia or hypotension. The corresponding relative risks were 37% and 8%. The latter is equivalent to a 92% relative risk reduction, which seems higher than may be clinically expected. A sample size of 56 syncope patients will have 85% power to detect a 60% relative risk reduction from a placebo outcome rate of 65%, using an unmatched 2-tailed test with alpha=0.05. To compensate for the report dropout rate we will inflate the sample by 15% to 64 subjects. A formal, blinded mid-way safety and efficacy analysis will be performed with a $p<0.01$ stopping rule for efficacy. This also will provide 85% power to detect an 80% relative risk reduction.

**4.5. Randomization:** Randomization will be carried out using a computerized algorithm. Patients will be randomized in a double-blind fashion to receive atomoxetine 40mg PO x2 or matching placebo with a 1:1 randomization ratio. Medication containers will be centrally filled and labeled with the randomization code number.

## V. ADVERSE EVENTS AND INCONVENIENCES

**5.1 Event types will be listed in the informed consent form.**

Study Diet: If you regularly drink caffeine, you may have a headache or be irritable from not drinking caffeine on the day of the study.
IV Cannulation: Having tubes put in your veins may be painful and may cause bleeding, bruising, or rarely infection.
Drawing blood may cause discomfort or bruising
The sticky patches on your skin may itch or cause a reaction.

Blood Pressure Measurement; The blood pressure measurements may be painful, or rarely cause bruising, numbness and tingling in the fingers. There will also be a short *time of poor blood flow in the arm/hand that is being cuffed during the measurements.
Tilt Table Test: There might be lightheadedness, dizziness, tremor, headache, nausea or fainting during the tilt table test. These symptoms usually resolve rapidly upon lowering of the table.

**5.1 Adverse Event (or Unanticipated Problem) Reporting:** Any adverse events of a serious nature will be reviewed immediately with the principal investigator. Serious adverse events will be reported in writing to the University of Calgary IRB, within 10 business days of the research team's first knowledge of the occurrence. Robert Sheldon MD PhD will be responsible for tracking adverse events in this study. The adverse event will be described with the following information: description of the event, outcome of the event, how long it lasted, relationship to study medications, whether the event required treatment or intervention, and the outcome.

The definition of events is as follows:

- Mild – transient and mild in nature, with no treatment necessary.
- Moderate – some intervention and treatment necessary, but subject completely recovers.
- Severe – an event that results in hospitalization, disability, death or is life threatening.

The investigator will state his opinion as to whether there is a reasonable possibility that the event or experience is related to the drug.

## VI. SUMMARY AND IMPLICATIONS

This will be the first adequately powered study of the ability of atomoxetine to prevent the vasovagal reflex. It will also provide insight as to whether norepinephrine transport inhibition functions here to maintain venous return or increase systemic vascular resistance. If positive, the study will provide a strong biomedical rationale and preliminary clinical results leading to POST 7: a randomized clinical trial of atomoxetine for the prevention of vasovagal syncope.

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