Phase 2 Norepinephrine Transporter Blockade, Autonomic Failure IND117394 12/28/12

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Table of Contents:

1.0 Specific Aims

Autonomic failure is a group of rare neurodegenerative disorders that primarily affect the autonomic nervous system. The presence and nature of the autonomic and neurological abnormalities depend on the location of the pathological lesion known as α-synuclein deposits. In multiple system atrophy (MSA), α-synuclein are found as glial cytoplasmic inclusions in basal ganglia or cerebellar structures causing impairment of central autonomic pathways crucial for autonomic cardiovascular control; the peripheral postganglionic sympathetic fibers are preserved.(1) In contrast, in pure autonomic failure (PAF) α-synuclein deposits are found in pre-ganglionic, postganglionic sympathetic fibers as well as in autonomic ganglia; central autonomic pathways are spared.(2)

Early in the course of the disease it is difficult to differentiate clinically between MSA and PAF; the main manifestation in both conditions is neurogenic orthostatic hypotension (NOH).(3) NOH is caused by impairment of autonomic reflexes that controls cardiovascular and neurohumoral adaptation to standing. Supine norepinephrine (NE) levels (normal in MSA and low in PAF) failed to increase upon standing. This leads to impaired sympathetic-mediated vasoconstriction that results in cerebral hypoperfusion(4) and symptoms such as lightheadedness, dizziness, syncope and falls(5) that contributes to morbidity, disability and death in this population.(6)

I hypothesized that the pharmacological agent, atomoxetine, a norepinephrine transporter (NET) blocker that increases the availability of NE at the level of the synapse by blocking its reuptake,(7) could induce an increase in blood pressure and be a potential treatment for NOH in autonomic failure. In normal individuals, atomoxetine, which is approved for the treatment of attention deficit hyperactivity disorder, has minimal hemodynamic effects because of a balance between its central and peripheral actions on the autonomic nervous system.(8) In central autonomic pathways, the increased NE levels diminish sympathetic activity by stimulating α-2 adrenergic receptors. In peripheral sympathetic fibers, the increased NE levels may stimulate sympathetic activity by acting on postganglionic α-1 adrenergic receptors.(9) Patients with autonomic failure have an imbalance between these central and peripheral autonomic pathways. In MSA, the peripheral sympathetic fibers are disconnected from its central input(10) unmasking any peripheral sympathetic-like effect and blood pressure response.

In a proof-of-concept clinical trial,(11) I determined the effect of 18 mg of atomoxetine on seated and standing blood pressure in 21 autonomic failure patients (10 MSA and 11 PAF). These preliminary data showed that an acute dose of 18 mg of atomoxetine increased seated systolic blood pressure (SBP) by ~50 mm Hg compared with placebo in MSA. In MSA patients, atomoxetine increased plasma NE levels by 26% suggesting a mechanistic link between the neurohumoral response and its hemodynamic effect. No significant blood pressor responses were observed in PAF patients who had very low plasma NE.

The sympathetic nervous system is maximally activated upon standing; plasma NE levels doubled on standing in normal subjects but failed to increase in autonomic failure patients. We hypothesized that atomoxetine by preventing the clearance of NE in the synapse would induce a greater blood pressure (BP) response upon standing compared with the direct α-1 adrenergic vasoconstrictor, midodrine. In a separate crossover study,(12) we compared the effect of a single dose of 18 mg of atomoxetine with midodrine (5,10 mg) and placebo on standing SBP and clinical symptoms in 69 patients with NOH and autonomic failure. Our results showed that atomoxetine and midodrine increased seated BP at the same magnitude. However, 18 mg of atomoxetine was more effective than midodrine in improving standing SBP (+7.5 mm Hg, **figure 4C**). Equally important, atomoxetine but not midodrine induced a significant reduction in clinical symptoms (lightheadedness and dizziness) compared with placebo, **figure 5**. Both studies strongly suggest that atomoxetine could be a potential treatment for NOH in autonomic failure, particularly in

patients with MSA. Additional studies are needed to conclusively determine its potential therapeutic role for these patients.

The response to an acute administration of a pressor agent, however, does not predict the long-term efficacy of the drug. We propose to test the hypothesis that prolonged (4-week) administration of the NET blocker, atomoxetine, improves clinical symptoms, activities of daily living, and increases standing blood pressure in patients with neurogenic OH. Repurposing atomoxetine for the treatment of NOH would be of a major advantage because this medication is commercially available, well-tolerated and previous pharmacoepidemiological studies(13,14) showed no increased risk of serious cardiovascular events among atomoxetine users.

2.0 Background

Autonomic failure is a group of neurodegenerative diseases of unknown cause involving two main subtypes: 1) MSA in which autonomic impairment is combined with an extrapyramidal or cerebellar movement disorder or both, and 2) PAF in which autonomic impairment (that is, NOH and bladder and sexual dysfunction) occurs alone. Other types of autonomic failure include the autonomic impairment associated with Parkinson Disease (PD).(3) Table 1 demonstrates the clinical and pathophysiological differences between these forms of autonomic failure. The presence and nature of the autonomic and neurological abnormalities depend on the location of the pathological lesion known as α-synuclein deposits. In MSA, α-synuclein precipitates are found as glial cytoplasmic inclusions in basal ganglia or cerebellar structures.(1) These patients have impaired central autonomic modulation but intact postganglionic sympathetic fibers as evidenced by the near normal plasma NE levels and normal cardiac NE uptake.(15) In contrast, in PAF α-synuclein deposits are located in neurons forming a characteristic pattern named Lewy bodies and are found in preganglionic and postganglionic sympathetic neurons as well as in autonomic ganglia.(2) Plasma NE levels are usually low in these patients.(16) The main clinical manifestation in MSA and PAF patients is NOH that results in cerebral hypoperfusion(4) and symptoms such as lightheadedness, dizziness, syncope and falls upon standing. In the early stages of the disease when NOH is the sole clinical presentation, MSA resembles PAF.(17) This period could last for years, measurement of plasma NE may help to identify patients with PAF, particularly when is very low (supine plasma NE<100 pg/ml), but this test has poor specificity and in the majority of cases it is inconclusive. A definitive diagnosis of PAF and MSA requires postmortem confirmation.(18)

Table 1. Clinical and pathophysiological characteristic in patients with MSA, PAF and Parkinson disease

Findings	MSA	PAF	Parkinson disease
NOH	+++	+++	+++
Movement disorder	+++	-	+++
Plasma norepinephrine	Normal	Low	Low
Cardiac noradrenergic uptake (MIBG or 6-[18F]fluorodopa	Normal	Low	Low
Glial cytoplasmatic inclusions	+++	-	-
Lewy bodies	-	++	++

MSA, multiple system atrophy; PAF pure autonomic failure. The presence of glial cytoplasmatic inclusions and Lewy bodies are detected during post-mortem examination.

Prevalence of Autonomic Failure

The precise prevalence of autonomic failure is unknown. Epidemiological studies are quite scarce and only available for MSA. In the Olmsted County, Minnesota, in the age group >50 years, the estimated annual incidence rate for MSA is 3 cases per 100,000 person-years.(19) Considering that the median survival is around eight years,(20) the estimated prevalence of this condition is 24 cases per 100,000 population. Similar prevalence has been reported in Europe.(21) Based on these data, it is predicted that approximately 21,000 individuals in the United States suffer from MSA (National prevalence was estimated using 2010 US census population estimates). The prevalence of PAF is thought to be lower than MSA, but there are no epidemiological data available to quantify the prevalence of this disease.

Management of Neurogenic Orthostatic Hypotension in Autonomic Failure

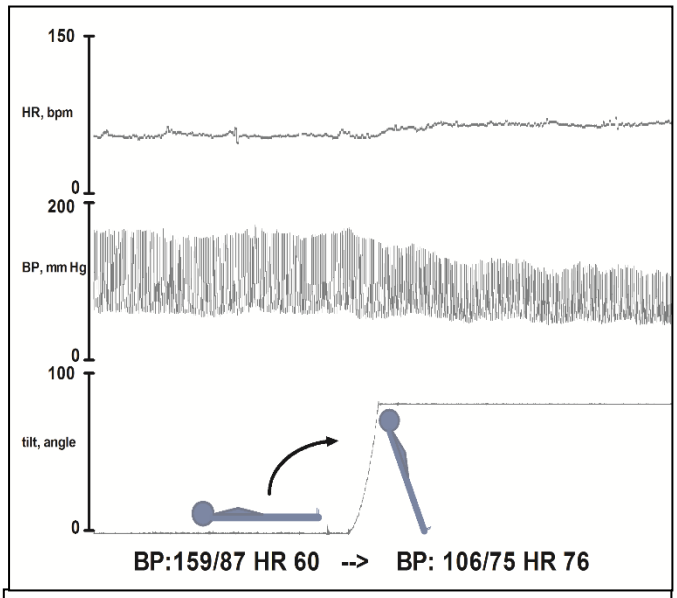


Figure 1. Changes in heart rate (first channel) and continuous blood pressure (second channel) in a patient with NOH during 70 degree head up tilt.

NOH is defined as a drop in SBP of at least 20 mm Hg or diastolic blood pressure (DBP) of at least 10 mm Hg within three minutes of standing or head-up tilt to at least 60 degree angle.(22) These patients have also a poor compensatory increase in their heart rate because of impaired baroreflex function. The average fall in SBP upon standing was 70±30 mm Hg in 237 patients registered in the Vanderbilt Autonomic Dysfunction Center database. **Figure 1** shows continuous blood pressure and heart rate recordings in a typical patient with NOH caused by autonomic failure. In this particular case, the decrease in SBP was ~53 mm Hg and the increase in hear rate (HR) was only 16 bpm during head up tilt (+70 degree tilt angle).

The profound decrease in BP upon standing induced a decrease in cerebral blood flow that led to pre-syncopal symptoms such lightheadedness and dizziness.(4) These patients have higher risk for hospitalizations, falls and syncope.(23,24) A stepwise approach is recommended based on the severity of the symptoms.[6,25] The first step includes the use of non-pharmacological measures such as rapid water drinking, use of compression stockings or abdominal binders. Patients should avoid situations such as excessive heat exposure or prolonged standing and medications that can cause or exacerbate OH (e.g. tricyclic antidepressants, vasodilators). In the majority of patients, however, non-pharmacological measures are unable to control symptoms or reduce the frequency of syncope and falls. Therefore, the use of pharmacological agents such as short-acting pressor agents is often needed. (26)

Since its approval by the FDA in 1996, the α_1 adrenergic agonist, midodrine has been the current standard of care for the treatment of NOH OH. The efficacy of midodrine in improving 1-minute standing SBP has been demonstrated in double-blind, placebo-controlled trials.(27,28) The use of midodrine, however, is limited in a fairly high number of patients by adverse effects such as pilomotor reactions (13%), pruritus of the scalp (10%), urinary retention (6%) and supine hypertension.(27,28) Furthermore, previous reports have described that midodrine may not work in a sub-group of patients with autonomic failure. In our single center's experience, approximately 36% of patients did not experience an increase in standing BP or improvement in OH-related

symptoms, 60 minutes post-drug administration, despite receiving therapeutic doses of midodrine (5 or 10 mg).(12) This lack of response could be due to different degrees of sensitivity to vascular α-adrenoreceptors.

In February 2014, the FDA approved droxidopa (L-dihydroxyphenylserine) a synthetic norepinephrine (NE) precursor for the treatment of NOH.(29) Droxidopa has a structure similar to NE but with a carboxyl group, it can be administered orally and is converted to NE through the enzyme dopadescarboxylase, which is found both centrally and in the periphery. The optimal dose varied between 300 and 1800 mg a day; patients require careful titration given different degrees of adrenergic denervation. This medication has been recently introduced in the market on September 2014; the long-term efficacy of this medication (beyond 2 weeks on therapy) for the treatment of symptomatic NOH is still under research. It is important to note that the two senior members of our group (Drs. Horacio Kaufmann and Italo Biaggioni (co-PI)) significantly contributed to the design, conduct, data interpretation and manuscript writing in the pivotal phase 3 study that evaluated the effect of droxidopa on symptomatic NOH**.**(30)

Significance

NOH is a cardinal feature of generalized autonomic failure and commonly is the presenting sign in patients with autonomic failure. NOH is a debilitating condition that can substantially reduce the patient's quality of life.(31) Patients commonly experience dizziness, syncope, or lose consciousness and fall, greatly increasing the risk of hip fracture and head trauma. These factors contribute to morbidity, disability, and death.(6,23)

Treatment of autonomic failure is challenging, and therapeutic options are scarce. There are only 2 FDA-approved drugs for the treatment of this condition in the US: midodrine an alpha-1 adrenergic agonist approved in 1996, and droxidopa a synthetic norepinephrine precursor approved in 2014. In 2010, the FDA proposed the withdrawal of midodrine from the market due to lack of evidence supporting its clinical benefit for the treatment of NOH.(32) This decision was revoked in 2012 pending the results of phase 4 clinical trials that address its clinical benefit.(33) It is still unknown, however, if this medication will remain in the market. Our single center's experience indicates that this medication only works in a limited number of subjects. In our most recent study,(12) 36% of patients with NOH did not improve their standing blood pressure with midodrine. The use of midodrine is also limited by the development of side effects such as pilomotor reactions (13%), pruritus of the scalp (10%), urinary retention (6%), and supine hypertension (4%).(27,28) These factors contribute to the poor persistence on midodrine treatment; I reported that 43% of midodrine users do not refill their medication after the first month on therapy.(24)

Droxidopa was introduced in the market on September 2014.(29) The beneficial effect of droxidopa past 2 weeks of treatment has not been determined. The long-term efficacy and safety of droxidopa is still under research. The use of this medication was associated with few cases of neuroleptic malignant syndrome in Japanese MSA patients because of its potential central pyrogenic effects.(34) Furthermore, droxidopa's efficacy is decreased when used in combination with dopamine decarboxylase inhibitors such as carbidopa because of the decreased peripheral conversion of droxidopa to NE.(35) Carbidopa is commonly used in combination with levodopa (Sinemet) in MSA and Parkinson disease for the treatment of motor symptoms. Finally, the prohibited cost of this medication (~$5,072 for a 30-day supply) limits its availability for patients with limited resources. Hence, there is an urgent need to identify new pharmacotherapies for the treatment of NOH in autonomic failure.

3.0 Preliminary Data

A Proof-of-Concept Clinical Trial: Selective NET Blockade Increases Seated and Standing Blood Pressure in MSA

The NET protein is responsible for ~90% reuptake of NE released in the synapse and is the primary mechanism by which the physiological effects of NE are terminated.(36) Atomoxetine, a selective NET blocker, increases NE concentrations by blocking its reuptake (**figure 2**, right panel). In central autonomic pathways, the increased NE levels diminish sympathetic activity by stimulating α-2 adrenergic receptors (sympatholytic effect).(9) In peripheral sympathetic fibers, the increased NE levels may stimulate sympathetic activity by acting on postganglionic α-1 adrenergic receptors (sympathomimetic effect). The effect on BP depends on a tight balance between these central and peripheral effects. Healthy subjects do not have any significant changes in BP.(8)

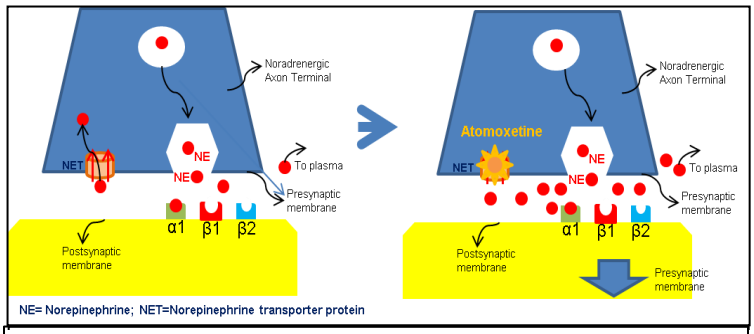


Figure 2. Approximately 90% of NE released in the synapse is reuptake by the NET. This is the primary mechanism by which the biological effects of NE are terminated (left panel). Atomoxetine is a selective NET blocker that increases NE concentrations in the synapse (right panel).

Our group hypothesized that treatment with a pediatric (18 mg) dose of atomoxetine should result in an increased BP in patients with autonomic failure, particularly MSA because of the balance between these central and peripheral autonomic pathways is lost.

We recruited 21 patients with severe autonomic failure (10 with MSA and 11 with PAF) from referrals to the Autonomic Dysfunction Center at Vanderbilt University. All the studies were conducted in the morning, at least 2.5 hours after breakfast to avoid any acute hemodynamic effects from eating, and in a postvoid state. On separate days, patients were given a pediatric dose of atomoxetine (18 mg) or placebo in a randomized, single-blind, crossover fashion. The study was conducted with the patients seated on a chair with their feet on

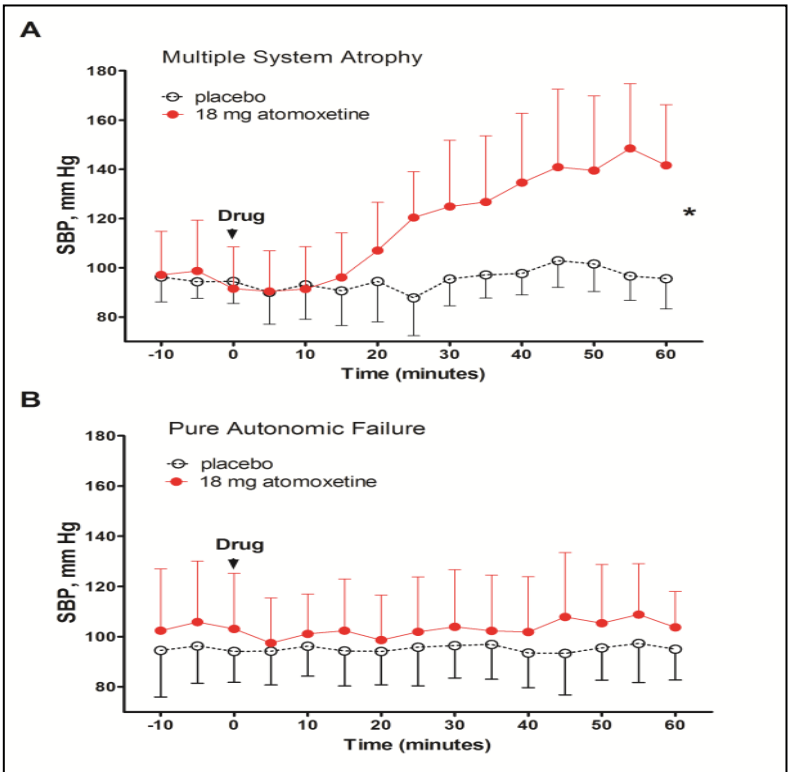


Figure 3. Changes in seated systolic blood pressure (SBP) with 18 mg of atomoxetine and placebo in patients with Multiple System Atrophy (MSA, A) and Pure Autonomic Failure (PAF, B).

the floor. BP and HR were recorded every 5 minutes with an automated brachial sphygmomanometer. Data were digitally acquired into a custom-designed database. Baseline parameters were measured for 30 minutes, then we measured BP and HR upon standing. BP was measured for 60 minutes after drug administration, when peak plasma levels are achieved. We repeated BP and HR measurements upon standing at the end of this period, as described previously.

Autonomic function tests performed at screening confirmed the diagnosis of autonomic failure; all subjects had severe sympathetic and parasympathetic involvement. As expected, patients with MSA had higher supine plasma NE and were younger as compared to patients with PAF (plasma NE 256±104 vs. 74±47 pg/ml; age 62±9 vs. 67±7 years old, P= 0.003, P= 0.06, (mean±SD) respectively). There were no significant differences in body mass index, supine SBP, or orthostatic changes in SBP between groups. SBP significantly increased with atomoxetine compared with placebo in MSA (slope difference between the atomoxetine and placebo days 0.92; 95% CI 0.73 to 1.11; P<0.001, **figure 3A**). In contrast, atomoxetine did not have a significant effect on SBP in PAF (slope difference between the atomoxetine and placebo days 0.16; 95% CI -0.02 to 0.34; P=0.08, **figure 3B**). In patients with MSA, atomoxetine increased seated SBP by 54±26 mm Hg and standing SBP by 45±23 mm Hg at the end of the 60 minutes trial (compared to 2±13 mm Hg (seated) and 2±17 mm Hg (standing) with placebo, P=0.004 and P=0.016, respectively). The pressor effect of atomoxetine in MSA was in part explained by increased availability of NE. In these patients, plasma NE tended to increase with atomoxetine (from 317±143 pg/mL at baseline to 430±83 pg/mL after atomoxetine, P=0.06).(11) Taken together, these findings offer a proof of principle to our hypothesis and additionally indicate that the use of atomoxetine is more effective in subjects with residual sympathetic function, measured by plasma NE levels, as was seen in MSA patients.

Expertise in The Evaluation of OH-Related Symptoms and OH-Impact on Daily Activities

Our group is experienced in the objective quantification of OH-related symptoms. OH causes disabling symptoms that interfere with the ability to perform everyday physical activities. Classic symptoms of OH such as lightheadedness and dizziness occur when standing and disappear when lying down. Until recently, there was no widely accepted validated scale to assess the comprehensive symptom burden and severity of OH. Co-PI (Dr. Horacio Kaufmann) validated a novel clinical rating scale, the Orthostatic Hypotension Questionnaire (OHQ), **table 2**. The OHQ is composed of 10 individual items: 6 items measure specific symptoms (the Orthostatic Hypotension Symptom Assessment [OHSA]), and 4 items measure the impact of those symptoms on a patient's daily activities (the Orthostatic Hypotension Daily Activity Scale [OHDAS]).(37) For the OHSA, patients are instructed to rate using a 0 to 10 point Likert scale (0 meaning "not experienced" and 10 meaning "worst possible"), how severe their symptoms for low BP pressure had been on average over the past week. For the OHDAS, patients are instructed to rate from 0 (no interference) to 10 (complete

Table 2. Orthostatic Hypotension Questionnaire

Symptoms		
1.	Dizziness, lightheadedness, feeling faint or feeling like you might black out	OHSA Composite; OHQ Composite
2.	Problems with vision	
3.	Weakness	
4.	Fatigue	
5.	Trouble concentrating	
6.	Head/neck discomfort	
Symptom Impact on Daily Activities that Require:		
1.	Standing for a short time	OHDAS Composite; OHQ Composite
2.	Standing for a long time	
3.	Walking for a short time	
4.	Walking for a long time	

interference) how the symptoms of NOH have interfered with daily life on average over the past week. The OHQ, composite score is calculated as the average, on a scale of 0 of 10, of the OHSA and the OHDAS composite scores.(37) Our group has experience using the OHQ, composite score during the conduct of the pivotal phase 3 study that led to the FDA approval of droxidopa for the treatment of NOH.(30)

We propose to use the OHQ, composite score as the primary endpoint in our clinical trial. We will use OHSA, question 1 as a secondary endpoint because this question has been identified by the FDA's Study Endpoints and Label Development (SEALD) core group as representing the cardinal symptoms of NOH and providing the best measurement of disease-defining symptoms. **(29)**

Acute administration of atomoxetine increased standing systolic blood pressure to a greater extent than midodrine, the standard of care

We previously reported that administration of 18 mg of atomoxetine increased BP in patients with MSA who are characterized by normal to high levels of plasma NE and residual sympathetic activity. In contrast, atomoxetine had no significant pressor effect in PAF patients who had very low levels of plasma NE.

The sympathetic nervous system is maximally activated upon standing; plasma NE levels doubled on standing in normal subjects but failed to increase in autonomic failure patients. We hypothesized that atomoxetine by preventing the clearance of NE in the synapse would induce a greater BP response upon standing compared with the direct α-1 adrenergic vasoconstrictor, midodrine. Hence, we compared the effect of acute administration of 18 mg of atomoxetine with midodrine (5 or 10 mg) and placebo on standing SBP and OH-related symptoms as measured by OHSA composite score and question 1 in autonomic failure patients with NOH.

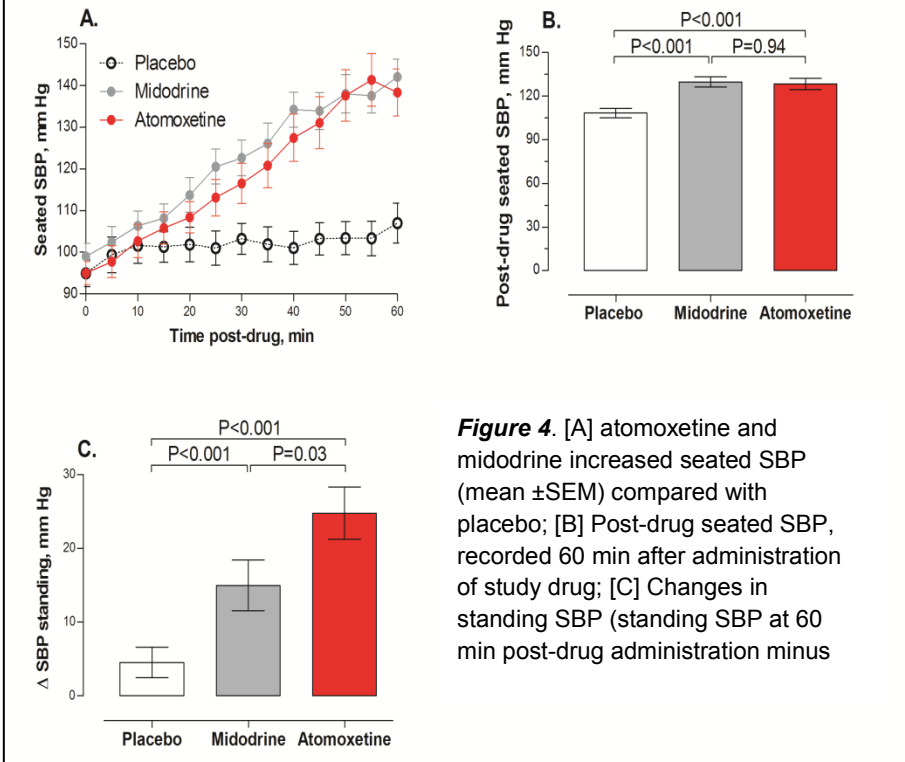


Figure 4. [A] atomoxetine and midodrine increased seated SBP (mean ±SEM) compared with placebo; [B] Post-drug seated SBP, recorded 60 min after administration of study drug; [C] Changes in standing SBP (standing SBP at 60 min post-drug administration minus

All studies were conducted in the morning, in a post-void state, at least 2.5 hours after breakfast to avoid the post-prandial hemodynamic effects. On separate days, patients were given atomoxetine (18 mg), midodrine (5 or 10 mg), or placebo in a randomized, single-blind, crossover fashion. Studies were conducted with the patients seated in a chair, with their feet on the floor.

We did not measure supine blood pressure during the study interventions because we followed standard of care (patients are instructed never to rest supine after receiving pressor agents).

During baseline, we measured BP and HR every 5 minutes for 30 minutes. We also obtained orthostatic vital signs at 1, 3, 5 and 10 minutes or until tolerated. We asked the patients to rate their OH-related symptoms using the OHSA questionnaire. We then administered the study drug, and hemodynamic parameters were assessed every 5 min for 60 min. We repeated the orthostatic vital signs assessment and symptom evaluation at the end of this period.

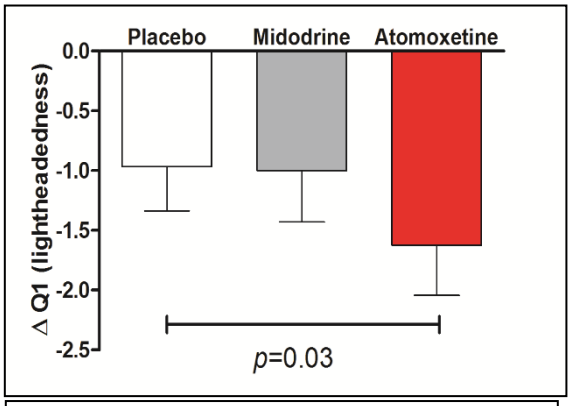


Figure 5. Atomoxetine significantly decreased lightheadedness and dizziness (OSHA, question 1, Q1) compared with placebo. Midodrine did not improve symptoms.

We studied 69 patients with NOH (26 with PAF, 21 with MSA, 12 with PD, and 10 with undetermined diagnosis). All patients had a profound decrease in SBP and DBP from the supine to the standing position (-63±29 and -29±16 mm Hg, respectively) without adequate increase in HR (+12±15 bpm). NE levels were low in supine posture (126±89 pg/mL) and did not increase appropriately during standing posture (257±249 pg/mL). Both atomoxetine and midodrine increased seated SBP by ~ 20 mm Hg compared with placebo (**figure 4A and 4B)**. However, atomoxetine was more effective in increasing standing SBP than midodrine (means difference = 7.5 mm Hg, 95% CI = 0.6 to 14.5, P=0.03), **figure 4C**. Furthermore, atomoxetine was the only drug effective in decreasing clinical symptoms as measured by OSHA (0.4 SQRT, 95% CI = -0.1 to -0.8, P = 0.02) and lightheadedness/dizziness, Q1 (0.6 SQRT points, 95% CI = -0.1 to 1.7, P = 0.03, **figure 5**), the study was published in Hypertension in 2014.(12)

In the studies presented, we did not measure supine blood pressure during the study interventions because we followed standard of care (patients are instructed never to rest supine after receiving pressor agents). In the proposed study we will assess the effect of prolonged use of atomoxetine on supine blood pressure as a safety endpoint.

In summary, atomoxetine, a selective NET blocker, increases standing BP and improves OH-related symptoms to a greater extent than midodrine, the current standard of care. Atomoxetine could be a new therapeutic alternative for the treatment of NOH in patients with autonomic failure, particularly those with MSA.

4.0 Inclusion/Exclusion Criteria

Inclusion Criteria:

- 40 years old or older
- Neurogenic Orthostatic Hypotension (defined by a reduction of systolic blood pressure ≥20 mmHg or a diastolic blood pressure ≥ 10 mmHg withing 3 minutes of standing or at least head-up tilt 60 degrees on a tilt table.

Exclusion Criteria:

- Pregnancy or breastfeeding
- Hypersensitivity to atomoxetine (severe allergic reaction, rash, urticaria, anaphylaxis)
- Use of other norepinephrine transporter inhibitors such as Wellbutrin (Bupropion), Cymbalta (Duloxetine), Effexor (venlafaxine), Pristiq (desvenlafaxine), Savella (milnacipran)
- Previous history (within 14 days prior to enrollment) and current use of monoamine oxidase inhibitors

- Concomitant use of strong CYP2D6 inhibitors such as delavirdine, paroxetine, fluoxetine, quinidine
- Pre-existing sustained severe hypertension (BP ≥ 140/90 mmhg in the sitting position at least two times 10 minutes apart)
- Impaired hepatic function (aspartate amino transaminase [AST] and/or alanine amino transaminase [ALT] >2 x upper limit of normal range)
- Impaired renal function (serum creatinine equal or more than 1.6 mg/dl)
- Myocardial infarction within 6 months prior to enrollment
- Congestive heart failure (LV hypertrophy acceptable)
- History of serious neurologic disease such as cerebral hemorrhage, or stroke
- Inability to comply with the protocol, e.g., uncooperative attitude, inability to return for follow-up visits, unlikelihood of completing the study, and mental conditions rendering the subject unable to understand the nature, scope, and possible consequences of the study
- Narrow-angle glaucoma

5.0 Enrollment/Randomization

The proposed study consists of an open–label, dose-optimization phase followed by a 2x2, double-blind, placebo-controlled, crossover phase. We estimated that we need to enroll 77 patients in the open–label, dose-optimization phase to have 40 responder patients randomized in the double-blind, placebo-controlled, 2X2 crossover phase (*study procedures*). We based our calculations on data collected during our previous study (*preliminary data*), the proportion of responders to atomoxetine was 64% (95% CI 52-76%) using the criteria proposed in the planned study. Atomoxetine responders will be defined as those who: 1) had a decrease in self-rating scale of ≥1 point in the OHSA, question 1 and 2) had an increase in standing SBP equal or more than 10 mm Hg from baseline, 60 minutes post-drug administration. Our target population is autonomic failure patients with NOH.

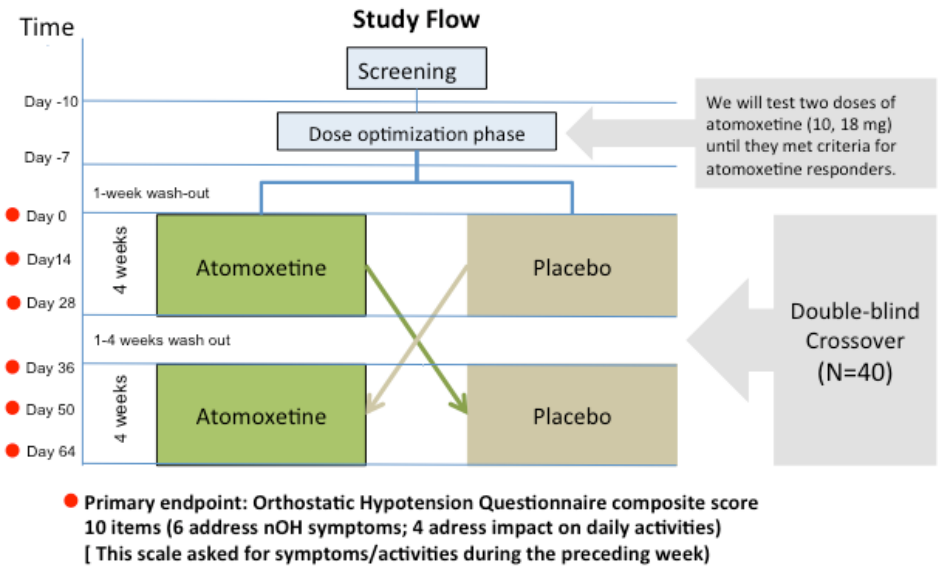
Patients with NOH and autonomic failure will be enrolled in two national referral centers that focus exclusively on disorders of the autonomic nervous system. The Vanderbilt Autonomic Dysfunction Center (PI: Dr. Cyndya Shibao) and the Dysautonomia Center at New York University (PI: Dr. Horacio Kaufmann).

6.0 Study Procedures

Specific Aim: Hypothesis: Prolonged administration of the NET blocker, atomoxetine, improves OH-related symptoms and OH-impact on daily activities compared with placebo in patients with autonomic failure and NOH.

The proposed study consists of an open–label, dose-optimization phase followed by a randomized, double-blind, placebo-controlled, 2x2 crossover phase. The overall study design is presented in **figure 6**. The schedule of activities is presented in the Appendix.

Screening (-10 day)



After informed consent is obtained, each patient will undergo a complete medical history and physical examination, and routine safety laboratory analysis, including electrolytes and serum creatinine, complete blood count, complete metabolic panel, urinalysis, and EKG. Subjects will be withdrawn from other pressor medications for 5 half-lives prior to administration of study medications. All other medications, including fludrocortisone, will be held constant throughout the study.

Evaluation of OH-related Symptoms and OH-impact on Daily Activities. We will use the OHQ composite score. Subjects will rate their presyncopal symptoms and daily activities, 7 days prior to enrollment.

Orthostatic Standing Test. Study patients will be studied in the morning, under fasting condition after midnight, to avoid the confounding effect of post-prandial hypotension. We will obtain BP and HR measurements with automated sphygmomanometer twice while supine for 10 min (with the torso and head elevated 30 degrees from horizontal) and after 1, 3, 5, and 10 min standing. The standing time will be measured with a chronometer. This initial measurement will allow us to determine if patients have NOH (inclusion criterion) and/or supine hypertension.

Supine and standing plasma NE. We will collect supine and standing plasma samples to measure NE using high-performance liquid chromatography with electrochemical detection.(38) If the subject is unable to stand up, plasma NE will be collected after the subject sits up with his torso upright for at least 10 minutes.

Autonomic Function Testing. All patients enrolled in this study will undergo autonomic function tests to determine the presence of autonomic failure. During these tests, we will monitor HR by EKG and BP continuously with tonometry or finger plethysmography and intermittently with an oscillometric device. These tests include sinus arrhythmia and valsalva maneuver. *Deep breathing-vagally mediated sinus arrhythmia (SA)* is assessed during controlled breathing

(pattern of 5 seconds inhalation and 5 seconds exhalation repeated over 90 seconds). *Valsalva maneuver.* The subject will exhale against a 40 mm Hg pressure. Changes in intrathoracic pressure produce autonomically modulated transient changes in HR and BP.

Open-Label Dose-Optimization Phase (days -10 to -7)

Procedures. We will test two doses of atomoxetine (10 and 18 mg) on separate days. We will perform all the assessments in the morning, under fasting conditions, to avoid the confounding effect of post-prandial hypotension. We will obtain BP and HR measurements with automated sphygmomanometer twice while supine for 10 minutes (with the torso and head elevated 30 degrees from horizontal) and after 1, 3, 5, and 10 minutes standing. We will ask the subject to rate his/her symptom using OHSA, question 1. We will administer atomoxetine (10 mg), and 60 minutes after dose administration, we will repeat the BP and HR measurements, supine and standing, and symptom assessment using OHSA, question 1. If the subject does not meet the definition of atomoxetine responders using 10 mg of atomoxetine, then we will test 18 mg of atomoxetine using the procedures outlined above on a separate day.

Atomoxetine responders will be defined as those who: 1) had a decrease in self-rating scale of ≥1 point in the OHSA, question 1; and 2) had an increase in standing SBP equal or more than 10 mm Hg from baseline, 60 minutes post-drug administration.

Subjects will be excluded if they 1) reached the maximum permitted doses of 18 mg and have not responded to the medication as defined previously or 2) had sustained blood pressure >180 mm Hg systolic or >110 mm Hg diastolic while standing, sitting or supine two consecutive BP measures taken 15 minutes apart.

Subjects will undergo a 7-day wash-out period after the completion of this phase.

Randomized, placebo-controlled, crossover phase (days 0 to 64).

A total of 40 subjects will participate in this study. We will recruit an equal number of male and female subjects. We will randomize the order of the medication assignment (atomoxetine or placebo) according to a computer-generated, randomization schedule. We will stratify the treatment assignment by clinical center and atomoxetine dose (10 or 18 mg twice a day). The investigational pharmacy will store, prepare, and label all the investigational agents, and maintain accurate drug storage and dispensing logs. At the time of randomization the research nurse will fax a copy of the consent form and a prescription containing the atomoxetine dose. The pharmacist will assign the subject a randomization number and provide the investigator with a 4-week supply of the blinded study medication. Upon completion of the 4-week treatment period (period 1), the investigator or research nurse will instruct the subject to discontinue the study medication for at least 1 week and a maximum time of 4 weeks (wash-out period). After this period, the subject will complete the second 4-week treatment period (period 2). During the 4-week treatment periods (period 1 and period 2) we will closely monitor the subjects. We will perform telephone visits at 1, 3, 5, and 7 days during the first week on treatment followed by weekly telephone visits. We will work diligently with the patients and care givers to maintain them throughout each of the 4-week treatment periods. We will also measure the primary endpoint and secondary endpoints twice at 2-week (days 14 and 50) and 4-week (days 28 and 64) intervals for each period.

Early crossover:

The primary comparison will be between atomoxetine and placebo on the primary endpoint collected two and four weeks into the treatment period. We will allow patients to early cross over after 2 weeks of treatment for patients who cannot remain on study medication for 4 weeks.

Outpatient monitoring. A research nurse/fellow will communicate with the patient or spouse at days 1, 3, 5, and 7 during the first week on treatment and after that on a weekly basis while the patient is in period 1 and 2 of the randomized crossover phase. These phone calls will be performed to ensure that there are no clinical problems, to collect BP and HR information measured at home, to coordinate the recording of hemodynamic data (24-hr ambulatory BP monitoring), non-hemodynamic data (OHQ, fall calendar and the Columbia-Suicide Severity Rating Scale), and to ensure that the patient's safety is maintained.

Hemodynamic evaluation

BP assessment during study visits. These measurements will take place at days 0, 14, 28, 36, 50, and 64 [before (pre-drug) and 60 minutes post-drug administration] during the randomized, placebo-controlled, crossover phase. We will perform all assessments in the morning, under fasting conditions, after midnight to avoid the confounding effect of post-prandial hypotension. We will obtain BP and HR measurements with automated sphygmomanometer twice while supine for 10 minutes (with the torso and head elevated 30 degrees from horizontal) and after 1, 3, 5, and 10 minutes standing.

Ambulatory BP monitoring. We will perform a 24-hour ambulatory BP monitoring with a positional tracking device during the randomized crossover phase two weeks after the initiation of study drug (period 1: day 14; period 2: day 50). Study subjects will be instructed to remain seated for 4 hours after taking their morning dose of the study drug. The goal of this evaluation is to assess the magnitude of the pressor response beyond 1 hour after drug administration and after multiple dosing. If during the 4-hour monitoring period the patient’s seated BP is increased beyond our established safety threshold (180/110 mm Hg), they will be withdrawn from the study with their primary endpoint taken at the exit visit.

Non-Hemodynamic Evaluation

Assessment of OH-related symptoms and OH-impact on daily activities. We will perform the OHQ composite score at 0, 14, 28, 36, 50, and 64 days (primary endpoint, **figure 6**).

Tracking of falls: We will use the calendar method of falls reporting which is considered the gold standard.(39) A fall will be defined as any event in which any part of the body above the ankle hits the floor, the ground, or a lower surface, including falls that occur on stairs. Patients will be trained at the baseline visit to record their experiences on the calendar each day, either placing an "N" in the box for the appropriate day if no fall has occurred that day or placing an "F" in the box if a fall has occurred that day. We will monitor the occurrence of falls at 0, 14, 28, 36, 50, and 64 days.

Standardization of care. Subjects will be provided written instructions on how to prevent supine hypertension, these include not resting supine in a horizontal position after taking the medication. Alternatively they can rest with the head of the bed elevated. Safety: Administration of concurrent monoamine oxidase inhibitors could result in a severe increase in BP. Therefore participants in this study will be provided a medical safety bracelet indicating that the subjects is participating in a clinical trial that involves the use of a norepinephrine transporter inhibitor (atomoxetine). Subject will wear this bracelet for the duration of the randomized crossover phase.

Evaluation of side effects: The study nurse will contact the patient at days 1, 3, 5, and 7 during the first week on treatment and after that on a weekly basis while the patient is in periods 1 and 2 of the randomized, placebo-controlled, crossover phase. The study nurse will inquire

about side effects during the study periods. We will use structured case report forms to assess compliance, concurrent medications, medical conditions, and adverse events.(40) Structured checklists are more effective in detecting adverse medication events than open-ended questions. All side effects will be reported and analyzed according to FDA guidelines.(41)

Endpoints

Efficacy measure: ***The primary endpoint*** will be the change from baseline of the OHQ, composite score. The OHQ will be administered during screening, before each treatment period, 2 weeks into the treatment period, and at the end of each of the 4-week treatment period (days 0, 14, 28, 36, 50, and 64, **figure 6**). ***Secondary endpoints*** include the improvement in the Likert scale for "dizziness, lightheadedness, feeling faint, or feeling like you might black out" (OHSA, question 1), the increase in standing SBP, 60 minutes post-drug administration compared to baseline, frequency of falls, plasma NE.

Safety will be assessed by adverse events.

Study-related visits or telephone communications will be scheduled within +/-3 calendar days of the schedule.

7.0 Statistical Considerations

Sample size justification: The primary endpoint is the change from baseline of the OHQ, composite score. In a study (30) co-authored by Dr. Horacio Kaufmann one of the study's PIs, droxidopa group had a mean (SD) change of -1.83 (2.07) units in OHQ composite score, versus -0.93 (1.69) in the placebo group. Assuming a similar effect will be achieved by atomoxetine, a sample size of 35 will give us 86% power to detect a difference in means of -0.9 (-1.83 versus -0.93), assuming a standard deviation of 1.7 for the within-subject differences using a paired t-test at 0.05 type I error rate. Assuming an about 10% drop-out rate, we plan to enroll 40 subjects. For our secondary endpoint, the increase in standing SBP, 60 minutes post-drug administration, our study sample size has >90% power to detect a difference of 45±23 mm Hg (preliminary data)(11) between placebo and atomoxetine.

Data analysis plan

For both primary and secondary endpoints, standard graphing and screening techniques will be used to detect outliers and to ensure data accuracy. Summary statistics for both numerical and categorical variables will be reported by study sequences to describe the study sample. Comparability among randomization sequences will be assessed.

The primary comparison will be between atomoxetine and placebo on the primary endpoint collected two and four weeks into the treatment period. It is important to note, however, that we may not be able to keep patients from crossing over to active treatment for those on placebo for the entire 4 weeks. Such crossover may bias the atomoxetine versus placebo comparison at week 4. However, from our past experience we are confident that we can keep patients on placebo for at least 2 weeks and will work quite diligently with the patients to keep them for 4 weeks. Thus, week 2 analysis will be primary. To avoid potential bias introduced by potential unblinding by such crossover, the primary endpoint OHQ will be collected by the study personnel who are blinded from such crossover information. The intention-to-treat analysis will be the primary analyses, and the per-protocol analysis will be secondary. Before data unblinding, the PI (Dr. Cyndya Shibao) and the study statistician and co-PI (Dr. Chang Yu) will review all protocol deviations and determine a list of protocol violators to be removed for the per-protocol analysis.

We will use a 2x2 crossover design. Although we have designed the study to avoid carry-over effect by having a one-week washout period, we will test for potential carry-over effect using the T-test approach described in Section 2.3 (page 21) of Jones and Kenwood (2003).(42) If there is evidence for a carry over effect, the traditional safe approach is to use data collected before the crossover to estimate the treatment effects. This would result in a loss of power; however it would ensure valid estimates. While we will use this approach in our analyses, we also planned to measure the primary endpoint right before study subjects take study medication (atomoxetine or placebo) at day 0 and at day 35 for the two treatment periods, respectively. These baseline measurements will allow us to estimate any residual carry over effect. This estimate will enable us to assess the atomoxetine versus placebo difference using data collected in both crossover periods in the presence of residual carry over effect.

The primary efficacy analysis will be unadjusted. We will calculate within-subject mean differences and 95% confidence intervals for the atomoxetine versus placebo comparison and test for treatment effect using paired t-test or Wilcoxon signed rank sum test depending on whether the data are normally distributed.

Additional adjusted analyses will be conducted using mixed effects models with a random subject effect and with treatment (atomoxetine versus placebo) as the fixed effect. We will include age and gender as covariates in the model. The secondary endpoints will be analyzed similarly as for the primary endpoint.

Due to the pharmacy error, at the end of the study, we will have lower dose (10mg) A and the higher dose (18mg) A (the doses with error used on patients until May 2018) and lower dose (10mg) B and the higher dose (18mg) B (the doses correctly compounded) versus placebo on each crossover. Our original plan is to pool the lower dose (10mg) B and the higher dose (18mg) B together for the paired treatment versus placebo comparison. Now we still plan on pooling all four doses together for the comparison. However, we will assess if there is any difference on safety and efficacy between A and B for the two doses separately. Based on the mechanism of action, we do not expect a difference between A and B for either dose. If we observe a difference, including lower dose (10mg) A or higher dose (18mg) A in the treatment versus placebo comparison will either enhance or attenuate the treatment versus placebo difference. We will report their impact accordingly in our findings.

Safety endpoints such as adverse events will be reported and analyzed according to FDA guidelines.(41)

We do not plan to conduct an interim analysis. We will have a Data and Safety Monitoring Board (DSMB) to independently monitor the conduct of the trial.

8.0 Risks

1. Supine hypertension: Around 50% of patients with autonomic failure develop supine hypertension.(43) Atomoxetine may induce or exacerbate supine hypertension particularly in patients with MSA. We designed our protocol to minimize this risk. **First**, we will only recruit patients who have seated BP less than 140/80 mm Hg. **Second,** we will use the minimal effective atomoxetine dose either 10 or 18 mg (pediatric dose). **Third**, we will exclude patients whose BP has increased above 180/110 mm Hg, 60 minutes after drug administration (safety threshold). **Fourth**, we will provide the patients with written instructions on how to prevent supine hypertension. These include not to rest supine on a

horizontal position after taking their medication. We will ask the patient to check their blood pressure at home with a calibrated automatic BP monitor. We will instruct subjects to rest with the head of the bed elevated at least 30 degrees, and we will monitor their BP at home on two occasions with a ambulatory BP monitor with a tracking position device.

2. NET blockade such as atomoxetine can cause severe hypertension when taken together with monoamine oxidase inhibitors. For this reason, subjects will be asked to wear a medical alert bracelet stating that they should not be given a monoamine oxidase inhibitor without first contacting the PI. Common (>10%) side effects associated with atomoxetine are headaches (2% to 19%), insomnia (2% to 15%), somnolence (4% to 11%), xerostomia (21%), nausea (7% to 21%), abdominal pain (7% to 18%), appetite decrease (11% to 16%), and vomiting (3% to 11%). Research subjects will be informed of all the potential side effects associated with the drug. During the randomized crossover phase, a research nurse will contact the patient on a weekly basis to collect information about potential adverse events. All potential adverse events will be ranked according to severity and will be reported according to the data and safety-monitoring plan described below.

3. Atomoxetine has been associated with suicidal ideation in children. The frequency of suicidal ideation is 0.37% (5/1,357) based on a recent meta-analysis. We have implemented a monitoring plan for prospectively assessing suicidal ideation and behavior The overall purpose of this plan is to ensure that any patient enrolled in the randomized crossover treatment phase who experiences suicidal ideation and behavior is properly recognized and adequately treated. For this purpose, we will use the C-SSRS survey for prospectively assessing suicidal ideation and behavior during at baseline (prior to randomization) and at the end of period 1 (day 28) and period 2 (day 64).

9.0 Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or Others

Any protocols will be reviewed and approved by the Vanderbilt Institutional Review Board (IRB) before any subject is enrolled. The PI will be responsible for ensuring both data integrity and for ensuring that study participants are safely cared for and that all AEs are noted, followed, and reported to the IRB, the DSMB, and the FDA. We will use the Guidance for Industry and Investigators for safety reported requirements for INDs and BA/BE studies published in the FDA website:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM227351.pdf

Definitions:
Adverse event (AE) means any untoward medical occurrence associated with the use of a drug in humans, whether or not consider drug related.
Suspected AE means any AE for which there is reasonable possibility that the drug caused the AE; “reasonable possibility” means there is evidence to suggest a causal relationship between the drug and the AE. An AE will be considered unexpected if it is not listed in the investigator brochure.
Serious AE means any AE that: a) results in death, b) is life-threatening, c) requires inpatient hospitalization or prolongation of existing hospitalization, d) results in persistent or significant disability or incapacity, e) is a congenital anomaly or birth defect.

Serious adverse events will be reported to the Chairman of the Data and Safety Monitoring Board (DSMB), the IRB, and the FDA no later than 7 calendar days after the PI's initial receipt of the information.

Suspected AE interpretable as single case (uncommon and strongly associated with drug exposure) will be reported to the FDA within 15 days from initial receipt.
Non-serious, unexpected adverse events will be reported to the IRB at the time of the annual continuing review.

Data and Safety Monitoring Board: The DSMB will provide objective review of treatment results as they relate to human safety and data quality. The committee will be comprised of Cheryl Laffer, M.D., Professor of Medicine, Division of Clinical Pharmacology; William DuPont, Ph.D., Professor of Biostatistics; Charles M. Stein, M.D., Professor of Clinical Pharmacology; and Ronald L. Cowan, M.D., Professor of Psychiatry. The DSMB will meet at least 3 times, once to review and ratify its charter and every 12 months to receive reports of the progress of the study. These reports will provide information regarding recruiting, safety reporting, data quality, and efficacy. The committee will assess safety data including development of hypertension, common adverse events, hospitalizations and other serious adverse events. The randomization will be blinded and presented on a coded basis (i.e. treatment periods, I and II) unless the Committee votes to receive unblinded data. The Committee will have the authority to modify the protocol or to terminate the study if it deems such actions to be warranted. The DSMB will provide summary reports to the IRB, the FDA and the investigators. The DSMB will review all serious adverse events. Committee members will be provided with all clinical data regarding the clinical occurrence. During regularly scheduled meetings, the DSMB will also be provided with a list of non-serious adverse events. The DSMB may choose to become unblinded; however, it is expected that such unblinding would not occur without reasonable concern related to either patient safety or data validity.

All studies will be registered in ClinicalTrials.gov prior to enrolling subjects.

Study Withdrawal/Discontinuation
Criteria for study withdrawal/discontinuation

- Drug-related toxicity
- Requirement for prohibited concomitant medications (see exclusion criteria)
- Pregnancy
- Request by subject to terminate treatment
- Clinical reasons believed life threatening by the physician, even if not addressed on the potential risk section
- Blood pressure more than 180/110 in any position (standing, seated, or lying down) on two consecutive readings within 15 minutes

10.0 Privacy/Confidentiality Issues

All data will be collected specifically for the proposed research project. A unique identification case number will be used to protect the confidentiality of the study participants. Only case numbers will be included in spreadsheets used for the statistical analysis. PHI and access to the key for the ID numbers will only be viewable by members of the research team. Member of the research team will have access to the patient's medical record during the screening visit and

throughout the study until the patient completes her participation in the study or meets any of the criteria for study withdrawal/discontinuation.

11.0 Follow-up and Record Retention

Research records will be maintained for at least three (3) years from the date the research is closed with the Vanderbilt University IRB. All research records will be accessible for inspection and copying by authorized representatives of the IRB, federal regulatory agency representatives, and the department or agency supporting the research.

All Health Insurance Portability and Accountability Act (HIPAA)-related documentation will be maintained for at least six (6) years from the date of the last use or disclosure of the Protected Health Information (PHI).

12.0 Data Coordinating Center

Given the study will recruit patients from two sites, Vanderbilt University Medical Center (VUMC) and New York University Medical Center (NYUMC), that effectively turns the study into a multicenter clinical trial. We plan to establish a Data-Coordinating Center (DCC) within this two-center RCT.

The DCC under Dr Yu's leadership proposes to serve the study by:
[a] Providing Biostatistical Expertise. The DCC will input on all biostatistical aspects of the clinical trial, including optimizing study design for increased accuracy and precision, assessing at the beginning and re-evaluating statistical power should the DSMB make such request, conducting the statistical analyses, serving as the central repository for data generated from the two clinical centers (VUMC and NYUMC), collaborating on presentations/publications, and preparing reports for the DSMB.

[b] Along with the trial coordinator, implementing and managing a REDCap database for the two study sites. The DCC will establish and manage a secure and confidential computerized system utilizing the REDCap to collect and manage study data. The REDCap is described in the resources section. It is a state-of-art system developed by a consortium of Clinical and Translational Science Research (CTSR) awardees led by Vanderbilt University.

[c] Coordinating and standardizing trial conduct among the two sites. The DCC will collaborate with PIs on protocol development and implementation, preparing the standard operating procedure, conducting training sessions on standard data collection and data entry, quality assurance, and generating reports for the DSMB and the funding agency.

Dr. Yu will assume the overall leadership for the DCC and will be directly involved with all biostatistical aspects for the program, except for unblinding the treatment should the DSMB request such. The staff statistician (TBN) will carry out much of the day-to-day operations and she/he may be unblinded. Should unblinding happen, the staff statistician will no longer be involved with any decision making for the trial to ensure the integrity of the study. Since we can leverage our past experience on the REDCap database described in [b] above, the DCC will primarily focuses on the biostaitstical aspects of the study.

Appendix:
Schedule of Study Activities

Table. Schedule of Activities

	Screening	Dose Optimization Phase		Randomized Crossover Phase		
		Day -10 to -7	1-4 weeks wash-out	Period 1	1-4 weeks wash-out	Period 2
Informed consent	x					
Medical History	x					
Physical exam	x					
Safety labs (CBCM BMP, U/A, EKG)	x					
Supine and standing catecholamines	x			x		x
Concomitant Medications	x					
Orthostatic Standing Test	x					
OHQ, composite score	x			X		X
Autonomic Function Tests	x					
Randomization (Day 0)				X (Day 0)		
Blood pressure assessments (supine, standing)		x		x		x
Medication administration (open label)		x				
Medication administration (blind)				X		X
Telephone visits				X		X
Side effect evaluation		x		X		X
Home blood pressure monitoring (24 h ABPM)				X		X
Columbia Suicide Severity Rating Scale				X		X
Falls diary				X		X
DNA collection		x				

ABPM, ambulatory blood pressure monitor, u/a urinalysis, CBC, complete blood count, CMP, comprehensive metabolic panel, ECG, electrocardiogram

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