VA Department of Veterans Affairs

VA RESEARCH CONSENT FORM

Version Date: April 29, 2019	**Page: 1 of 12**
Subject Name:	**Informed Consent Date:**
Principal Investigator: Jill M. Wecht, EdD	**VAMC: James J Peters**
Title of Study: Blood Pressure, Cerebral Blood Flow and Cognition in SCI: 30 day study	
Protocol #: WEC-13-066	

1. Purpose of study and how long it will last:

You are being asked to participate in a research study. The purpose of this study is to determine if the effects of increasing your blood pressure with midodrine compared to placebo (no medication), over a 10-week period improves blood flow to your brain, your ability to think, and your quality of life. The 10-week period includes 30-days (4 weeks) of taking the drug, a 14-day (2 weeks) washout period, and another 30-days (4 weeks) of treatment. We also want to know if giving midodrine to you over a 4-week period is safe so we will monitor your blood pressure very closely and will ask you to complete questions on the symptoms that are related to autonomic dysreflexia (AD) or other possible side effects. You are being asked to participate in this research study because you are between the ages of 18 and 85 with Spinal Cord Injury (SCI) for over one (1) year and you have low blood pressure. This study is sponsored by the National Center for the Medical Consequences of SCI, and is also funded by the Craig H. Neilsen Foundation. You will be one of approximately 40 subjects in this study, which is being conducted at James J. Peters VA Medical Center and Kessler Institute of Rehabilitation. Your participation will involve six (6) laboratory visits, which will occur over the course of about 10 weeks. You are eligible for this research study because you have low blood pressure and do not have a very bad history of AD. In addition, you met the following screening criteria:

Inclusion Criteria:

- SCI between the ages of 18 – 85 years old
  - Any level of injury
  - non-ventilator dependent
  - Any AIS grade of SCI
  - SCI duration > 12 months
  - Wheelchair dependent
- Able to provide informed consent
- Low blood pressure
  - Males - systolic blood pressure < 110 mmHg or diastolic blood pressure < 70 mmHg
  - Females – systolic blood pressure < 100 mmHg or diastolic blood pressure < 70 mmHg
- Fluent in English
- Right handed
- You have completed the acute (single-dose) trial and 30 day observational study

Exclusion Criteria:

- Current illness or infection
- Individuals with frequent or severe autonomic dysreflexia
  - More than 3 symptomatic events per week
  - BP ≥140/90 mmHg
  - Significant adverse subjective symptoms reporting
- Hypertension
- I have supine hypertension (greater than 140 systolic and 90 diastolic mm Hg);
- History of Traumatic Brain Injury (TBI)
- Any neurological condition other than SCI (Alzheimer's disease, dementia, stroke, multiple sclerosis, Parkinson's disease, etc.)
- History of epilepsy or other seizure disorder
- Diagnosis of a psychiatric disorder such as schizophrenia or bipolar disorder
- Mini mental status exam score of less than 24
- Vision impaired- more than 20/60 in worst eye (with prescription eyewear)
- Known artery disease
- Had major surgery in the last 30 days
- Pregnant

2. Description of the Study Including Procedures to be Used:

If you consent to participate in this research study, you will be asked to visit the laboratory 6 times over the course of about 10 weeks. All 6 visits will include monitoring of your heart rate, breathing rate, blood pressure, blood flow to your brain and completion of an AD survey. On 2 of the visits, in addition to monitoring of your heart rate, breathing rate, blood pressure, blood flow to your brain, you will be asked to complete several thinking tests and to answer a few quality of life surveys (see Protocol Time Line below).

Protocol Time Line

		Arm 1				Washout		Arm 2			
	Week 0	Week 1	Week 2	Week 3	Week 4	14 days	Week 6	Week 7	Week 8	Week 9	Week 10
	Initial Visit 1		Interim Visit 2		Post Visit 3		Initial Visit 4		Interim Visit 5		Post Visit 6
Seated BP	X		X		X		X		X		X
Seated CBFv	X		X		X		X		X		X
Seated HR	X		X		X		X		X		X
24-hour BP	X				X		X				X
Thinking Tasks	X				X		X				X
Quality of Life Surveys	X				X		X				X
AD symptoms reporting	X		X		X		X		X		X
Phone calls to report side effects		x		X				x		X	
Spasticity Survey	X	x	X	X	X		X	x	X	X	X

Treatment Phase – You understand that you will be given either active drug (midodrine) or matching placebo (a pill with an inactive substance that looks like the study drug). Neither you nor the investigators will know which you are getting during the first or second 4-week treatment phase. You will be sent home with three vials of medication; 2 vials will contain 3-days' worth of medication or placebo (about 10 pills each), the other vial will contain 24 days' worth of study medication or placebo (about 80 pills). You will first take 2.5 mg dosages of medication for three days. If you do not experience hypertension (systolic blood pressure greater than 140 mmHg) and no increased symptoms of autonomic dysreflexia (AD) (a condition where blood pressure increases higher than normal usually because of a painful stimulus below the level of your spinal cord injury). You will increase the dosage to 5.0 mg for three days. If you do not experience any of the above stated side effects, you will increase the dosage to 10 mg for the remaining 24 days. The vials will be labeled clearly with the order in which they should be taken.

During each 4-week treatment period you will be asked to take the study medication 2-3 times/day. We suggest that you take one pill at about ***8AM, 12 noon and 4PM*** with a glass of water while in the seated position and asked you to strictly follow these instructions:

- ***Do not take the study medication after 4PM*** on any given day unless you have discussed this with study investigators.
- ***Do not take the study medication within 1 hour prior to your bowel care routine,*** no matter what time of day this occurs.
- ***Do not take study medication within 3 hours of bedtime.***
- ***Monitor, document and transmit BP 1 hour after taking study medication and during routine bowel care,*** using a brachial BP, which will be provided.
- ***Monitor and document significant symptoms of AD.***
- ***Adhere to*** scheduled weekly phone calls and laboratory visits.

At your 1st visit you will be given a BP monitor and will be shown how to use it. You will be asked to record and transmit your BP values every day, 1 hour after taking the study medication, during your routine bowel care program and at any time that you feel that you're BP may not be normal. Your blood pressure will be transmitted via either your cell phone or your land-phone directly to the VA and Dr. William Bauman or Dr. Miroslav Radulovic will monitor your blood pressure and any symptoms you may be feeling. If any data is missing from the BP recordings or if there is evidence of a blood pressure above 140/90 mmHg, the research team will call you immediately. In addition, investigators will call you weekly for an update on your well-being. If any significant adverse event occurs that may be related or un-related to the study medication, you should report this immediately (within 1 hour) to the research team.

On laboratory visit days, you will be asked to take your morning dose of study medication prior to each laboratory visit; the initial and post visits will be conducted over 3-4 hours and the interim visits will be about 1-2 hours.

Baseline Testing (all visits) - Upon arrival to the laboratory on all 6 visits you will remain quietly seated in your wheelchair for 30-minutes while the research team applies instrumentation. There will be a 5-minute recording of continuous heart rate, breathing rate, blood pressure and blood flow to your brain. After baseline testing you will be asked to answer several questions related to your symptoms of AD (autonomic dysreflexia is a condition where blood pressure increases higher than normal, usually because of a painful stimulus below the level of your spinal cord injury). On interim visits 2 and 5 testing will be concluded and you will leave the laboratory. On visits 1, 3, 4 & 6 after completion of baseline testing you will be given several thinking tests, which will take about 40 minutes. During these thinking tests your heart rate, breathing rate, blood pressure and blood flow to your brain will be continuously recorded. After completion of the thinking tests you will be asked to

take a few surveys which will evaluate your quality of life, these surveys can be taken while you are in the laboratory or when you get home from your computer. Before leaving the laboratory on visits 1, 3,4 & 6 you will be instrumented with a 24-hour blood pressure monitor which will record your heart rate and blood pressure every 20 minutes during the day and at 30-minute intervals during the nighttime.

Heart rate (HR) - 3 electrodes (small sticky pads) will be placed on your chest and abdomen and will be used to determine HR and breathing rate (BR). Both HR and BR will be continuously monitored during each study visit and will be recorded twice during the seated baseline and continuously during each cognitive battery of tests.

Blood Pressure (BP) – Blood pressure will be taken from the upper arm using standard procedures at 1-minute intervals during rest and the thinking tests. In addition your blood pressure will be monitored continuously at rest and during the thinking tasks at your middle and ring fingers.

Brain Blood Flow (CBFv) - will be monitored continuously at rest and during the thinking tests using a transcranial Doppler (TCD) ultrasound probe to visualize the middle cerebral arteries (MCA).

Thinking Tests –These tests will take about 40 minutes to complete and will evaluate different types of thinking (cognition) such as your short term, and long term memory, attention processing speed, and working memory, reasoning and mental flexibility (executive function). During these tests we will continuously monitor and record your heart rate, breathing rate, blood pressure and blood flow to your brain using the equipment attached to you.

Health Related Quality of Life Assessment (HRQOL) – This assessment tool encompasses several domains of life satisfaction including physical-medical health & secondary complications (pain, toileting, muscular, skin, temperature, fatigue, cardiovascular, bone, autonomic dysreflexia), emotional health (resilience, loss/grief, self-esteem, sadness/depression, positive emotions, other emotions, anxiety/fear), and social health participation (interpersonal relationships, significant other role, leisure, work, stigma, independence).

Side Effects Survey: You will be called by the study coordinator at weeks 1, 3, 7 and 9 and once during the 14-day wash out period to report any side effects that you have which may or may not be related to the study drug.

Spasticity Survey: You will be asked by the study coordinator once a week to fill out questionnaires on your spasticity

Autonomic Dysreflexia (AD) Symptoms Survey: You will be asked to fill out an AD symptoms questionnaire. If you experience any symptoms that are unlike what you usually experience you will be asked to contact study investigators immediately. On the survey, you will be asked to answer questions related to AD; this survey will include recording your blood pressure and any/all symptoms (un-well feelings). Other symptoms may include those expected from the study medication (headaches, blurred vision, pounding in the ears, slow pulse, increased dizziness, fainting, etc.) as well as those not expected (fever, infection, illness, etc.). The more information you can record the more the investigators will know about the safety of this medication.

3. Description of any Procedures that may Result in Discomfort or Inconvenience:

You have been told that the study described above may involve the following discomforts:

- You may experience some discomfort when electrodes are removed from skin and some skin irritation at the site of electrode placement.
- You may experience some discomfort when the blood pressure cuffs around my upper arm and index finger are inflated.
- You may feel discomfort with head harness that is used to secure the ultrasound probe to your head for assessment of brain blood flow.
- Possibly frustration may occur during the thinking tests. You will be encouraged to take breaks as needed and you may stop a test at any time and for any reason.
- There may be symptoms of discomfort from taking the study medication as described in the next section.
- Risks and discomforts that cannot be foreseen may arise.

4. Expected Risks of Study:

- Heart rate, breathing rate, and blood pressure: are all non-invasive measurements and are not associated with any known risks.
- Your blood pressure may be elevated above what is considered to be the normal range (>140/90 mm Hg) following midodrine administration.
- Symptoms of autonomic dysreflexia (AD) may become more frequent or worse while taking midodrine. If this happens, you will call us immediately and we will guide you through the AD treatment plan. We will instruct you to sit upright to prevent too much blood flowing to your head; you will be asked to loosen any tight clothing or braces that

you are wearing; and we will ask you to check and empty your bladder and bowel. If your blood pressure remains high for more than 30 minutes after we take these non-drug measures, you will call 911. In our experience with midodrine, the need for an emergency room visit would be very unlikely.

- Risks of midodrine include blurred vision, cardiac awareness (irregular heartbeat or shortness of breath), headache, pounding in the ears, increased dizziness, slow pulse, fainting, tingling and itching of the scalp, goosebumps, chills, constipation, superficial venous thrombosis (a blood clot in a vein), vascular ischemia (blockage of blood supply in an artery), urinary retention, the urge to urinate, and temporary muscle spasms.
- As with any research, there may be unforeseen risks and discomforts.

5. Expected Benefits of the Study:

There may be no direct benefit to you from this study, but information we get from this study may help others.

6. Other Treatments Available:

Participation in the study is voluntary and you understand that the only alternative is to not participate in the study.

7. Use of Research Results:

We will let you and your physician know of any significant new findings made during this study which may affect your willingness to participate in this study. All research material generated from the study will remain in the possession of Dr. Wecht and her study team. De-identified electronic data will be stored on secured VA networks, behind VA firewalls, in access-restricted folders. Coded physical data will be stored at the James J. Peters VA Medical Center in the Center of Excellence in locked file cabinets behind locked doors. Access to the research materials generated from the study will be restricted to Dr. Wecht's research team. Your coded data may be shared with Dr. Dyson-Hudson and his research team at the Kessler Institution for Rehabilitation. Your medical records will be maintained according to this medical center's requirements and all electronic and hard copy Research Records will be retained according to National Archives and Records Administration, Records Schedule Number DAA-0015-2015-000.

Research Investigator files will be destroyed six years after the end of the fiscal year when the research project has been completed per Records Schedule DAA-0015-2015-0004-0032, Section 7.6, Research Investigator Files.

☐_____ By checking this box and initialing, you agree to be contacted by the Principal Investigator or her investigative team at a future date for additional studies being conducted in the Center of Excellence for the Medical Consequences of SCI.

If results of this study are reported in medical journals or at meetings, you will not be identified by name, by recognizable photograph, or by any other means without your specific consent. No information by which you can be identified will be released or published unless required by law. In order to comply with federal regulations, research records identifying you may be reviewed by the following: Authorized representatives of the Bronx VAMC (e.g. Institutional Review Board, Research Compliance Officer) and VA, including the Office of Research Oversight (ORO), Federal Agencies such as the Government Accounting Office (GAO), VA Office of Inspector General (OIG), Food and Drug Administration (FDA), and the Office for Human Research Protections (OHRP).

Clinical Trials

"A description of this clinical trial will be available on http://www.ClinicalTrials.gov , as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time."

8. Special Circumstances:

If you are a patient, a copy of this consent form will be placed in your medical record.

9. Compensation and/or Treatment in the Event of Injury:

The VA must provide necessary medical treatment to a research subject injured by participation in a research project approved by a VA R&D Committee and conducted under the supervision of one or more VA employees. Further information about compensation and medical treatment may be obtained from the medical administration service at this VA medical center. A veteran-participant does not have to pay for care received as a participant in a research project, except in accordance with federal law that certain veterans have to pay co-payments for medical care and services provided by the VA.

10. Voluntary Participation:

You are not required to take part in this study; your participation is entirely voluntary you can refuse to participate in this study or withdraw your participation in this study after you consent without

penalty or loss of VA or other benefits to which you are entitled. During the course of the study, you will be told about any new findings within the investigation or about information reported in the literature or reported verbally to the investigators that might affect your willingness to remain in the study. A signed copy of this consent form will be given to you.

11. Termination of Participation:

You can refuse to participate now or you can withdraw from the study at any time after giving your consent. This will not interfere with your regular medical treatment, if you are a patient. The investigator also has the right to withdraw you from the study at any time for reasons including, but not limited to, medical concerns (your health and safety are in jeopardy with continued participation in the study), non-compliance (you miss several scheduled appointments without notification) and protocol deviations (exclusion/inclusion criteria change and you are no longer eligible to participate).

12. Costs and Reimbursements:

As a veteran or non-veteran, you will not be charged for any treatments or procedures that are part of this study. For veterans who are required to pay co-payments for medical care and services provided by VA, these co-payments will continue to apply for medical care and services provided by VA that are not part of this study.

You have been told that you will receive up to $500 for participation in this research study according to the following schedule:

ARM 1	ARM 2
Initial visit (1) – 4 hours - $100.00	Initial visit (4) – 4 hours - $100.00
Interim visit (2) – 2 hours - $50.00	Interim visit (5) – 2 hours - $50.00
Post visit (3) – 4 hours - $100.00	Post visit (6) – 4 hours - $100.00

You understand that payment will be processed after each study visit based on the above schedule, and that you will be paid for each study visit you attend and complete. You understand that if you cannot complete both study visits you will be paid for the testing session that you complete. The reimbursement will be sent in the form of a check or electronic fund transfer (EFT) sent directly to your bank. You understand that if you choose to receive reimbursement through EFT, you will be required to provide the research staff information that includes; name of your bank, routing number and account number.

13. Contact Person(s):

If you have any questions, at any time, about this research, or want to discuss any possible study-related injuries, please call telephone number 718-584-9000, ext. 3122 for Dr. Wecht. In addition after-hours you can contact Dr. Wecht at (201) 390-0487 or one of the medical doctors affiliated with this study: Dr. William Bauman at (914) 329-4772 or Dr. Marinella Galea at (917) 513-6758.

You understand that should you wish to discuss your participation in this study with any other doctor or layperson; you can contact **Mary Sano, Ph.D., ACOS-R&D** by requesting an appointment at (718) 741-4228 hospital extension 4228, first floor in the research building, room 1F-01. If you have any questions, concerns and/or complaints concerning the research study, you can ask one of the researchers listed above or contact **Dr. Sano**. Medical problems during the course of the study should be addressed to the investigator at the phone listed above."

If you have problems, concerns, and questions about the research and research subject's rights, you can contact Dr. Sano, who is not affiliated with this research study, to obtain information or to offer input. If you still have questions regarding the study or your rights as a participant in the study you may discuss them with an administrator of the Institutional Review Board at the Veterans Affairs Medical Center, Bronx, NY at telephone number (718) 741-4228.

RESEARCH SUBJECTS' RIGHTS:

You have read or have had read to you all of the above. Dr. Jill M. Wecht, EdD or her delegate has explained the study to you and answered all of my questions. You have been told of the risks or discomforts and possible benefits of the study. You have been informed of other choices of treatment available to me.

I understand that I do not have to take part in this study, and my refusal to participate will involve no penalty or loss of rights to which I am entitled. I may withdraw from this study at any time without penalty or loss of VA or other benefits to which I am entitled.

The results of this study may be published, but my records will not be revealed unless required by law. This study has been explained to me. I have had a chance to ask questions. I voluntarily consent to participate in this study. I will receive a signed copy of this consent form.

Subject Signature	Date	Time

Person Obtaining Informed Consent (Print Name) (Investigator or Delegate as indicated on Assurance Page)	Signature of Person Obtaining Informed Consent	Date

VERBAL CONSENT IF THE PARTICIPANT LACKS UPPER LIMB FUNCTIONS TO COMFORTABLY WRITE

_____ is unable to sign the consent form due to impaired arm function. I certify that I have carefully explained the purpose and nature of this research to him/her in appropriate language and he/she has had an opportunity to discuss it with me in detail. I have answered all of his/her questions and he/she has consented t participate in this research. He/She has also given me permission to initial each page of the consent form with his/her initials as we review it. I, therefore, am signing the consent form to document that he/she has given his/her consent to participate in this research study.

Person Obtaining Consent:

Name: _____

Signature: _____

Date: _____

Witness Name: _____

Signature: _____

Date: _____

Background and Significance

Individuals with tetraplegia and paraplegia above T5 struggle with persistent hypotension,[4-11] episodic orthostatic hypotension (OH) [12-16] and post-prandial hypotension.[17] Although we routinely observe and have reported a systolic BP (SBP) below 100 mmHg, [63, 64] most of these individuals remain overtly asymptomatic. There is a growing body of evidence supporting associations between asymptomatic hypotension and cognitive deficits. In otherwise healthy non-SCI individuals, asymptomatic hypotension is associated with slowed cognitive speed, [19] fewer word recall, [20] decreased accuracy of response,[21] limited attention,[20] prolonged reaction times,[19, 21, 22] and reduced memory and concentration capacity. [21, 22] We recently reported preliminary evidence of significant deficits in memory and marginal deficits in attention and processing speed in hypotensive individuals with spinal cord injury (SCI) compared to a normotensive SCI cohort.[33] Therefore, although many hypotensive individuals with SCI remain asymptomatic and do not raise clinical suspicion warranting intervention, chronic hypotension may have significant adverse cognitive consequences.

Furthermore, the superimposition of hypotension and cognitive impairment on the physical, social and emotional limitations already experienced by many individuals with SCI can severely impact autonomy, social independence and quality of life (QOL).[36, 37] In the 1990's the British Journal of Medicine published a series of papers on the association between low BP and mood disorders.[24, 31, 32, 65] The findings suggest that, compared to normotensive individuals, those with chronic hypotension report significantly increased incidence of depression,[23-30] anxiety,[25, 26] unexplained tiredness,[24, 31] and poor perception of well being.[32] Because these associations were made in large epidemiological studies the clinical implication has met with some skepticism.[66] With that appreciated, a more recent report, which aimed to determine the influence of high BP on depression and anxiety found an inverse relationship, suggesting that low BP may confer greater risk.[67] Significantly increased reporting of depression and anxiety have been repeatedly reported in the SCI population,[68-70] and we found significantly increased Becks Depression Index score in hypotensive individuals with SCI compared to the normotensive SCI cohort.[33] Despite these data, chronic asymptomatic hypotension has not attracted clinical attention; in a retrospective chart review we found that nearly 40% of veterans with SCI had clinical BP values entered into the medical record indicative of hypotension;[71] however less than 1% carried the diagnosed or were prescribed anti-hypotensive therapy.[52]

Although as early as 1927 individuals with low BP were described as those who lacked stamina, tired easily, complained of cold extremities and showed an inability to do prolonged mental or physical work; [1] the notion that hypotension may be a clinical concern has yet to gain substantial traction. In fact, several more recent papers have challenged the notion that low BP is a health concern, suggesting that hypotension is the ideal "normal" BP and a benefit to longevity and cardiovascular health.[3, 72] In addition, there is a general lack of consensus regarding the definition of hypotension, as well as whether chronic hypotension exists,[73] or is a problem. [2, 74] In 1978, the World Health Organization (WHO) defined hypotension as a SBP ≤ 110 mmHg for males and ≤ 100 mmHg for females, without regard to diastolic BP (DBP). However, much of the literature on hypotension is equivocal regarding its definition. Large epidemiological studies discuss hypotension as BP in the lowest 5-30% of the population,[25, 26, 28] while smaller studies report cut-offs to define systolic hypotension of between 100 and 120 mmHg.[24, 27, 31, 32, 65] In addition, there is discussion about whether or not "constitutional hypotension" exists, [73] and while several Eastern European countries diagnose and treat individuals with hypotension, many English speaking countries are not convinced that low BP is a clinical syndrome, and actually believe that hypotension conveys significant cardiovascular benefit.[3] Yet, compared to normotensive males, 13-year mortality risk for all causes and cardiovascular disease was 2.4 to 3.4 times greater, respectively, in men ages 40-49 with systolic hypotension; by comparison, systolic hypertension conveyed a 1.7 fold increase in all cause mortality. [62]

We understand that the diagnosis and treatment of disease is usually based on causal associations between symptoms and physiological pathology;[2] and the "non-disease state" was described as the diagnosis of a particular disease when confirmatory 'symptomology' is not readily apparent, [75] as in the case of low blood pressure.[2] Therefore, the clinical diagnosis of hypotension is most often made based on the presence of significant symptomology, which includes dizziness, light-headedness, pre-syncope and syncope, as well as non-specific symptoms of generalized weakness, fatigue, nausea, cognitive slowing, blurry vision, leg buckling or headache. Because most hypotensive individuals with SCI remain asymptomatic, the vast majority is not diagnosed, let alone treated, which is in sharp contrast to persons diagnosed with asymptomatic hypertension,

and aggressive treatment if often recommended. Moreover, OH was defined in 1996 by the American Autonomic Society and the American Academy of Neurology as a fall in SBP of greater than or equal to 20/10 mmHg within 3 minutes of standing, regardless of symptoms, [76-79] and in fact, a dissociation between OH and orthostatic dizziness has been reported.[58, 60, 80] Regardless of symptoms, however, several large epidemiologic studies report associations between OH and increased hospitalizations,[81] incidence of ischemic stroke[54] and coronary heart disease risk[59] and higher mortality in the elderly subjects after controlling for confounding factors.[57, 60, 61] While the predominance of information on OH and mortality has been reported in elderly cohorts, several investigators have demonstrated significantly poorer prognosis among younger individuals (early to mid 40s) who were OH positive compared to OH negative individuals.[55, 58, 59] Of note, these individuals were otherwise healthy and remained asymptomatic during episodes of OH, and therefore, did not raise clinical concern.[55, 58]

There is a clear discrepancy between the empirical evidence, which indicates adverse consequences in association with chronic asymptomatic hypotension and the clinical diagnosis, treatment and appreciation of this condition. Because our unpublished data suggest that the incidence of hypotension is 2.5 fold increased in veterans with SCI compared to veterans without SCI, gaining a better understanding of the possible causal association between asymptomatic hypotension and clinically relevant outcomes should be a priority in this population.

Laboratory evidence in the general medical literature suggests that elevation in BP improves cognitive performance in healthy subjects and in post-acute stroke patients.[38, 39, 82] Compared to placebo, administration of an alpha-adrenergic agonist (midodrine hydrochloride) induced significant elevations in BP which were associated with increased resting cerebral blood flow (CBF) and a more pronounced rise in CBF with the execution of a cued reaction time task.[38] Moreover, subjects who received midodrine experienced greater improvement in attentional performance than those who received placebo, and the degree of performance enhancement was positively correlated to the increase in resting CBF.[38, 39] In addition, cognitive function was significantly improved, in association with reduced hypoperfused tissue on neuro-imaging scans of the brain, following induced BP elevation in a randomized-comparative group trial in 15 post-stroke patients.[82] Although the effects of induced BP elevation on cognitive performance have not been described in persons with SCI, we have demonstrated that 10 mg midodrine increases orthostatic BP during a head-up tilt maneuver and attenuates the orthostatic fall in CBF.[43, 44] Further, our preliminary evidence suggests diminished CBF responses to cognitive testing in persons with SCI compared to controls, which may contribute to poor test performance.[35]

Midodrine hydrochloride [d,1-alpha-(2'5'-dimethoxyphenyl)-β-(glycinamidoethanol); $C_{12}H_{19}N_2O_4Cl$] is a pro-drug that undergoes enzymatic hydrolysis in the systemic circulation to form the active metabolite desglymidodrine; midodrine is nearly completely absorbed after oral administration,[83] even in models of NOH in which gastroparesis is common.[84] It has been shown that midodrine does not cross the blood brain barrier; therefore, it is not associated with central nervous system effects.[85] A few relatively small multi-center, randomized placebo-controlled clinical trials have been conducted to determine the efficacy of midodrine to treat symptomatic OH in various models of autonomic failure (Bradbury-Eggleston [pure autonomic failure], Shy-Dragers syndromes [multiple system atrophy], Parkinson's disease and diabetic neuropathy).[46, 84, 86, 87] Compared to placebo, 10 mg midodrine TID increased standing BP and improved symptoms of dizziness or light-headedness during standing.[46, 84, 86, 87] Of note, two reports suggest that midodrine improves subjective reporting of energy level and depression.[46, 47]

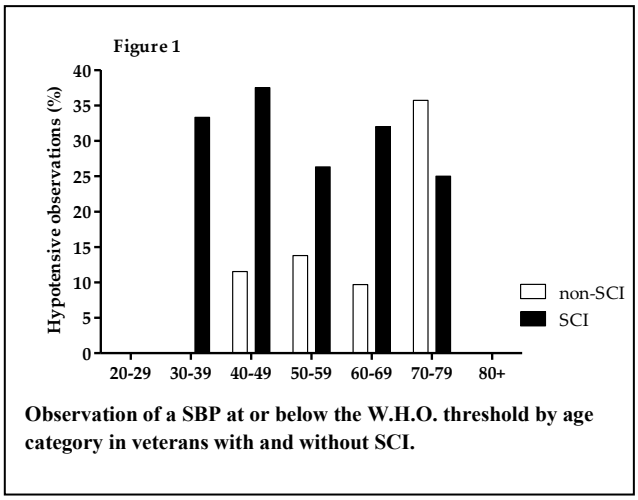
Although our data indicate that between 39% and 70% of the SCI population is hypotensive, less than 1% of veterans with SCI is diagnosed or prescribed treatment for this condition.[52, 71] Disparity between the prevalence of hypotension and the diagnosis in the SCI population is disturbing because of the possible deleterious effects on cognitive function, mood and QOL; adverse effects which may be magnified in individuals with a long-term physical disability.[36, 37] Further, although these individuals do not complain of symptoms, a recent report found significantly increased incidence of ischemic stroke in the Taiwan's SCI population compared to age-, sex- and propensity-matched controls, which may relate to persistent cerebral hypoperfusion, secondary to systemic hypotension.[88]

Preliminary Studies

Dr. Jill Wecht has been funded since 2000 by the VA RR&D Service to investigate the consequences of decentralized cardiovascular autonomic control on BP in persons with SCI. She has received four investigator-initiated Merit Reviews (#B3203R, #F6980R, #B6999R and #B7537R), two Career Development Awards (RCD #B3346V and CDA II #A6161W), and she is the Principal Investigator of the Cardiovascular Autonomic Program in the Center of Excellence for the Medical Consequences of SCI (CoE: B4162C). Dr. Wecht's VA funded research has involved the study of the mechanisms of BP control as well as testing the efficacy and safety of therapeutic treatment options for hypotension and OH in persons with SCI. Although Dr. Wecht has been successful in securing funding for these investigator-initiated projects, her studies have been limited by relatively small in sample sizes. It must be appreciated that before long term treatment of chronic asymptomatic hypotension should be recommended in the SCI population, a large -scale randomized placebo -controlled clinical trial must be conducted. It is our primary objective that the data generated by this investigation will provide the preliminary evidence to power such a large -scale study to determine the effects of sustained elevation in BP, to normotensive levels (SBP 111 -139 mmHg), on CBF, cognitive function, mo od and QOL in persons with SCI . Until that time, the following text describes advances made on several research initiatives conducted by Dr. Wecht and her associates to identify the prevalence and adverse consequences of hypotension in persons with SCI.

Prevalence of hypotension in veterans with SCI

In 2008, Dr. Wecht and colleagues had a Pilot Merit Review application funded by the RR&D Service (#B6999R) entitled "Prevalence of Blood Pressure Abnormalities among Veterans with SCI". The investigation determined the rates of BP abnormalities diagnosed and treated in a veteran SCI population based on the medical record charting over a 5-year span of time and rates observed in a subset of veterans with SCI. The data, which have been accepted for publication (Appendix 3), suggest an increased prevalence of hypotension among veterans with SCI (28.79%) compared to a matched non-SCI veteran cohort (11.89%) (χ^2=10.4; p<0.01). Further delineation by age indicates that the prevalence of hypotension is increased from the 3rd decade of life in those with SCI, but an increased observation of hypotension does not become obvious until the 7th decade of life in the matched non-SCI veteran cohort (Figure 1).



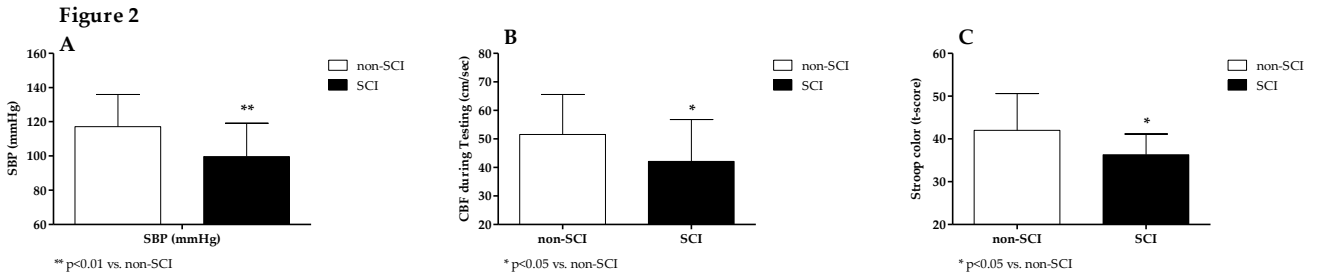
Observation of a SBP at or below the W.H.O. threshold by age category in veterans with and without SCI.

Although the prevalence of hypotension was increased in veterans with tetraplegia (T [C3-C8]: 35.07%) and high paraplegia (HP [T1-T6]: 26.59%) compared to those with low paraplegia (LP [T7 and below]: 4.42%), the use of anti-hypotensive agents was comparable, and essentially negligible, among the 3 groups (0.1, 0.5 and 0.3%, respectively). Furthermore, prescription of anti-hypertension agents was substantially increased compared to anti-hypotensive agents and was comparable among individuals with T (54%), HP (55%) and LP (54%); although the diagnosis of hypertension was significantly reduced in those with T (39.1%) and HP (44.2%) compared to veterans with LP (59.6%; p<0.05). Thus, the prevalence of hypotension is increased in veterans with SCI; the incongruously low prescription of anti-hypotensive agents may reflect general lack of clinical appreciation of the adverse affects of hypotension on QOL and/or a paucity of data supporting the safe and efficacious use of these agents in the SCI population.

Hypotension and Cognitive Performance in Persons with SCI

In 2008 the VA RR&D Service funded an Associate Investigator Award to Adejoke Jegede , PhD (# B4968R) entitled "Relationship between Blood Pressure, Cerebral Blood Flow, and Learning in Persons with Spinal Cord Injury"; Dr. Wecht was her Primary Mentor. The findings, which have been published in two reports, [33, 35] suggest that hypotensive individuals with SCI, regardless of level of lesion, years of education or premorbid IQ, perform significantly more poorly on neuropsychological tasks of memory and attention & processing speed compared to normotensive individuals with SCI; it should be noted that the self-reported

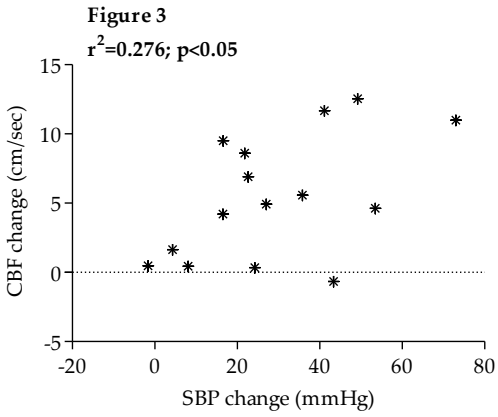
incidence of traumatic brain injury was comparable between the hypo- and normotensive cohorts. [33] Findings from a second manuscript suggest an inappropriate reduction in CBF during cognitive testing in individuals with SCI compared to a statistically significant increased in CBF during testing in the non-SCI controls. Although we were unable to establish a relationship between BP, CBF and cognitive performance, subjects with SCI, regardless of lesion level, had significantly reduced SBP [A], CBF during testing [B] and poorer test performance on the Stroop color task [C] compared to the non-SCI controls (Figure 2). In fact, 62% of the SCI group met criteria the WHO for hypotension (100±20 mmHg), compared to 38% of the non-SCI controls (117±19 mmHg) and, 46% of the SCI cohort had cognitive t-scores 1.5 standard deviations below the normative mean (mild cognitive impairment) compared to 19% of the controls. These observations strongly support an increased prevalence of hypotension in the SCI population and suggest that relatively reduced CBF in concert with systemic hypotension may be associated with diminished cognitive performance.



Systolic BP [A], and CBF [B] during cognitive testing and cognitive t-score on the Stroop color task [C] in the non-SCI (open bars) and SCI (closed bars) groups.

Effects of Midodrine on BP, CBF and Cognitive Performance in P ersons with SCI

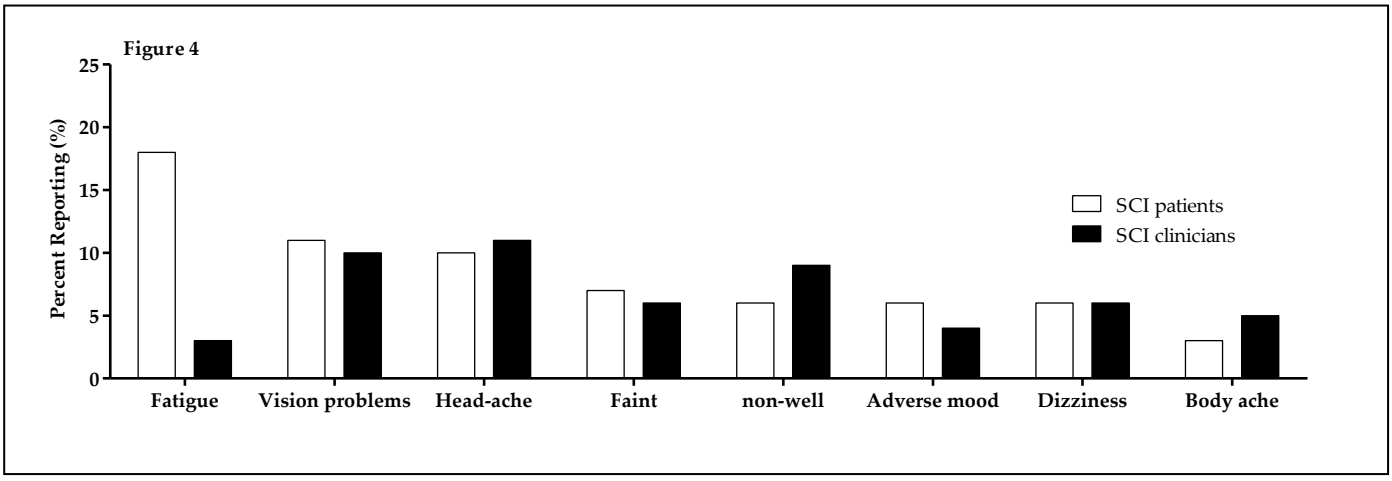
In 2006 The VA RR&D Service renewed Dr. William A. Bauman's CoE (#B4162C), and a component of the Cardiovascular Autonomic Program within the CoE was entitled "Determination of the Efficacy of an α-Agonist on BP and CBF in Patients with Tetraplegia". The results of this initiative have been published in two manuscripts. [43, 44] We documented an increase in BP and an attenuated fall in CBF during head-up tilt in persons with SCI following midodrine 10 mg administration.[44] In addition, a portion of Dr.Wecht's CDA II award (#A6161W) was determined the effect of midodrine (10 mg) on 4-hour seated BP, CBF and performance on a serial subtraction task in hypotensive individuals with SCI. Data collection is ongoing but testing is complete in 14 individuals with lesions from C3-T4. There was a significant increase in seated BP from the baseline (BL: 90±12/58±11 mmHg) to the 4-hour post drug (midodrine) average (119±18/76±14 mmHg; p<0.0001) and a statistically significant increase in CBF (39±9 to 44±11 cm/sec, respectively; p<0.01). Further the relationship between the change in SBP and the change in MFV following administration of midodrine was statistically significant (Figure 3). To address the impact of significant increases in SBP and CBF on cognitive performance subjects performed a serial subtraction task, to assess intellectual efficiency, before and after midodrine administration. Following midodrine administration the number of attempts was increased from BL (50.7±29.6 vs. 43.2±28.2, respectively; p<0.05), and the number of correct response was also significantly increased (44.6±30 vs. 40.0±28.7, respectively; p<0.05) in subjects with SCI. Although these data suggest that improved cognitive performance may be associated with elevation in BP and CBF following midodrine administration, this work was performed in a relatively small number of subjects, and the multiple regression model between physiological increases (i.e., change in BP and CBF) and cognitive improvements (i.e., # correct responses after drug) was not statistically significant (r^2=0.264; p=0.19).



The relationship between the change in systolic BP and the change in mean flow velocity (MFV) from seated baseline to the average of the 4-hour seated observation after administration of midodrine.

BP Dysregulation and Quality of Life in Persons with SCI

In 2010, Dr. Wecht was awarded a Merit Review by the VA RR&D Service (#B7537R) entitled "Development of the Blood Pressure Symptom Subdomain for the SCI-QOL". This project will use qualitative research techniques and validated psychometric analysis (i.e., Item Response Theory) to develop a bank of questions which will help identify the impact of BP dysregulation (BPD) on QOL, and will assist in efforts to determine the efficacy of treatments for BPD on Patient Reported Outcomes (PROs) in persons with SCI. The results of the first phase of investigation, focus group testing, has been accepted for publication (Appendix 3); the findings suggest that individuals with SCI and SCI clinical experts, with at least 5 years experience, were readily able to identify areas of everyday life that may be adversely impacted by the inability to appropriately



regulate BP (Figure 4). While there was relatively good coherence in symptoms reporting between the patients and clinicians, reporting of fatigue, in association with BPD, was greater in the patients (18%) than providers (3%). The total BPD item bank (BPQOL), which contains 196 unique and validated items, is currently being field tested in a sample of 600 persons with SCI.

Research Design and Methods

We propose to determine the effects of midodrine, administered in a randomized, double blind, placebo-controlled, outpatient trial to normalize BP over a 30-day period, on CBF, cognitive function, mood and QOL Our primary objective is to generate pilot data describing the effect size of change in CBF, cognit ive test score, mood and QOL following sustained elevation in BP, to normal levels, in hypotensive individuals with SCI. .

Approximately 50 subjects with SCI will be screened for study eligibility. We anticipate that approximately 40 of the subjects screened will be eligible and will undergo a 4-hour laboratory dose-effect trial. Once dose has been determined subjects will be randomized by IVAN (Interactive Touch Tone Randomization System) to receive either midodrine or placebo for the 30-day out-patient drug treatment intervention. Randomization will occur in a double-blinded manner, and individuals that use an abdominal binder regularly will be stratified equally as will those with a positive history of traumatic brain injury (TBI). Our recruitment target is 20 subjects per randomization category. We estimate approximately 10% attrition during the 30-day out-patient treatment protocol; as such, complete data will be available in ~36 subjects. Study medication and placebo will be distributed by the James J Peters VAMC Pharmacy Service. The study is proposed to be completed in two years. Total enrollment will be accomplished within 18 months of obtaining full IRB approval, which should be complete within 6 months of funding, and subject participation is estimated to last about 6-8 weeks.

Eligibility Criteria – Inclusion Criteria: (1) males and non pregnant females; (2) 18 – 65 years of age; (3) chronic SCI (≥ 1 year post injury); (4) ability to provide informed consent; (5) laboratory or clinical evidence of hypotension (WHO criteria - SBP ≤ 110 mmHg in males and ≤ 100 mmHg in females). Exclusion Criteria: (1) SBP > 110 mmHg for males and > 100 mmHg for females (2) documented history of: (a) coronary artery disease, (b) stroke, (c) diabetes mellitus, (d) current pregnancy or lactation, (e) cardiac arrhythmias; (f) significant systemic, hepatic, cardiac or renal illness, (g) suspected malignancy, (h) neurological disease other

than SCI; (i) history of frequent and/or severe autonomic dysreflexia (AD)*; (j) known drug allergy to midodrine; (k) acute current illness or infection (l) psychiatric disorders and (m) substance abuse.

*The incidence of AD is reported to be between 48-90% during rehabilitation in individuals with tetraplegia and high paraplegia (above T6), [89-91] and may increase with time post-injury.[90] However, in our review of the medical record, the diagnosis of AD was about 6% of veterans with tetraplegia and high paraplegia (T1-T6), the diagnosis of AD was less than 1% in those with lower thoracic lesions (T7 and below).[52] Because administration of midodrine may worsen BP elevations during episodes of AD, and we cannot rely on the medical record for an accurate report of this condition, we will administer an AD questionnaire (Appendix 4) to all participants, any potential subject with frequent (3+ episodes/week) or severe (BP elevation ≥ 150/95 mmHg and/or self-reported adverse symptomology) episodes of AD will be excluded. To evaluate the impact of midodrine on BP elevations during AD, eligible subjects will be sent home with the same survey, modified to include: subject number, the date and the BP readings.

Screening Visit – Individuals with SCI will be approached by investigators and asked to provide informed consent to participate in the Screening Phase to determine eligibility. Any subject taking a vasoconstrictor agent will be asked to stop these medications 2 days or 5 half lives (whichever is longer) prior to the screening visit. The screening assessments will include: medical intake information (Appendix 5), medical history (Appendix 6), physical examination, American Spinal Cord Injury Impairment Scale (AIS) classification, clinical symptoms survey for OH and BP monitoring. The BP monitoring will include brachial manual assessments for 10 minutes in the seated and 10 minutes in the supine position and will be recorded each minute. Individuals will be eligible to participate if the average seated or supine recordings meets the WHO criteria and there is no evidence of sustained elevation in BP >135/85 mmHg. This visit will take about 2 hours.

Dose Determination Visit – The dose determination visit will be scheduled to begin no less than 2 days and no more than 14 days after completion of the screening visit. Our preliminary data suggest that midodrine 10 mg normalized seated SBP during a 4-hour laboratory observation in 55% of the patients with SCI tested. Therefore, it is anticipated that the 10 mg dose of midodrine will be adequate to normalize seated BP in about half of our sample. However, we appreciate that some subjects with SCI will not respond adequately to 10 mg dose (our preliminary data suggest that 28% may require a higher dose), and others may have a hypertensive response (>139 mmHg: 17%, based on preliminary evidence). Eligible participants will be administered midodrine 10 mg, open-label, and BP will be monitored for 4-hours; individuals with an average 4-hour seated SBP between 111-135 mmHg will be randomized to receive 10 mg midodrine (or placebo) during the Treatment Phase. However in those with inadequate responses to 10 mg, a second open-label trial will be carried out to determine 4-hour seated SBP responses at a higher dose (15 mg) for individuals with an average SBP ≤ 110 mmHg, and at a lower dose (5 mg) for those with an average SBP > 135 mmHg. Individuals that respond to midodrine, at any of the doses tested, with two or more consecutive BP observations of >135/85 mmHg, will be excluded from the treatment phase of the investigation. Brachial BP will be recorded at 15 minute intervals and these visits will take about 5 hours.

Pre- and Post -Treatment Visits – Within 1 week of determining the appropriate dose of midodrine for each subject, eligible participants will return to the laboratory for pre-randomization testing including: (1) laboratory BP and heart rate (HR) assessments, (2) CBF measurement at rest and during cognitive testing, (3) cognitive testing, (4) mood and QOL surveys, (5) 24-hour ambulatory BP monitoring and (6) 24-urine volume. Subjects will arrive at the laboratory between 10AM and 1PM after a 4 hour fast, and having avoided alcohol, caffeine, and nicotine for 12-hours. Subjects will remain in their wheelchair for instrumentation, which will include: 1) electrocardiogram (ECG): three surface electrodes will be applied to the chest for continuous 3-lead recording of heart rate (HR); 2) brachial BP: will be monitored using a manual sphygnomometer and finger arteriolar beat-to-beat BP will be recorded using a photoplethysmograph placed around the middle and index fingers of the left hand; 3) CBF: will be monitored and recorded from the right and left middle cerebral artery (MCA) using transcranial Doppler ultrasound technology. Subjects will remain in the seated position for 30 minutes of baseline (BL) data collection; HR, BP, CBF will be monitored continuously for 5-minutes at 0, 10 and 20 minutes, brachial BP will be monitored and recorded at 30-second intervals during each of the 5-minute data collections periods. After the BL assessments subjects will be asked to participate in a complete neuropsychological battery (Appendix 7) which will include assessments of: pre-morbid intellectual abilities, attention & concentration, information processing, memory, and executive control. The NP battery will take

about 60 minutes to complete and HR, BP, and CBF will be monitored and recorded during this testing. After the NP battery is complete, subjects will be asked to answer questions related to how BPD impacts their mood and QOL (Appendix 8); these short form questionnaires were developed for use in the SCI population and will take about 15-minutes to complete. In addition, to scales developed for use in the SCI population, because fatigue was ranked highest in terms of the adverse impact of hypotension on QOL by subjects with SCI from our focus group sessions (Figure 4), we will assess fatigue specifically using the PROMIS short form and the fatigue severity scale (Appendix 8). Finally, subjects will be equipped with a 24-hour BP monitor, and will be sent home with a log to record their activities of daily living (ADL) in association with the BP recordings (Appendix 9). In addition, subjects will be sent home with a 24-hour urine collection contained and will be asked to empty their leg bag, or to urinate into this contained at each voiding for a 24-hour period to assess hydration status. Post-randomization testing will be scheduled for approximately 30±3 days after randomization and, prior to returning to the laboratory, subjects will be asked to take their morning dose of the study medication. These visits will take about 4 hours.

Treatment Phase –After pre-randomization testing, subjects will be randomized to either midodrine (at the individually effective dose) or matching placebo and will be sent home with a one-month (30±3 day) supply. Subjects will be asked to take the study medication three times per day, at approximately 8 am, 12 noon and 4 pm; however, each patient will establish his/her daily regimen with Dr. Galea based on their individual sleep/wake schedules and ADLs. Subjects will be asked to keep a log of the time of day each dose was taken along with their BP and any adverse events (Appendix 10). Three BP values will be recorded and uploaded directly to www.HealthVault.com at the time of dosing and 1 hour after taking each daily dose (total of 18 BP entries daily). Only study investigators will have access to; this website, which will be password protected and the data will be stored behind the VA firewall. Study investigators will review daily BP entries and will contact the subject if data are missing or if there is evidence of a hypertensive episode. Subjects will be asked to report, immediately (within 1 hour), any significant AE, and study investigators will contact each subject weekly to discuss study specific information and general health and wellbeing. If an individual develops a fever or any other symptom of an acute illness or infection they will be taken off study medication and discontinued from participation and will be encouraged to visit their primary care physician for an evaluation. If after treatment of the illness or infection the subject is cleared for participation by the treating physician he/she may resume participation beginning with pre-randomization testing.

Interim Visit : Subjects will be asked to return to the laboratory approximately 10 days after randomization, in the late morning or early afternoon, after taking their scheduled daily dose for assessment of BP, HR and CBF and AE reporting. This visit will take about 2 hours.

Follow -up Visit – A follow-up visit will be scheduled 7 to 10 days after completion of the Treatment Phase to collect information on any AE(s) experienced after discontinuation of study medication and for a final laboratory assessment of HR, BP and CBF. This visit will take about 2 hours.

Data and Statistical Analysis – The objectives of this proposed investigation are to determine the effects of normalizing BP for 30-days on with midodrine hydrochloride compared to matching placebo, in hypotensive individuals with SCI, on: 1) CBF at rest and during cognitive testing, 2) cognitive function, 3) mood and QOL, and (4) the number and severity of AE reporting. A similar proposal was submitted to the VA Cooperative Studies Program, but was not funded due to the lack of convincing preliminary data demonstrating that increases in systemic BP, secondary to extended use of midodrine in hypotensive individuals with SCI, raises CBF at rest and during cognitive testing and improves test performance (Appendix 11). Therefore, this project will test the following hypotheses in an effort to provide sufficient and convinci ng data to support a large -scale clinical trial to determine the long term benefits of normalizing BP in individuals with SCI across multiple VA sites through the VA Cooperative Studies Program.

Study Objective s:
Based on our pilot data we believe that the proportion of individuals classified as normotensive will be increased after 30-days of treatment with midodrine compared to those treated with placebo. We plan to classify individuals as normotensive if SBP is within the target range of 111-139 mmHg for ≥ 50% of the 24-hour observation (i.e., about 60 BP recordings) during the post-treatment period and the post-treatment relative risk of hypotension in the midodrine group versus placebo group will be assessed. Relative risk will be

determined by casting raw data into simple counts in a 2x2 contingency table, from which the proportion of cases that are classified as hypotensive in the midodrine group will be divided by the proportion of hypotensive cases in the placebo group. The 95% confidence interval for the relative risk value will be constructed, as described by Newcombe and Altman.[92] In addition, clinical relevance will be quantified by calculating the number needed to treat (NNT) from the relative risk calculation as follows: NNT = 1 / (hypotension rate in midodrine group – hypotension rate in placebo group).

We hypothesize that, during a typical 24-hour day, the proportion of SBP observations within the target range of 111-139 mmHg will be increased after treatment with midodrine compared to placebo, after controlling for the baseline proportion. We anticipate that about >50% of the subjects randomized to midodrine will have normal 24-hour SBP after 30-days of treatment. In contrast we expect < 25% of individuals randomized to receive placebo to have normal 24-hour SBP after the 30-day intervention. If our postulated values are accurate, the relative risk for hypotension for the subjects on midodrine would be ~0.67, which represents about a 33% reduction in the rate of hypotension in subjects treated with midodrine compared to those randomized to placebo. The resulting NNT is ~ 4, which suggests that about 4 subjects with SCI would need to be treated with midodrine to normalize BP in one subject.

We will then determine the effect of increasing SBP to normal levels on the following outcome parameters:
Cerebral Blood Flow:

- Analysis of covariance (ANCOVA) will be used to determine the change in CBF at rest and during cognitive testing following randomization to midodrine versus placebo. Pre-randomization CBF will be used as the covariate. Our hypothesis is that there will be a significant increase in CBF, both at rest and during cognitive testing, after 30-days treatment with midodrine compared to placebo.

Memory and Attention Processing :

- ANCOVA will be used to determine the change in cognitive function from baseline to post-treatment following randomization to midodrine versus placebo, using the pre-randomization t-score as the covariate. Our hypo thesis is that there will be a significant improvement in cognitive function in individuals treated with midodrine as assessed by standardized cognitive tests of memory and attention & processing speed compared to those randomized to placebo.

Depression, Anxiety and Fatigue :

- ANCOVA will be used to determine the change in mood and QOL score from baseline to post-treatment following randomization to midodrine versus placebo, using the pre-randomization QOL score as the covariate. Our hypothesis is that there will be a significant improvement in QOL in individuals treated with midodrine as assessed by the BPQOL compared to those randomized to placebo.

Adverse Events Reporting :

- To determine the differences in AEs reported at the end of 30-days treatment following randomization to midodrine versus placebo. Our hypothesis is that there will be an increase in mild and moderate drug-related AEs in individuals treated with midodrine compared to those on placebo. A few AE's may be expected to include supine hypert ension (may not have been present prior to drug **administration), exacerbation of AD (elevated BPs recorded during known trigger's for AD, such** as bowel care, bladder distension, transfers), pruritis, urinary retention and more severe or more frequent heada ches.

Secondary Analyses :

- Our conceptual model is that prescription medication class, use of support stockings, abdominal binders and history of TBI may function as mediator variables between SCI and the dependent variables. To explore this mediation, at a first level of analysis we will examine the bivariate relationships between the mediator and dependent variables. Second, we will build hierarchical multiple regression models in which a potential mediator variable and SCI status (dummy coded) are both forced into the model. In addition, examination of the partial correlation between SCI and dependent variables (after partialing out the effect of the mediators relative to the zero order correlation will provide insight into the effect size.