Study Title: The role of pharmacological agents in restoring neuronal excitability after chronic SCI

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Participant Name:Click or tap here to enter text. Date:Click or tap to enter a date.

Title of Study: The role of pharmacological agents in restoring neuronal excitability after chronic SCI

Principal Investigator: Lynda Murray, PhD VA Facility: James J. Peters VAMC

KEY SUMMARY INFORMATION ABOUT THIS STUDY

You are being asked to participate in a research study. Before you decide to take part, it is important for you to know why the research is being done and what it will involve. This includes any possible risks to you and any potential benefits you might receive.

Read the information below closely and take your time to decide. You may discuss it with your family and friends if you wish. If there is anything that is not clear or you would like more details, please inform the study staff. If you do decide to take part, your signature on this form will represent that you have received and understood all information below and discussed any questions and concerns with the study staff.

WHAT IS THE STUDY ABOUT AND HOW LONG WILL IT LAST?

This study will shed light on the potential role and mechanisms of three Food and Drug Administration (FDA) approved medications: cyproheptadine, carbidopa-levodopa, and atomoxetine, when delivered in combination with hand training exercises. The study will investigate the short-term effects of each study drug, compared to placebo, on normalizing and restoring central nerve system excitability and muscle strength in individuals with weak hand motor function after cervical spinal cord injury (SCI). By doing this study, we hope to find combinations of study drugs and hand/wrist exercises that may temporarily improve nerve transmission to your hands.

Your participation in this research will last up to 7 visits over roughly 5 weeks.

WHAT ARE KEY REASONS YOU MIGHT CHOOSE TO VOLUNTEER FOR THIS STUDY?

If you decide to participate:

- The study medication has the potential to temporarily improve different body systems/functions, and nerve transmission to your hand muscle function.
- You may learn more information about how your body responds to these study medications.
- You may learn more information about the nerve transmission between your brain and your hand muscles.
- Also, the information we get from this study might help others with your condition.

For a complete description of benefits, refer to the Detailed Information section of this form.

WHAT ARE KEY REASONS YOU MIGHT CHOOSE NOT TO VOLUNTEER FOR THIS STUDY?

It is important for you to know that you may not get any benefit from taking part in this research study. This study will not lead to a cure or to permanent improvements from your SCI.

The study involves magnetic and electrical stimulation – sometimes stimulation may be uncomfortable. We can stop at any time.

There is a risk of adverse events such as fatigue or increased muscle spasms. There is also a very small risk of seizure.

The are the potential side effects from the study medications.

For a complete description of risks, refer to the Detailed Information section of this form.

DO YOU HAVE TO TAKE PART IN THE STUDY?

Taking part in this study is completely voluntary. If you are receiving clinical care at James J. Peters Veterans Affairs Medical Center (JJPVAMC), your clinical care will continue to the best of our ability whether or not you participate.

If you decide to take part in the study, it should be because you really want to volunteer. You will not lose any services, benefits or rights you would normally have if you choose not to volunteer.

WHAT IF YOU HAVE QUESTIONS, SUGGESTIONS OR CONCERNS?

The person in charge of the study is Lynda Murray, PhD, at JJPVAMC. If you have questions, suggestions, or concerns regarding this study or you want to withdraw from the study his contact information is:

Dr. Lynda M. Murray, Ph.D.
During the Day: 718-584-9000 x5426
After Hours: 347-399-7231

DETAILED INFORMATION ABOUT THE STUDY

There are no established drug treatments to promote recovery following SCI. A number of medications have been shown to affect nerve excitability by influencing neurotransmitters such as serotonin, dopamine, and epinephrine. The key idea behind this strategy is that these systems play a critical role in how neurons communicate. This study will shed light on the potential role and mechanisms of three FDA approved medications: cyproheptadine, carbidopa-levodopa, and atomoxetine, when delivered in combination with hand training exercises. The study will investigate the short-term effects of each study drug, compared to placebo, on normalizing and restoring CNS excitability and muscle strength in individuals with weak hand motor function after cervical SCI.

This study wouldn't be possible without the support of the study sponsor, the Craig H. Neilsen Foundation (CNF; www.chnfoundation.org).

WHAT IS THE PURPOSE OF THIS STUDY?

You are being asked to participate in a research study. **The purpose of this study is to investigate the short-term effects of cyproheptadine, carbidopa-levodopa, and atomoxetine on motor responses when delivered in combination with hand training exercises.** You are being asked to participate in this research study because you are between the ages of 18 and 80 and you have a cervical spinal cord injury that happened more than 12 months ago.

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By participating in the study, you will undergo a series of experimental research tests that are not part of usual medical care. Firstly, the study involves the off-label use of three FDA approved drugs called cyproheptadine, carbidopa-levodopa, and atomoxetine, as well as the use of several well-established magnetic and electrical stimulation techniques for assessing changes in the CNS. These responses will be examined before and after the administration of the study drug(s), or a look-a-like placebo, in combination with hand training exercises.

All procedures will take place at the JJPVAMC's Spinal Cord Injury Research Center (SCIRC; www.scirc.org), 7th floor, Suite A-13.

HOW LONG WILL I BE IN THE STUDY?

There are 7 visits in total, including the initial evaluation and clinical assessment session. You will be required to participate in all visits. Should a study drug visit be aborted, you will be given the option to repeat the session following adequate washout (optional). The experiments will be performed in a randomized order with at least one-week break between experimental drug visits. Each visit will last roughly up to 5 hours or less. We plan to enroll 28 participants with cervical SCI over a two-year period.

WHAT WILL HAPPEN IF I TAKE PART IN THE STUDY?

If you consent to participate in this research study, you can expect the following:

General: All participants will undergo the same procedures. You will come to our research center in Suite 7A-13 of the JJPVAMC main hospital building for all your visits. You will be seated in an adjustable upholstered reclining chair in our testing room within the research center. Alternatively, the experiment can be performed in a manual or powered wheelchair.

Clothing: During the clinical evaluation, we need access to your arms and legs to test sensation and perform manual muscle testing. It is also important that we have access to your full arm for us to locate sites of stimulation and placement of electrodes during each visit. You will be asked to wear light loose-fitting clothing such as a short-sleeved t-shirt or shorts. Alternatively, a sleeved top or pant that can be lifted/rolled up will be okay. A surgical gown can be provided if inappropriate clothing is worn.

Visit 1 (approximately four hours)

In-person screening: Accompanying an initial phone screening, you will be asked to attend an in-person screening to discuss risks, discomforts, and potential benefits of the study. After authorizing HIPAA and providing informed consent, the following eligibility assessments will be administered:

Questionnaires: Routine demographics and other questionnaires (e.g., TMS screening) will be completed ensure there will be no issues with you taking any of the study drug(s) and/or receiving the stimulation performed in the study. A review of your medical and SCI history will be performed. This will determine if you have a medical history of any other condition(s) that would make you ineligible to participate in the study. This is partly to protect your safety. Capabilities of Upper

Extremity Questionnaire (CUE-Q), patient-reported assessment of upper extremity functional capacity, will also be performed.

Clinical examination: A routine physical and neurological exam will be performed (lasting 30-40 minutes) after you are helped to transfer onto a treatment table. The examination includes a test of your sensory function at key levels above and below your spinal injury and strength of key hand and arm muscles. If we are unable to detect some ability to partially move your fingers or wrist voluntarily during this visit, you will not be eligible for further participation in the study.

Preliminary screening of experimental tests:

- Muscle activity recording: Activity within your muscles will be measured using several surface electrodes attached to the skin overlaying key muscles of your hands and arms. For the electrodes to adhere to the skin and give clean uninterrupted recording, the skin may need to be cleaned, shaved and lightly exfoliated. The electrodes are secured in place with hypoallergenic tape or tegaderm, a clear sticky film. These electrodes are only used to record muscle activity and do not stimulate. A computer will record any signals generated during the following test procedures. If we are unable to detect enough responses in your hand or wrist muscles with the following test procedures, you will not be eligible for further participation in the study.

- Noninvasive brain stimulation testing: This test measures your muscle responses to stimulation of

your brain. A transcranial magnetic stimulator and hand-held coil with neuronavigation capabilities will be used to deliver short magnetic pulses of stimulation over the skin on an area of your head where the brain sends signals to your hand muscles. Due to some overlap of the hand and face muscles on the motor area in the brain, you might find that this stimulation activates several areas causing twitches in your face and arm muscles at the same time. These twitches are normal and will be recorded. Regardless of injury, anatomical differences (i.e., skull shape and thickness) may reduce the effectiveness of the stimulation. Non-responders will still be able to participate in the study as long as the hand dexterity test is achievable.

- Noninvasive spinal stimulation testing: This test measures your muscle responses to stimulation of nerves exiting your spinal cord. A surface electrode will be placed on your skin over the spinal location known to control hand and wrist circuits. The electrodes are similar to the ones used to deliver transcutaneous electrical nerve stimulation (TENS) and will be secured in place with hypoallergenic tape or tegaderm. We will deliver a series of short electrical pulses at low intensity to your spine. This type of stimulation causes multiple muscles to twitch- twitches are normal and will be recorded.

- Noninvasive peripheral nerve stimulation testing: This test measures your muscle responses to stimulation of nerves located in your wrist and elbow. A surface electrode will be lightly pressed to the skin over a nerve and a series of short electrical pulses at a low intensity will be

applied to the nerve via the same stimulator as the spinal stimulation. This type of stimulation causes a twitch in the muscle(s) being tested – this is normal. The electrodes used to deliver the electrical pulses are adhesive and lined with a gel-like substance to ensure the delivery of electrical current to the skin is safe and painless.

- Muscle strength testing: In this test we will measure the amount of force you can produce while performing an action with a gauge placed in your hand. We will measure the best force you can produce out of three attempts with 100% effort.

- Hand dexterity: In this test we will measure your ability to move items from one compartment/hole to another. We will measure the best time it takes you to complete the task.

Autonomic function tests: Throughout each visit we will perform frequent checks of your seated blood pressure, heart rate, and oxygen saturation levels.

Safety and side effects questionnaires: As the study involves the ingestion of a study drug(s), or look-a-like placebo, and the delivery of various types of stimulation, it is important that we monitor your experiences as they feel to you. A set of questionnaires will ask questions regarding your comfort level and the presence of any adverse side effects (e.g., a headache, nausea, or skin irritation). These questionnaires will be administered at multiple timepoints throughout your visit to monitor any change(s).

If there are any major issues or problems during the first visit, such as significant changes in blood pressure accompanied by shortness of breath, or other significant discomfort(s), the procedure will be halted immediately, and appropriate medical care will be provided. Depending on the event(s), for your own safety you may not be eligible to participate further in the study.

Blood test: All participants will be required to give a blood sample for the purposes of checking liver and kidney function prior to participating in the study. You will have approximately 2 teaspoons (10 mL) of blood withdrawn (once, prior to commencing the study).

A phlebotomy-trained study staff will: clean the skin, put an elastic band (tourniquet) above the area to get the veins to swell with blood, insert a needle into a vein (usually in the arm inside of the elbow or on the back of the hand), pull the blood sample into a vial or syringe, take off the elastic band and remove the needle from the vein. Your blood will be appropriately discarded after the test is completed. If the test shows signs of liver or kidney disease, for your safety you will not be eligible to participate in the study.

Visit 2+3 (approximately one and a half hours each)

Hand training exercise practice visits: This light exercise session, resembling motor tasks that are usually performed on a day-to-day basis, such as writing, using keys, stringing beads, lacing/braiding yarn, holding/flipping cards, and picking up small objects. Exercises will be challenging enough that you can complete 50-75 % of the work without assistance. The purpose of these practice sessions are to assess your ability to complete different activities and give you time to understand and practice the task.

Autonomic function test will also be performed.

Visits 4-7 (approximately five hours each)

General: The study staff will collect the drug, or look-a-like placebo, from the VA Pharmacy the day of the experiment. The Pharmacy is responsible for randomizing the order of the drug and placebo in a blinded fashion. This means that you and the study staff will not know what the tablet contains until all data has been collected at the end of the entire study. Identity of the study drug will remain blinded unless there is a medical event that occurs during a testing session.

Set-up: Using the same testing techniques described above in Visit 1 (noninvasive brain, spine and peripheral nerve stimulation), and surface electrodes for muscle activity recording and stimulation, you will receive a series of magnetic and electrical pulses to confirm correct targeting of stimulation over muscle "hotspots", and to measure stimulation "thresholds" that will be used to calculate the intensity needed in different testing techniques. The set-up, including hotspot and threshold testing, will take approximately 30 minutes and will only need to be performed once at the start of every visit. Muscle strength and hand dexterity will also be assessed as described in Visit 1.

Intervention: For every visit, the intervention requires you to ingest two capsules (contents disguised) with up to 180 mL (6 Oz) of water, on an empty stomach (minimum 2 hours without food). Depending on the VA Pharmacy's coded randomization, one of four interventions will be performed: **1**) cyproheptadine + hand training; **2**) carbidopa-levodopa + hand training; **3**) atomoxetine + hand training; and **4**) placebo + hand training. After ingesting the capsules, you will spend 50 minutes performing five different upper arm/hand exercises for 10 minutes/exercise. For example, finger and thumb isolation exercises, stringing beads, lacing/braiding yarn, holding/flipping cards, stacking and/or sorting small objects, etc. There will be a 10-minute rest before all baseline experimental tests are repeated.

Pre- and post-intervention testing: The same baseline experimental tests will be performed 60 minutes after drug ingestion, as described in Visit 1. Autonomic function tests and symptom questionnaires will be performed frequently throughout the entire visit to ensure you are not experiencing any adverse effects due to the study drug or the stimulation. Muscle activity in response to different stimulation protocols and strength and dexterity of key muscles will be measured. These testing techniques will take approximately 60 minutes to complete and are designed to see if your muscles respond better to the study drug(s) versus placebo when delivered in combination with hand motor exercises.

The tests performed in this study are for research purposes and not the same as regular medical care. They are performed for specific research purposes and are not set up to find abnormalities. However, on occasion we may notice a finding that should be followed up by your primary care doctor. If you are a Veteran, we will arrange for a visit with your VA primary doctor. If you are a Veteran and you do not have a primary care doctor, we will refer you to one within the VA system. If you are not a Veteran, we will advise you to follow up with your primary care doctor. **You can**

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decide at any time not to continue participating in the study. Your future care or privacy at the VA will not be affected by leaving the study.

WHAT IS EXPECTED OF ME IF I TAKE PART IN THIS STUDY?

Keep your study appointments. If you need to miss an appointment, please contact the research staff to reschedule as soon as you know you will miss the appointment.

While participating in this research study, do not take part in any other research project without approval from our team. This is to protect you from possible injury from things such as extra blood drawing. Taking part in other research studies without first discussing it with our team may invalidate the results of this study, as well as that of the other studies.

Tell the investigator or research staff if you believe you might be pregnant.

Ask us any question(s), at any time.

WHAT POSSIBLE RISKS OR DISCOMFORTS MIGHT I HAVE IF I TAKE PART IN THIS STUDY?

Discomfort or Inconvenience

You are being asked to participate in a study that requires a time commitment of 7 visits, performed at roughly the same time of day for every visit. During these visits we will frequently check your blood pressure, heart rate, and oxygen levels throughout the procedure. This may be an inconvenience. Repeating an aborted session may also be an inconvenience, however this will be optional.

A blood sample of 10 mL (2 teaspoons) will be required to rule out any liver and kidney issues that could pose a risk when taking the study drug. The blood collection will involve the use of a needle piercing the skin and as such may be uncomfortable for some.

The study involves three FDA-approved drugs used in an off-label manner. Cyproheptadine, carbidopa-levodopa, and atomoxetine have been associated with headaches, dizziness, drowsiness, tiredness, nausea, vomiting, diarrhea, constipation, urinary hesitation/retention, erectile dysfunction, irregular/painful menstruation, changed appetite, stomach pain, increased sweating, dry mouth, blurred vision and feelings of anxiety and depression, with or without suicidal tendencies. However, many people using these medications do not have side effects, and if you do have side effects, they will likely wear off quickly since you are only getting one dose of the drug. Tell us immediately if you notice any symptoms of a serious allergic reaction, such as: rash, itching/swelling (especially of the face/tongue/throat), severe dizziness, or trouble breathing. If you tell us or we notice any significant symptoms or changes in your vital signs, we will halt the procedure immediately, unblind the study drug, and provide appropriate medical care.

Skin irritation at the site of electrode application may occur. Areas with too much hair will be shaved prior to adhesive application. Any open skin wounds will be avoided; however, location or severity of a wound may prevent your participation.

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The Brainsight transcranial magnetic stimulation (TMS) tracking system uses passive reflecting stickers. Although this is a passive detection device, skin irritation from the reflector piece being adhered to the forehead by fashion body tape may occur. Alternatively, a snug head strap can be used.

Other discomforts including headache (which may include migraine), local pain, neck pain, toothache, and facial numbness/tingling are possible with magnetic stimulation but almost always mild and transient. Usually, headaches cease as the stimulation ceases. These symptoms will be minimized with adequate rest breaks, and acetaminophen (Tylenol) if necessary. To reduce the occurrence, we will screen out people who suffer from frequent severe migraines or other types of headaches.

Sometimes a muscle in your scalp, forehead, or neck might twitch from the stimulation- this is normal. The stimulation also produces a 'clicking' noise that may cause some irritation over the ear and possible hearing loss. This can be minimized with the use of earplugs. The stimulation may cause some people to clench their jaw, in these cases a mouthguard can be provided. If you do feel discomfort, it should not last more than a few seconds. You can decide to stop the procedure at any time.

Whether it's over the head, neck or arm, the applied stimulation could cause brief irritation or discomfort of the skin around surrounding areas. All forms of stimulation will cause your muscle(s) to twitch – this is normal. When nerves in the forearm or wrist are stimulated, you may feel it as sharp but tolerable. If you feel discomfort, you should tell us. We will reduce the intensity or stop the stimulation altogether.

Electrical stimulation applied over your neck may theoretically cause symptoms such as nausea, light-headedness, and sweating. If you notice any of these symptoms, we will stop the procedure immediately and provide appropriate medical care.

The devices used in this study are for research purposes only. In the future, versions of these devices may be available for home use, but not at this time. Therefore, the devices used in this study will not be available for your use outside of the study or after your participation is completed.

Expected Risks of Study

There is a small risk of falling during transfers between different chairs and treatment tables; with the risk of falling, is the risk of bone fracture. The study staff are trained and experienced in the care of participants with limited mobility, including extensive safety experience in preventing falls. You will never be left unattended during a test session.

With blood being drawn at the start of the study, there are some risks of discomfort, bruising, and rare but possible fainting or infection. If there are symptoms of dizziness or lightheadedness, you might be instructed to lie down during the blood collection. The collection of blood will be performed by a health care professional or a phlebotomy-trained study staff.

There may be a risk of allergic reaction to cyproheptadine, carbidopa-levodopa, and atomoxetine ingestion, depression with or without suicidal ideation (carbidopa-levodopa, and atomoxetine), very rare risk of neuroleptic malignant syndrome (carbidopa-levodopa, upon sudden discontinuation of long-term use), as well as an associated risk of liver toxicity, low white blood cell count, and/or cardiovascular problems. Note that these medications have all been FDA-approved for use in other conditions such as Parkinson's disease. Thus, serious side effects are unlikely given the safety record in other patient populations and that participants only receive a single dose of cyproheptadine, carbidopa-levodopa, and atomoxetine on separate occasions. There may be an instance where your experiment is aborted, and you are given the option of repeating the session. It is unlikely that a single repeat, upholding the washout period, will increase the risk of adverse reactions. Nevertheless, prior to consenting, you will undergo a comprehensive pre-screening evaluation including blood tests and will be excluded if at risk of these rare reactions.

We do not advise stopping or decreasing your usual doses of other medications to participate in this study. In general, there are risks with suddenly stopping medications (i.e., antidepressants and antiepileptics) or greatly decreasing the dose. Rebound or withdrawal symptoms, including seizures, may occur. To minimize these risks, participants will be instructed to continue the medications as prescribed by their physician. Medication must be stable for ≥ 30 days prior to screening.

TMS carries several potential risks. The most serious risk of TMS is induction of seizures or "convulsive syncope" (fainting with seizure-like movements). TMS-induced seizures are usually focal, but in some cases can become generalized. Seizure induction with the type of TMS used in this study is extremely rare. The risk of seizure is extremely small, roughly 8 per 100,000 sessions. TMS-induced seizures are usually focal, but in some cases can become generalized. To minimize this risk, participants with history of severe brain injury requiring neurosurgery will be excluded from participation (see full list under Exclusion Criteria). Furthermore, the applied stimulus intensities fall below the recommended safe guidelines delineated by an international workshop on TMS safety (Rossi et al. 2009, 2021). As brain stimulation is expected to produce a muscle response in the targeted muscle, we will visually and electrically monitor different muscles in the same arm and in the opposite hand to ensure there has been no spread of excitation across different brain regions that might be indicative of increased seizure risk. Furthermore, the co-investigator, Dr. Noam Harel, is a board-certified neurologist experienced in treating seizures. All procedures take place within the JJPVAMC, where there is access to all forms of life-support equipment, medications, and medical personnel. In the unlikely event of a seizure during this study, you should be aware of the implications a seizure could have on your future employment, insurance and eligibility to drive. Since such an event would be considered a response to the procedure and not an underlying disease, Dr. Harel would provide a letter to you documenting that this event does not indicate any underlying disease that could affect your employability, driver's license, or health/life insurability.

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If there are any symptoms of dizziness or lightheadedness, which could potentially be warning signs of convulsive syncope, we will halt the procedure immediately, investigate and take steps to end the symptoms. If you feel as though you will pass out. We will lie you down and elevate your legs. Those with previous history of syncope will be assessed for eligibility by Dr. Harel (Co-Investigator).

There is a theoretical risk of TMS causing acute psychotic or manic symptoms in patients with depression. This risk is not clearly above the natural rate of psychotic or manic symptoms that may arise in subjects with depression. Regardless any subject with history of bipolar disease, active psychotic symptoms, or history of suicide attempt will be excluded.

TMS pulses generate loud auditory clicks. Risk of hearing changes due to the 'click' of the stimulator will be minimized by using earplugs during the experiment. Individuals who complain of hearing loss, ringing in the ears (tinnitus), or ear pressure following completion of TMS will be referred to the appropriate medical care. To further reduce risk of hearing loss, we will closely monitor you to make sure the earplugs do not loosen or fall out and halt the procedure if they do. While individuals with cochlear implants will be excluded, others with pre-existing hearing issues will be assessed for eligibility.

Although extremely rare, we will also monitor for other potential complications such as uncomfortable visual changes. Any such complications will result in immediate cessation of the protocol.

The electro-magnetic field generated by TMS exerts forces on ferromagnetic objects such as implanted spine stimulators, deep brain stimulators, vagal nerve stimulators, cardiac pacemakers, cochlear implants, or aneurysm clips. For safety, anyone with such implants will be excluded from participating. Furthermore, jewelry, glasses, and other potentially conducting or magnetic objects worn on the head will be removed during TMS experiments. Participants need to avoid wearing eye makeup such as eyeliner, mascara, and eye shadow. It is worth noting that chronic exposure to electro-magnetic fields appears safe at levels even greater than those possible with TMS.

The research team has delivered TMS pulses extensively in prior and ongoing IRB-approved clinical studies. No study participants have ever experienced a seizure in any of our studies since we began using TMS in 2011. A standardized form to assess TMS side effects is used at the end of each TMS session. The type of stimulation we deliver, as well as all the other precautions and exclusion criteria we will follow, far exceed the recommended guidelines established by TMS experts.

Electrical pulses may be transiently irritating or painful. Stimulation will be reduced or halted if you are too uncomfortable. Electrical stimulation of the upper spinal cord may theoretically alter activity in vagal or other "autonomic" nerve circuits. The most likely adverse risks of autonomic activation would be nausea, light-headedness, sweating, or fainting.

There is a possible but unlikely risk that magnetic or electric stimulation could cause a heart rhythm problem. However, the stimulation procedure used in this study will not cause current to cross over the heart muscle. Nevertheless, to provide further caution against cardiac damage or rhythm problems, participants with significant coronary artery disease, cardiac conduction disease, or implanted pacemaker/defibrillators, or history of recurrent autonomic dysreflexia (AD) will be excluded from participation. To provide further caution, the procedure will be conducted with continuous monitoring of vital signs. Any significant change in blood pressure or oxygen level with symptoms will lead to us immediately stopping the procedure and providing medical evaluation and treatment.

In subjects with SCI, there is a risk of "autonomic dysreflexia" (AD) – this is defined as a syndrome of sudden rise in blood pressure accompanied by symptoms such as headache, facial flushing, sweating, nasal congestion, and blurry vision. It usually occurs due to problems such as bowel or bladder obstruction. There is a theoretical risk that it could occur in response to magnetic or electrical stimulation. Potential subjects who have a history of recurrent AD within the past 6 months will be excluded. The study staff will be monitoring your blood pressure, heart rate, and symptoms the entire time. If AD is suspected, the procedure will be halted so that the study team can sit the subject upright and address bowel, bladder, or other triggers as necessary. This is a standard approach to managing episodes of AD. Subjects who experience AD during any session may be withdrawn from further participation.

This research may have unknown effects on an unborn child. For female born participants, the study should not be performed during pregnancy. A pregnancy test may be requested. You also agree to avoid becoming pregnant during the study.

There always exists the potential for loss of private information, however there are procedures in place to minimize the risk (explained below).

There may also be potential risks that are unknown.

WHAT ARE THE POSSIBLE BENEFITS OF THIS STUDY?

It is important for you to know that you may not get any benefit from taking part in this research study. Others may not benefit either. However, any information we get from the study can help others with SCI (including you) in future studies. This study may result in the development of better rehabilitation strategies for people who have a neurological disorder.

HOW WILL MY PRIVATE INFORMATION BE PROTECTED?

Your participation in the study will be included in the VHA health record. A copy of the signed informed consent and signed HIPAA authorization for participation in the study will be in your health record. The study staff has no real or apparent conflicts of interest involving the study.

Only the study staff will have access to the research materials obtained from you during this study. These materials will be secured in a locked cabinet in SCIRC (7A-13) as well as on a password-protected file on the VA secure network (S:\SCI Research\Neurorehab Studies\Active

studies). Your identifiable and personal health information (PHI) will be protected by coding your identity. Only research personnel approved by IRB, R&D, PO, and ISO, as applicable, will have access to identifiable research data. The code is kept in a locked cabinet and secured on password-protected electronic servers. The code will not be used to link information back to you without your permission, unless required to do so by law. This code is different from the VA Pharmacy randomization code used to decide the drug order.

We will let you and your primary care physician know of any significant findings made during this study that are clinically relevant or which may affect your willingness to participate.

Your medical records will be maintained according to the Medical Center's requirements. Records will be retained according to National Archives and Records Administration, in accordance with Records Schedule RCS-10-1. In order to comply with federal regulations, research records identifying you may be reviewed by the following: Representative of the study sponsor [CNF]; Authorized representatives of the JJPVAMC (i.e., IRB, Research Compliance Officer), including the Office of Research Oversight, and similarly authorized representatives of the Mount Sinai Medical System; Federal Agencies such as the Government Accounting Office (GAO), and FDA; The Office for Human Research Protections (OHRP); Office of Inspector General (OIG). The Bronx Veterans Medical Research Foundation, Inc. (BVMRF) for participant payments. Greenphire, provider of ClinCards for payment.

Because this research involves articles regulated by the FDA, the FDA may choose to inspect and copy medical or research records that identify individual research subjects.

A description of this study will be available on www.clinicaltrials.gov. This website will not include information that can identify you. At most, the website will include a summary of the results.

If you allow our team to arrange for your transportation, please note that your identifiable contact information and mobility details will be given to our transportation provider, essential for organizing appropriate transportation.

Photography, audio and video consent (optional)

We may ask to photograph or video record you during study procedures for the purposes of academic presentations, publications, or study advertising. Any media will be stored on a password-protected secure VA network drive, coded by subject number, date and activity. No other identifying information will be attached to the recordings. If results of this study are reported in medical journals or a meeting, you will not be identified by name, recognizable in photographs, 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.**

The purpose of this section is to document your consent to the Department of Veterans Affairs' (VA) request to obtain, produce, and/or use a verbal or written statement, photograph, digital image, video, and/or audio recording containing your likeness or voice. By signing this **optional** section below, you are authorizing the production or use only as specified. You may rescind your

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consent at any time prior to, during, or upon completion of the media production by supplying a written request. You may rescind your consent after production is completed at the discretion of the VA/study staff due to the burden of complying in regard to the financial and administrative costs, the ease of compliance, and the number of parties involved. The VA/study staff will comply as long as the request is reasonable. All requests must be made in writing.

I hereby give my permission to Dr. Murray to use any photography, digital image, video and/or audio recording material taken of myself whilst enrolled and undergoing study procedures for current protocol, entitled "The role of pharmacological agents in restoring neuronal excitability after chronic SCI". I have read and understood the foregoing, and I consent to the use of photography, digital image, video, verbal and/or written statements that include(s) my likeness and/or voice as specified for the above-described purpose(s). I understand that no royalty, fee, or other compensation of any kind will be made to me by the United States for such use. I understand that consent to obtain, produce, and/or use photography, digital image, video, verbal and/or written statements containing my likeness and/or voice is voluntary, and my refusal will not adversely affect my participation in the study or access to any present or future VA benefits for which I am eligible. The following requests apply:

The following requests apply. Select all that apply (tick or cross box):

- ☐I request my face not to be in view
- ☐I request my face to be blurred / barred
- ☐I do not mind my face being seen
- ☐I permit use for presentations
- ☐I permit use for publications
- ☐I permit use for the Laboratory's website.

_____ _____ _____

Participant Signature Date Time

☐ *By checking this box, I agree to be contacted by the Principal Investigator or study staff at a future date for additional studies being conducted at the Center.*

WHAT ARE THE COSTS TO ME IF I TAKE PART IN THIS STUDY?

As a Veteran or non-Veteran, you or your insurance will not be charged for any treatments or procedures that are part of this study. If you usually pay co-payments for VA care and medications, you will still pay these co-payments for VA care and medications that are not part of this study.

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Effective Date: November 6, 2025

You will be reimbursed to offset any travel expenses and inconveniences you may endure as a result of your participation in the study. You will be reimbursed $50 for the evaluation and screening (Visit 1); $25 each for the hand training practice sessions (Visit 2+3) and $100 per experimental session (Visit 4-7) thereafter. The total amount for participating in all sessions adds up to $500. If a session is repeated, you will be reimbursed the nominated value for that session. You will be reimbursed according to the number of visits that you complete.

Payment may be in the form of a check, received approximately 4-6 weeks after participating in the study, or a reloadable Greenphire ClinCard. Greenphire is a company working on behalf of The Bronx Veterans Medical Research Foundation (BVMRF) to support this reimbursement process. In order for you to get paid, Greenphire will need to process certain personal information about you, including your Name, Address, and Date of Birth, in order to be able to set up and facilitate your reimbursement via the ClinCard. This information will be collected from you by the study staff and given to Greenphire.

Greenphire will collect and use your information for the following purpose(s): ClinCard. You may be issued a Greenphire ClinCard, which is a debit card that your funds are loaded onto. When a study visit is completed, funds will be approved and loaded onto your ClinCard. The funds will be available within 1 business day and can be used to pay for anything you need. Protect this card like cash. If you lose the ClinCard, please contact the study team, they can provide you with a new one that will transfer any monies you have available.

Greenphire has administrative, physical, and technical safeguards that reasonably and appropriately protect the confidentiality, integrity, and availability of your personal information. Your personal information will be used and disclosed only to support the described research activities, including to service providers who assist us in managing, administering, or delivering the Services. Your personal information will not be shared by Greenphire or sold, used, or distributed for any other purpose. Your information will be kept for as long as necessary to provide the described activities and for compliance with applicable laws. You can exercise your rights to access, correct, modify, or delete your information at any time by contacting the staff from this study. If you exercise your rights or take away your consent, the study staff will not further transfer your personal information to Greenphire; however, this may not affect processing that occurred before you took away consent.

Payment received as compensation for participation in research is considered taxable income. If payment exceeds $600 in any one calendar year, BVMRF (if opting for check payment) or Greenphire will file a 1099 (Miscellaneous Income) form on behalf of BVMRF. BVMRF/Greenphire will need your Name, Address, and Social Security Number.

WHAT WILL HAPPEN IF I AM INJURED BECAUSE OF MY BEING IN THE STUDY?

If you are injured as a result of taking part in this study, the VA will provide necessary medical treatment at no cost to you unless the injury is due to non-compliance by a study participant with

study procedures or if the research is conducted for VA under contract with an individual or non-VA institution.

If you are injured as a result of taking part in this study, you will not receive additional compensation. You will not give up any legal rights or release the VA from any liability by signing this form.

If you should have a medical concern or get hurt or sick because of taking part in this study, call Dr. Noam Y. Harel, M.D. Ph.D. (Co-investigator and Study Physician):

Dr. Noam Y. Harel, M.D. Ph.D.

During the Day: 718-584-9000 x1742

After Hours: 917-428-7258

DO I HAVE TO TAKE PART IN THE STUDY?

You are not required to take part in this study. **Your participation is entirely voluntary**. You can refuse to participate, 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 Veteran.**

If you are a VA employee or student, your refusal to take part in the study will in no way influence your employment, ratings, subsequent recommendations, or academic progress as applicable.

RIGHT OF INVESTIGATOR TO TERMINATE MY PARTICIPATION

If you decide to withdraw from this study, please notify one of the study staff. This will not interfere with your regular medical treatment at the VA. Alternatively, your participation may be terminated by us without regard to your consent under certain conditions, including, but not limited to, medical concerns (your health and safety are in jeopardy with continued participation in the study), noncompliance (you miss several scheduled appointments without notification) and protocol deviations (exclusion/inclusion criteria change and you are no longer eligible).

WHO DO I CONTACT ABOUT THIS STUDY IF I HAVE QUESTIONS?

If you have questions about your rights as a research subject and would like to speak to someone outside of the research team, you may contact the Associate Chief of Staff for Research (ACOS/R) Office at (718) 741-4228 or the hospital extension 4228 first floor in the research building, room 1F-01 to request an appointment with the ACOS/R or designee.

WILL I BE TOLD NEW INFORMATION ABOUT THIS STUDY?

The research tests we perform in this study are not standard clinical tests, so the findings are not directly clinically relevant.

However, if we learn anything during the course of this research study that might change your opinions about staying in the study, we will tell you about it and discuss with you whether you want to continue in the study. For example, if we learn that unacceptable side effects such as

worsened pain or spasms consistently result from study participation, we would tell you about it and modify the study as needed. That can result in changes to this consent form. If you decide to continue in the study, you might be asked to sign an updated informed consent form.

If you decide to withdraw from the study for this or any other reasons, your regular medical care will continue. Your research doctor could also decide it to be in your best interests to withdraw you from the study. If so, he or she will explain the reasons and arrange for your usual medical care to continue.

AGREEMENT TO PARTICIPATE IN THE RESEARCH STUDY

Dr./Mr./Ms_____ _____ has explained the research study to you. You have been told of the risks or discomforts and possible benefits of the study. You have been told of other choices of treatment available to you.

You have been given the chance to ask questions and obtain answers.

By signing this document below, you voluntarily consent to participate in this study. You also confirm that you have read this consent, or it has been read to you. You will receive a copy of this consent after you sign it.

I agree to participate in this research study as has been explained in this form.		
_____ Participant's Name	_____ Participant's Signature	_____ Date
_____ Person Obtaining Informed Consent (Investigator or Delegate as indicated on Assurance Page)	_____ Signature of person obtaining informed consent	_____ Date

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Participant Name:Click or tap here to enter text. Date:Click or tap to enter a date.

Title of Study: The role of pharmacological agents in restoring neuronal excitability after chronic SCI

Principal Investigator: Lynda Murray, PhD VA Facility: James J. Peters VAMC

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 to participate in this research. 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 informed consent

_____	_____	_____
Printed name	Signature	Date

Witness to consent

_____	_____	_____
Printed name	Signature	Date

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