STU#: 00078099

PROTOCOL TITLE: Altering activations patterns in the distal upper extremity after stroke

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VERSION NUMBER: 7

VERSION DATE: January 8, 2019

OBJECTIVES:

Aim 1: Determine the capability of an anti-serotonergic agent to reduce hyperexcitability poststroke without compromising voluntary strength.

Aim 2: Assess the efficacy of using a multimodal intervention combining an anti-monoaminergicagent with upper extremity training.

Hypothesis: We investigators hypothesize that the group receiving the combined cyproheptadine and active movement therapy will have better outcomes than the groups receiving passive therapy or placebo.

BACKGROUD:

Chronic sensorimotor impairment of the upper extremity is prevalent in more than 6 million stroke survivors in the U.S. (Go, et al., 2013), especially in the distal upper extremity (Trombly, 1989). In our studies of the impairment mechanisms of hand motor control after stroke, e.g., (Cruz, et al., 2005; Kamper, et al., 2006; Triandafilou, et al., 2011), we have been struck by two phenomena which arise following the original brain lesion: i) involuntary hyperexcitability of the motor units in certain muscles and ii) the difficulty in producing and controlling voluntary muscle activation. We propose to directly treat both of these phenomena simultaneously in order to improve motor control of the hand and arm. We will reduce motoneuronal hyperexcitability through administration of an anti-serotonergic drug which does not increase weakness, and we will guide the generation of proper muscle activation with a custom device and computer program. We believe that our multimodality treatment approach is innovative in that we combine the use of pharmacological agents with individualized movement therapy in a manner that can be used with patients with poor initial motor control. In separate preliminary studies, we were able to show that a single dose of the agent cyproheptadine could reduce unwanted muscle excitation without decreasing voluntary strength (Seo, et al., 2011) and that active motor training, assisted by an electromyographically (EMG) controlled actuated glove, could lead to statistically significant improvement both in measures of impairment and task performance. In this study, we will combine these approaches to create a novel treatment paradigm for improving motor control of the distal upper extremity after stroke. These techniques are amenable to rapid and widespread integration into the clinic for the arm and hand, and could be applied to the lower extremity as well.

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INCLUSION AND EXCLUSION CRITERIA:

The following groups of individuals will be excluded from this study:
- Adults unable to consent
- Individuals who are not yet adults (infants, children, teenagers)
- Pregnant women
- Prisoners

In this study, we will recruit stroke survivors who:
- *are between the ages of 18 to 80;*
- *have sustained a single, unilateral stroke at least 6 months prior to enrollment;*
- *have substantial hand impairment as rated at Stage 2 or Stage 3 on the Stage of Hand section of the Chedoke-McMaster Stroke Assessment (Gowland, et al., 1993).*

Subjects are excluded if they have:
- *excessive pain in the paretic upper limb;*
- *cerebellar involvement;*
- *contracture in the paretic upper limb;*
- *hemispatial neglect (as assessed by the Behavioural Inattention Test (Wilson, et al., 1987));*
- *apraxia of the paretic upper limb (as assessed by the FABERS battery (Power, et al., 2010));*
- *rheumatoid arthritis or other orthopaedic impairments restricting finger or wrist movement;*
- *conditions which necessitate the use of medication that may interfere with neuromuscular function.*
- *history of seizure disorder*
- *altered dose of anti-spasticity medication (within 1 month of study start)*
- *botulinum toxin injection(s) to the upper extremity (within prior 6 months of study start)*
- *contraindicated conditions of the study drug, cyproheptadine (including hypersensitivity to cyproheptadine and other drugs of similar chemical stucture; monoamine oxidase inhbitor (MAOI) therapy, angle-closure glaucoma, stenosing peptic ulcer, symptomatic prostatic hypertropy, bladder, stomach or bowel obstruction, eldery debilitated patients*

STUDY-WIDE NUMBER OF PARTICIPANTS: N/A

STUDY-WIDE RECRUITMENT METHODS: N/A

MULTI-SITE RESEARCH: N/A

STUDY TIMELINES:

After completing a preliminary screening and enrolling in the study by signing the informed consent, each subject will undergo a medical examination with the study doctor to verify suitability for participation. A clinical assessment will be conducted to allow for a stratified group randomization based upon the Fugl-Myer Assessment (FMA) upper extremity score. The subject will then be added to the queue to begin participation.

A subject in the study will be asked to participate for a total of 13 weeks. Training sessions will occur within a 6-week span, starting Week 4. These training sessions will be divided into 3 1-

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hour visits a week, for a total of 18 sessions. Additionally, participants will be asked to come to the Arms and Hands Lab for 7 evaluation sessions, each lasting approximately 2 hours. These will take place during the titration phase (baseline and end of weeks 1, 2, and 3), at the midpoint of training (end of week 6), at the end of training (end of week 9), and one month following (end of week 13) (see Fig 1).

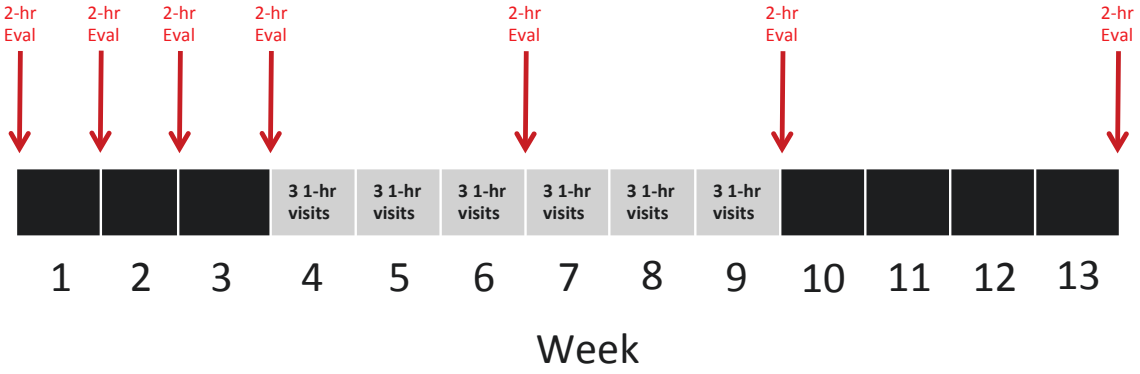

Figure 1: Timeline for evaluation visits (baseline and end of weeks 1-3, 6, 9 and 13) and treatment therapy sessions (3 visits per week for weeks 4-9). Note that you will also be escorted to the outpatient lab area at the baseline visit and the end of week 3 (during chronic drug dose) to have your blood drawn.

- Anticipated enrollment of participant's completion date: October 2020.
- The estimated date for the investigators to complete this study: October 2022

STUDY ENDPOINTS:

Primary Outcome Measure:

Change in mean completion time for Graded Wolf Motor Function Test (GWMFT)

Secondary Outcome Measure:

Change in grip relaxation time (following a maximum voluntary contraction (MVC)) Time required for muscle electromyographic (EMG) signals to reduce to within 3 SD of pre-MVC EMG activity.

PROCEDURES INVOLVED:

Study Design:

Treatment, Parallel Assignment, Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor), Randomized, Efficacy Study.

Over the course of the study, subjects will participate in a therapy regimen involving either active practice of hand and arm movements or passive stretching of the digits, while concurrently receiving either cyproheptadine or placebo. Thus, the study has two experimental factors: Drug (cyproheptadine hydrochloride/placebo) and rehabilitative movement training (active/passive). Subjects will be randomly divided into four groups, stratified by initial FMA score, consisting of the four combinations of Drug and Training:

- cyproheptadine with active movement training
- placebo with active movement training

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- cyproheptadine with passive stretching
- placebo with passive stretching.

Twenty-five subjects in each group will complete the study for a total of 100 participants. The therapists, other research personnel (including the PI), and the subjects will all be blinded as to which agent each subject is taking.

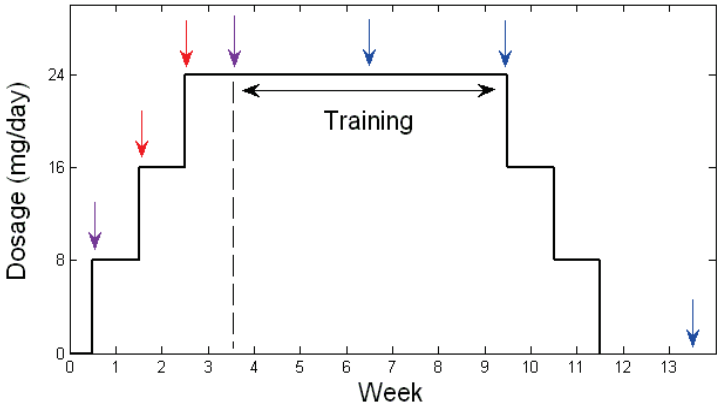

Fig. 2. Dosage and evaluation scheduling for the subjects. During the titration period, dosage is increased each week from 8 mg/day toward the target chronic dose of 24 mg/day. The 6 weeks of training will occur once the chronic dose has been established. Arrows indicate evaluation sessions.

As cyproheptadine can have side effects, the dosage is generally titrated over time to the desired chronic daily dose in order to permit accommodation to the drug. This dosing schedule can alleviate the severity of some of the side effects. For this study, both cyproheptadine and the placebo will be titrated in the same manner, beginning at up to 8 mg (up to 4 mg taken 2 times daily) and increasing the next week to up to 16 mg (up to 8 mg taken 2 times daily) and reaching the desired dose level of up to 24 mg per day (up to 8 mg taken 3 times daily) the following week (Fig. 2). If side effects occur at higher doses, but not at lower doses, the subject will be maintained at the highest dose tolerated for the remainder of the treatment phase. Participants will maintain this daily dosage for 6 weeks, during which time training will be performed. After completion of the training period, dosage levels will be reduced back to zero over a two-week period. The drug dosage may be reduced from the target level as recommended by the study doctor.

The hospital pharmacy will dispense the allotment of the study drug to research staff at each change in dosage over the course of the study (5 dispenses). All pills will be encapsulated by the Research Pharmacist so that both cyproheptadine and placebo will be identical in appearance and weight. Only the Research Pharmacist and study Statistician will have the key identifying which drug each subject was given. In this manner all other study personnel, including the PI, and the subjects will remain blinded as to group membership until the study is complete, or the revealing of this information is deemed medically necessary. Each week during the titration period, the subject will come to the Arms and Hands lab to receive his/her weekly allotment of pills from study staff. Examination by the study doctor will occur at baseline, midpoint, and at the end of the study. To monitor type and severity of potential adverse side effects of the medications, the study doctor or a study team member will complete a checklist for each subject weekly. All subjects, even those in the placebo group, will be given this checklist. Adverse side effects will be rated as “none”, “moderate”, or “severe” based on subject report. If a subject feels unable to

continue the study due to any side effects, she may end her study participation at that time. Transportation can be arranged to convey subjects to and from the Shirley Ryan AbilityLab during this period in order to preclude the need for subjects to drive when they may be experiencing dizziness or somnolence from the medication. Weekly pill counts will be performed to gauge subject compliance with taking the medication. Participants will receive the subsequent allotment of pills at each dosage change.

Once the chronic dosage is attained, therapeutic training will begin for all subjects. The sensorimotor therapy, consisting of 18 one-hour sessions held over 6 weeks, will focus on the impaired upper extremity, particularly the hand.

Active Movement Therapy (AMT), VAEDA:

A Voice and EMG-driven Actuated hand orthosis, the VAEDA glove, will be worn by all subjects during these therapy sessions. The VAEDA glove contains cables (Spectra kite wire) which run across the back of the digits in order to provide extension and resist flexion (Fig 3). Forces are transmitted through the cables from a DC micromotor (1724, Faulhaber, Inc), located remotely, to the digits. The single actuator controls torque or displacement in the cable. Tension in the cable is measured directly with a custom tension sensor; cable displacement is estimated from the motor encoder (IE2-16, Faulhaber, Inc.). The cable travels from the actuator through a Bowden cable to a forearm splint, at which point it is attached to the 5 cables running to the digits. Along the digits, the cables traverse through custom plastic blocks, which serve both to guide the cable and to prevent joint hyperextension. The weight of the glove with the cables and cable guides is 2.2 N and the forearm splint is an additional 1.5 N, thereby making the total weight on the arm less than 4 N.

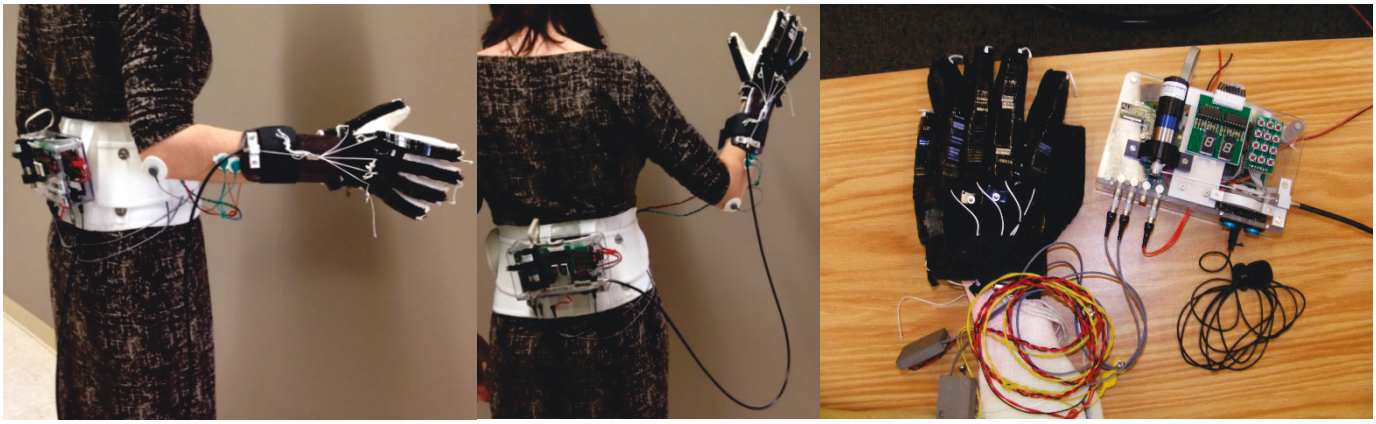

Fig. 3. Picture of the VAEDA glove system. Cables run through cable guides on the dorsal side of the glove to facilitate extension and resist unwanted flexion (Left). The cable is driven by a single actuator located remotely on the electronics box which can be worn on the back (Center). EMG signals, which control the glove, are processed by custom amplifiers before being transmitted to the microcontroller (Right).

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The VAEDA glove can be controlled with up to 3 channels of EMG. Custom pre-amplifiers process the EMG signals before transmitting the data to the microcontroller (RabbitCore® RCM 4510, Digi International, Inc., Davis, CA). For this study, electrodes will be placed above flexor digitorum superficialis (FDS) and extensor digitorum communis (EDC). Assistance of hand opening can be provided by the VAEDA glove, but only if appropriate EMG activity is detected. For example, the EDC EMG signal must reach a specified threshold before extension assistance will be provided. Similarly, the FDS EMG signal has to surpass a threshold level during hand closing before the user is allowed to flex the digits. Additionally, maximum allowable FDS activity during hand opening and EDC activity during hand closing can be specified to address coactivation issues. Feedback of muscle activity and of opening force provided by the VAEDA glove is available to the user through a custom graphical user interface (Fig. 4). As detection of movement intent from EMG for even simple tasks, such as hand opening and closing, can be challenging in stroke survivors with significant impairment, the system also contains a voice recognition system, (VRS), (SR-07 Electronic Express, NY), which can be trained specifically for each user within minutes. The entire device can be worn, with the actuator, VRS, microcontroller, and batteries (Tenergy 7.4V Heavy Duty LIPO, Tenergy Corp Freemont, CA) on the lower back (Fig. 3). Alternatively, they can be placed on a tabletop for a seated user.

Fig. 4. Graphical user interface for the VAEDA glove. Either the magnitude of EMG signals or the force in the cable can be displayed to provide feedback to the user and/or therapist. Green and yellow bars show the magnitudes of EDC and FDS muscles, respectively. The force graph displays the actual readings from the sensor in real-time. Data recorded during hand opening.

Active Movement Therapy (AMT), EMG Video Game:

The alternate session will consist of directly training muscle activation patterns by playing a computer game. A cursor, or "game piece" will be controlled by the patterns recorded from surface EMG electrodes (Bagnoli, Delsys, Inc.) positioned over a subset of the following muscles: FDS, EDC, thenar eminence, hypothenar eminence, first dorsal interosseous, flexor carpi radialis (FCR), and extensor carpi ulnaris (ECU). We will use principal component analysis (PCA) to determine basis vectors which can be used to explore the activation workspace defined by these muscle groups for each subject. Actions on the computer screen are associated with activation of specific principle components (PCs) (Fig. 5). For example, activation levels of the first and second PCs can correspond to the x- and y-coordinates for the user's game piece. Movement of the game piece can then be used to spell specific words (Fig. 5b), reveal a hidden picture (Fig. 5c), navigate a maze, or play a version of Asteroids. As the user progresses, the PCs controlling the game piece will be periodically cycled, such that the third and fourth PCs control the x- and y-coordinates, for example. Desired PCs can also be explicitly created from the graphical user interface, such as to have the user focus on activating individual muscles. If simultaneous control of 2 PCs proves too difficult, one-dimensional versions of the letter and hidden picture games can be used. Again, half of the subjects in this active training group will be concurrently taking cyproheptadine while the other half will be taking a placebo.

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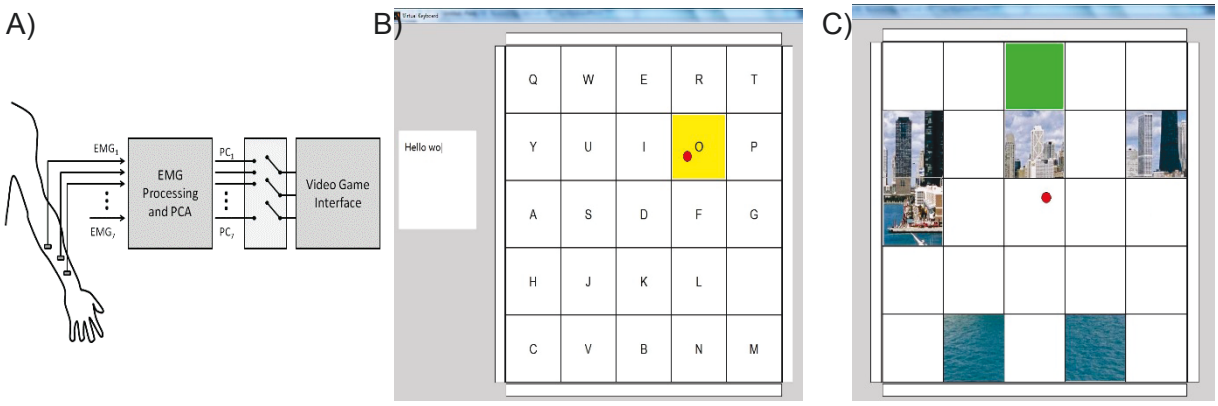

Fig. 5. Computer games to guide exploration of the activation workspace. A) EMG signals are converted into PCs in real-time to drive a computer video game. B) Control of two PCs moves the game piece (here, a red dot) along the horizontal and vertical axes to reach the indicated letter (which turns color from green to yellow when the red dot is properly positioned). C) User moves the red dot to the correct tile (highlighted in green) to remove the tile and

Passive Stretching, VAEDA glove:

We recognize that exposure to a novel device such as the VAEDA glove and regular visits to the Coleman Hand Rehabilitation Laboratory could have a placebo effect by focusing attention on the impaired upper extremity. Thus, the comparison group, comprised of the other half of the subjects, will have similar exposure to the laboratory and device, but will not undergo active movement therapy. Instead, they will wear the VAEDA glove while it moves their digits from a flexed posture to full extension and then allows them to return to the flexed resting posture at a rate of roughly 15 cycles per minute. We have found this passive, cyclical stretching to have a transient impact on motor control, although the effects did not seem to carry over from one day to the next in individuals with chronic impairment (Triandafilou, et al., 2014). For each session, subjects will receive two 20-minute stretching sessions, with 10 minutes of rest in between. Half of this group will concurrently be taking cyproheptadine while the other half will be taking a placebo.

Outcome Measures:

Subjects will be tested at the Arms and Hands Lab at baseline and the end of each week during the titration phase. Thus, data will be collected prior to administration of any agent, after one week at the lowest dosage of up to 8 mg per day, after one week at the next dosage of up to 16 mg per day, and after one week at the highest dosage of up to 24 mg per day. Data from the 4 testing sessions will be used to assess the impact of cyproheptadine on stroke. All outcome measures will be collected during each testing session. Pill counts will be performed each week as well to gauge subject compliance.

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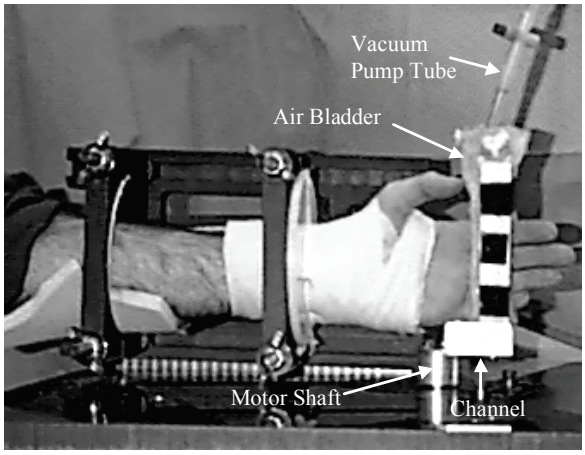

Fig. 6. Depiction of the interface between the fingers and the device. The motor shaft rotates the U-piece coupled to the proximal phalanges of the fingers. For the spasticity experiments, the proximal and distal interphalangeal joints will be fixed in neutral with finger splints.

Three potential manifestations of motoneuronal hyperexcitability will be quantified: spasticity, excessive coactivation during voluntary contraction, and prolonged muscle relaxation time. Spasticity will be precisely measured using techniques we have successfully employed in the past in which all four fingers are coupled to a servomotor through a custom jig (Fig. 6). Rotation of the servomotor shaft produces equivalent rotation of the MCP joints. The servomotor will impose constant-velocity rotation of the MCP joints in order to stretch the long finger flexors. Fast MCP rotation (300°/s) will be applied to evoke a stretch reflex. Slow MCP rotation (10°/s) will be imposed to measure nominally passive resistance. Wrist orientation and position will be fixed with a fiberglass cast which is subsequently clamped to a table (Fig. 6). MCP angle, angular velocity, and torque are recorded for analysis of spasticity. EMG recordings will be obtained with surface electrodes (Bagnoli) from EDC and FDS. Subject strength will also be assessed, by having subjects perform maximum voluntary MCP flexion and extension in the same testing jig while the servomotor provides resistance. The EMG data recorded during these isometric contractions will be used to quantify coactivation. Finally, FDS relaxation time will be determined by having the subject create maximal grip force in the jig and then relax upon hearing the termination of an auditory tone, as we have done previously. Both upper extremities may be tested in a subset of participants in order to determine the impact of cyproheptadine on the non-paretic (ipsilesional) side.

Clinical assessments will be performed at the baseline, pretreatment (week 3), mid, post and follow up evaluation sessions by the study research therapist and study team. This battery of assessments includes the GWMFT, FMA, Chedoke McMaster Stroke Assessment – Stage of Hand (CMSA-H), grip and pinch strengths, the Modified Modified Ashworth Scale (MMAS), the Jebsen Hand Function Test, the Nine-Hole Peg Test, the Box and Blocks Test (BBT), and the Semmes Weinstein Monofilament Touch test.

In addition to these neuromechanical measurements, subjects will be evaluated in terms of sleepiness, depression, and weight gain. These are side effects that could dissuade use of the medication. The Epworth Sleepiness Scale (ESS) will be given to subjects at each testing session (Johns, 1991). This instrument consists of a self-assessment of the propensity to doze (ordinal scale, 0-3) during each of 8 activities of daily living (e.g., sitting and talking to someone). We will use the Beck Depression Inventory-II (BDI-II) for assessing depression in our subjects. The BDI-II is a self-report of 21 items rated on an ordinal scale from 0-3 (Beck, et al., 1996). The BDI-II, a revised version of the Beck Depression Inventory (Beck, et al., 1961), was developed to remove possible bias for older adults from the original instrument. Additionally, subjects will be weighed each week to track fluctuations in weight.

DATA AND SPECIMEN BANKING: N/A

DATA AND SPECIMEN MANAGEMENT: N/A

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PROVISIONS TO MONITOR THE DATA TO ENSURE THE SAFETY OF PARTICIPANTS:
A medical monitor will periodically evaluate the data collected regarding harms to determine whether participants remain safe. Findings from the medical monitor will be reported to the IRB during scheduled continuing reviews.

The data monitor will have access to all data collected, including side effects checklists, surveys and untoward events. This information is collected at the evaluation study visits beginning with the medical examination with the study doctor and Baseline evaluation. The data monitor will perform monitoring every 6 months for the first 1-2 years of the study, then annual if no change to the unanticipated adverse effects of this study.

WITHDRAWAL OF PARTICIPANTS:
Non-compliance with study protocol, or if it is deemed appropriate for the subject's safety by the study doctor or PI, will result in removal from the study.

If a subject chooses to stop involvement in the study prematurely, the study doctor will be notified, and will recommend beginning the titration process for weaning the subject from the study drug. This will be handled on a case-by-case basis which would involve at least one additional visit with the study doctor.

RISKS TO PARTICIPANTS:

The primary risks for involvement in this study are associated with the pharmacological agent to be tested. Although cyproheptadine hydrochloride itself is not being used or administered differently than the FDA approved method, it is being used for a potentially different outcome, namely reduced unwanted muscle tone following stroke.

Some of the potential side effects of taking cyproheptadine include: diminished mental alertness, drowsiness, dizziness, hallucinations, insomnia, muscle weakness, chest congestion, headache, hypertension, increased appetite, upset stomach, diarrhea, difficulty urinating, vision problems, skin rash and dry mouth, nose, and throat, and convulsions. Although reported clinical experience has not identified differences in responses between the elderly and younger patients, elderly patients should be more cautious of possible risks. These risks may include decreased hepatic, renal or cardiac function.

To minimize these risks, we will begin with low levels of the drug and gradually titrate (increase) up to the optimal target dose for the study, which is still well within the safe level of this drug. Patients will be evaluated weekly and will be able to contact the study doctor at any time with questions or concerns. As a precautionary measure, liver profiles (requiring blood draws) will be run prior to initiation of drug administration and at the end of week 3 (chronic drug dose) to check drug impact on liver function although liver damage is not a known side effect. Following the medical screening, additional labs may be ordered at the discretion of the study doctor. Adverse events, including falls, will be assessed weekly at minimum.

Additionally, the medication may have side effects when combined with other types of drugs and/or alcohol. Some side effects of taking combined drugs may lead to confusion, high blood pressure, high fevers, tremor or muscle rigidity, and increased activity.

The effects of the study drug, cyproheptadine, on human sperm and eggs have not been studied and are therefore unknown. The effects of cyproheptadine in humans have not shown to cause negative conditions in either the mother or the fetus during pregnancy.

However, studies in animals have shown an increased risk of birth defects and fetal hormonal imbalances. The effects of this medication in women who are nursing have been shown to produce hormonal imbalances in the newborn.

Although not in the FPI for cyproheptadine, risks of falls, cognitive decline and increased mortality have been associated with use of other such drugs with antihistaminic and anticholinergic effects.

There are also risks with the use of the actuated hand orthosis, the VAEDA glove, to provide extension assistance or stretching. This device, as well as the motor used during the evaluations, has the potential to cause too much stretching, which may cause pain or damage to the joint. A number of safety features, however, have been implemented to attempt to reduce these risks, such as mechanical stops and limit switches. Additionally, the subject will be monitored continuously by research staff while using this equipment.

Skin irritation could result from the use of self-adhesive surface electrodes. This will be minimized by cleaning the skin with alcohol before and after their application. In case of any incident, emergency medical services are routinely available at the Rehabilitation Institute of Chicago and at the adjacent Northwestern Memorial Hospital emergency room.

Due to the repetitive motions of the arm and hand, subjects also risk experiencing fatigue, muscle pain, or soreness.

The electrical stimulation used to measure muscle activation can cause pain; for some people it is sharp like a prick of a needle. We will use a series of stimulation pulses that we have found to be least painful. Additionally, we will carefully adjust the stimulation level to minimize discomfort.

The cast saw used to remove the fiberglass cast placed around the wrist for the evaluations could produce burns if left for too long in one place. All study personnel will be trained in the proper use of this saw.

Some questions we ask from the BDI-II examination may be upsetting or make the subject feel uncomfortable. If they do not wish to answer a question, they may skip it and go to the next question. A BDI-II total score above 13 will be reported to the study doctor immediately, and a private consultation with the study doctor arranged. Likewise, any suicidal ideations revealed through the BDI, regardless of total score, will be reported to the study doctor. In either case, the individual will be advised to seek counseling.

POTENTIAL BENEFITS TO PARTICIPANTS:

Although it has been shown that some benefit may be derived from taking cyproheptadine or from performing repetitive motion tasks or stretching, subjects are not guaranteed any direct benefit from participating in this research study. Participation in this study may aid in our understanding of the nature of movement impairment after stroke and may eventually improve rehabilitation of upper extremity function.

VULNERABLE POPULATIONS: N/A

COMMUNITY-BASED PARTICIPATORY RESEARCH: N/A

SHARING OF RESULTS WITH PARTICIPANTS:

PROTOCOL TITLE:

This study is registered on clinicaltrials.gov NCT02418949. Therefore, study results for the outcome measures will be available at the completion of the study. Individual laboratory test results will not be shared with participants unless deemed necessary by the study doctor nor will they be available on clincicaltrials.gov.

SETTING:
All training, hand evaluation sessions will be held in the Arms and Hands Lab (22 floor) of the Shirley Ryan AbilityLab, 355 E. Erie St. Chicago, IL 60611. This is also where subjects will be given their allotment of pills for each change in dosage and see the study doctor for examinations. Research staff will escort subjects to the outpatient lab for blood draw at baseline and the end of week 3 (before beginning therapy treatment) to monitor the drugs effect on your liver function.

RESOURCES AVAILABLE:
The Shirley Ryan AbilityLab will provide all space and resources required for the completion of the proposed study, including areas to conduct subject assessments and experiments, offices for the Principal Investigator, Dr. Elliot Roth, and the other project personnel, and administrative and information system support. Specifically, the proposed study will be conducted in the Arms and Hands Lab of the Shirley Ryan AbilityLab, which contains 17 laboratories devoted to the study of human sensorimotor integration and control.

The RIC is a 182-bed specialty hospital in the downtown Chicago area with full accreditation by the Joint Commission on Accreditation of Healthcare Organizations and the Commission on Accreditation of Rehabilitation Facilities. The RIC brings together high quality comprehensive care for individuals with disability, research into the mechanisms and management of disabling conditions, and training of professionals and the public about disability and approaches to its management. It provides acute inpatient rehabilitation, day rehabilitation, outpatient clinics, and home health for stroke, spinal cord injury, traumatic brain injury, and orthopedic patients. The RIC is an academic affiliate of the Northwestern University Feinberg School of Medicine and is the home of its Department of Physical Medicine and Rehabilitation.

Stroke survivors who are willing to participate in the proposed study will be drawn from the outpatient facility of the Shriley Ryan AbilityLab. In addition, the Sensory Motor Performace Program (SMPP) maintains an Institutional Review Board (IRB) approved Clinical Neuroscience Research Registry of over 900 stroke survivors who wish to be contacted for possible participation in research studies.

Shirley Ryan AbilityLab has its own pharmacy. Cyproheptadine and placebo will be dispensed from this pharmacy.

Shriely Ryan AbilityLab is highly supportive of research and is striving to further integrate research and clinical care. Therapists working in SMPP typically split their time between SMPP and the clinic. RIC currently hosts a number of federally funded centers, including the Rehabiltiation Research and Training Center for Stroke, sponsored by the National Institute on Disability and Rehabilitation Research. Dr. Roth is the PI and Director for this Center. Additionally, RIC is constructing a replacement facility to open in 2017, two blocks from its current site. The concept for the new facility is to infuse biomedical science and research into the clinical environment. Thus, research laboratories will sit adjacent to clinical therapy space and a culture of interaction and cooperation will be fostered. As a model, in the current facility RIC opened the Patient Recovery Unit in which patients receive intensive, customized therapy guided by the latest research findings.

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PRIOR APPROVALS: N/A

RECRUITMENT METHODS:
Recruitment for potential participants will be done through the IRB approved research registry. Flyers will be placed in Shirley Ryan AbilityLab, clinics, and the Life Center and on the clinical trials webpage for the Shirley Ryan AbilityLab Referrals from the study doctor or other colleagues will also be screened.

Following the initial screening with the research staff, further participation will require passing a medical examination with the study doctor as well as completing a clinical assessment for randomization purposes prior to study enrollment. The stipend is $20 for this visit.

During the study, the stipend for each treatment session is $20 and the stipend for each evaluation session is $40. These funds are provided to help support time and travel associated with participation. If a session needs to be repeated at the behest of the study doctor, PI, or due to researcher conflicts and/or equipment malfunction the stipend will be duplicated.

RIC is moving away from using petty cash. During this transition period you may be paid in cash or by ClinCard. If a ClinCard is available when you enter into the study, you will be paid by card. If a ClinCard is not available, then you will receive cash payments on the day of your research visit.

NUMBER OF LOCAL PARTICIPANTS:
We are targeting 100 subjects to complete the study.

This would break down into four groups of 25:
- Cyproheptadine and Active Hand Therapy
- Placebo and Active Hand Therapy
- Cyproheptadine and Passive Stretching
- Placebo and Passive Stretching

We estimate needing to enroll 200 subjects in order to reach our target due to participants not meeting inclusionary/exclusionary criteria or to dropping out of the study.

CONFIDENTIALITY: N/A

PROVISIONS TO PROTECT THE PRIVACY INTERESTS OF PARTICIPANTS:
A private room may be provided to the subject during administration of the side effects checklist, medical examinations, or other surveys, such as BDI-II, where sensitive information is discussed. As always, the subjects have the right to refuse to answer any questions which may make them feel uncomfortable.

The study doctor may access medical records or sensitive information for recruiting purposes.

COMPENSATION FOR RESEARCH-RELATED INJURY:

If a subject becomes ill or gets an injury or illness as a result of study medications or procedures, you should seek medical treatment through your doctor or treatment center of choice. You should promptly tell the study doctor about any illness or injury.

The hospital will not pay for medical care required due to an injury or illness as a result of their participation in this research study. However, this does not keep them from seeking to be paid back for care required because of a bad outcome. Subjects are welcome to seek medical treatment through their doctor or treatment center of choice.

ECONOMIC BURDEN TO PARTICIPANTS:
There will be no costs to participants for being in this study. The cost of the drug, the therapies and the lab work tests will be covered by the study.

CONSENT PROCESS:
This study will obtain written informed consent from all study participants. The consenting process will take place at Shirley Ryan AbilityLab, 355 E. Erie St., Chicago IL, 60611 with an approved member of the study team. A full discussion about the study will take place before the medical examination; research staff will be available to answer any questions. Subjects will be given ample time to meet with family or friends to discuss details of the study prior to giving consent. For documentation of the consent process, a participant's signature may be obtained electronically.

Adults Unable to Consent
The individuals from whom permission will be obtained in order of priority: durable power of attorney for health care, court appointed guardian for health care decisions, spouse, and adult child.

PROCESS TO DOCUMENT CONSENT IN WRITING:
Informed consent will be documented in writing through our Consent and HIPAA Authorization for Research form and uploaded to the Nitro Study Tracker.

DRUGS OR DEVICES:
The drugs used in this study will be administered by the Shirley Ryan AbilityLab pharmacy for each subject. A study team member will deliver the prescription to the participant during a scheduled visit. If there is any time the drug will be in the lab prior to this delivery, it will be temporarily locked in a designated cabinet approved by the pharmacy.