Department of Veterans Affairs

RESEARCH CONSENT FORM

Version Date: (03/18/2024)

Participant Name: _____ Date:_____

Title of Study: **A randomized placebo-controlled trial of methylphenidate in Veterans with a diagnosis of post-traumatic stress disorder and recent cerebral stroke**

Principal Investigator: __Chen Lin, MD_____ VA Facility: __Birmingham (521)_

KEY SUMMARY INFORMATION ABOUT THIS STUDY

This research is being sponsored by the VA Office of Clinical Science Research and Development. 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 potential risks to you, as well as any potential benefits you might receive. Taking part in this study is completely voluntary.

WHAT IS THE STUDY ABOUT AND WHY ARE WE DOING IT?

This study is about treating patients with stroke and post-traumatic stress disorder (PTSD). Veterans with PTSD that suffer stroke, will tend to have worsening PTSD and stroke outcomes. Of major concern, Veterans with stroke are typically excluded from PTSD clinical trials due to their stroke. Methylphenidate is a central nervous stimulant and currently approved by the FDA to treat narcolepsy and attention deficit hyperactivity disorder. Methylphenidate has been researched and shown to improve PTSD symptom severity and stroke clinical outcomes, separately. Most importantly, it has also been shown to be safe in these studies. This study aims to fill this gap in knowledge by investigating the impact and mechanism of methylphenidate on clinical outcomes in Veterans with both recent stroke and PTSD.

WHAT DOES THE STUDY INVOLVE AND HOW LONG WILL IT LAST?

Your participation in this research will last about 16 weeks. The purpose of this research is to gather information on the safety and effectiveness of methylphenidate, an FDA-approved medication, as a treatment for PTSD in patients that have suffered stroke. You will receive either methylphenidate or placebo for 12 weeks. The final visit will be 30 days after finishing the taper.

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

If you agree to take part in this research study, there may not be a direct benefit to you. Potential benefits to you may include a reduction in PTSD symptoms or improvement in stroke symptoms. The investigators hope the information learned from this research study will benefit other Veterans with PTSD and stroke in the future.

For a complete description of benefits, refer to the Detailed Consent.

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

Methylphenidate has independently been studied in patients with PTSD only and patients with Stroke only to help improve PTSD symptoms and stroke symptoms, respectively. However, methylphenidate has not been studied when patients have both PTSD and stroke. All interventions have risks.

Methylphenidate HCl: Nervousness and insomnia are the most common adverse reactions reported in clinical trials and post-marketing surveillance. In addition, patients have reported loss of appetite, abdominal pain, weight loss during prolonged therapy, and tachycardia. Other side effects include:

- Cardiac: angina, arrhythmia, palpitations, pulse increased or decreased, tachycardia.
- Gastrointestinal: abdominal pain, nausea.
- Immune: hypersensitivity reactions including skin rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme, and thrombocytopenic purpura.
- Metabolism/Nutrition: anorexia, weight loss during prolonged therapy.
- Nervous System: dizziness, drowsiness, dyskinesia, headache, rare reports of Tourette's syndrome, toxic psychosis
- Vascular: blood pressure increased or decreased; cerebrovascular vasculitis; cerebral occlusions; cerebral hemorrhages and cerebrovascular accidents.
- Blood/Lymphatic: leukopenia and/or anemia
- Hepatobiliary: abnormal liver function, ranging from transaminase elevation to hepatic coma
- Psychiatric: transient depressed mood, aggressive behavior
- Skin/Subcutaneous: scalp hair loss

This study is called "double-blind" because neither you nor the study doctor will know which combination you will receive; however, the doctor can get this information in case of emergency. You will be assigned to a group by chance, which may prove to be less effective or to have more side effects than the other study group(s) or alternatives.

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For a complete description of risks, refer to the Detailed Consent.

WHAT IS THE PURPOSE OF THIS STUDY?

This study is a randomized double-blind placebo-controlled trial of methylphenidate in Veterans to evaluate PTSD and stroke outcomes. The overarching goal of our proposal is to determine if MPH improves PTSD and stroke outcomes in Veterans with both PTSD and stroke. The high prevalence of PTSD in Veterans with stroke provides strong justification for development of interventions that effectively and simultaneously target both conditions. This could improve symptomatic and functional outcomes. To better understand the overlapping brain changes from stroke and PTSD, you will also have an MRI of the brain.

HOW LONG WILL I BE IN THE STUDY?

This research study is expected to take approximately 5 years. Your individual participation in the project will take approximately 16 weeks.

WHAT WILL HAPPEN AND WHAT CAN I EXPECT IF I TAKE PART IN THIS STUDY?

Baseline and Randomization: After screening for study eligibility and reviewing your medical history, you will have a baseline visit which includes the assessments listed in Table 1. If you continue to meet eligibility criteria on or up to 28 days after the baseline assessment, you will be randomized (like a coin flip) to either the methylphenidate or placebo treatment group.

Medication Protocol: The study drug is dispensed from the VA pharmacy according to the assignment after the medication order is entered by the investigator. In this double-blind design, both you and research team will remain blinded of which treatment you are receiving (methylphenidate or placebo) for the duration of the trial; however, pharmacy has procedures for breaking blind for emergency situations to non-research provider of care. At randomization, the study personnel will provide you the instructions for taking the drug. The dose of methylphenidate for this study will be similar to that used in prior PTSD trials. **Study drug will be initiated over a 2-week titration period: 10 mg once daily (1 pill daily) for the first week, and 10 mg twice daily (1 pill in the morning and 1 in the afternoon for a total of 20 mg daily) for the second week. After the second week, if tolerated, you will then be on 20mg twice daily (2 pills in the morning and 2 pills in the afternoon, for a total of 40mg) dosing until week 10. After week 10, you will start a 2-week taper period. The first week taper will be at 10 mg twice daily (1 pill in the morning and 1 pill in the afternoon totaling**

20 mg daily), followed by 10mg once daily (1 pill daily) for a week, and then stop the medication. If an adverse effect is believed to be associated with medication, your dose will be held or decreased to a prior dose instead of proceeding with the scheduled increases. **Follow-up Procedures**: Following randomization, you are assessed in-person every 4 weeks (4, 8, 12) and conclude with a final follow-up at 30 days **after completing taper**. You will also have a telephone assessment every 2 weeks when not evaluated in-person (week 2, 6, and 10) for treatment-emergent side effects. Schedule of events for in-person visits are listed in Table 1. At each monthly assessment, medication adherence is determined by self-report, verified by pill counts, and recorded as % adherence. Specifically for the CAPS-5 measure, the measure will be recorded by a VA-approved audio recorder. Co-investigators will review the recording to ensure agreement in scoring.

Table 1: Schedule of Events

Assessments	Screen	Baseline	Wk 4	Wk 8	Wk 12	30 days after taper
Informed Consent and HIPAA	X					
Demographics, Medical History, Physical, Height, ECG, Labs.	X					
Verify Eligibility Criteria	X					
Ohio State University TBI	X					
Emory Treatment Resistance Interview for PTSD	*X*					
Life Events Checklist	X					
Vital Signs and Weight	X	X	X	X	X	X
CAP-5 past week	X	X	X	X	X	X
PTSD Checklist for DSM-5		X	X	X	X	X
Columbia-Suicide Severity	X	X	X	X	X	X
Patient Health Questionnaire 9		X	X	X	X	X
modified Rankin Score		X	X		X	X
Fatigue Severity Scale		x			x	x
Montreal Cognitive Assessment		X	X		X	X
Stroke Impact Scale-16		X	X		X	X
Study Drug Adherence			X	X	X	
Concomitant Medication			X	X	X	X
Adverse Events			X	X	X	X
Review PTSD therapies completed	X					X
Neuroimaging		X				X

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Neuroimaging: Before and after intervention, you will return for an MRI scanning session and a repeat of the questionnaires that were done at your first visit. This visit should take approximately 1-hour for MRI scanning. MRI takes advantage of the magnetic properties of water in your body to take pictures. The MRI machine consists of a very strong (3.0 Tesla) magnet. The MRI scanner is commonly used in clinical care and **is** safe **and commonly used in medical care**. You will be asked to lie on a long narrow padded table for approximately 60 minutes while the MRI scanner gathers information. The space within the magnet that you lie in is somewhat confined. If you feel claustrophobic (an unpleasant feeling of being closed in) you can discontinue the scan at any time. During the scan, you will be exposed to a magnetic field and radiofrequency magnetic fields, but you will not feel either. You will hear repetitive noises; however, you will wear earplugs or headphones to reduce the noise. You will be given a squeeze ball that activates an alarm if you need to stop the scan at any time.

Continuing your current medications: You may remain on antidepressants, prazosin, or sleep medications if every effort is made for the doses to remain stable during the study. Opiates and other medications for pain conditions will be allowed and recorded in the concomitant medication inventory. All concomitant medication you use will be carefully documented. While dose stability is the goal, any changes in dosages during participation that are medically warranted are recorded and may be leveraged in outcomes data interpretation. The following psychotropic medications are not allowed during the study: mood stabilizers (lithium,
carbamazepine, valproate, lamotrigine), benzodiazepines, and neuroleptics. Treatment with trauma-focused therapy (e.g., CPT, PE, or EMDR) for PTSD within two weeks of baseline (if you are receiving therapy, you must complete treatment prior to entering study) is not allowed. If you want this type of treatment, you may enroll in a course of treatment and complete it prior to study participation of after study completion. You may attend supportive-educational appointments that were initiated prior to entry.

Rescue Medication: From the screening point forward, diphenhydramine or a nonbenzodiazepine sedation medications, such as zolpidem, zaleplon, and eszopiclone may be used sparingly (not to exceed three times per week) for severe insomnia or agitation.

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

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Any intervention has possible risks and discomforts. The procedures in this study may cause all, some, or none of the risks or side effects listed. Rare, unknown, or unexpected risks also may occur.

Physical Risks

Methylphenidate: You will be screened by the eligibility criteria and be excluded if you have any contraindications to methylphenidate including hypersensitivity reactions such as angioedema and anaphylactic reactions to methylphenidate.

Nervousness and insomnia are the most common adverse reactions reported in clinical trials and post-marketing surveillance. In addition, patients have reported loss of appetite, abdominal pain, weight loss during prolonged therapy, and tachycardia. Other potential side effects include:

• Cardiac: angina, arrhythmia, palpitations, pulse increased or decreased, tachycardia.
• Gastrointestinal: abdominal pain, nausea.
• Immune: hypersensitivity reactions including skin rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme, and thrombocytopenic purpura.
• Metabolism/Nutrition: anorexia, weight loss during prolonged therapy.
• Nervous System: dizziness, drowsiness, dyskinesia, headache, rare reports of Tourette's syndrome, toxic psychosis
• Vascular: blood pressure increased or decreased; cerebrovascular vasculitis; cerebral occlusions; cerebral hemorrhages and cerebrovascular accidents.
• Blood/Lymphatic: leukopenia and/or anemia
• Hepatobiliary: abnormal liver function, ranging from transaminase elevation to hepatic coma
• Psychiatric: transient depressed mood, aggressive behavior
• Skin/Subcutaneous: scalp hair loss

Very rare reports of neuroleptic malignant syndrome (NMS) have been received, and, in most of these, patients were concurrently receiving therapies associated with NMS. In a single report, a ten-year-old boy who had been taking methylphenidate for approximately 18 months experienced an NMS-like event within 45 minutes of ingesting his first dose of venlafaxine. It is uncertain whether this case represented a drug-drug interaction, a response to either drug alone, or some other cause.

The investigators will closely monitor you for all possible side effects and adverse events. This study uses a low dose and duration of methylphenidate, which reduces the chances of an adverse event.

Clinical Testing: The functional assessments used in the proposed study are routine clinical assessments of gait and stroke impairments used in stroke outpatient and therapy clinics. The experimental protocol to be used in this portion of the proposal involves minimal risk and is considered standard clinical practice.

MRI Neuroimaging: The MRI scanner contains a very strong magnet. Therefore, you will be excluded from the study if you have certain types of metal implanted in your body, for example, any pacing device (such as a heart pacer), any metal in your eyes, or certain types of heart valves or brain aneurysm clips. Although there is no indication that MRI is unsafe during pregnancy, if you are female, you will be asked to take a urine pregnancy test to verify that you are not pregnant. There is not much room inside the MRI scanner. You may be uncomfortable if you do not like to be in close spaces ("claustrophobia"). If you become uncomfortable at any time, you can request that the scan be stopped. All participants will pass an MRI screen to decrease risk of adverse events.

Psychological Risks

You may feel that the PTSD interview process, and completion of the self-report forms are a source of triggered anxiety or embarrassment. While answering questions regarding your psychological symptoms, you may experience temporary anxiety, discomfort or embarrassment, or distressing memories of traumatic experiences may be triggered. These are research risks, not therapeutic risks.

You may experience prolongation or worsening of stroke, PTSD, insomnia, or depression because of ineffectiveness of drug or placebo. Those with PTSD are at risk for also having other psychological conditions and are also at risks of having suicidal thoughts or behaviors. Study staff will assess suicidality and adhere to the suicide prevention plan. These are research risks but may also be partly attributed to the course of illness.

Economic, Legal, and Social Risks

You may have to miss work and lose income or spend money on transportation or childcare to attend the assessment visits. These are research risks, not therapeutic risks. An unlikely legal or social risk associated with participating with this study may be invasion of privacy or breach

of confidentiality in the remote chance that there is a loss of data containing PHI **(protected health information)** or PII **(personally identifiable information).** These are research risks, not therapeutic risks.

There is always a chance that any procedure can harm you. The procedures in this study are no different. In addition to the risks described above, you may experience a previously unknown risk or side effect.

Risks of the usual care you receive are not risks of the research. Those risks are not included in this consent form. You should talk with your health care providers if you have any questions about the risks of usual care.

WHAT ARE THE POSSIBLE BENEFITS OF THIS STUDY?

If you agree to take part in this research study, there may not be a direct benefit to you. Potential benefits to you may include a reduction in your symptoms. However, your PTSD and stroke symptoms may get better, get worse, or may not change. The investigators hope the information learned from this research study will benefit other Veterans with PTSD and Stroke. The knowledge gained from this study will serve to inform future research and clinical care for veterans.

WHAT OTHER CHOICES DO I HAVE IF I DO NOT WANT TO JOIN THIS STUDY?

You may choose not to participate in this study. Instead of being in this research study, you may discuss with your doctor other treatment options such as lifestyle changes and different medication regimens.

HOW WILL MY PRIVATE INFORMATION BE PROTECTED?

Every effort will be made to maintain the confidentiality of your study records. Your identity will remain confidential unless disclosure is required by law. All data will be identified by code numbers. These data will be stored in locked file cabinets that will be accessible only to study staff. The key listing names and code numbers will be kept in a separate locked filing cabinet or separate secure computer drive. All computer data, including any audio recordings, will only

be accessible to study personnel. All private data will be stored behind a VA firewall- and password-protected on VA computers in a research folder. During the study, records will be released only with your written consent and HIPAA authorization to appropriate VA research team members including, if requested and warranted, people from the Food and Drug Administration, the General Accountability Office, the Office of the Inspector General, the VA Office of Research Oversight, the VA Central Institutional Review Board (IRB), the VA Research and Development Committee, and the VA Drug Monitoring Committee. Destruction of all research records pertaining to this study will be in accordance with the Federal Policy of the Department of Veterans Affairs and will be retained for a minimum of 6 years after the end of the study.

Your imaging information will be released to University of Alabama-Birmingham, Department of Radiology at the Highlands Neuroimaging Laboratory. The information obtained in this study may be published, but your identity will not be revealed. The VA personnel VA Institutional Review Board (IRB), and other federal oversight agencies reserve the right to inspect both the research data and your medical records. The information from the research may be published for scientific purposes; however, your identity will not be given out.

We will put information about your participation in this study into your medical record. This electronic medical record will be kept in accordance with the VA-approved records retention schedule. Authorized users of electronic VA medical records can access your medical record.

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

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

You will not be charged for any treatments or procedures that are part of this study. All study treatment is free of charge to study participants. 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.

WILL YOU BE PAID TO PARTICIPATE IN THIS RESEARCH STUDY?

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You will receive $50 each after completing the following visits: baseline visit, week 4, week 8, and week 12 visits. $100 for completing the final 1-month follow-up. The money will be issued via direct deposit after your visit. The direct deposit may take up to 12 weeks to hit your account. The total for completing the entirety of the study including the final 1-month post-intervention follow-up is $300.

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

If you are injured because 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 with study procedures. The Department of Veterans Affairs does not normally provide any other form of compensation for injury. By signing this form, you have not released this institution from liability for negligence.

If you should have a medical concern or get hurt or sick because of taking part in this study, call:

DURING THE DAY:

Dr. Chen Lin at **(205) 934-0634 or (205) 240-6552** and

AFTER HOURS:

The VA Emergency Room at 205-558-4725 after hours for urgent medical issues.

Dr. Chen Lin at **(205) 934-0634**

Emergency and ongoing medical treatment will be provided as needed.

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DO I HAVE TO TAKE PART IN THE STUDY?

PARTICIPATION IS VOLUNTARY

It is up to you to decide whether to take part in this study. If you decide to take part, you may still withdraw at any time. If you do not wish to be in this study or leave the study early, you will not lose any benefits to which you are entitled. If you are a VA employee, refusal to take part in this study will in no way influence your employment. If you do not take part, you can still receive all usual care that is available to you. Your decision not to take part will not affect the relationship you have with your doctor or other staff, and it will not affect the usual care that you receive as a patient. If you decide to stop taking study medication you will be asked to come to the remaining visits, but again, this is voluntary, and you will not be penalized for declining. If you withdraw completely from the study and discontinue study interventions and study follow-ups, data that has already been collected as part of the study can be utilized by the study team.

RIGHT OF INVESTIGATOR TO TERMINATE MY PARTICIPATION

The study staff may end your participation in the study if they believe it is in your best interest or if you are not following study requirements. If so, your study doctor will explain the reasons and arrange for your usual medical care to continue. Termination from the study will not affect the relationship you have with your doctor or other staff, and it will not affect the usual care that you receive as a patient.

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

If you have questions about your rights as a study participant, or you want to make sure this is a valid VA study, you may contact the Institutional Review Board (IRB). This is the Board that is responsible for overseeing the safety of human participants in this study. The IRB Administrator phone number is 205-558-4747if you have questions, complaints, or concerns about the study or if you would like to obtain information or offer input.

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WILL I BE TOLD NEW INFORMATION ABOUT THIS STUDY?

Sometimes during a research study, new information becomes available about the treatments being studied that might change a person's decision to stay in the study. If this happens, your study doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw from the study, your study doctor will arrange for your medical care to continue. If you decide to continue in the study, you might be asked to sign an updated informed consent form.

Individual research results from this study will not be available and/or disclosed to participants at any time. However, a summary of the overall results will be available at the end of the study in the following website: http://www.ClinicalTrials.gov. In addition, participants will be notified of their treatment assignment when the study ends.

FUTURE USE OF DATA

The information collected about you during the study will be stored in a research database maintained by the local investigators until destroyed according to VA regulations. The database will be shared per VA policy and applicable Federal requirements among the researchers involved in this project and others in the future who have a VA-approved agreement to use the study data. Information that discloses your personal identity will not be released without your permission unless required by law. Your personal information will always be kept separate from the research database.

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.

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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. A copy of this signed consent may also be put in your medical record per local VA policy.

I agree to participate in this research study as has been explained in this document.		
_____ Participant's Name	_____ Participant's Signature	_____ Date