LARA Quarterly Progress Report: 9/1/2022-10/15/2022
2022 Veteran Marijuana Research Grant

Investigating the Therapeutic Impact of Cannabinoids on Neuroinflammation and Neurobiological Underpinnings of Suicide Ideation in Veterans with PTSD

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Project Aims:

This study, referred to here as the 'Neuroimaging Study,' is a supplement (add-on) to our ongoing VMR study (Wayne State Warriors Marijuana Clinical Research Program: Investigating the Impact of Cannabinoids on Veterans' Behavioral Health", PIs: Lundahl and Ledgerwood), which will be referred to as the 'Parent Study'. **The Neuroimaging Study will be the first-ever neuroimaging study of cannabis treatment in US armed forces veterans with PTSD, or in any population.** The Parent Study involves randomizing 200 Michigan veterans with PTSD into one of four different THC (∆9-tetrahydrocannabinol) : CBD (cannabidiol) dose conditions (High THC:High CBD; HighTHC:Low CBD; Low THC:High CBD, and Low THC:Low CBD) for a 12-week treatment phase. For this Neuroimaging Study, half of the 200 participants from the Parent Study (N=100; 25 of the 50 participants in each dose condition) will additionally complete two brain imaging assessments: one before (i.e., 'baseline' scan) and one after the 12-week treatment period (i.e., 'post-treatment' scan). **Primary outcomes include:** A) neuroinflammatory state as measured via positron emission tomography (PET) imaging with the radiotracer, α-[11C]methyl-L-tryptophan (AMT); B) resting or 'basal' neural network communication as measured via functional magnetic resonance imaging (fMRI); and C) brain activation during well-validated inhibitory control (Go/No-Go) and emotion regulation (Emotional Stroop) tasks as measured via fMRI. We will focus on brain regions that are consistently linked to both PTSD symptom severity and suicidal ideation, and that are densely populated with cannabinoid receptors (which are modulated by acute cannabis/cannabinoid administration). Further, the collection of whole-brain, multi-modal neuroimaging data (structural MRI, functional MRI, and PET imaging data) during the same session will allow us to explore the impact of cannabis/cannabinoid administration on the relationship between neuroinflammatory state and neural network activation and interactions throughout the brain, and link these brain metrics to clinical outcomes (e.g., reduction in suicidal ideation or PTSD/depression symptoms over time). This highly innovative approach will provide unprecedented insight into the neurobiological underpinnings of PTSD and suicidal ideation and the potential therapeutic effects of cannabis (and associated brain mechanisms) on these and other critical outcomes (e.g., quality of life, depressive symptoms). Findings from this Neuroimaging Study may also identify veterans who will benefit most from cannabinoid therapeutics and specific THC:CBD dose combinations therein, and thus, may inform a personalized medicine approach for veterans with PTSD in the future.

1. Project Milestones

• Percent (%) completion of the project objectives

Preparation for Neuroimaging Study Launch: 20%
Neuroimaging Study Progress: 0%
Neuroimaging Study Analyses/Findings Communication: 0%

• Project Progress – Brief outline of the work accomplished during the reporting period and the work to be completed during the subsequent reporting period(s).

Since receiving the grant funds in September 2022, we have begun to develop our protocols and the infrastructure needed to support the Neuroimaging Study. In particular, we have developed the consent forms, screening forms, and protocols to be submitted to the Wayne State University Institutional Review Board in October 2022. This involves close coordination between our study team and the Parent Study team, including the Co-PIs (Drs. Lundahl and Ledgerwood) and the study coordinator. Our study team has also begun to develop our internal protocols for quality assurance, and attended CRA and stakeholder meetings.

Once we receive IRB approval, we will submit our MR protocol to the MRI Research Committee. Once approved, we will test all of the parameters and sequences during pilot testing MRI scans. We have already begun to develop some of the computer and MRI tasks that will be tested in the MRI scan environment. After IRB approval, the PET scanning protocol will be submitted to the PET Center's Radioactive Drug Research Committee for review.

In early September, Co-PIs Marusak and Woodcock met with Pavan Jella, MR Technician, and Dr. Mark Haacke, the Director of the MR Research Facility, to discuss our research design, proposed MRI protocol, and safety procedures. We have been working closely with Mr. Jella and Dr. Haacke to develop a comprehensive 4-tiered protocol for screening participants for MRI safety. Our 4-tiered MRI safety screening protocol includes a detailed MRI safety questionnaire, review of medical records, and two pass-by metal detector screenings: one to be used at the screening visit and one on scan day. At present, we identified and demoed the metal detector, and are in process of purchasing two high-sensitivity pass-by metal detectors for this study: one to be mounted in our laboratory and the other to be mounted in the MRI center. This reflects a significant advancement over previous MRI safety protocols. Once implemented, this new comprehensive MRI safety protocol will maximize participant safety throughout the Neuroimaging Study.

In preparation for study launch, we have worked with our administrative team to establish a new budget index and accounting processes, add key personnel to the study, and begun to establish new vendors for purchasing supplies, equipment, and consultants. We have also worked with our HR administrator to create a new job posting for a computer scientist/research technician position and a research assistant position, and we started to interview potential candidates for both positions. In addition, we purchased two computer workstations for neuroimaging data processing and visualization, and one computer workstation for research administration. We also purchased a centrifuge and are in the process of purchasing an ultra-low freezer for processing and storage of biological samples.

Finally, our research laboratory has been allocated additional space by the Department of Psychiatry and Behavioral Neurosciences to significantly expand and re-

organize. The Substance Abuse Research Division (SARD), which will administer all four Wayne State University Veteran Marijuana Research Grants, is in the process of adding more than 3,600 square feet, including 4 new participant testing and interview rooms, a new phlebotomy and biological sample storage room, and a new physiological testing room. This expansion will add office space for 5 new research assistants, 2 new research coordinators, 4 new Postdoctoral Fellows, 10-12 'hot desk' workstations for students and research volunteers, and a new conference room. Once complete, the SARD will occupy an entire floor in the Tolan Park Medical Building located in Detroit, MI and will serve as the largest clinical cannabis research laboratory in Michigan (and possibly the country). In addition, we converted a conference room to create a comfortable waiting room to accommodate caretakers and family members who accompany Veterans on their lab study days. Study days can be long and we want to provide a comfortable and welcoming space, with reading areas, workspaces, and TV/lounge area for Veterans and their family members or caretakers. We also converted an office to a calming room/safe space for participants should they experience any acute anxiety or discomfort during study procedures. This expansion will provide more usable space for our study participants and staff, and demonstrates the commitment of support from the Department to these VMR projects.

• Noteworthy Accomplishments – Identify and describe any milestones reached or noteworthy accomplishments completed during the period.

N/A – The study is in the Study Preparation phase.

2. **Delays – Brief description of problems or delays, real or anticipated, which should be brought to the attention of the Grant Administrator.**

None.

3. **Statement concerning any significant deviation from previously agreed-upon Statement of Work.**

None.

• Attachments and Other Materials – Provide project materials developed and implemented during the reporting period (e.g. newspaper articles, newspaper advertisements, forms, brochures, announcements, studies, reports, analyses, audits, etc.)."

This project, along with other VMR-funded projects, has received local interest and some media coverage which may serve to facilitate study activities and recruitment within the community. This included interviews at the University level (https://today.wayne.edu/medicine/news/2022/08/04/state-awards-wsu-researchers-additional-125-million-to-study-risk-and-benefits-of-cannabis-in-veterans-behavioral-health-care-49016) and local media outlets (https://www.detroitnews.com/story/news/local/michigan/2022/08/08/michigan-marijuana-research-veterans-use-wayne-state-university-of-michigan/10088266002/).

4. Financial expenditures of grant money and other contributions to the project, in-kind and/or direct funding.

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CATEGORY	TOTAL BUDGET	Expenses - thru 10/12/22	% of Budget Spent
Personnel/Fringe	2,182,687	4,627	
Equipment	42,000	-	
Supplies/Other	966,334	1,250	
Computers	12,000	3,396	
Consultants	12,000	-	
Travel	-	-	
DIRECT TOTALS	**3,215,021**	**9,273**	**0.29%**
Indirect Costs- 10%	321,503	927	
BUDGET TOTALS	**3,536,524**	**10,201**	**0.29%**

Respectfully submitted,

Hilary A. Marusak, Ph.D.
Lead/Contact Principal Investigator

October 13, 2022