LARA Quarterly Progress Report: 9/1/21 – 12/31/21

Wayne State Warriors Marijuana Clinical Research Program: Investigating the Impact of Cannabinoids on Veterans' Behavioral Health

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Project Aims:

In this randomized, controlled clinical trial we will recruit veterans with PTSD who report using cannabis. **We will conduct two studies that are complementary and linked via their aims and methodology**. In **Study 1**, 200 veterans will be randomized into one of four different THC:CBD dose conditions (High THC:High CBD; High THC: Low CBD; Low THC:High CBD, and Low THC:Low CBD) for a 12-week treatment phase. In **Study 2**, 150 veterans will be assigned into *either* a naturalistic group that will be followed as they continue to use cannabis as they normally do (observation only), or into a "THC reduction group" in which veterans are asked to switch from their typical cannabis product to using a lower THC/higher CBD product; adherence to this switch will be incentivized using contingency management. **Both studies** involve assessments bi-weekly throughout a 12-week treatment phase, and at 3- (post-treatment), 6-, 9-, and 12-months post-baseline. Study 1 will also include additional weekly assessments. **Primary outcomes** include clinical assessments of PTSD symptom severity, mood and anxiety symptoms, and suicidality. **Secondary measures** include (1) neurocognitive function; (2) overall health, sleep quality, pain, healthcare utilization, and quality of life; (3) individual differences in fear learning and extinction associated with PTSD symptom severity; (4) saliva for DNA analysis to examine genetic and epigenetic markers associated with the endocannabinoid system; and, (5) blood and saliva samples to quantify levels of endocannabinoids and their metabolites (e.g., anandamide [AEA] and 2-AG), as well as THC and CBD and their metabolites, to examine whether these levels vary as a function of THC:CBD dose mixtures and differentially affect outcomes. Data will be analyzed to determine which THC and CBD levels might be associated with the outcome measures. These data will be used to (1) develop a predictive algorithm that will help determine personalized profiles of patients who may be at increased risk for suicide; and, (2) develop a profile of who might most benefit from cannabinoid therapeutics.

• Project Milestones – Percent (%) completion of the project objectives

N/A. We are currently in the start-up process and the study has not yet begun.

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

For this first quarter we focused on establishing the infrastructure needed to recruit for and conduct the studies, hiring and training research and clinical staff, procuring the equipment and supplies needed to successfully perform study-related tasks, and obtaining the necessary university review board approvals. The Department of Psychiatry and Behavioral Neurosciences (DPBN) requires that all research protocols involving human participants be reviewed and approved by a Departmental Review Board (DRB) prior to submission to the broader University Institutional Review Board (IRB). We submitted our initial DRB application in early December

and are finalizing edits and revisions to the protocol based on the DRB's suggestions, concerns, and feedback. We anticipate receiving DRB approval of our final protocol within the next week and will submit the protocol to the Wayne State University IRB in mid-February, 2022.

Below are specific tasks in which we are currently engaged *or* have completed:

Research personnel

- Hired and trained research assistants and study coordinator
- Trained research personnel on use of OnCore, a system for tracking clinical trials participants
- Training staff in all procedures and measures
- Research Team meets on a bi-weekly basis
- Lead PI Dr. Lundahl and study coordinator meet weekly
- Lead PI Dr. Lundahl and co-PI Dr. Norrholm meet weekly
- Leadership meetings as needed

Regulatory

- Submitted DRB application
- Revising protocols and methodology, particularly around safety issues, in response to DRB feedback
- Completing IRB application for submission mid-February, 2022
- Uploading study to clinicaltrials.gov
- Consulted with attorney specializing in cannabis regulatory issues on issues regarding cannabis delivery, procurement, etc.

Protocol

- Set up account for processing ClinCard payment cards for participants
- Developed detailed methods and protocols; revising according to DRB feedback
- Refined timeline of study methods
- Developed Informed Consent Forms for screening and for study
- Updated literature search to select appropriate THC/CBD doses and strains for medical use
- Building a library of VR-scenarios identified as trauma relevant by Servicemembers (SMs) and Veterans; constructing new environments reported as traumatic by SMs and Veterans but have not yet been available in research applications. Study team is building VR environments linked to those SMs who worked with battlefield victims and mortuary affairs to be included in this study's cue reactivity assessment
- Working with Dr. Krishnarao Maddipati (Lipidomics Core at WSU) to refine our protocol for collecting plasma samples and analyzing endocannabinoids. Integrated this into our protocol and consent forms.

Supplies/Needs

- Ordered portable blood pressure monitor and secured blood collection supplies

- Completed application with STORZ & BICKEL to purchase medical vaporizers for cannabis administration
- Identified cannabis supplier (currently awaiting prices, availability from two licensed suppliers)
- Working with Alex Leonowicz (COO and General Counsel at Redbud Roots) to identify cannabis flower strains for the RCT and how product will be delivered to the research team
- Identified vans that will serve as the Pharmacology Lab Vans (PLV) for the delivery of study drug, and specified modifications needed to conduct field assessments; they will be purchased through the University and the purchase orders are currently under review at the University
- Contracted with WSU to use University Health vans while waiting for new van delivery
- Purchased computers/laptops
- Developed Qualtrics versions of necessary questionnaires and measures
- Loaded software and measures needed (neurocognitive testing)
- Purchased BIOPAC psychophysiology equipment, which is currently en route to WSU

Safety

- Arranged for medical coverage and backup during screening and study
- Interviewed several security-guard companies to identify appropriate level of coverage during Pharmacology Lab Van visits
- Developed Data Safety Monitoring Plan for identifying and reporting Adverse Events, safety protocols for increased symptomatology and/or suicide risk; maintaining confidentiality; securing data, etc.

Data

- Developed databases for securely storing participant information

Recruitment and Screening

- Developed scripts for telephone screening and recruitment
- Developed advertisements for online postings and flyers
- Researched social media and local recruitment sites
- Developing website dedicated to recruitment and information for the study
- Developed study “brand” and logo for recognition/recruitment

During the next quarter, we will submit an application for IRB approval, which we expect will be granted after a round of revisions. Once our protocol is approved we will be able to begin recruiting and screening for study enrollment. We will place ads, post flyers on main campus at around the VA hospital, and reach out to veterans’ groups to recruit potential participants.

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

N/A – Still in study start-up

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

We experienced a delay in obtaining DRB approval to move forward with our IRB application because board reviewers expressed concern about the virtual reality trauma cue exposure. This task involves exposing participants to personalized trauma-related cues in a virtual reality format and assessing their physiological and psychological reactions before and after the treatment trial. The DRB reviewers felt that presenting trauma cues, especially in such a realistic format, might be "triggering" and cause an escalation in PTSD symptoms or suicidal ideation, which they concluded was too risky for this population. The reviewers also felt that the cue exposure might be so aversive that participants would drop out of the study prematurely, which would compromise the feasibility of completing the study. The board concluded that they would approve the protocol only if we were to remove the virtual reality cue exposure task from the studies. We agree with their feedback. As the main focus of this grant is the cannabis treatment trial, we have dropped the cue exposure task from the trial protocol so the main studies can be launched more quickly and with improved safety.

• 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.)."

As expected, this project has received local interest and some media coverage which may serve to facilitate study activities and recruitment within the community. This coverage has included interviews at the University level (https://today.wayne.edu/podcast/s2-e2) as well as in local media outlets (https://www.thesouthend.wayne.edu/features/article_45acf82e-2d53-11ec-a989-5ff6b79f18b0.html; https://www.dbusiness.com/daily-news/wayne-state-university-granted-7m-for-cannabis-research-for-veterans/).

Respectfully submitted,

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Jan 18, 2022