State of Michigan
Department of Licensing and Regulatory Affairs
Marijuana Regulatory Agency

VETERAN MARIJUANA RESEARCH (VMR) GRANT PROGRAM

2022

REQUEST FOR PROPOSALS

VETERAN MARIJUANA RESEARCH (VMR) GRANT

RESPONSE DOCUMENT

ESTIMATED TIMELINE	
Issue Date	April 1, 2022
Inquiries Due	April 15, 2022
Inquiries Response Posted	May 1, 2022
Proposals Due	June 1, 2022
Anticipated Start Date	July 30, 2022

PART V: INFORMATION REQUIRED FROM APPLICANT(S)

Applicant(s) must submit one proposal. Electronically submitted proposals must have a scanned signature or e-signature and cannot exceed 15 MB.

Applicant(s) must provide responses to each section below. Be as descriptive as possible and answer each question in its entirety; some questions have multiple components. In your responses, provide a straight-forward, concise description of the applicant(s)'s ability to meet the requirements of the RFP. Questions that do not apply should be answered "N/A."

V-A Identification of Organization

State the full name and address of the organization, the organization's federal identification number, the organization's telephone and fax numbers, and what percentage of the organization is located in Michigan.

BEGIN APPLICANT RESPONSE

Wayne State University

Sponsored Program Administration

5057 Woodward Avenue

13th floor, Suite# 13202

Detroit, MI 48202-4050

Federal ID # 38-6028429

Tele: (313) 577-2653

Fax: (313) 577-5055

100% located in Michigan

END APPLICANT RESPONSE

V-B Authorized Negotiator

State the name of one (1) contact person and his/her telephone number, fax number, and electronic mail address. The contact person must be authorized to be the negotiator for the proposed Grant Agreement with the State.

BEGIN APPLICANT RESPONSE

Patty Yuhas Kieleszewski

Associate Director, Contract Administration

Sponsored Program Administration

5057 Woodward Avenue

13th floor, Suite 13203

Detroit, MI 48202-4050

Tele: (313) 577-9227

Fax: (313) 577-5055

Email: aa6841@wayne.edu

END APPLICANT RESPONSE

V-C Method for Addressing the Problem

State in succinct terms the applicant(s)'s proposed method for addressing the problem presented in Section III-B, Problem Statement. Describe any significant obstacles the applicant(s) has had coordinating and managing clinical trial research.

BEGIN APPLICANT RESPONSE

I. EXECUTIVE SUMMARY

Post-traumatic stress disorder (PTSD) is a debilitating anxiety disorder that disproportionately affects US armed forces veterans and is linked with increased risk for suicide. One of the most effective treatments for PTSD is Prolonged Exposure (PE) therapy, however, many military veterans prematurely discontinue PE and more than a third who complete PE do not report significant symptom improvement. There is a clear and urgent need for novel approaches to treat PTSD, and emerging evidence indicates that cannabinoids like THC and CBD potentially could enhance the effects of PE. ***We propose to conduct the first randomized, controlled, large-scale clinical trial to examine whether cannabinoids used as adjunctive treatment (i.e., PE+cannabis) can improve the effectiveness of PE, an empirically-based behavioral treatment for PTSD.***

II. VISION STATEMENT

Our overall vision is to improve the quality of life of military veterans suffering from Posttraumatic Stress Disorder (PTSD), suicidality and other mental health problems by improving the effectiveness of medication and psychosocial treatments for these conditions. Consistent with this vision, the proposed study will explore the impact of cannabinoids (THC and CBD) for improving the effectiveness of prolonged exposure (PE), an intervention that has extensive evidence for its efficacy, but is also limited as many patients who start this treatment do not complete it. The proposed study has many strengths that are necessary to meeting our vision including: research aims that are highly significant from both a scientific and public health standpoint; a boldly innovative approach to addressing the use of cannabinoids in the treatment of PTSD and suicidality; a rigorous clinical trial methodology; an exceptionally experienced team with all of the pertinent skills to accomplish our aims; and a supportive and well-established research environment in which to complete the work.

Our long-term goals are to establish a clinical research center that will allow us to advance the science related to the use of cannabinoids in PTSD care. With the recent LARA-based funding of our new clinical trial to examine whether cannabinoids can improve mental health functioning among military veterans, we have established the umbrella *WarriorCare Center* within the Department of Psychiatry and Behavioral Neurosciences at Wayne State University. With the development of the center, we can leverage our current and subsequent LARA grants to extend cannabinoid therapeutics to the aim of enhancing current therapies that we know work to a moderate extent, but need to work much better if they are to benefit the broad population of veterans with PTSD. Our work will also have

benefits for the broader veteran and clinical communities through its impact on education, health care policy and improved healthcare utilization.

Our proposed treatment outcome trial would be the first randomized, controlled clinical trial to examine whether cannabinoids improve the effectiveness of an empirically-based behavioral treatment for PTSD. This trial is innovative (cutting-edge) and methodologically rigorous, and will have real-life implications for treating veterans who experience PTSD and chronic suicidality (high public health significance). Strong methodological elements of this clinical trial include random assignment to treatments, different THC:CBD combinations, placebo control condition, well-validated assessments, extensive clinician training, thorough measurement of treatment fidelity, long-term follow-up of research participants, and intent-to-treat analysis (i.e., assessment of all participants regardless of whether they complete the intervention). This rigorous and comprehensive approach will ensure our research has a high impact in the scientific literature, thus increasing the possibility that treatment providers and organizations will have access to, and ultimately will implement, our findings.

If effective, the addition of cannabis to PE will confer direct benefits to this community, as it could be immediately translated into clinical practice. Locally, the expansion of our work to PE also has the potential of greatly expanding services to veterans in underserved areas of South East Michigan where there are relatively few providers. Cannabis has substantial value as a potential therapy both as a stand-alone medication and as an adjunct to other interventions such as PE. Our WarriorCare Center provides a dedicated space for veterans to take part in these important and innovative clinical trials, and with our recent LARA funding, we are well on our way to making our vision a reality. **Support for the proposed project will greatly enhance our ability to address fundamental and timely clinical and scientific questions related to the use of cannabis for the treatment of mental illness.**

III. OBSTACLES

At least four primary obstacles to this line of research can be effectively addressed through the Veteran Marijuana Research program. These obstacles are noted below:

(1) Federal regulations are currently and largely prohibitive to conducting human cannabis research. Compelling data from animal studies suggest that cannabis, related cannabinoid compounds, and the mammalian endocannabinoid system should be a principal area of empirical study to better understand their roles in trauma-, stressor-, anxiety-, mood-, and substance-related disorders as well as improving existing treatments and developing novel treatments for these disorders. ***Drs. Lundahl and Greenwald have the necessary FDA, DEA, and NIH licenses and certificates, and a wealth of experience navigating regulatory requirements, to conduct human cannabis research and have been doing such studies for over 20 years.***

(2) Sources of extra- and intramural funds to support large-scale, community-based studies of cannabis and its potential therapeutic benefits are few despite the infrastructure and expertise being readily available within the Wayne State University system. ***Funding through the Veteran Marijuana Research Program will support the first large-scale, randomized, placebo-controlled clinical trial examining the ability of cannabinoids to improve the efficacy of a frontline, gold-standard behavioral treatment for PTSD in US armed forces veterans.***

(3) Recruitment, enrollment, and retention of Veterans in clinical research studies can have its unique set of barriers, both institutional (e.g., VA regulations and policy) and logistical (e.g., Veterans' access to healthcare and research opportunities), and psychological (e.g., distrust of medical or government research). ***We will leverage the partnerships with Veterans' groups and associations that we have already begun to build for our current VMR project to recruit Veterans for this proposed treatment trial, and will create on-line and mobile systems to support study participation and maintenance to overcome these barriers. We have also established the WarriorCARE Center, which includes a welcoming and comfortable reception and waiting area for Veterans and family members who might accompany them to their study sessions. By providing a warm and comfortable setting, with snacks, beverages, and access to workspace and WiFi, we hope to make study participation as***

convenient and as pleasant as possible.

(4) Despite a growing evidence base of potential therapeutic indications coupled with Veteran reports of cannabinoid use for treating their symptoms, at present the Department of Veterans Affairs does not support cannabinoid therapeutic trials. ***Providing the proposed gold-standard behavioral treatment (PE) combined with cannabis administration to increase retention in treatment and improve treatment outcomes, may reduce anxiety and fear, improve mood, and decrease rates of suicide in Veterans. This may represent a viable and attractive alternative approach for treatment-seeking Veterans. Optimistically, positive results might also provide impetus for the Department of Veterans Affairs to reconsider their stance on therapeutic trials with cannabis.***

END APPLICANT RESPONSE

V-D Management Summary

(1) Describe management procedures that will be used by the organization to complete the proposed project.

(2) Describe the organization's quality control measures, including measures for ensuring compliance as well as eligibility determination. In your description, include information regarding separation of duties.

(3) Selected applicant(s) must provide fiscal control and financial accounting procedures that will assure that grant funds will be accounted for and properly dispersed in a way that will allow the Issuing Office to clearly review and verify all grant related expenditures. Describe the organization's internal control policy:

- Identify the type of accounting system/software the organization will use to account for grant funds,
- Identify how duties will be separated,
- Describe how the organization will account for grant funds, i.e., will grant funds be placed in a separate bank account, will the grant funds be assigned a unique code(s) within the organization's overall accounting system. Ensure funds are maintained in a non-interest-bearing account.
- Indicate whether internal and external audits of the organization's operations are performed on an annual basis. Selected applicant(s) must provide a copy of the organization's most recent audited financial statement as well as a copy of the organization's most recent single audit as required by OMB Circular 200.36

(4) Describe your agency's data security plan.

BEGIN APPLICANT RESPONSE

(1-3) Management Procedures, Quality Control Measures, and Financial Accounting Procedures

Wayne State University (WSU) has a Sponsored Program Administrative (SPA) department that all grant awards must go through. Once the grant is awarded, we are notified by our SPA office and an index or account number is set up for that specific grant or fund award. The SPA office prepares the financial reports for the agency at each reporting period. They also send notifications and reminders if progress reports are due. The SPA office will load the budget based on what was submitted to the agency in our BANNER Accounting system.

At the department level, once a grant index number is established, our administrative team meets to review the contract. Cordell Crutchfield is our grant & contract administrator within the department of Psychiatry. Sonya Blair is our HR program specialist, Michelle Caton and Valerie Felder are purchasing agents, and Jennifer Ballard-Traynor is the administrative director. The administrative team meets to review the contract with the PI. The purpose of the initial meeting is to understand the project, review the budget, and read through the contract so we are all on the same page with the requirements.

Sonya will add effort to the grant based on the budget and the PI's sign off on who is actually working on the grant. This is done through an Electronic Personnel Action Form (EPAF), which is an online system for making personnel changes. Once she processes, it is reviewed by Jennifer, then by individuals in HR and the School of Medicine's Business Affairs office. All approvers will review the budget loaded in our Banner Accounting system, to ensure there are funds in the "personnel" expense account before approving.

The research team, including Co-PIs, Co-Is, or research coordinator will submit orders via email to either Michelle or Valerie. The orders are then placed in our WayneBuy Procurement System. At WSU, all purchasing orders must be pre-approved before making the purchase. Upon receiving the order form from the research team, Michelle and/or Valerie will enter that order in WayneBuy. Once submitted, there are several approvers that must review the order before a Purchase Order is submitted to the vendor. Jennifer reviews all orders that are placed within the department. She reviews the grant budget to determine if the good/service was initially budgeted for. If it was, she approves it, if it was not, she will reach out to the PI for justification of the purchase. All charges on the grant must be 100% for that specific study. Once approved, it then goes to Business Affairs to review against the budget posted in Banner. Then it goes to the SPA office to review to ensure compliance with that specific grant. Lastly, a representative from the Purchasing office will review to ensure the requisition is compliant with the University. There are several approvers in this process to create a separation of duties and to ensure compliance for both the granting agency and the University.

Once the PO is approved, it is sent to the vendor to fulfill the order. The vendor will then submit an invoice to WSU for payment. Invoices under $1,000 do not require departmental review. Any invoice over $1,000 needs to be reviewed by the department to ensure the good or service was received. Then a receipt is entered in the WayneBuy system which prompts Disbursements to make the payment. All payments are made by the Disbursement office and do not go through the Department. Departments at WSU do not have the ability to issue payments to vendors.

All travel has to be preapproved in our Concur TravelWayne system. In this system, the user needs to estimate the expenses, enter the conference or research related travel information, indicate the index number to charge, and upload the conference brochure or research purpose. The request needs to be approved by Jennifer for grant compliance and budget review and to the Chair, Dr. David Rosenberg. In the Department of Pharmacy Practice, the complimentary counterparts are Lucy Snyder, the business administrative officer, and Dr. Lynette Moser, the Department Chair. Once approved, the traveler can submit receipts to an expense report in the system. These are reviewed first by Jennifer and then by the Business Affairs office. Once fully approved, the expense is posted to the grant index in Banner.

WSU uses the Clincard System to pay out research subject incentives. These are debit cards that are loaded with funds once a research participant completes a milestone. Jennifer sets up the studies in the Clincard system based on the approved IRB protocol for the study. She will enter the study name, grant index number, and the payment milestones. The physical cards are ordered through the Procurement office. The cards do not have funds on them until they are loaded through the Clincard system. We do not keep cash or preloaded debit/gift cards for the purpose of paying subjects. Users are given access to the Clincard system to load the cards once a participant is seen. A separate user will be added as a card approver once funds are loaded. The approver does not have access to the clincards as to separate duties. The system also requires social security numbers for each subject being paid, and the university runs reports on a regular basis to ensure no SSN matches a WSU employee's SSN. The university front loads funds to the Clincard system and each month charges are

posted to Banner based on the index number for each study.

WSU uses the Banner ERP system to manage student and employee information and financial data for all funding received. Access to Banner relies on strict security measures and is only given to eligible employees. To separate duties, administrative employees in the Department of Psychiatry only have read-only access to Banner. The grant budget is loaded by SPA, the personnel expenses are added by the above EPAF system, expenses are added as WayneBuy and TravelWayne expenses are approved and paid, and research subject payments are posted monthly as they are paid out.

Our SPA office will invoice the granting agency on a monthly basis (unless otherwise stated in the contract) for all expenses that have been posted to the grant in Banner. Invoices are normally to be paid 30 days upon receipt of the invoice. Once the invoice is paid, it is recorded under the grant so that we can track the revenue in that same index number.

An audit or review is performed each year in compliance with regulatory requirements or Board of Governor mandates. In certain instances, to achieve efficiencies, these audits may be performed biannually. Below is a link to our internal auditor web page with information on what systems are audited, the timeliness of audits, best practices, safeguarding assets, etc. https://internalaudit.wayne.edu/

(3) All clinical research and participant encounters performed as part of this project will be subject to at least four levels of oversight from the Departmental to the Federal level. First, the Department of Psychiatry and Behavioral Neurosciences in the Wayne State School of Medicine has a Departmental Review Board (DRB) that reviews and approves research conducted by faculty in the Department. This is a prerequisite step to submission to Wayne State University's Institutional Review Board (IRB), the principal research oversight committee located at the University. Additionally, Dr. Lundahl, one of the project's Principal Investigators, is required to submit progress reports regularly as part of her approved and funded program of studies using cannabinoids to both the US Food and Drug Administration (FDA) and the US Drug Enforcement Administration (DEA).

(4) Data Security

Access to the Database

All data collected for this project will be stripped of all identifiable information and each participant will be assigned an individual code. These codes will be kept in a master file, separated from the identifiable information, by using a different passcode and kept in a different folder in a password protected server. No data will have participant names on them, except for consent forms, which are stored separately from other questionnaires in a locked file cabinet. The master code is the only list that will link the names of the participants with their participant numbers and will be kept in a secure, password- protected computer account on a separate drive from research coded data and will be accessible only to IRB- approved members of the research team. All the data for this project will be collected specifically for research purposes. All information obtained during this study is strictly confidential, except when there is either a danger to self or others. Members of the research teams will not divulge any information about interviews or other tests to non-study staff personnel. Data that may be reported in scientific journals will not include any information that identifies any person as a participant in this study. Hard copy files will be kept in locked file cabinets within locked offices to which only authorized research personnel have access. Electronic data (e.g., digital audio-files or video-files of prolonged exposure sessions used for assessing therapist competence and treatment fidelity) will be stored electronically on Emory University's secure, HIPAA-compliant OneDrive and Dr. Rabinak's secure, HIPAA-compliant private server located in WSU's central IT Data Center. Behavioral, fMRI, and psychophysiological data will be stored in password-protected computer files, such as encrypted Microsoft Excel files, (except for a single tracking file) on a password and firewall-protected private lab server as well as in an Electronic Data Capture system with a CFR Part 11 compliant audit trail (Castor). All paper forms (e.g., therapist notes and checklists) will be stored in a locked cabinet at Co-

PI Lundahl's research site. Therapists will transfer paper forms to the research site as soon as possible when conducting PE sessions.

Participants will be asked to use their personal smartphones or other recording device to record (audio only) their PE therapy sessions for later use in homework assignments. Participants may choose to utilize the PE Coach application (https://mobile.va.gov/app/pe-coach) to store and manage their recordings, however this is not mandatory. If a participant does not have access to an audio-recording device, they may borrow one from Dr. Rabinak for use during their participation in the study. Audio recordings of PE sessions will be handled and stored by the participant on their personal device(s) and will not be accessed or stored for research purposes (i.e., by the research staff).

Back-up of Database

The site research coordinator will back up the data from Castor on a weekly basis onto the secure research server at Wayne State University. WSU will permit study monitors and oversight boards with access to data files and scanned case report forms stored on a WSU Box account. The study monitor will download a copy of the data files and scanned case report for data collection and quality assurance purposes. Our statistician will create static analytic files for interim and final analyses and will report the date the data is finalized, and number of subjects included in that database.

END APPLICANT RESPONSE

V-E Work Plan

Provide clear and concise work plans for meeting the following components, with detailed explanation:

1) Provide for the coordination and overseeing of clinical trial(s) to determine the efficacy of marijuana in treating the medical conditions of U.S. armed services veterans and preventing veteran suicide.
2) Recruit and evaluate researchers to accomplish the goals of this grant.
3) Demonstrate the ability to work with researchers who can garner the United States Food and Drug Administration approval for the clinical trials.
4) Ensure the maximum amount of grant dollars are used to coordinate and oversee clinical trials with a minimal amount of grant dollars used for administrative costs.
5) Work with organizations closely tied to veterans and veterans' programs.
6) Provide the Grant Administrator with a grant budget to which monitoring and reporting will be tied. Please see attachment A for the budget template to be used.
7) Establish research goals, approve projects, exercise financial and management oversight, and document and review results.
8) Publish the results of the clinical trials.

BEGIN APPLICANT RESPONSE

Item 1 is addressed in the **Work Plan**, below.
Items 2-3. We have compiled a clinical research team with the necessary experience and expertise to successfully meet the aims and goals of the proposed clinical trial. Drs. Lundahl and Greenwald have decades of experience navigating regulatory requirements (e.g., FDA INDs, DEA, NIH) to conduct their human drug administration and behavioral pharmacology studies. Our team has expertise in designing and conducting clinical

trials, working with veterans, other traumatized populations, and substance users, as well as experience using advanced brain imaging techniques to characterize fear responding. Our consultants are national experts in cannabinoid research (Dr. Vandrey), use of cannabinoids for anxiety and PTSD in veterans (Dr. Bonn-Miller), and co-Investigator Dr. Rauch is a certified trainer in the use of Prolonged Exposure Therapy for PTSD. Collectively our team has successfully managed and completed many multi-million dollar federally- and privately-funded projects. Of note, our team also was awarded a VMR grant in the last funding cycle, and we will leverage much of the infrastructure already put into place for that project.

Item 4. Our administrative costs (salary and fringe benefits) account for *approximately 1.34% of the overall budget.*

Item 5. Our research team has ongoing collaborations with Veterans Affairs Healthcare Systems, including Detroit and Ann Arbor. We have initiated partnerships with and are currently working with several organizations to recruit veterans for study participation, including Wayne State University Student Veterans Organization, the Detroit Chapter of Team Red, White, and Blue, Veterans of America, Michigan Veterans Affairs Agency, Veterans of Foreign Wars (VFWs), VetLife, Volunteers of America (MI), and Piquette Square, among others. Dr. Rauch has conducted research with the DOD and the Veterans Administration. We have started to build a recruitment network capable of reaching Veterans either for whom cannabis is an existing treatment strategy or might be an attractive intervention for them to alleviate their symptoms of PTSD, depression, and suicidality.

Item 6: A Budget Justification and Attachment A Budget are attached to this application.

Items 7-8 are addressed in the **Work Plan**, below.

Work Plan

Wayne State Warriors Marijuana Clinical Research Program: Cannabinoid Adjunct to Prolonged Exposure & Recovery (*CAPER*)

Specific Aims

Post-traumatic stress disorder (PTSD) is a serious, often debilitating, stress-induced anxiety disorder characterized by numbing, avoidance, reexperience of trauma (e.g., nightmares), persistent distress, and excessive, inappropriate fear responses (e.g., hypervigilance, flashbacks) [1]. PTSD disproportionately affects US armed forces veterans; an estimated 13-31% of US veterans experience PTSD, compared to 6-10% of the general population. Individuals with PTSD are at increased risk for suicidality [2], and rates of suicide among United States military veterans are alarmingly high. In 2019, more than 6,200 US veterans died by suicide [3], which is equivalent to more than 17 suicides per day. Veterans make up only 8% of the US population, yet they accounted for 13.7% of all suicide deaths in US adults. These high rates of suicide in veterans are thought to be related to untreated or undertreated depression and post-traumatic stress disorder (PTSD) as well as psychological problems associated with these disorders [4].

A gold-standard, first-line behavioral treatment for PTSD is Prolonged Exposure (PE), a type of cognitive behavioral therapy that utilizes extinction learning principles [5]. PE teaches patients to gradually approach and process trauma-related memories, feelings and situations that patients may have been avoiding due to the trauma [5]. The beneficial effects of exposure therapy have been shown to derive from neurophysiological processes typical of fear extinction. Specifically, these benefits include significant post-therapy increases in prefrontal cortex (PFC) activity in conjunction with decreases in amygdala (AMYG) activity [6]. Although considered one of the most effective treatments for PTSD, up to 39% of patients prematurely discontinue PE [7–9], and more than 30% of military veterans who complete PE do not report significant improvement in PTSD symptoms at the end of treatment [10]. Clearly there is room for improvement, and a medication that could enhance the neural and neurochemical substrates of extinction and recall of extinction learning could improve PTSD treatment outcomes [11–13].

Emerging data indicate that cannabinoids like Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD) could potentially enhance the effects of PE. Recently, Co-PI Rabinak showed that administration of dronabinol (synthetic THC) prior to fear extinction facilitated the subsequent recall of extinction learning in healthy humans and in patients with PTSD using a similar behavioral design as proposed in the current project [14]. Taken together, rodent and human data reveal that

the combination of CBD and THC could modulate aspects of PTSD related to impaired fear extinction and its recall, while potentially improving other correlates of PTSD such as anxiety, depression, hyperarousal, chronic pain, and sleep disturbance. Therefore, a critical next step is to examine whether cannabis facilitates PE therapy in individuals with PTSD. ***In the proposed project, we will examine the ability of THC and CBD to increase the effectiveness of PE therapy in veterans with PTSD.***

In this proposed randomized, double-blind, placebo-controlled clinical trial, we will recruit veterans with PTSD who report limited prior use of cannabis along with interest in trying cannabis as a therapy. A total of 350 veterans will be randomized into one of five different THC (Δ^9-tetrahydrocannabinol:CBD (cannabidiol) dose conditions (High THC:High CBD; High THC: Low CBD; Low THC:High CBD, Low THC:Low CBD, and placebo). All participants will undergo a standardized 10-session prolonged exposure (PE) treatment protocol [15], consisting of two introductory/preparation sessions followed by eight exposure sessions. One to two sessions will occur each week. Just prior to beginning actual exposure sessions 1-4, participants will receive their assigned THC:CBD (or placebo) dose. We will assess treatment response (e.g., reduced PTSD symptom severity and suicidal ideation) at each subsequent PE visit, to detect rate of improvement, and again at 3-, 6-, and 9-months following treatment to explore long-term effects of PE coupled with THC:CBD vs. placebo. **Primary outcomes** include treatment response (i.e., clinical assessments of PTSD symptom severity, mood and anxiety symptoms, suicidality, and disability). **Secondary measures** include: (1) neurocognitive and reward decision-making functions (which could moderate the effects of cannabis and PE on treatment outcomes); (2) overall health, sleep quality, pain, healthcare utilization, and quality of life; (3) individual differences in fear reactivity, which has been associated with PTSD symptom severity; (4) saliva for DNA analysis to examine genetic and epigenetic markers associated with the endocannabinoid (eCB) system; and (5) blood, urine, and saliva samples to quantify levels of eCBs 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 in combination with evidence-based behavioral treatment.

Few US researchers can administer cannabis to human clinical trial and laboratory study participants because of restrictions imposed by federal (e.g., FDA, NIDA, DEA), state, or local agencies, institutions, or organizations. Further constraining important research on potential cannabis therapeutics are limited drug supply (there are few federal suppliers of cannabis for research in the US), lack of established laboratory practices for conducting such research, and few funding sources. Our highly experienced clinical research team at Wayne State has conducted cannabis and cannabinoid administration studies for over 20 years. We are accustomed to navigating FDA, DEA, and IRB regulatory requirements to conduct this work with human volunteers. The current proposed project will fill a huge unmet need for treatment options to reduce PTSD and suicidality in US armed forces veterans. This work will foster investigation of potential therapeutic effects of cannabis/cannabinoids to improve patient quality of life and reduce PTSD and depressive symptoms that can precede suicidality. These efforts, in turn, could improve existing therapies and guide development of novel approaches to PTSD treatment, with the goal of improving veterans' health outcomes and lowering their healthcare utilization rates and costs.

The overall strategy is to recruit veterans with PTSD who report minimal current cannabis use but are interested in or considering therapeutic cannabis to manage mental health symptoms (anxiety, depression, PTSD and/or suicidality). The specific aims of this clinical trial are to:

AIM 1: Examine the effects of varying THC:CBD cannabis mixtures administered before prolonged exposure sessions 1-4 (i.e., PE+cannabis) on PTSD symptom severity and frequency and severity of suicidal ideation in veterans with PTSD during and after PE treatment. *Hypothesis*: When administered in combination with exposure therapy, THC:CBD mixtures will reduce severity of PTSD symptoms and suicidal ideation, relative to placebo.

AIM 2: Examine the effects of varying THC:CBD cannabis mixtures administered before each PE session (PE+cannabis) on responder (defined as at least 50% reduction in symptom severity on the CAPS-5 and/or 50% reduction in the C-SSRS suicidal ideation intensity scale) or remission (defined as loss of PTSD diagnosis plus a score <20 on the CAPS-5) status. *Hypothesis*: When administered in combination with exposure therapy, THC:CBD mixtures

will increase the proportion of treatment responders and remitters, relative to placebo.

AIM 3: Examine the effects of THC:CBD cannabis mixtures administered before each PE session (PE+cannabis) on fear reactivity. *Hypothesis*: When administered in combination with exposure therapy, THC:CBD mixtures will reduce fear reactivity (fMRI brain activation and psychophysiological outcomes), relative to placebo.

AIM 4: Characterize psychiatric symptoms, health, pain, sleep, and quality of life in relationship to PE+cannabis treatment. *Hypothesis*: When administered in combination with exposure therapy, THC:CBD mixtures will generally improve behavioral health, relative to placebo.

Exploratory Aims:
AIM 5a: Determine whether plasma, urine, and saliva THC and CBD levels during and following PE+cannabis treatment correlate with changes in PTSD, mood, anxiety, and suicidal symptoms.

AIM 5b: Determine whether circulating plasma and saliva endocannabinoids (eCBs) during and following PE+cannabis treatment correlate with changes in PTSD, mood, and suicidal symptoms.

This project will assess whether THC:CBD cannabis mixtures (vs placebo) used in combination with an evidence-based, gold standard PTSD behavioral intervention improves treatment outcomes for veterans with PTSD. The proposed study has high scientific and public health significance as it will elucidate important mechanisms related to the use of cannabinoids for treatment of mental health symptoms among military veterans. It is highly innovative as no prior study has explored the administration of THC and CBD alone and in combination for enhancing PE. Our study also utilizes scientifically rigorous clinical trial methodology. Finally, our study team and environment are exceptionally suited to conducting this clinical trial as we have experts in cannabinoid administration and pharmacology, behavioral therapy, advanced neuroimaging approaches; endocannabinoids and stress regulation and psychiatric risk, and treatment clinical trial methodology, as well as DEA-licensed laboratory facilities that exist in only a small number of universities across the country. This project will also build on the existing Infrastructure created for our current cannabis and PTSD in veterans program awarded in the last funding cycle.

Background and Significance

PTSD, Suicidality and Mental Health among US Military Veterans

Up to 31% of US Veterans experience posttraumatic stress disorder (PTSD), a stress-induced illness characterized by excessive, inappropriate fear responses (e.g., hypervigilance, flashbacks) [3], compared to 6-10% of the general population. Moreover, the burden of PTSD on military veterans and society is significant, as those with the disorder often experience loss of productivity [16], require more healthcare resources [17], are more likely to develop medical illness [18], and experience problems in occupational [19], interpersonal [19–22], and parental/family domains [23,24].

Additionally, individuals with PTSD also report depression-related disturbances in daily life including stress, anxiety, hyperarousal, negative mood, executive function (cognitive) deficits, pain, and poor sleep quality [25]. Suicidality is among the most pernicious mental health problems facing military veterans with PTSD [2]. In 2019, more than 6,200 US veterans, about 17 per day, died by suicide [3]. Although veterans make up only 8% of the US population, they account for 13.7% of all suicide deaths among US adults. These unacceptably high rates of suicide in veterans are thought to be related to untreated or undertreated depression and PTSD as well as psychological problems associated with these disorders [4].

Prolonged Exposure Therapy & Limitations

PTSD symptoms include *impairment in fear extinction*, that is, memories of an aversive experience are strongly preserved long after the trauma has occurred. PTSD is due in part to decreased activation in brain regions including the prefrontal cortex and hippocampus, which are pivotal for inhibiting inappropriate fear responses, fear extinction, and recall of extinction learning (i.e., extinction retention) [26–32]. *Prolonged Exposure (PE)* therapy is a first-line intervention for PTSD [5] that relies on extinction learning principles. It aims to generate new, safe memories by repeatedly exposing the patient to feared objects, memories, images, and situations to integrate disconfirming/corrective information that will diminish trauma-related fears [5]. Treatment involves repeated exposures to trauma memories (imaginal exposure) and avoided situations (*in vivo* exposure) and practice exposures (e.g., listen to tapes of imaginal exposure, carry out *in vivo*

exposure) outside of PE sessions as “homework”. This cognitive processing is a critical part of extinction retention over time in PE. The beneficial effects of exposure therapy have been shown to derive from neurophysiological changes that occur during fear extinction, including post-therapy increases in activity in the brain’s prefrontal cortical regions [6].

Although PE produces clinically meaningful improvements for many PTSD patients there is still substantial room for improvement. Many patients prematurely discontinue PE (e.g., 13-39% [7–9]) and even among patients who show reductions in PTSD symptoms, 60-72% still meet criteria for PTSD diagnosis after completing PE [10,33,34]. *PTSD remains a difficult-to-treat disorder, thus, a medication that enhances the neural and neurochemical substrates of extinction and recall of extinction learning could solve this challenge and improve PTSD treatment outcomes* [11–13].

Cannabis to Relieve PTSD and other Mental Health Symptoms among US Military Veterans

Marijuana, or cannabis, contains many chemicals, known as cannabinoids, that have unique behavioral effects. Common cannabinoids include: delta-9-tetrahydrocannabinol (THC), the primary psychoactive compound in the marijuana plant; cannabinol (CBN), which is not psychoactive; and cannabidiol (CBD), which is commonly used over-the-counter for several conditions, although empirical studies for the efficacy of CBD are still in progress. Cannabis and CBD can be consumed in multiple forms (e.g., flower, hash, oil, wax, food products, tinctures), using several different routes of administration such as inhalation (smoking or vaporizing), ingestion, and topical application.

Use of marijuana and cannabinoids is prevalent in the military veteran community and many traumatized individuals report that cannabis use can alleviate stress, anxiety, depressed mood, and disturbed sleep. A recent national survey of military veterans [25] indicated that 75% would consider using cannabis as a treatment option for pain or mental health issues. About 83% supported legalization of medical cannabis, and 68% believed the US Department of Veterans Affairs should allow research exploring the use of cannabis as a therapeutic option. Notably, although cannabis remains a Schedule I controlled substance and federal regulations prevent clinicians in the VA system from recommending or prescribing cannabis as medicine, 20% of veterans acknowledged having used cannabis for medical purposes including PTSD.

The role of cannabis use in suicidal behavior is unclear. Lifetime prevalence of cannabis use disorder has been linked to suicide attempts in veterans, even after controlling for PTSD, depression, and substance use disorders [35]. However, currently it is not known whether cannabis use increases suicidal behavior among veterans with mental health problems [36] or whether veterans with mental health problems and elevated suicidality are more likely to use cannabis to manage symptoms. Indeed, epidemiological data from the 2012 Canadian Community Health Survey revealed that cannabis use may reduce the association of PTSD with severe depression and suicidality [37]. Thus, research is needed to establish whether cannabis use might be linked to a decreased risk of veteran suicide. Furthermore, emerging data link both PTSD and depression [38,39] to disruption in the brain’s endogenous cannabinoid (or *endocannabinoid*, eCB) system, which plays a key role in regulating stress, emotion regulation, and fear extinction [40]. However, few studies have examined the impact of cannabis or cannabinoid administration on circulating eCB levels, and whether changes in circulating eCBs correspond with changes in PTSD, mood, and suicidal symptoms.

An important contributor to persistent PTSD, suicidality and cannabis use may be *anhedonia*, which refers to the loss of pleasure/interest in rewarding life activities. Anhedonia is a key feature of depression [41–45]. Furthermore, anhedonia may amplify the use of and reinforcing effects from cannabis, which could alter mood and treatment outcomes for PTSD and suicidality. This project will systematically assess anhedonia, reward processing and reward preference, which we will examine as moderators of fear responding and exposure therapy outcomes.

Cannabis Might Facilitate Prolonged Exposure and Improve Treatment Outcomes

Compelling new data from rodent studies of fear learning indicate that activating cannabinoid signaling within the prefrontal cortex and hippocampus may regulate fear extinction and recall of extinction learning. For instance, drugs that block cannabinoid receptors or genetic deletion of cannabinoid receptors within these structures prevent recall of extinction learning, whereas activating the eCB system with drugs such as THC can promote recall of extinction learning [46]. CBD administration has also been shown to decrease PTSD symptoms, improve sleep, focus, mood, and decrease anxiety [47,48]. In addition, drugs that increase brain eCB levels during fear extinction enhance recall of extinction learning and prevent recurrence of extinguished fear in rats (i.e., inappropriate fear responses do not return) [46].

Studies in Co-PI Rabinak’s lab using fMRI found that oral THC (vs. placebo), administered to healthy volunteers and

individuals with PTSD, modulates prefrontal and hippocampus activation during a recall test of extinction learning [14,49]. Together, rodent and human data indicate that chemicals found in cannabis modulate brain regions involved in fear extinction and its recall, therefore, *a critical next step is to examine the efficacy of cannabis to facilitate PE therapy in individuals with PTSD*. Co-PI Rabinak is currently conducting a clinical trial in civilian patients with PTSD to test whether an acute oral dose of THC alone can improve the efficacy of PE, using a similar design as to the proposed study.

A therapeutic goal in the treatment of PTSD is to re-learn emotional memories to reduce their intensity and thus decrease threat response. Accumulating data indicate that both endogenous and exogenous cannabinoid agonists may acutely decrease stress reactivity and enhance extinction of fear responding [50]. Thus, THC alone or in combination with CBD may have anxiolytic effects; however, this has yet to be tested in the context of fear extinction or gold-standard treatments, such as PE. To address this gap, we propose to examine whether cannabis that contains THC and CBD in varying ratios *will increase the effectiveness of PE therapy in PTSD by modulating brain regions involved in fear extinction*. Collectively, these exciting findings suggest that *activating CB1 receptors in specific neural circuits can enhance the efficacy of fear extinction and recall of extinction learning in individuals with PTSD, who exhibit impaired recall of extinction learning and associated aberrant ventromedial prefrontal cortex-hippocampal function.*

The overarching objective of this project is to use varying ratios of THC:CBD cannabis as a "cognitive enhancer" during PE therapy to increase the likelihood that PTSD patients will benefit from PE. If successful, the novel use of cannabis could benefit veterans with other disorders for which exposure-based treatment (e.g., Cognitive Behavioral Therapy (CBT)) is empirically supported (e.g., panic disorder, social phobia, generalized anxiety disorder). Although it is currently unknown which particular THC:CBD ratios will provide the optimal outcome, this study will examine four different THC:CBD combinations and the results should offer excellent guidance for future clinical research and healthcare.

Of note, this study is poised to benefit veterans living in Southeast Michigan, where rates of trauma exposure and PTSD are much higher than the national average. Indeed, the proposed study will be centered in the city of Detroit, which consists of a large population of urban-dwelling, lower-income Black residents. Southeast Michigan is also home to one of the largest populations of Middle Eastern/North African individuals in the US. Lower-income minority groups often have less access to evidence-based mental health treatments and our current treatments more often fail to help these individuals. Further, research shows that Black veterans experience higher rates of PTSD and show more severe PTSD symptoms as compared to White veterans. Therefore, given that this study will occur in the heart of Detroit, this project is well-positioned to benefit a diverse population of veterans living in Southeast Michigan, and to address socioeconomic disparities in health outcomes in this at-risk population.

High Innovation and Impact of this Research

Our proposed treatment outcome trial would be the first randomized, controlled, and large-scale clinical trial to examine whether cannabinoids improve the effectiveness of an empirically-based behavioral treatment for PTSD. This trial is innovative (cutting-edge) and methodologically rigorous, and will have real-life implications for treating veterans who experience PTSD and chronic suicidality (high public health significance). Strong methodological elements of this clinical trial include random assignment to treatments, several THC:CBD combinations, placebo control condition, well-validated clinical and biological assessments, extensive clinician training, thorough measurement of treatment fidelity, long-term follow-up of research participants, and intent-to-treat analysis (i.e., assessment of all participants regardless of whether they complete the intervention). This rigorous and comprehensive approach will ensure our research has a high impact in the scientific literature, thus increasing the possibility that treatment providers and organizations will have access to, and ultimately will implement, our findings.

Unique Expertise and Preparedness to Conduct this Research

Our team has extensive experience conducting randomized controlled trials (the gold standard) for numerous mental health conditions. Of note, **we are the only research group in the Midwest that has the federal and state licenses that permit us to administer cannabis and cannabinoids to human volunteers,** which uniquely positions us to conduct this significantly impactful clinical trial. Our team has extensive experience (1) administering THC and CBD, alone and in combination, and assessing their effects in randomized, double-blind, placebo-controlled laboratory studies as well as in clinical trials; (2) recruiting and retaining military veterans in studies on PTSD; (3) designing and conducting

long-term clinical treatment trials; (4) conducting laboratory measures of fear conditioning in veterans with PTSD; (5) assessing and treating psychiatric disorders, including depression, anxiety, PTSD, and suicidality; and, (6) successfully completing large-scale, complex studies with multiple investigators across multiple sites. Our team also has expertise in (7) advanced neuroimaging approaches to study neurobiological mechanisms that may facilitate therapeutic effects; and (8) the role of endocannabinoids in stress regulation and psychiatric risk. We will incorporate neuroimaging to examine changes in brain regions involved in fear extinction, and we will examine changes in circulating eCB concentrations and associations with symptom improvements, during the trial.

Crucially, we will leverage our progress in the ongoing LARA/CRA-funded clinical trial that is examining whether 12-week treatment with cannabis containing varying THC:CBD combinations improves mood and anxiety symptoms and decreases suicidal ideation in veterans with PTSD. As a team, we have established our umbrella Warrior Care program in the Department of Psychiatry and Behavioral Neurosciences (DPBN) at Wayne State University. As noted below in the Research Settings section, we have a dedicated suite in the Tolan Park Medical Building for this and related studies. We also have strong support from the DPBN department Chair and the School of Medicine administration. Thus, as highlighted here and elsewhere in this proposal, we have unique and ample administrative, infrastructure/space, collegial and regulatory resources to ensure that this proposed project is successfully completed.

Approach

Study Design Overview. This randomized, double-blind, placebo-controlled, mixed between- and within-subject trial will examine whether THC and CBD enhance the therapeutic effects of PE on self-reported PTSD symptom severity and suicidal ideation in US armed forces veterans in an outpatient setting. A total of 350 treatment-seeking veterans will be randomized into one of five groups (70 in each: High THC:Low CBD, High THC:High CBD, Low THC:High CBD, Low THC:Low CBD, and placebo). A 10-session standardized PE treatment protocol will be followed, where Sessions 1-2 are psychoeducational and Sessions 3-10 involve actual exposure. Assigned doses of THC and CBD will be administered just prior to Sessions 3-6 (i.e. the first 4 sessions with actual exposure; PE+cannabis). We will assess treatment response (i.e., reduced PTSD symptom severity, reduced or absent suicidal ideation) at each subsequent PE session to examine rate of improvement, and again at post-treatment, then 3-, 6-, and 9-months following treatment to explore long-term effects of PE+cannabis. We will also use a well-validated Pavlovian fear conditioning paradigm to measure brain activation during fear extinction. In this paradigm, fear acquisition, extinction learning, extinction recall and renewal will occur during fMRI scanning. These assessments will occur prior to PE treatment and within one week of completing treatment (following PE Session 10). Primary clinical assessments (Clinician-Administered PTSD Scale for DSM-5 [CAPS-5] and self-reported PTSD Checklist 5 [PCL-5]) will occur at study pre-treatment, during treatment, after treatment, and again at 3-, 6-, and 9-month post-treatment follow-up. Additional interview and self-report assessments are listed in Table 2. Study duration for each participant will be approximately 12-months from the time he/she is enrolled in the study.

Data Platform: Castor. Castor is a secure electronic data capture system and will be used to collect participant questionnaire and assessment data. Each week participants will be sent a secure electronic link. When participants click on the link using their computer, tablet, or smartphone, they will be able to complete their weekly questionnaires (described below) online in Castor. Each user (research staff and participant) has their own unique login information and Castor uses a CFR Part 11 compliant audit trail.

Participant Recruitment, Selection, and Retention

Participants aged 18-60 years will be included in the study. There will be no enrollment restrictions based upon gender, race or ethnic origin.

The number of treatment-seeking PTSD veterans expected to participate in this study is 350, with 70 randomly assigned to each group. Based on our experience with similar studies we expect about 30% attrition, so we anticipate that about 50 participants per group will complete the study, for a total sample size of 250 completers. Participants will be recruited via Veterans groups and associations, local newspaper ads, social media (e.g., Craigslist, Facebook), word-of-mouth referrals, and flyers posted throughout the Wayne State medical campus and at local Veterans organizations and fairs.

The Wayne State University IRB will approve all procedures. ***Inclusion criteria.*** To be enrolled in the trial, each participant must: (1) be a healthy veteran who has served in a branch of the US armed forces; (2) report using cannabis

on at least one occasion in their lifetime up to 1x/week; (3) be willing to use cannabis immediately prior to the four PE therapy sessions; (4) significant PTSD severity indicated by a Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) diagnosis and score ≥25 for at least the month prior to study entry (PTSD will be identified as the patient's primary concern); (5) be between 18-60 years old; (6) not be seeking treatment for Cannabis Use Disorder; (7) be psychiatrically stable on psychotropic medications and/or in psychotherapy (and not experiencing acute symptoms) before the study begins (participants cannot be in treatment for PTSD); and, (8) agree to adhere to study procedures.

***Exclusion criteria*.** Candidates will be excluded if they: (1) are pregnant (urine HCG), lactating (self-report), or heterosexually active women and not using medically-approved birth control (oral or depot contraception, IUD, condom/foam, sterilization, tubal ligation); (2) have current or past bipolar or psychotic disorder as determined using the SCID-5; (3) are determined to be at immediate high risk for suicide based on the C-SSRS; (4) meet DSM-5 criteria for Substance Use Disorder other than Alcohol (Mild or Moderate) or Nicotine Use Disorder; (5) have allergies or other contraindications for smoking or vaporizing cannabis; (6) are taking medication known to have level 1 evidence for severe drug-drug interactions with THC or CBD that are taken daily; (7) have a current diagnosis or evidence of significant or uncontrolled hematological, endocrine, cerebrovascular, cardiovascular (e.g. systolic BP >140 or <95 mmHg, diastolic BP >90 mmHg, abnormal ECG), systemic (e.g., liver, renal, inflammatory), pulmonary (e.g., asthma, COPD), immunocompromising (e.g., AIDS, COVID-19), or neurological disease (e.g., seizures, dementia, traumatic brain injury); (8) exhibit cognitive impairment (<80 IQ); (9) may not comply with or have difficulty completing the PE clinical trial; (10) are currently receiving psychotherapy (exposure-based or otherwise) for PTSD or have previously received exposure-based therapy; (11) have insufficient memory of the traumatic event (i.e., only a vague sense or feeling that trauma occurred, no actual memory); and, (12) are unable to provide informed consent.

***Inclusion/Exclusion Criteria: Brain Imaging Substudy*.** Although all 350 participants will be offered the opportunity to participate in the brain imaging substudy, due to strict safety criteria (e.g., no metal in the body, no history of moderate-to-severe traumatic brain injury), it is likely that only a relatively small subset of participants will qualify for the MRI scans. Thus, only volunteers who are interested and meet safety inclusion/exclusion criteria will undergo brain imaging procedures. Veterans who are interested in participating in the brain imaging substudy must not: (1) be exclusively left-handed (i.e., score of -100.00 on Handedness Questionnaire); (2) have had moderate or severe traumatic brain injury, defined by The American Congress of Rehabilitation as a person who has had a traumatically-induced physiological disruption of brain function (i.e., the head being struck, the head striking an object, and/or the brain undergoing an acceleration/deceleration movement (i.e., whiplash) without direct external trauma to the head), as manifested by at least one of the following: loss of consciousness >30 min; loss of memory for events immediately before or after the injury and/or alteration in mental status at the time of the incident lasting >24 hr; or focal neurological deficits that may or may not be transient; (3) be unable to tolerate small, enclosed spaces without anxiety (e.g. claustrophobia), based on self-report; and, (4) have ferrous-containing metals within the body (e.g., aneurysm clips, shrapnel/retained particles). Based on our prior experience conducting neuroimaging studies of this type, we anticipate that about 165 participants will meet criteria and enroll in the brain imaging substudy, with about 125 completing all four (4) scans.

Screening Procedures

Individuals interested in the main study can complete a confidential pre-screening survey online (via our WarriorCARE website, www.Warriorcare.net) or speak over the phone with our research staff. Those who appear to meet eligibility criteria will be invited to attend 1-2 in-person screening visits (screening measures are described below). During the first screening session the PI or her designee will describe study procedures and requirements. Candidates will be asked to read the consent form. Particular attention will be given to reviewing required procedures (e.g., abstaining from use of non-study cannabis during the trial) and possible side effects of the drugs (THC and CBD) with candidates. Measures used to ensure confidentiality will be reviewed with candidates. After answering candidates' questions, if their understanding is satisfactory to study staff, the consent form will be signed in the presence of the PI and a witness. Female participants must sign a form agreeing to immediately notify the experimenter if they become pregnant.

Screening Measures

The ***Shipley Institute of Living Scale*** [51] yields an estimated IQ score. Candidates must score >80 to give informed consent. The ***Medical History Questionnaire*** is a comprehensive self-reported assessment of participant medical history routinely used in our lab. The ***Semi-structured Clinical Interview for DSM-5* (SCID)** [52] will be used to assess psychiatric and substance use symptoms (for exclusion) and to ascertain Substance Use and other psychiatric Disorder diagnoses. The ***Clinician-Administered PTSD Scale for DSM-5 Total Severity Score* (CAPS-5)** [53] will be used to

assess and confirm PTSD diagnosis. The ***Drug History and Use Questionnaire*** **(DHUQ)** is an extensive alcohol and drug use questionnaire we developed and have published on; it will be used to establish that potential participants have limited prior experience smoking cannabis and to characterize other drug use. Menstrual cycle phase is a possible confound. We will record females' self-reported menstrual cycle phase at screening and during the study and will examine the data to determine whether THC- or CBD-induced effects vary between males and females at differing cycle phases. To maintain progress on the proposed study, it is not feasible to control time of drug exposure, but we will have these data to include as statistical covariates.

Retention

Strategies for participant retention will be discussed regularly in weekly research meetings, and will be practiced for optimized retention such as contact with the PIs and the research team during the study, phone reminders/confirmation of visits, established contact with the study coordinator, arrangements for transportation at each visit, and payment for participants' time and effort. Also, office hours are flexible (e.g., 7am-7pm during the week with weekend availability). We also have a welcoming and private reception area with comfortable seating, access to snacks and beverages, and WiFi access to accommodate family members who accompany veterans to sessions. To ensure we do not lose contact with participants between assessments, we will collect information on several points of contacts (e.g., address, home and cell phone numbers, email addresses), send out occasional holiday cards or reminder letters, and obtain contact information for one or more emergency contact individual who may be able to facilitate contact with the participant if we cannot reach him/her. Based on these strategies, we anticipate that drop-out will be minimized.

Study Procedures.

Drug Dose Selection, Preparation and Administration

Cannabis (THC and CBD). Cannabis flower will be purchased in bulk* from a federally-registered cannabis supplier for research (e.g., GroffNA or BRC) and prepared using a digital scale with weight adjustments to achieve the exact dose conditions shown in Table 1. The four active cannabis dose conditions have been carefully selected based on what is reported in the literature as most often available in dispensaries and used by medical cannabis patients, as well as on our own experience administering smoked and vaporized THC and CBD to participants in our laboratory. Further, the recommended starting dose of medical marijuana is 2.5 mg, with doses up to 20 mg administered to cannabis-naive individuals (e.g., [54]). Our data and those from others demonstrate these concentrations have excellent safety profiles. Placebo cannabis material (containing 0 mg THC and 0 mg CBD) will be obtained either from NIDA Drug Supply or one of the federally-registered suppliers.

Table 1: Cannabis Dosing Conditions

	THC mg	CBD mg
Placebo	0 mg	0 mg
High THC: High CBD	10 mg	10 mg
High THC: Low CBD	10 mg	2.5 mg
Low THC: High CBD	2.5 mg	10 mg
Low THC: Low CBD	2.5 mg	2.5 mg

**NOTE: If available, cannabis might also be obtained from the National Institute on Drug Abuse (NIDA) Drug Supply Program, which has provided cannabis for Dr. Lundahl's previous studies. Dr. Lundahl and Dr. Greenwald (co-investigator) already hold all the necessary DEA licenses and FDA certifications to obtain cannabis from NIDA.*

Administration. Immediately prior to the start of exposure sessions 3-6, participants will be seated in an experimental chamber equipped for cannabis administration. They will vaporize 300 mg of cannabis (equivalent to about 1 marijuana cigarette, or joint) using a Mighty® vaporizer (Storz & Bickel, Germany). Per Table 1, this fixed amount of plant material will contain differing proportions of THC and CBD. Standardized puff topography will be: 5-sec prepare, 5-sec inhalation, 10-sec breath-hold, 5-sec exhalation, and 40-sec inter-inhalation interval. Thus, participants will

prepare/inhale/hold/exhale over 20-sec, wait 40-sec, then initiate the next inhale/hold/exhale sequence (cued by research assistant). The smoking episode will take ≈10-min. Immediately prior to and after vaporizing the dose, vital signs will be recorded and subjective drug effects will be assessed. The prolonged exposure session will then begin. Both participants and research staff will be blind to the cannabis condition. Because the flower is placed within dosing capsules inserted directly into the Mighty® the flower is never visible to the participants, which will help maintain the blind (in our experience, placebo cannabis often differs visually from active cannabis). Only Dr. Lundahl or Dr. Greenwald will know which cannabis dosing condition each participant is in.

Storage. Cannabis will be kept in a locked freezer in a locked room (per DEA guidelines) in the Human Pharmacology Laboratory at Tolan Park; only Drs. Lundahl and Greenwald have access to this room. Cannabis will be humidified for 24-hr prior to administration sessions.

Pavlovian Fear Conditioning Paradigm

Following baseline assessments and prior to beginning PE therapy, participants will complete a Pavlovian fear conditioning paradigm using visual stimuli. This fMRI protocol uses an event-related design developed and validated in Dr. Rabinak's lab (Figure 1).

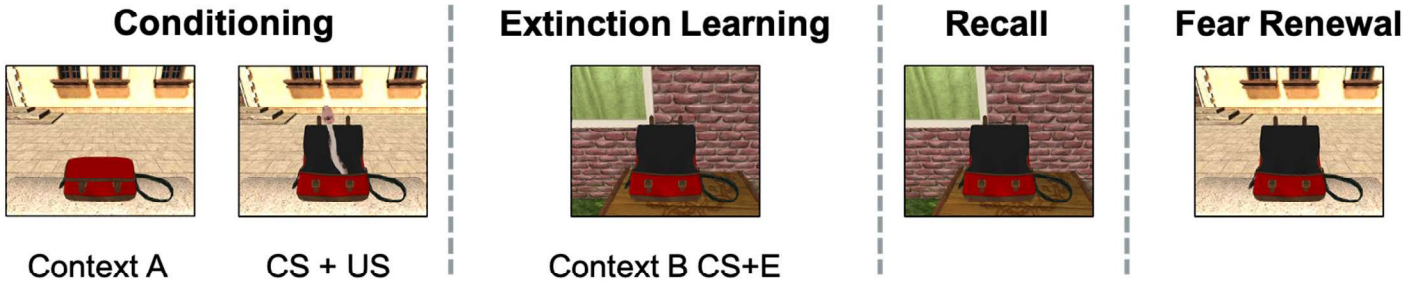


Figure. 1: Schematic of fear conditioning and extinction paradigm.

In the first phase, participants undergo fear conditioning in which we train them to learn that a neutral cue (CS), like a messenger bag of a particular color (e.g., red) might contain an aversive stimulus (US), like a snake. Prior to conditioning, the bag doesn't elicit any type of fear response, but after repeated pairings with a snake popping out the bag begins to take on properties of the snake, such that when the participants sees the red bag, they may start to feel anxious. The participant has learned a fear association between the red bag and the occurrence of a snake. In the next session, extinction learning, participants are shown the different colored messenger bags again. Those bags that were previously paired with the snake will elicit fear responses (e.g., anxiety) in participants at the beginning of the session. But during extinction learning none of the bags ever contain the snake. In this phase we are teaching participants that the bag is no longer negative and we begin to see fear reduce over repeated, unreinforced trials (CS+E). The next day we can bring participants back to the lab and show them the messenger bags again, without a snake (CS+E), and see if they respond with fear (suggesting they are accessing their initial fear memory) or if they do not respond with fear (suggesting they are accessing the safe extinction memory). However, the context or environment plays a role in gating the behavioral response. For instance, participants are expected to show low fear when tested in the same context (Context A; e.g., 'plaza'') as that in which extinction took place (Context A). Testing outside of this context (Context B; e.g., 'garden') should elicit a fear response. If a participant is trained that the red bag no longer signals a snake in Context A, but is tested in Context B we will see a fear response. However, if they are tested in Context A we should see a low fear response, because they learned the bag was no longer dangerous in this context. In PTSD, individuals have difficulty retrieving the extinction memory even when tested in the same context. They tend to default to high fear no matter if they extinguished their fear during extinction learning. Fear responses are measured via two ways: changes in skin conductance response (SCR), or sweating, (psychophysiological measure) or by subjective report called an expectancy rating (US expectancy). We ask participants to rate whether they think the bag will contain a snake every time they are presented with the bag and before it is opened. Stimulus parameters will be like those conducted in our previous studies. All phases of this fear conditioning paradigm will be conducted in the MRI scanner with simultaneous recording of SCR and US expectancy ratings, except in the event a participant is unable to be scanned, in which case these visits will be conducted outside the scanner in Dr. Rabinak's research laboratory. Participants will complete the entire fear conditioning paradigm (i.e., fear acquisition, extinction, recall) two times- once before beginning PE treatment and again after treatment completion. When the paradigm is completed for the second time (i.e., post-treatment), novel

contexts (e.g., ‘garden’ and ‘plaza’) and stimuli (e.g., black, white, and gray messenger bags) will be used.

Prolonged Exposure (PE) Treatment

PE treatment will consist of 10, 60-min sessions [20]. PE therapy will be administered using the Prolonged Exposure Therapy for PTSD therapist guide and patient workbook. Therapists will utilize interview and recording forms included in the therapist guide, and participants will complete homework assignments using the forms and handouts included in the patient workbook. Sessions 1 and 2 will consist of psychoeducation that includes discussion of reactions to trauma, treatment rationale, breathing retraining, and review of Subjective Units of Distress Scale (SUDS) to assess level of distress from 0 to 100 (100=extreme anxiety/distress) when facing fears. Sessions 3-10 will consist of repeated exposures to trauma memories (imaginal exposure) and avoided situations (in vivo exposure). As is standard, patients will also practice exposures (e.g., listen to tapes of imaginal exposure, carry out in vivo exposure) outside of PE sessions as “homework”. At each of the first four exposure-focused sessions (Sessions 3-6) cannabis (THC:CBD) or placebo will be administered just before the session begins. Due to rapid-onset effects of vaporized cannabis, we will begin PE immediately after the dose has been administered. (Cannabis administration and the PE session will take place in the same room.) To track symptom change for each participant, the PCL-5 will be completed at the pre-treatment baseline assessment and at each PE session (using the same timeline), and at the 3-, 6-, and 9-month follow-ups. The CAPS-5 will be conducted at the pre-treatment baseline assessment, at PE Session 6, at the last PE session [Session 10; review of therapeutic gains/relapse prevention/assessments], and at the 3-, 6-, and 9-month post-treatment follow-up. Participants who complete at least 4 exposure-based sessions of PE+cannabis will be considered treatment completers. PE sessions will occur at least once per week and will be completed within 10 weeks.

Therapist Adherence and Competence Methods: The study therapists will be Clinical Psychologists (Drs. Lundahl and Ledgerwood) and PhD-level postdoctoral fellows. All study therapists will be trained and certified in administering PE therapy and licensed to practice in the state of Michigan. PE therapy will be administered using the Prolonged Exposure Therapy for PTSD therapist guide and patient workbook [55]. Therapists will utilize interview and recording forms included in the therapist guide, and participants will complete homework assignments using the forms and handouts included in the patient workbook. Study therapists will be blind to drug conditions. PE therapy sessions will be conducted in offices in the Human Pharmacology Laboratory at Tolan Park. All PE sessions will be audio-recorded to ensure therapist competence and to assess fidelity to the treatment protocol. These digital audio-recordings will be stored at Wayne State University on a HIPAA-compliant secure, dedicated server.

All study therapists will be supervised by Dr. Sheila Rauch, who is a leading expert in the development and implementation of psychotherapeutic interventions for anxiety disorders and PTSD. She has over 20 years of experience conducting clinical research (including DOD, VA, and NIH-funded clinical trials) focused on understanding mechanisms involved in the pathology and treatment of PTSD in addition to training providers in PE therapy. Meetings between the Co-PIs and/or study coordinator, Dr. Rauch, and the study therapists will occur weekly or as needed throughout the study to discuss any participant-related questions or concerns and to ensure adherence to the study protocol. Twenty percent of session tapes will be rated for fidelity by Dr. Rauch, who will be blind to drug conditions.

Study Measures

See Table 2 (below) for a schedule of assessments. All instruments will be administered by trained, master’s-level psychology graduate students and trained research assistants under the supervision of Drs. Lundahl and Ledgerwood, who are both licensed clinical psychologists.

Table 2: Assessment Schedule

		Pre- Treatment			PE Sessions											Post-Treatment			Follow-Up		
			FMRI					Exposure with THC:CBD or PBO				Exposure without THC:CBD or PBO				FMRI					
	Screening, Informed Consent & Study Entry	Baseline	Fear Acquisition & Fear Extinction	Extinction Recall Test	1	2	Randomization	3	4	5	6	7	8	9	10	Post-Treatment	Fear Acquisition & Fear Extinction	Extinction Recall Test	3-Month Follow Up	6-Month Follow Up	9-Month Follow Up
SCID-5	✓																				
LEC-5	✓																				
Shipley Institute of Living	✓																				
Medical History Questionnaire & Physical	✓																				
DHUQ	✓																				
Race/ Ethnicity Form	✓																				
Gender Identity Questionnaire	✓																				
Handedness Questionnaire	✓																				
MR Safety Form	✓																				
Vital signs	✓	✓			✓	✓		✓	✓	✓	✓	✓	✓	✓	✓						
Urine Samples	✓	✓						✓	✓	✓	✓				✓						
Concomitant Medication Form	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
PCL-5	✓				✓			✓	✓	✓	✓	✓	✓	✓	✓	✓			✓	✓	✓
Healthcare Utilization	✓				✓							✓			✓	✓			✓	✓	✓
CGI-S	✓				✓										✓					✓	
Timeline Follow-Back	✓				✓	✓		✓	✓	✓	✓	✓	✓	✓	✓				✓	✓	✓
ESS	✓							✓	✓	✓	✓	✓	✓	✓	✓	✓			✓	✓	✓
Blood Draw	✓										✓				✓						
CAPS-5	✓											✓			✓	✓			✓	✓	✓
BPI	✓														✓	✓			✓	✓	✓
DDT	✓															✓			✓		
SF-36	✓															✓			✓	✓	✓
QOL	✓															✓			✓	✓	✓
Effort Expenditure for Rewards Task		✓														✓			✓		
Monetary Delay Discounting		✓														✓			✓		
Probabilistic Reward Task		✓														✓			✓		
MID Task		✓														✓			✓		
Wechsler Memory Scale		✓														✓			✓		
Visual Working Memory scale		✓														✓			✓		
California Verbal Learning Test		✓														✓			✓		
Wisconsin Card Sorting Task		✓														✓			✓		
Iowa Gambling Task		✓														✓			✓		
SHAPS		✓																			
C-SSRS		✓														✓			✓	✓	✓
SBQ-R		✓			✓			✓	✓	✓	✓	✓	✓	✓	✓	✓			✓	✓	✓
STAI		✓			✓			✓	✓	✓	✓	✓	✓	✓	✓	✓			✓	✓	✓
BDI-II		✓			✓			✓	✓	✓	✓	✓	✓	✓	✓	✓			✓	✓	✓
SCR			✓	✓													✓	✓			
US Expectancy			✓	✓													✓	✓			
SUDS			✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓		✓	✓			
Debriefing Interview				✓												✓		✓			✓
UTI						✓		✓	✓	✓	✓	✓	✓	✓	✓						
Saliva Samples								✓	✓	✓	✓										
Subjective Cannabis Effects Rating								✓	✓	✓	✓										
SES								✓	✓	✓	✓										
CGI-I												✓			✓					✓	
SUF												✓			✓				✓	✓	✓
CSQ-8															✓						

Primary Outcome Measures.
The primary outcomes of the proposed study include changes from baseline (pre-treatment) to the end of the 12-week treatment phase (post-treatment) in PTSD symptom severity and suicidal ideation as a function of cannabis (THC:CBD mixture) dose. PTSD will be assessed with the ***Clinician-Administered PTSD Scale for DSM-5 Total Severity Score* (CAPS-5)** [56] and ***Post-Traumatic Stress Disorder Symptom Checklist for DSM-5* (PCL-5)** [57]. The CAPS-5 is a well-validated, semi-structured clinician interview that determines the presence and severity of PTSD symptoms and diagnosis consistent with the DSM-5 and allows for assessing changes in symptom severity over time [58]. PTSD diagnosis is based on meeting the DSM-5 symptom cluster criteria (minimum threshold of symptoms with a score ≥ 2) with a qualifying criterion A index trauma. The CAPS-5 Total Severity Score is calculated by summing the total score for each of the four symptom categories to assess past-month PTSD symptoms on a specific traumatic event: intrusion (Category B), Avoidance (Category C), Mood and Cognition (Category D), and Hyperarousal (Category E). CAPS-5 Total Severity scores range from 0–80, where higher scores indicate worse PTSD severity. Suicidality will be assessed using the ***Columbia Suicide Severity Rating Scale* (C-SSRS)** [59], and ***Suicide Behavior Questionnaire-Revised* (SBQ-R)** [60]. The C-SSRS is a clinician-administered measure of suicidal thoughts and behaviors over time. A baseline form is used to assess lifetime suicidal ideation, intensity, and behavior, and can be compared to current suicidal ideation and intensity assessed over the clinical trial. The SBQ-R is a brief (4-item), self-administered questionnaire that captures four dimensions of suicidality (lifetime ideation/attempt, frequency of recent ideation, risk of suicide attempt and self-reported likelihood of future suicidal behavior), and will be measured at all time-points.

Measures of Treatment Response: We will assess change in the severity of PTSD symptoms and frequency and severity of suicidal ideation in addition to changes in secondary measures (e.g., anxiety, depression, and disability). **Responder status** will be defined as at least 50% reduction in symptom severity on the CAPS-5 and/or 50% reduction in the C-SSRS suicidal ideation intensity scale. **Remission** from PTSD is loss of PTSD diagnosis plus a score <20 on the CAPS-5. The CAPS-5 and C-SSRS will be administered by trained research assistants who will be blind to drug conditions. Interviews will be conducted by multiple, trained raters, and inter-rater reliability will be examined to ensure good reliability (kappa coefficient ≥0.6).

Secondary Measures.
Demographics including age, sex, gender identity, marital status, race/ethnicity, education, employment status (hours per week; type of job; hourly income), annual income, and handedness will be assessed. The **Life Events Checklist for DSM-5 (LEC-5)** is a self-report measure designed to screen for potentially traumatic events in a person's lifetime [61]. The **Beck Depression Inventory-II (BDI-II)** [62] assesses neurovegetative depressive symptoms. **The State Trait Anxiety Inventory Form Y (STAI)** [63] is a 40-item questionnaire with 2 scales assessing state and trait anxiety (somatic and cognitive symptoms). The **Concomitant Medication Form** will be reviewed and updated (if applicable) at each study visit. Additional clinical assessments will include: (1) **Clinical Global Impression Severity Scale (CGI-S)** is a 1-item scale asking the evaluator to assess the patient's overall level of illness severity. The evaluator integrates all aspects of the patient's condition when using this scale; (2) **Clinical Global Impression Improvement Scale (CGI-I)** is a 1-item scale asking the investigator to assess the patient's overall improvement compared to the patients' condition at study entry. The evaluator integrates all aspects of the patient's condition when using this scale; (3) **Study Update Form (SUF)** will be used to collect information about treatment and changes since the previous assessment. This will be collected at PE Session 6 (mid-point of treatment), PE Session 10 (post-treatment), and at the 3-, 6-, and 9-month follow-up assessments. Versions of this form have been used in multiple clinical trials conducted by Co-I Rauch; (4) The **Client Satisfaction Questionnaire (CSQ-8)** will be completed as a self-report assessment at the last PE session to examine acceptability and feasibility of PE. This measure has demonstrated good reliability and validity; (5) The **Utility of Techniques Inventory (UTI)** will be used at PE sessions 2-10 to assess participants' adherence to/completion of homework assignments and perceived helpfulness of learned techniques. The **Snaith-Hamilton Pleasure Scale (SHAPS)** is a 14-item validated questionnaire that measures anhedonia, i.e. loss of interest/pleasure [64].

We will administer **behavioral tasks that measure reward decision-making**, which are predicted to be sensitive to levels of anhedonia, PTSD and depression symptoms and, potentially, the effect of experimental cannabinoids on exposure therapy response.

(1) The Effort Expenditure for Rewards Task (EERT; [65]) involves dopamine-mediated limbic-prefrontal cortex circuitry [66–71], and is sensitive to depression [72] and cannabis use [73,74]. In addition to dopamine, glucocorticoids – which are implicated in PTSD and depression symptomatology – may also be involved in reward-processing deficits

[75].
(2) Monetary Delay Discounting (MDD), which has been shown to be sensitive to suicidality [76], anxious-depressive traits [77], anhedonia [78] and cannabis use [79].
(3) The Probabilistic Reward Task (PRT; [80]) is related to anhedonia and the NIMH Research Domain Criteria 'Positive Valence' system [81], and to reinforcement learning [82]. In people with depression, probabilistic learning on this task has been associated with treatment outcomes [83,84] although neural markers of reduced learning may persist after treatment remission [85].
(4) The Monetary Incentive Delay (MID; [86]) task measures anticipatory and consummatory phases of reward-related brain activation (particularly in ventral striatum). The MID task has been shown to be related to anhedonia [87] and task-induced ventral striatum activation is greater in those with remitted depression compared to non-depressed controls [88], and differs in chronic cannabis users [89,90], although one recent report did not find this difference [91]. Brief treatment with the antidepressant duloxetine improved reward function on this task [92]. Interestingly, CBD did not alter reward function on the MID task [93].
(5) The Iowa Gambling Task (IGT) is a computer-based measure of decision-making in which participants are given a hypothetical amount of money to play, and must choose between four decks of cards (labeled A, B, C and D) that are presented on the computer screen [94]. Decks A and B are associated with higher (hypothetical) monetary rewards, but also associated with higher punishment (money lost) than decks C and D. Overall, decks A and B result in losses, while decks C and D result in gains. The gains and losses associated with each card turn are not predictable. Risky decision-making is associated with more selection from decks A and B than decks C and D.

SUDS. Subjective Units of Distress Scale [95] measures subjective fear on a scale from 0 (absolutely calm) to 100 (worst distress). It is a self-report measure made on the computer via a sliding bar from 0 to 100.

Executive Function/Neurocognitive Assessment: Working Memory will be assessed using the Wechsler Memory Scale-Fourth Edition, Visual Working Memory scale [96] and the California Verbal Learning Test 3rd Edition (CVLT3) [97]. The Wisconsin Card Sort Task (WCST) assesses abstraction and the ability to shift or maintain cognitive set [98,99]. Inability to shift cognitive set in the face of new information is indicative of perseveration. All of these measures will be administered prior to and after PE treatment to see if there are changes in memory and executive function as a result of PE+cannabis treatment.

Health/Quality of Life: The Short Form 36 (SF-36) is a brief measure of overall self-reported health that is associated with other objective health measures [100]. The Quality of Life Inventory (QOL) [101] assesses satisfaction in 17 life areas (work, health, recreation, goals, etc.) and will be used to assess quality of life changes over time. Brief Pain Inventory (BPI) [102] will be included to assess pain, and will be completed at baseline, post-treatment, and at each follow-up assessment. Daytime sleepiness, which is indicative of sleep problems, will be assessed using the Epworth Sleepiness Scale (ESS) [103]. We will also assess the number of times participants utilize emergency room, urgent care, specialist, and general practitioner services on a monthly basis (healthcare utilization).

The Timeline Follow-Back will be conducted at the weekly PE sessions to record any alcohol, cannabis, or other drug use (biologically verified using saliva testing). If participants do not show up for their weekly PE session, they will be sent a text reminder to complete the assessments online using Castor. Research staff will also contact them to complete the clinician-administered measures over the phone.

Subjective Cannabis Effects Rating Form [104]. Immediately after the cannabis vaporizing episode prior to each PE+cannabis session, participants will complete VAS ratings of "good drug effect," "bad drug effect," "strength of drug effect," liking," "sedated," and "desire to take again," and indicate whether they thought they received active drug or placebo.

Subjective Effects Scale VAS (SES). These 33 items are adapted from Haney et al. [105] and include the phrase "I feel…" followed by adjectives describing a mood (e.g., "anxious", "friendly," "down," etc), a drug effect (e.g., "high," "stimulated", "a good drug effect") or a physical symptom (e.g., "hungry," "tired," "restless"). These visual analog scale (VAS) items are presented as a series of horizontal 100-mm lines, anchored on the left by 0 ("not at all" or "dislike a lot" depending on the item) and 100 ("a lot" "extremely" or "very much" depending on the item) on the right. Each line is labeled with a phrase and participants are instructed to place a mark on each line (i.e., from 0-100) indicating how they feel at the moment. These will be administered immediately after the cannabis vaporizing episode prior to each PE

session.

Physiological and Biological Measures

Vital signs (heart rate, oxygen saturation, and blood pressure) will be assessed at screening, baseline, prior to start of each PE session, and immediately after the PE session. Heart rate and blood pressure will also be assessed continuously throughout each PE session, for safety reasons. Urine samples will be collected at baseline, pre- and post-acute cannabis administration, post-PE+cannabis sessions (i.e., after PE session 6), and post-PE treatment and used to measure creatinine-normalized THC, CBD, and metabolite concentrations (e.g., ▵9-THC, 11-OH-THC, THCCOOH, 7-COOH-CBD). Saliva samples will be collected at pre- and post-acute cannabis administration (i.e., during PE sessions 3-6). To collect saliva samples the subject will hold a cotton salivette at a fixed position in his/her mouth, without chewing, for 2 min. Salivettes will be centrifuged and saliva will be transferred to cryogenic tubes, frozen at –20º C, put on dry ice and sent to the Lipidomics Core Facility at WSU for analyses and assay of cortisol.

Blood samples will be collected at screening, post-PE+cannabis sessions (i.e., after PE session 6), and at post-PE treatment. Saliva and plasma will be analyzed to determine endocannabinoid concentrations. Blood draws will be performed by a trained member of the research team who is certified in phlebotomy. During each draw, 5 ml whole blood will be collected to yield ≈2.5 ml plasma. This volume is consistent with published ethical guidelines for blood sampling in adults (<5 ml/kg in any one 24 hr period). If the first attempt at the blood draw is unsuccessful, the research team will ask the participant if they are willing to attempt again, with up to three possible attempts at any time. The participant will be free to decline with no penalty. Blood samples will be obtained using a butterfly needle and 10 ml vacutainers (BD Vacutainer® K2EDTA Blood Collection Tubes). Blood samples will be immediately processed (<10 min after collection) to limit ex vivo production of eCBs. Blood will be centrifuged and plasma will be aliquoted, immediately frozen at –20º C in the Human Pharmacology Laboratory on-site freezer, and sent to the Lipidomics Core Facility at WSU for analyses of plasma and saliva levels of eCBs, THC, CBD, and metabolites. Plasma samples will be used to determine plasma concentrations of eCBs (i.e., AEA, 2-AG, OEA, PEA) using ultra performance liquid chromatography tandem mass spectrometry (UPLC/MS/MS). This approach is standard for assessment of eCBs and is routinely used in the Lipidomics Core lab. Procedures are described in detail in Gachet et al., [106].

Skin Conductance Response (SCR): SCR is a measure of sweating on the skin and changes in SCR are used as an index of fear. The SCR signal will be amplified and recorded with a BIOPAC Systems SCR module connected to a laptop. All data will be continuously sampled at 1000 Hz. AcqKnowledge software (BIOPAC Systems) will be used for off-line analysis.

Genotyping: DNA extraction and genotyping of the rs324420 (FAAH) variant will be completed in Dr. Burghardt's laboratory in Pharmacy Practice at WSU. If the participant signs the DNA consent form, DNA will be extracted from buccal swabs using Qiagen buccal DNA kits.

fMRI Scanning: Magnetic resonance scanning at WSU will be performed on a 3.0 Tesla Siemens Magnetom Verio System using an industry-leading 32-channel head-coil for superior image quality. We will use a multi-band echoplanar imaging sequence [TR [repetition time] = 2000ms; TE [echo time] = 30ms; Flip angle = 73°; 128x128 matrix; FOV [field of view] = 256 mm; 66 slices; 2.0 x 2.0 x 2.0 mm voxels], which were used Co-PI Rabinak's K01 and R61 projects and are currently used in her R33 clinical trial. A high-resolution structural image will provide precise anatomical localization. Whole-brain fMRI blood oxygen-level dependent (BOLD)-related signal measures will be acquired to measure task- and drug-related effects and to minimize susceptibility artifact (signal loss) at the medial temporal lobe (including the amygdala and the ventromedial prefrontal cortex).

Research Design

In this randomized, double-blind, placebo-controlled clinical trial, veterans with PTSD (n=350) will be randomized into one of five cannabis (with varying THC:CBD ratios) conditions and complete a 10-session PE treatment protocol. Cannabis will be administered immediately before the start of the first four exposure-focused sessions; cannabis will not be administered during the remaining exposure sessions. All participants will undergo fear conditioning assessment prior to and after the PE treatment, with a subset of participants who meet safety criteria also undergoing fMRI scans with the fear conditioning measures. Clinical assessments will occur at baseline (pre-treatment), weekly at each PE session, pre- and post-cannabis administration, and post PE-treatment, with additional post-treatment follow-ups at 3-, 6-, and 9-months. Assessment measures are described above and shown in Table 2. Study flow is presented in Figure 2.

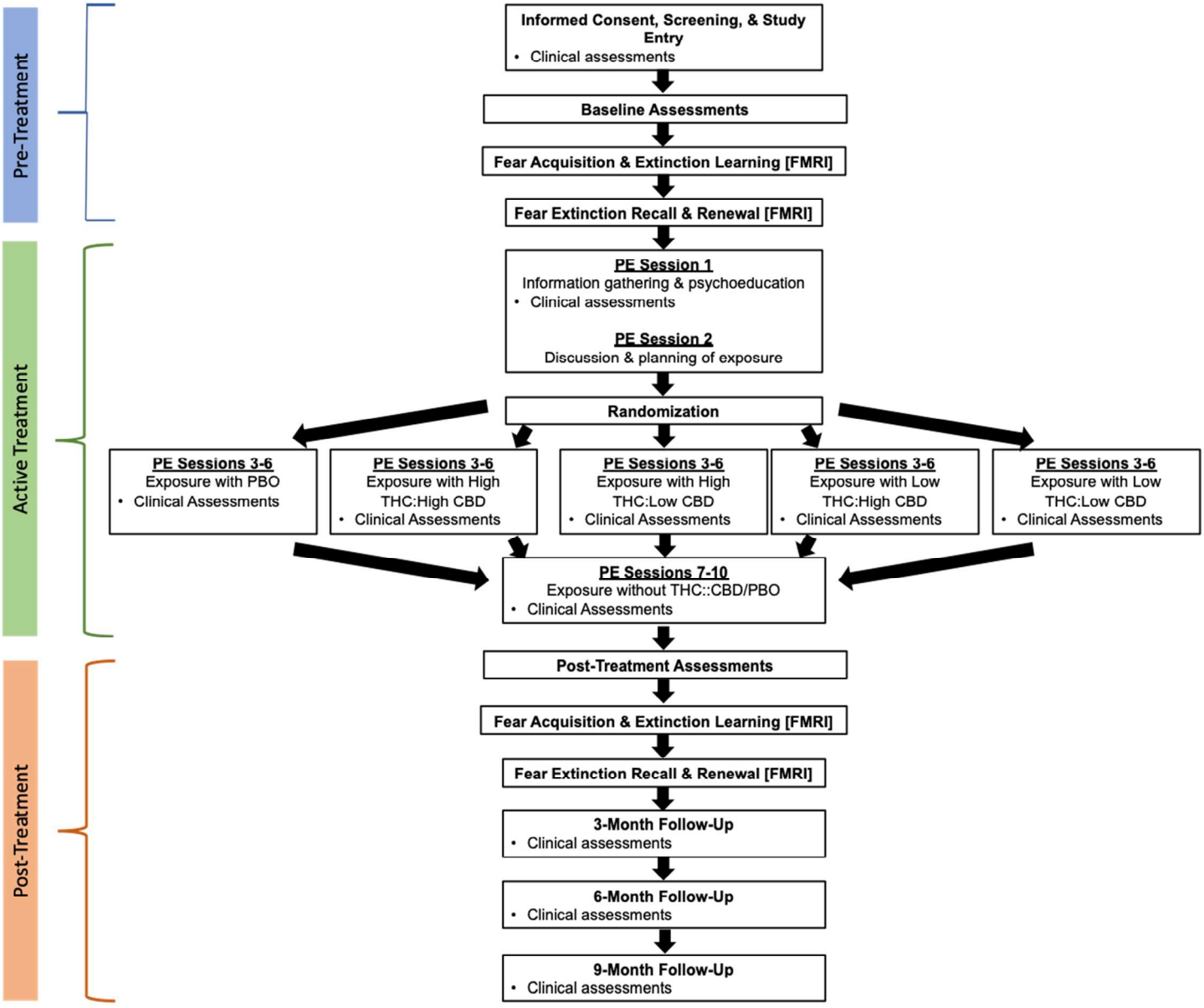


Figure 2. Study Flow.

Baseline Sessions. Participants will be asked not to use any alcohol or drugs for 24-hr before arriving at the lab, but will be allowed to smoke 1 tobacco cigarette just prior to the session. Upon arrival at the Human Pharmacology Laboratory, participants will provide urine and breath samples to test for recent drug or alcohol use. At approximately 0900, baseline assessments will begin. These include **physiological** (heart rate, oxygen saturation, skin temperature, blood pressure, saliva sample for DNA analysis, blood sample to analyze plasma endocannabinoids, THC, CBD, and metabolite levels); **psychological** (PCL-5, C-SSRS, SBQ-R, BDI-II, STAI, SHAPS, EERT, MDD, PRT, MID); **neurocognitive** (WMS, WCST, IGT, CVLT); and **overall health** (Brief Pain Inventory, Epworth Sleepiness Scale, Short-Form 36, Quality of Life) testing. These assessments will occur in randomized and counterbalanced order. Participants will be provided with lunch and offered periodic breaks.

Pre-treatment Fear Conditioning. In the week prior to beginning PE, participants will undergo the pre-treatment fear conditioning and extinction assessment. This session is expected to last approximately 1.5 hr and will take place either in the fMRI scanner (for those in the MRI substudy) or in Dr. Rabinak's laboratory. The fear extinction recall session with scan will be scheduled to occur the day after, but no more than 5 days following fear conditioning and extinction. These two sessions (pre-treatment fear conditioning, extinction, and recall test) need to occur prior to the start of the first PE session.

10-Week PE Treatment Phase. Participants will then begin the 10-week PE treatment phase, during which participants will undergo 10, 60-min sessions that occur at least once per week. All the PE sessions (1-10) will occur in the WarriorCARE suite and the Human Pharmacology Lab at Tolan Park. Sessions 1 and 2 involve pre-exposure psychoeducation that includes discussion of reactions to trauma, treatment rationale, breathing retraining, and how to report level of distress from 0 to 100 (100=extreme anxiety/distress) when facing fears. Sessions 3-10 will consist of repeated exposures to trauma memories (imaginal exposure) and avoided situations (*in vivo* exposure). Prior to each of the first four exposure-focused sessions (Sessions 3-6) participants will vaporize the THC:CBD dose to which they were randomized, according to the administration procedure described above. Exposure will begin immediately after doses have been administered. Changes in PTSD symptoms and suicidal ideation, along with other clinical measures and vitals, will be assessed each week at these sessions.

Upon arrival at TP, participants will provide urine and breath samples to test for recent drug or alcohol use. At approximately 0900, clinical assessments will occur, followed by 1-hr PE sessions. For sessions 3-6, at 0900 hrs pre-cannabis administration assessments will occur, followed by cannabis vaporization of each participant's assigned dose. Post-cannabis administration measures will be gathered, and immediately followed by the exposure-focused PE session. Because cannabis is administered, participants will be required to stay in the HPL for 4 hours after vaporization to ensure that all cannabis effects have dissipated before they are discharged from the lab following sessions 3-6. The non-cannabis PE sessions are expected to last about 1.5 hours.

Post-treatment Phase Assessments. The day after (or up to 5 days after) the final PE session (i.e., Session 10), participants will undergo a post-treatment assessment, which will include most of the measures obtained during Baseline. These include **psychological** (CAPS-5, PCL-5, C-SSRS, SBQ-R, BDI-II, STAI, SHAPS, EERT, MDD, PRT, MID; CGI-I; CGI-I); **neurocognitive** (WMS, WCST, IGT, CVLT); Timeline Followback of substances recently used, and **overall health** (Health Care Utilization, Brief Pain Inventory, Epworth Sleepiness Scale, Short-Form 36, Quality of Life) testing. A debriefing interview will also be conducted to provide information to and gather feedback from participants. This assessment will occur in the WarriorCARE suite at Tolan Park.

Post-treatment Fear Conditioning. Within 1 week following the completion of the last PE session, participants will undergo the post-treatment fear conditioning and extinction assessment. This session is expected to last approximately 1.5-hr and will take place either in the fMRI scanner for those in the MRI substudy or in Dr. Rabinak's laboratory. The fear extinction recall with scan will be scheduled to occur the day after, but no more than 5 days following fear conditioning and extinction. This session will also last approximately 1.5-hr. Both the post-treatment fear conditioning, extinction, and recall test sessions need to occur following the last PE session.

Post-Treatment Follow-Up Assessments. Post-treatment follow up assessments will occur at 3-, 6- and 9-months post-treatment. Measures collected will be a subset of those conducted at Baseline and include: **psychological** (CAPS-5, PCL-5, C-SSRS, SBQ-R, BDI-II, STAI); Timeline Followback of substances recently used, and **overall health** (Health Care Utilization, Brief Pain Inventory, Epworth Sleepiness Scale, Short-Form 36, Quality of Life) testing. These sessions will occur either in the WarriorCARE suite at Tolan Park or participants may elect to complete questionnaires online via Castor with clinician interviews conducted over the phone or telehealth visit.

Termination Criteria

Study participation may be terminated for any of the following reasons: (a) participant request to exit or withdraw consent; (b) development of risk of harm to self or others that requires immediate intervention; (c) alcohol, drug, medication use that would interfere with the study drug; (d) development of a systemic, medical, neurologic, or psychiatric illness requiring treatment that would exclude participation; (e) clinical deterioration (see below); (f) non-compliance with study protocol requirements; (g) pregnancy; any other reason determined by the Co-PIs.

Patients will be asked to consider discontinuing their participation if they fail to appear for three consecutive treatment sessions or do not fully engage in treatment (e.g., do not perform assigned work in or outside the treatment session). We will make every effort to ensure that the treatment is accessible (i.e., scheduling treatment sessions during evening and weekend hours). The protocol for non-compliance is to ensure that patients receive appropriate treatment. If a patient decides to end treatment, which they are free to do at any time without consequence, the Co-PIs will coordinate a thorough exit evaluation and provide treatment referrals including pharmacotherapy and/or locally available

psychosocial treatment, as appropriate. Patients will be informed of this protocol before treatment.

A patient may be withdrawn from therapy early (i.e., fail to complete all 10 sessions) and still complete the other non-therapeutic study visits (i.e., Visits 14-17). The Co-PIs (Lundahl & Rabinak), in consultation with Co-I Rauch, will determine whether a patient who does not complete therapy (e.g., due to non-compliance with therapy requirements, lack of treatment response, or patient decision to end therapy) will remain in the study or be removed from the study on a case-by-case basis. So long as remaining in the study is not harmful to the patient and they are compliant with the non-therapy study procedures, the patient may be kept in the study to examine outcomes in treatment non-completers.

A patient who is withdrawn from the study (e.g., due to becoming ineligible, non-compliance with the study requirements, patient withdrawal of consent) may continue to receive PE therapy sessions (up to 10 total) with their assigned therapist if they wish to do so. The Co-PIs (Lundahl & Rabinak), in consultation with Co-I Rauch, will determine whether a patient who is removed from the study may continue to receive PE therapy on a case-by-case basis. Patient safety and clinical benefit will be considered. Some limited measures may continue to be collected by the study team as clinically necessary (e.g., CAPS-5, PCL).

Inadequate Clinical Improvement or Clinical Deterioration

It is possible that some participants will not experience clinical improvement, as expected, or that participants could experience clinical deterioration during this protocol (e.g., worsening of PTSD symptoms or functioning). This risk will be explained fully to participants at study entry and during informed consent. If the participant is willing to continue with treatment and is not at imminent suicidal or homicidal risk (see below), they will be permitted to continue in the study. Determinations about whether clinical deterioration warrants terminating a participant from the study will be made by the PI in consultation with Co-PI Lundahl, Co-I Ledgerwood and/or Co-I Rauch, and will be handled on a case-by-case basis. If, and when, clinical deterioration warrants ending a participant's participation, the Co-PIs and/or research staff will immediately refer the patient to receive appropriate clinical treatment.

Clinical Plan for Addressing Elevated Suicidality

Due to the nature of the study, it is probable that we will experience situations where participants experience increases in suicidal ideation. Exacerbations in suicide risk may be detected in a variety of ways: 1) a participant may report increased suicidality or suicidal behaviors to a research assistant; 2) participants may note increased suicidality on the C-SSRS, SBQ or BDI-II; or 3) we may become aware of increased suicidality through a clinical or collateral source such as a therapist or family member.

The presence of suicidal ideation is evaluated at the initial assessment, every exposure-based session, and again at 3-, 6-, and 9-months follow-up to reflect real world practice. If a participant reports suicidal ideation, either at the initial study intake or during the study, research staff will complete the Safety Plan worksheet together and both parties will keep a copy. Research staff will also immediately contact Drs. Lundahl and/or Ledgerwood who are licensed clinical psychologists in the State of Michigan. Both Drs. Lundahl and Ledgerwood have experience working with individuals who have depression and express suicidal ideation. Dr. Lundahl and/or Ledgerwood will meet with the participant and conduct a risk assessment. Important components of a suicide risk assessment include assessment of the presence of suicidal ideation, past attempts, plan for an attempt, lethality of the suicide plan and past attempts, and accessibility to means for a suicide attempt. Dr. Lundahl and/or Ledgerwood will assess each of these specific domains. In cases where the participant is not at immediate risk (i.e., the participant is experiencing mild thoughts about death, has no intention or plan to commit suicide, reports many things to live for, has a strong social support network and has a forward-looking perspective), Dr. Lundahl or Ledgerwood will continue to monitor the individual, make frequent assessments of his/her suicidality at subsequent visits and assessment time-points, and will refer the individual to outpatient mental health treatment (or notify the individual's current therapist, after consent to do so is obtained). Assessments of suicidality are routinely conducted every week in the study, but Dr. Lundahl and/or Ledgerwood will conduct more frequent follow-up in cases where the participants' risk of suicide is significantly elevated from prior assessment time-points. In cases where the suicide risk is high (i.e., wish to die, suicide plan, access to methods, etc.), or unknown, Dr. Lundahl and/or Ledgerwood will conduct further assessment, and may arrange for a warm transfer to a crisis line, meeting with another licensed mental health professional, or arrange for the participant to be transported to the nearest Emergency Room if s/he believes that the participant may attempt suicide after the lab visit. If there is risk of immediate physical harm to the research staff, WSU campus police will be alerted. We have adopted a similar policy in our ongoing studies.

Emergency contact information will be required for each participant and will be stored separately from study data or links to data and will only be accessible by key personnel listed on the study. Paper copies will be stored with the consent forms (i.e., in a locked cabinet in the study coordinator's office at WSU). We also request contact for and permission to contact outside therapists and clinicians to contact should a participant report an increase in suicidal ideation or symptom severity. Co-PI Lundahl and Co-I Ledgerwood will serve as the on-call contacts for handling psychiatric and medical emergencies including situations involving imminent suicidal or homicidal risk and/or severe, adverse drug reactions. Co-PI Lundahl and Co-I Ledgerwood will each be notified in advance of all scheduled study visits.

Research staff will follow the steps outlined in the "Emergent Suicidal or Homicidal Risk Assessment and Action Standard Operating Procedures", which will be in a Regulatory Binder prepared for this trial.

We will also establish a Data and Safety Monitoring Board, composed of outside experts in cannabinoid pharmacology, PTSD, and psychiatry. This board will meet prior to beginning recruitment, and then yearly to discuss progress and monitor safety. They may also be convened in the event of an unexpected reaction during the study to discuss whether changes to the protocol are needed.

Compensation

Participants will be paid for their time and inconvenience. Those who participate in screening sessions but do not qualify for the study will be paid for attending screening visits ($75 for Visit 1 and $75 for Visit 2). Those who enroll and complete the study will receive $100 for the Baseline assessment session; $40 for each of the 4 fear acquisition/extinction with MRI Scan sessions; $30 for PE sessions 1, 2, and 7-9 (which do not involve cannabis administration); $60 for each of the 4 PE+cannabis sessions (PE sessions 3-6; these sessions last longer as participants must stay in the lab for 4-hr post-cannabis administration for safety reasons); $50 for PE Session 10 (this session is longer because of additional clinical assessments); $100 for the Post-treatment assessment; and $50 for each of the 3 follow-up sessions. There is an additional $200 bonus for finishing the entire PE treatment and all 4 MRI scans, as well as an additional $100 bonus for completing all 3 follow-up sessions. Thus, study completers will earn a total of $1290. Participants who withdraw prior to completing the study will receive partial payment based on the number of sessions they completed.

Study Timeline

The proposed study will take about 5 years. In the first three months we will hire additional research staff, train existing staff, set up study questionnaires on Castor, purchase necessary supplies, obtain IRB approval, and start recruiting. We will also file any necessary regulatory paperwork (e.g., FDA IND application, file protocols with the DEA). We anticipate needing to recruit and screen about 525 candidates to enroll 350 volunteers. Based on our previous studies, we expect 30% attrition, and thus will end with about 250 completers. We will recruit new participants until the end of the 4th year, with all participants completing their follow-ups in the 5th year. Each participant is involved in the study for about one year after they enroll in the study (including the 3-, 6-, and 9-month post-treatment follow up sessions).

Data Analyses

Preliminary Analyses: The proposed project uses a repeated-measures, independent sample design. First, we will examine the distribution of each variable. We will then check for out-of-range values, outliers and abnormal values using graphical methods (e.g., boxplots and histograms) and descriptive summaries to ensure that all values are within expected ranges. We will verify that the distributions of measures meet the assumptions of the statistical tests to be used, applying a formal test such as the Shapiro-Wilk's test. Sphericity will be verified (Mauchly's Test) prior to repeated-measures analysis of variance and Huynh-Feldt correction for repeated measures will be applied. Transformations will be used when distributional assumptions are not fulfilled for inferential tests. Tests will be conducted to identify potential relationships of baseline demographic and clinical variables to our dependent variables (e.g. resumption of smoking, delay discounting) and to see whether they are balanced between groups. If a baseline variable is not balanced between conditions and is correlated with the dependent variable ($r>.30$), we will include this variable as a covariate in subsequent analyses. All tests described below will each have a .05 two-tailed alpha-level.

Aim 1 (Examine the effects of varying THC:CBD cannabis mixtures administered before PE sessions on PTSD symptom severity and frequency and severity of suicidal ideation in veterans with PTSD during and after PE treatment). Least-squares mean score changes from baseline to post-treatment will be analyzed using a mixed between-within subjects model for repeated measures (MMRM), with cannabis dose as the between and time (pre-, post-treatment) as the

repeated factor. We will also examine differences in PTSD symptom severity and suicidal ideation between the PE+Cannabis and the PE sessions. This MMRM analysis will be based on the missing at random (MAR) assumption to estimate the treatment effect that would have been observed had participants continued their assigned treatment, to incorporate the actual treatment received and treatment retention into the treatment effect assessment. Separate analyses will be run for PTSD symptom severity, suicidal ideation, psychiatric symptoms, health, pain, quality of life and other continuous variables. We will also be able to examine trends in symptom severity over time at each post-treatment follow-up assessment.

Aim 2 (Examine the effects of varying THC:CBD cannabis mixtures administered before each PE session on responder (defined as at least 50% reduction in symptom severity on the CAPS-5) or remission (defined as loss of PTSD diagnosis plus a score <20 on the CAPS-5) status) will be analyzed using either non-parametric tests for categorical data or regression, with responder and remission status as outcomes and cannabis condition (THC:CBD doses) and time (pre-post PE treatment) as predictor variables. We plan to examine cannabis dose differences both at post-PE treatment, and at each session within treatment (e.g., trend in a logistic outcome). PTSD symptom severity, mood/anxiety and suicidal ideation will all be analyzed separately.

Aim 3 (Examine the effects of THC:CBD cannabis mixtures administered before each PE session on fear reactivity) will use a conventional alpha level of 0.05 and all tests will be two-tailed. To evaluate the main effects, Analysis of Variance will be used for neuroimaging (brain activation) and peripheral measures of fear (e.g., SCR, US expectancy ratings). We will also include covariates such as gender if found unbalanced and correlated (r>0.30) with the outcome variable (e.g., MANCOVA, ANCOVA). Drug groups (THC:CBD doses, placebo) will be used as the between-subjects factor and extinction recall (pre-treatment, post-treatment) as the within-subject factor. If significant multivariate analysis will be followed by univariate analysis, which if significant, will be followed up with simple effects analyses (e.g., independent t-tests, paired t-tests). In addition to omnibus tests, planned comparisons will be used to test specific hypotheses such as THC:CBD dose (vs. placebo) on fear extinction in PTSD, as well as comparisons between THC:CBD doses; if there is no significant difference between THC:CBD doses we will examine potential trends with varying ratios of THC:CBD. To evaluate relationships, Pearson correlations will be used along with scatterplots to examine the nature of relationships. Hochberg step-down multiplicity adjustment will be used to control for all multiple comparisons. Confidence intervals and effect sizes will also be calculated.

Aim 4 (Characterize psychiatric symptoms, health, pain, sleep, and quality of life in relationship to PE+cannabis treatment over a one-year period) will be analyzed using a generalized linear mixed-effects model (GLMM). GLMM allows for within- and between-subjects comparisons but is superior to repeated measures analysis of variance by incorporating all data under the assumption that missed data are missing at random. Separate analyses will be run for PTSD symptom severity, suicidal ideation, psychiatric symptoms, health, pain, quality of life and other continuous variables. We will be able to examine trends in symptom severity over time at each of the follow-up time-points. We may also use other statistical methods depending on the specific questions we are exploring including repeated measures ANOVA, multiple regression and logistic regression analyses. We will focus on symptom changes from baseline to each of the post-treatment follow-up time periods (3-, 6-, 9-months).

Exploratory Aims 5a (Determine whether plasma, urine, and saliva THC and CBD levels during and following PE+cannabis treatment correlate with changes in PTSD, mood, anxiety, and suicidal symptoms) and 5b (Determine whether circulating plasma and saliva endocannabinoids (eCBs) during and following PE+cannabis treatment correlate with changes in PTSD, mood, and suicidal symptoms) will be analyzed using correlational methods.

Lipidomics Core Analyses

Analysis of eCBs in any biological matrix is possible by state-of-the-art LC-MS methods, as demonstrated by published protocols [29, 40-43]. Yet, caution is required during sample collection and processing for LC-MS analysis to prevent hydrolysis of fatty acyl ethanolamides by fatty acid amide hydrolase (FAAH) and non-enzymatic isomerization of 2-acylglycerols. Addition of FAAH inhibitors in the sample during collection and use of aprotic solvents for extracting eCBs helps alleviate these problems [29]. These are part of standard protocols at our Lipidomics Core Facility. Blood samples (1-2 mL each) will be collected into Vacutainer tubes containing EDTA as an anticoagulant. Each tube will be inverted several times then centrifuged at 900g for 15 min to obtain plasma fraction. Plasma will be transferred to cryogenic tubes a. Saliva samples will be collected under non-stimulated conditions via oral swab (Salimetrics®, State College, PA) placed under the subject's tongue for ~2min. After collection, swabs will be returned to a storage tube containing

the FAAH inhibitor.

We will measure four primary eCBs: AEA, 2-acyl-glycerol (2-AG), palmitoylethanolamide (PEA), and oleoylethanolamide (OEA). Importantly, the analytic method includes all eCBs simultaneously without increased costs, thus we will also examine other eCBs including all fatty acid variants of ethanolamides, 2-fatty acyl glycerols, epoxy eCBs [44], and prostaglandin ethanolamides. Our analytical method for the eCB system is similar to a published protocol [41] with the following differences: Samples are spiked with internal standards for AEA-d8, 2-AG-d8, 1-AG-d8, oleoylethanolamide-d4, and 1-PGE_2-d4 glycerol along with URB597 to inhibit FAAH. Methanol is added to the sample to a final concentration of 15% and applied to pre-conditioned StrataX C18 SPE cartridges (Phenomenex, 30 mg sorbent, 1 ml). The loaded columns are washed with water containing 15% methanol, dried under vacuum, and eluted with a 1:1 mixture of acetonitrile and ethyl acetate. The eluates are dried under a stream of nitrogen, the residue is reconstituted in HPLC mobile phase mixture consisting of methanol – water – ammonium formate – formic acid (Mobile Phases A: 5:95:2mM:0.1; B:95:5:1mM:0.1, respectively) at 15%B. The reconstituted samples are subjected to HPLC on Luna C18(2) (3µ, 2x150 mm, Phenomenex) column. The gradient program with respect to the composition of B is as follows: 0-1 min, 50%; 1-8 min, 50-80%; 8-15 min, 80-95%; and 15-22 min, 95%. The flow rate is 0.2 ml/min. The HPLC eluate is directly introduced to ESI source of QTRAP5500 mass analyzer (SCIEX) in the positive ion mode with following conditions: Curtain gas, GS1, and GS2: 35 psi, Temperature: 600 ˚C, Ion Spray Voltage: 5100 V, Collision gas: low. Declustering potential and collision energy used for each eCB are the same as published [41]. The eluate is monitored by Multiple Reaction Monitoring (MRM) method to detect unique molecular ion – daughter ion combinations for each eCB. The MRM is scheduled to monitor each transition for 120 s around the established retention time for each eCB. Mass spectra for each detected eCB are recorded using the Enhanced Product Ion (EPI) feature to verify the identity of the detected peak in addition to MRM transition and retention time matched with the standard. Data is collected using Analyst 1.6.2 software and the MRM transition chromatograms are quantified by MultiQuant software (both from SCIEX). The internal standard signals in each chromatogram are used for normalization for recovery and relative quantitation of each analyte.

Psychophysiological data (SCR, HR/HRV) will be analyzed using AcqKnowledge data analysis packages in Dr. Rabinak's lab. These will be used to process, filter and summarize the physiological data for the fear conditioning tests.

Research Settings

Tolan Park Medical Building (WSU medical campus). The Tolan Park (TP) Medical building is centrally located near Detroit Medical Center and the John D. Dingell VA Medical Center. The Warrior Care Center, new space designated to conduct our current, ongoing LARA/CRA-funded cannabis trial, is housed on the first floor of TP, and consists of a reception area, small kitchen, conference room, and two private interview rooms for testing. Co-PI Dr. Lundahl and Co-Investigators Dr. Ledgerwood and Dr. Greenwald have offices and laboratory space on the 2nd floor of TP, in the Human Pharmacology Laboratory. All screening, baseline, treatment, post-treatment, and follow-up assessments (except for fear conditioning) will occur in the Warrior Care Center and the Human Pharmacology Laboratory (HPL) at TP. Cannabis administration immediately preceding the prolonged exposure sessions will occur in the HPL in uniquely equipped and ventilated rooms specifically designed and built for cannabis and other drug administration, behavioral testing, intensive physiological monitoring, and data collection. Test rooms are linked to a central monitoring suite on the same hallway (occupied by the research assistants) for audio-visual surveillance. The laboratory includes at least three rooms available for participant testing and for PE therapy sessions. Free street-level parking is available adjacent to the TP building. The main entrance is staffed by a guard and all other entrances are locked. Entrance to office suites is gained via card swipe and visitors must be accompanied by staff escort.

Rabinak Laboratory: Co-PI Rabinak's Translational Neuropsychopharmacology Laboratory (www.tnp2lab.org) totals approximately 1,000 square feet of research-dedicated space, located at Wayne State University's Department of Pharmacy Practice in the Eugene Applebaum College of Pharmacy and Health Sciences (EACPHS) building. Co-PI Rabinak's laboratory, the HPL, and Wayne State's shared resources infrastructure have the resources required to perform all the work proposed in the study. The research laboratory maintains the necessary computer infrastructure to carry out clinical assessments, behavioral testing/training, and data collection related to fMRI, psychophysiological, and electrophysiological research. In particular, the lab has four new quad core processor workstations (Dell Quad Core HT, 3.40GHz Turbo, 8GB 1600MHz DDR3 memory, 1TB 3.5" SATA hard drive, 2nd 3.5" HDD Caddy), one single processor workstation (Dell Eight Core, 3.1GHz, 20M, 8.0GT/s, Turbo+ with 128GB, DDR3 RDIMM Memory, three 2TB 3.5" STAT 6GB/s hard drives, RAID 5, with 16 1GbE Ports), two standard computers for stimulus presentation (Dell Quad Core,

3.20GHz Turbo, 4GB 1600MHz DDR3 Memory, 500GB hard drive) and 2 Dell laptops for data acquisition (2 Dell Dual Core, 2.50GHz, 8GB 1600MHz DDR3L, 500GB Solid State Hybrid Drive). Archival storage is done via high-speed networking to two external 30TB network drives with redundant backups (one onsite and one offsite); another onsite RAID array is available for high-speed local processing. The laboratory has hardware and software support necessary to analyze neuroimaging (e.g., fMRI) and psychophysiology data. The laboratory also contains an advanced virtual reality (VR) platform from Vizard. The laboratory includes at least three rooms available for participant testing and therapy. There is a parking structure across the street and the Brady Street entrance to the College is staffed by a guard; visitors without proper ID must be escorted. The Mack Ave entrance and loading dock area are always locked from the outside.

Design Considerations

(1) We carefully considered whether to include participants who are already using cannabis to manage their symptoms or focus on individuals who have limited experience with cannabis but are open to trying it, in conjunction with an established behavioral therapy. Ultimately, we decided to recruit veterans with minimal current cannabis use to be sure that we can detect any potential cannabis effects, which may be difficult with individuals who are already using cannabis heavily for symptom management. (2) We are not concerned about recruitment efforts being hampered through "competition" with recruitment for our current VMR-funded cannabis trial, as there is very little overlap between the two trials. Potential participants for the proposed project will not be regular cannabis users (as they are in our ongoing study), and they will also be seeking behavioral treatment (PE) for PTSD (not the case for the ongoing study). Because both the ongoing trial and the proposed trial are multi-year studies, it is certainly possible that veterans who meet study criteria for both studies may participate in both studies (although participants must wait one year after completing one study before enrolling in the other).

Dissemination of Findings. We expect that at least 2-3 manuscripts per year will be submitted to high-quality, peer-reviewed scientific journals starting in Year 3. Preliminary findings will be presented at annual professional conferences, including International Cannabinoid Research Society, the American Psychological Association, the American Psychiatric Association, Society of Biological Psychiatry, the American College of Neuropsychopharmacology, and the International Society for Traumatic Stress Studies and in public communications and community engagement. We will share findings with our partnered veterans groups and associations, local cannabis dispensaries and cultivars, on social media, and to the State of Michigan CRA. Data from the proposed project would also be used in support of NIH grants designed to continue and expand on cannabinoid science and the therapeutic potential of cannabinoids.

Future Directions

Results from the proposed trial will provide valuable and novel information about the use of cannabis and cannabinoids in adjunct with evidence-based behavioral treatments for PTSD. Although prolonged exposure therapy is a frontline, gold standard treatment approach for PTSD, it is not efficacious for everyone and relapse rates are high. Studying cannabis as an add-on component to act as a "cognitive enhancer" for treatment introduces another potential therapeutic indication for cannabis, to improve an existing therapy. As such, these findings will significantly advance scientific knowledge about this area which, in turn, could inform treatment and public policy. In addition, results from these studies will inform future clinical trials designed to assess the most efficacious use of cannabinoids for reducing PTSD severity and suicidality among veterans. Specifically, data from this trial can be used to identify the optimal THC:CBD ratio that may confer benefit with lower risk. Data from our genotyping could be used to support research on personalized medicine, in which we might be able to predict, based on genetics, symptom severity, and response to cannabis, who might or might not do well on specific THC/CBD ratios and doses. Depending on the findings of our proposed studies, we anticipate that future clinical trial work may focus on: using cannabis as adjuncts to pharmacotherapeutic approaches, such as selective serotonin reuptake inhibitors (SSRIs) during treatment; examining other cannabis products, e.g. edibles or concentrates; exploring potential targets of cannabinoid intervention such as anxiety, depressive symptoms, pain, and sleep impairment, all of which may be important in reducing suicidal ideation. Data from the current proposed project would provide compelling support for NIH applications proposing any of these future avenues of research. Training in PE for local providers (Drs. Lundahl, Ledgerwood, postdoctoral fellows, psychology interns, practicum students) will increase the number of clinicians available who can offer PE therapy in the community, which will increase access to treatment for veterans. Access to evidence-based treatments is badly needed in Southeast Michigan, where rates of trauma exposure and PTSD exceed national averages.

References

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. Fifth Ed. Arlington, VA: American Psychiatric Association; 2013.
2. Panagioti M, Gooding PA, Tarrier N. A meta-analysis of the association between posttraumatic stress disorder and suicidality: the role of comorbid depression. Compr Psychiatry. 2012;53:915–930.
3. Affairs USD of V. 2020 National Veteran Suicide Prevention Annual Report. 2020.
4. Olenick M, Flowers M, Diaz V. US veterans and their unique issues: enhancing health care professional awareness. Adv Med Educ Pract. 2015:635.
5. Foa EB, Hembree E, Rothbaum B. Prolonged Exposure Therapy for PTSD: Therapist Guide. Oxford University Press; 2015.
6. Hauner KK, Mineka S, Voss JL, Paller KA. Exposure therapy triggers lasting reorganization of neural fear processing. Proc Natl Acad Sci. 2012;109:9203–9208.
7. Hembree EA, Foa EB, Dorfan NM, Street GP, Kowalski J, Tu X. Do Patients Drop Out Prematurely from Exposure Therapy for PTSD? J Trauma Stress. 2003;16:555–562.
8. Eftekhari A, Ruzek JI, Crowley JJ, Rosen CS, Greenbaum MA, Karlin BE. Effectiveness of national implementation of prolonged exposure therapy in veterans affairs care. JAMA Psychiatry. 2013;70:949–955.
9. Norton PJ, Hayes-Skelton SA, Klenck SC. What happens in session does not stay in session: Changes within exposures predict subsequent improvement and dropout. J Anxiety Disord. 2011;25:654–660.
10. Steenkamp MM, Litz BT, Hoge CW, Marmar CR. Psychotherapy for military-related PTSD: A review of randomized clinical trials. JAMA - J Am Med Assoc. 2015;314:489–500.
11. Graham BM, Milad MR. The Study of Fear Extinction. Mech Psychiatr Illn. 2011;5:1255–1265.
12. Bitencourt RM, Pamplona FA, Takahashi RN. Facilitation of contextual fear memory extinction and anti-anxiogenic effects of AM404 and cannabidiol in conditioned rats. Eur Neuropsychopharmacol. 2008;18:849–859.
13. Stevens JS, Ely TD, Sawamura T, Guzman D, Bradley B, Ressler KJ, et al. Childhood Maltreatment Predicts Reduced Inhibition-Related Activity in the Rostral Anterior Cingulate in Ptsd, But Not Trauma-Exposed Controls. Depress Anxiety. 2016;33:614–622.
14. Rabinak CACACA, Angstadt M, Sripada CSCSCS, Abelson JLJLJLJL, Liberzon I, Milad MRMR, et al. Cannabinoid facilitation of fear extinction memory recall in humans. Neuropharmacology. 2013;64:396–402.
15. Foa EB, Hembree EA, Rothbaum BO. Prolonged exposure therapy for PTSD: Emotional processing of traumatic experiences: Therapist guide. 2007.
16. Hoge EA, Austin ED, Pollack MH. Resilience: research evidence and conceptual considerations for posttraumatic stress disorder. Depress Anxiety. 2007;24:139–152.
17. François C, Despiégel N, Maman K, Saragoussi D, Auquier P. Anxiety disorders, major depressive disorder and the dynamic relationship between these conditions: treatment patterns and cost analysis. J Med Econ. 2010;13:99–109.
18. Jakupcak M, Luterek J, Hunt S, Conybeare D, McFall M. Posttraumatic Stress and Its Relationship to Physical Health Functioning in a Sample of Iraq and Afghanistan War Veterans Seeking Postdeployment VA Health Care. J Nerv Ment Dis. 2008;196:425–428.
19. Norman SB, Stein MB, Davidson JRT. Profiling Posttraumatic Functional Impairment. J Nerv Ment Dis. 2007;195:48–53.
20. Amaya-Jackson L, Davidson JR, Hughes DC, Swartz M, Reynolds V, George LK, et al. Functional impairment and utilization of services associated with posttraumatic stress in the community. J Trauma Stress. 1999;12:709–724.
21. Dekel R, Solomon Z. Marital relations among former prisoners of war: Contribution of posttraumatic stress disorder, aggression, and sexual satisfaction. J Fam Psychol. 2006;20:709–712.
22. Riggs DS, Byrne CA, Weathers FW, Litz BT. The quality of the intimate relationships of male Vietnam veterans: Problems associated with posttraumatic stress disorder. J Trauma Stress. 1998;11:87–101.
23. Cohen LR, Hien DA, Batchelder S. The Impact of Cumulative Maternal Trauma and Diagnosis on Parenting Behavior. Child Maltreat. 2008;13:27–38.

24. Jordan BK, Marmar CR, Fairbank JA, Schlenger WE, Kulka RA, Hough RL, et al. Problems in families of male Vietnam veterans with posttraumatic stress disorder. J Consult Clin Psychol. 1992;60:916–926.
25. Boden MT, Babson KA, Vujanovic AA, Short NA, Bonn-Miller MO. Posttraumatic stress disorder and cannabis use characteristics among military veterans with cannabis dependence. Am J Addict. 2013;22:277–284.
26. Myers KM, Davis M. Mechanisms of fear extinction. Mol Psychiatry. 2007;12:120–150.
27. Bouton ME, Westbrook RF, Corcoran KA, Maren S. Contextual and Temporal Modulation of Extinction: Behavioral and Biological Mechanisms. Biol Psychiatry. 2006.
28. Quirk GJ, Beer JS. Prefrontal involvement in the regulation of emotion: convergence of rat and human studies. Curr Opin Neurobiol. 2006;16:723–727.
29. LeDoux JE. Emotion circuits in the brain. Annu Rev Neurosci. 2000;23:155–184.
30. Herry C, Ciocchi S, Senn V, Demmou L, Müller C, Lüthi A. Switching on and off fear by distinct neuronal circuits. Nature. 2008;454:600–606.
31. Milad MR, Pitman RK, Ellis CB, Gold AL, Shin LM, Lasko NB, et al. Neurobiological basis of failure to recall extinction. 2010;66:1075–1082.
32. Milad MR, Orr SP, Pitman RK, Rauch SL. Context modulation of memory for fear extinction in humans. Psychophysiology. 2005;42:456–464.
33. Resick PA, Nishith P, Weaver TL, Astin MC, Feuer CA. A comparison of cognitive-processing therapy with prolonged exposure and a waiting condition for the treatment of chronic posttraumatic stress disorder in female rape victims. J Consult Clin Psychol. 2002;70:867–879.
34. Schnurr PP, Friedman MJ, Engel CC, Foa EB, Shea MT, Chow BK, et al. Cognitive Behavioral Therapy for Posttraumatic Stress Disorder in Women. Jama. 2007;297:820.
35. America I and AV of. 2019 Member Survey. 2019.
36. Kimbrel NA, Newins AR, Dedert EA, Van Voorhees EE, Elbogen EB, Naylor JC, et al. Cannabis use disorder and suicide attempts in Iraq/Afghanistan-era veterans. J Psychiatr Res. 2017;89:1–5.
37. Lake S, Kerr T, Buxton J, Walsh Z, Marshall BD, Wood E, et al. Does cannabis use modify the effect of post-traumatic stress disorder on severe depression and suicidal ideation? Evidence from a population-based cross-sectional study of Canadians. J Psychopharmacol. 2020;34:181–188.
38. Hill MN, Bierer LM, Makotkine I, Golier JA, Galea S, McEwen BS, et al. Reductions in circulating endocannabinoid levels in individuals with post-traumatic stress disorder following exposure to the World Trade Center attacks. Psychoneuroendocrinology. 2013;38:2952–2961.
39. Hill MN, Miller GE, Ho WSV, Gorzalka BB, Hillard CJ. Serum endocannabinoid content is altered in females with depressive disorders: A preliminary report. Pharmacopsychiatry. 2008;41:48–53.
40. deRoon-Cassini TA, Stollenwerk TM, Beatka M, Hillard CJ. Meet Your Stress Management Professionals: The Endocannabinoids. Trends Mol Med. 2020;26:953–968.
41. Treadway MT, Zald DH. Reconsidering anhedonia in depression: Lessons from translational neuroscience. Neurosci Biobehav Rev. 2011;35:537–555.
42. Le Heron C, Holroyd CB, Salamone J, Husain M. Brain mechanisms underlying apathy. J Neurol Neurosurg Psychiatry. 2019;90:302–312.
43. Rizvi SJ, Pizzagalli DA, Sproule BA, Kennedy SH. Assessing anhedonia in depression: Potentials and pitfalls. Neurosci Biobehav Rev. 2016;65:21–35.
44. Wang S, Leri F, Rizvi SJ. Anhedonia as a central factor in depression: Neural mechanisms revealed from preclinical to clinical evidence. Prog Neuro-Psychopharmacology Biol Psychiatry. 2021;110:110289.
45. Olson EA, Kaiser RH, Pizzagalli DA, Rauch SL, Rosso IM. Anhedonia in Trauma-Exposed Individuals: Functional Connectivity and Decision-Making Correlates. Biol Psychiatry Cogn Neurosci Neuroimaging. 2018;3:959–967.
46. Mayo LM, Rabinak CA, Hill MN, Heilig M. Targeting the Endocannabinoid System in the Treatment of Posttraumatic Stress Disorder: A Promising Case of Preclinical-Clinical Translation? Biol Psychiatry. 2021. 24 July 2021. https://doi.org/10.1016/j.biopsych.2021.07.019.
47. Elms L, Shannon S, Hughes S, Lewis N. Cannabidiol in the Treatment of Post-Traumatic Stress Disorder: A Case Series. J Altern Complement Med. 2019;25:392–397.
48. Forsythe ML, Boileau AJ. Use of cannabinoids for the treatment of patients with post-traumatic stress disorder. J Basic Clin Physiol Pharmacol. 2022;33:121–132.

49. Rabinak CA, Angstadt M, Lyons M, Mori S, Milad MR, Liberzon I, et al. Cannabinoid modulation of prefrontal-limbic activation during fear extinction learning and recall in humans. Neurobiol Learn Mem. 2014;113:125–134.
50. Haney M, Evins AE. Does Cannabis Cause, Exacerbate or Ameliorate Psychiatric Disorders? An Oversimplified Debate Discussed. Neuropsychopharmacology. 2016;41:393–401.
51. Zachary R. Shipley Institute of Living Scale: revised manual. Los Angeles: Western Psychological Services; 1991.
52. First MB, Williams JBW, Karg RS, Spitzer RL. User's Guide for the Structured Clinical Interview for DSM-5 Disorders, Research Version (SCID-5-RV). Arlington, VA: American Psychiatric Association; 2015.
53. Weathers FW, Blake DD, Schnurr PP, Kaloupek DG, Marx B, Keane TM. Clinician-Administered PTSD Scale for DSM-5 (CAPS-5). PTSD Natl Cent PTSD. 2015:1–18.
54. Bhattacharyya S, Morrison PD, Fusar-Poli P, Martin-Santos R, Borgwardt S, Winton-Brown T, et al. Opposite effects of δ-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology. Neuropsychopharmacology. 2010;35:764–774.
55. Foa EB, Hembree EA, Rothbaum BO, Rauch SAM. Prolonged Exposure Therapy for PTSD. New York: Oxford University Press; 2019.
56. Weathers FW, Blake D, Schnurr PP, Kaloupek DG, Marx BP, Keane TM. The Clinician-Administered PTSD Scale for DSM-5 (CAPS-5). Available from WwwPtsd.vaGov. 2013. www.ptsd.va.gov.
57. Weathers FWFW, Litz BTBT, Keane TMTM, Palmieri PPA, Marx BPBP, Schnurr PPPP. The ptsd checklist for dsm-5 (pcl-5). vol. 5. 2013.
58. Weathers FW, Bovin MJ, Lee DJ, Sloan DM, Schnurr PP, Kaloupek DG, et al. The Clinician-Administered PTSD Scale for DSM–5 (CAPS-5): Development and initial psychometric evaluation in military veterans. Psychol Assess. 2018;30:383–395.
59. Posner K, Brown GK, Stanley B, Brent DA, Yershova K V., Oquendo MA, et al. The Columbia–Suicide Severity Rating Scale: Initial Validity and Internal Consistency Findings From Three Multisite Studies With Adolescents and Adults. Am J Psychiatry. 2011;168:1266–1277.
60. Osman A, Bagge CL, Gutierrez PM, Konick LC, Kopper BA, Barrios FX. The Suicidal Behaviors Questionnaire-Revised (SBQ-R):Validation with Clinical and Nonclinical Samples. Assessment. 2001;8:443–454.
61. Weathers FW, Blake D, Schnurr PP, Kaloupek DG, Marx BP, Keane TM. The Life Events Checklist for DSM-5 (LEC-5). Natl Cent PTSD. 2013;5:Instrument available from the National Center for. www.ptsd.va.gov.
62. Beck AT, Steer RA, Brown G. Beck Depression Inventory-II. Psychol Assess. 1996. 1996.
63. Spielberger CD. Manual for the State-Trait Anxiety Inventory STAI (form Y)('self-evaluation questionnaire'). 1983.
64. Snaith RP, Hamilton M, Morley S, Humayan A, Hargreaves D, Trigwell P. A Scale for the Assessment of Hedonic Tone the Snaith–Hamilton Pleasure Scale. Br J Psychiatry. 1995;167:99–103.
65. Treadway MT, Buckholtz JW, Schwartzman AN, Lambert WE, Zald DH. Worth the 'EEfRT'? The Effort Expenditure for Rewards Task as an Objective Measure of Motivation and Anhedonia. PLoS One. 2009;4:e6598.
66. Floresco SB, Ghods-Sharifi S. Amygdala-Prefrontal Cortical Circuitry Regulates Effort-Based Decision Making. Cereb Cortex. 2006;17:251–260.
67. Randall PA, Pardo M, Nunes EJ, López Cruz L, Vemuri VK, Makriyannis A, et al. Dopaminergic Modulation of Effort-Related Choice Behavior as Assessed by a Progressive Ratio Chow Feeding Choice Task: Pharmacological Studies and the Role of Individual Differences. PLoS One. 2012;7:e47934.
68. Salamone JD, Correa M, Yohn S, Lopez Cruz L, San Miguel N, Alatorre L. The pharmacology of effort-related choice behavior: Dopamine, depression, and individual differences. Behav Processes. 2016;127:3–17.
69. Salamone JD, Correa M, Yang J-H, Rotolo R, Presby R. Dopamine, Effort-Based Choice, and Behavioral Economics: Basic and Translational Research. Front Behav Neurosci. 2018;12.
70. Walton ME, Bannerman DM, Rushworth MFS. The Role of Rat Medial Frontal Cortex in Effort-

Based Decision Making. J Neurosci. 2002;22:10996–11003.
71. Yohn SE, Errante EE, Rosenbloom-Snow A, Somerville M, Rowland M, Tokarski K, et al. Blockade of uptake for dopamine, but not norepinephrine or 5-HT, increases selection of high effort instrumental activity: Implications for treatment of effort-related motivational symptoms in psychopathology. Neuropharmacology. 2016;109:270–280.
72. Horne SJ, Topp TE, Quigley L. Depression and the willingness to expend cognitive and physical effort for rewards: A systematic review. Clin Psychol Rev. 2021;88:102065.
73. Lawn W, Freeman TP, Pope RA, Joye A, Harvey L, Hindocha C, et al. Acute and chronic effects of cannabinoids on effort-related decision-making and reward learning: an evaluation of the cannabis 'amotivational' hypotheses. Psychopharmacology (Berl). 2016;233:3537–3552.
74. Taylor MB, Filbey FM. Residual Effects of Cannabis Use on Effort-Based Decision-Making. J Int Neuropsychol Soc. 2021;27:559–569.
75. Lamontagne SJ, Melendez SI, Olmstead MC. Investigating dopamine and glucocorticoid systems as underlying mechanisms of anhedonia. Psychopharmacology (Berl). 2018;235:3103–3113.
76. Bryan CJ, Bryan AO. Delayed reward discounting and increased risk for suicide attempts among U.S. adults with probable PTSD. J Anxiety Disord. 2021;81:102414.
77. Ludwig VU, Nüsser C, Goschke T, Wittfoth-Schardt D, Wiers CE, Erk S, et al. Delay discounting without decision-making: medial prefrontal cortex and amygdala activations reflect immediacy processing and correlate with impulsivity and anxious-depressive traits. Front Behav Neurosci. 2015;9.
78. Lempert KM, Pizzagalli DA. Delay discounting and future-directed thinking in anhedonic individuals. J Behav Ther Exp Psychiatry. 2010;41:258–264.
79. Strickland JC, Lee DC, Vandrey R, Johnson MW. A systematic review and meta-analysis of delay discounting and cannabis use. Exp Clin Psychopharmacol. 2021;29:696–710.
80. Pizzagalli DA, Jahn AL, O'Shea JP. Toward an objective characterization of an anhedonic phenotype: A signal-detection approach. Biol Psychiatry. 2005;57:319–327.
81. Kangas M. DSM-5 Trauma and Stress-Related Disorders: Implications for Screening for Cancer-Related Stress. Front Psychiatry. 2013;4:2–4.
82. Huys QJ, Pizzagalli DA, Bogdan R, Dayan P. Mapping anhedonia onto reinforcement learning: a behavioural meta-analysis. Biol Mood Anxiety Disord. 2013;3:12.
83. Vrieze E, Pizzagalli DA, Demyttenaere K, Hompes T, Sienaert P, de Boer P, et al. Reduced Reward Learning Predicts Outcome in Major Depressive Disorder. Biol Psychiatry. 2013;73:639–645.
84. Brown VM, Zhu L, Solway A, Wang JM, McCurry KL, King-Casas B, et al. Reinforcement Learning Disruptions in Individuals With Depression and Sensitivity to Symptom Change Following Cognitive Behavioral Therapy. JAMA Psychiatry. 2021;78:1113.
85. Whitton AE, Kakani P, Foti D, Van't Veer A, Haile A, Crowley DJ, et al. Blunted Neural Responses to Reward in Remitted Major Depression: A High-Density Event-Related Potential Study. Biol Psychiatry Cogn Neurosci Neuroimaging. 2016;1:87–95.
86. Knutson B, Fong GW, Adams CM, Varner JL, Hommer D. Dissociation of reward anticipation and outcome with event-related fMRI. Neuroreport. 2001;12:3683–3687.
87. Green IW, Pizzagalli DA, Admon R, Kumar P. Anhedonia modulates the effects of positive mood induction on reward-related brain activation. Neuroimage. 2019;193:115–125.
88. Schiller CE, Minkel J, Smoski MJ, Dichter GS. Remitted major depression is characterized by reduced prefrontal cortex reactivity to reward loss. J Affect Disord. 2013;151:756–762.
89. Enzi B, Lissek S, Edel M-A, Tegenthoff M, Nicolas V, Scherbaum N, et al. Alterations of Monetary Reward and Punishment Processing in Chronic Cannabis Users: An fMRI Study. PLoS One. 2015;10:e0119150.
90. Spechler PA, Stewart JL, Kuplicki R, Aupperle R, Bodurka J, Feinstein J, et al. Attenuated reward activations associated with cannabis use in anxious/depressed individuals. Transl Psychiatry. 2020;10:189.
91. Skumlien M, Mokrysz C, Freeman TP, Wall MB, Bloomfield M, Lees R, et al. Neural responses to reward anticipation and feedback in adult and adolescent cannabis users and controls. Neuropsychopharmacology. 2022. 6 April 2022. https://doi.org/10.1038/s41386-022-01316-2.
92. Ossewaarde L, Verkes RJ, Hermans EJ, Kooijman SC, Urner M, Tendolkar I, et al. Two-Week Administration of the Combined Serotonin-Noradrenaline Reuptake Inhibitor Duloxetine Augments

Functioning of Mesolimbic Incentive Processing Circuits. Biol Psychiatry. 2011;70:568–574.
93. Lawn W, Hill J, Hindocha C, Yim J, Yamamori Y, Jones G, et al. The acute effects of cannabidiol on the neural correlates of reward anticipation and feedback in healthy volunteers. J Psychopharmacol. 2020;34:969–980.
94. Bechara A, Damasio AR, Damasio H, Anderson SW. Insensitivity to future consequences following damage to human prefrontal cortex. Cognition. 1994;50:7–15.
95. Wolpe J, Lazarus AA. Behavior therapy techniques: A guide to the treatment of neuroses. Elmsford, NY, US: Pergamon Press; 1966.
96. Wechsler D. Wechsler Memory Scale, 4th Edition. 4th ed. Pearson Assessments; 2009.
97. Delis DC, Kramer JH, Kaplan E, Ober BA. California Verbal Learning Test, 3rd Edition. 3rd ed. Pearson Assessments; 2017.
98. Berg EA. A Simple Objective Technique for Measuring Flexibility in Thinking. J Gen Psychol. 1948;39:15–22.
99. Milner B. Effects of Different Brain Lesions on Card Sorting. Arch Neurol. 1963;9:90.
100. Ware JE, Sherbourne CD. The MOS 3-item Short-Form Health Survey (SF-36). Med Care. 1992;30:473–483.
101. Frisch MB, Cornell J, Villanueva M, Retzlaff PJ. Clinical validation of the Quality of Life Inventory. A measure of life satisfaction for use in treatment planning and outcome assessment. Psychol Assess. 1992;4:92–101.
102. Cleeland CS, Ryan K. Pain Assessment: Global Use of the Brief Pain Inventory. Ann Acad Med Singapore. 1994;23:129–138.
103. Johns MW. A New Method for Measuring Daytime Sleepiness: The Epworth Sleepiness Scale. Sleep. 1991;14:540–545.
104. Haney M, Ward AS, Comer SD, Foltin RW, Fischman MW. Abstinence symptoms following smoked marijuana in humans. Psychopharmacology (Berl). 1999;141:395–404.
105. Haney M, Hart CL, Ward AS, Foltin RW. Nefazodone decreases anxiety during marijuana withdrawal in humans. Psychopharmacology (Berl). 2003;165:157–165.
106. Gachet MS, Rhyn P, Bosch OG, Quednow BB, Gertsch J. A quantitiative LC-MS/MS method for the measurement of arachidonic acid, prostanoids, endocannabinoids, N-acylethanolamines and steroids in human plasma. J Chromatogr B. 2015;976–977:6–18.

END APPLICANT RESPONSE

V-F Current and Prior Experience and Funding Disclosure

Current and prior experience in administering clinical trials is important to the selection process. Each applicant(s) must provide a copy of the organization's most recent audited financial statement and single audit (if applicable). The audited financial statement and single audit must be sent under separate cover.

Proposals submitted by applicant(s) should include:

(1) A description of the organization's experience in conducting the type of work proposed. Include current activities and activities for the previous ten years. Include project results.

(2) If applicant(s) received a similar grant award from the State of Michigan in prior years for the type of project proposed, provide a summary of project accomplishments. Include a plan for addressing and resolving past problems.

(3) Current funding source(s) and the level of funding for the current year and the previous ten years.

BEGIN APPLICANT RESPONSE

(1) Wayne State University is a premier, public, urban research university located in the heart of Detroit where students from all backgrounds are offered a rich, high-quality education. Our deep-rooted commitment to excellence, collaboration, integrity, diversity and inclusion creates exceptional educational opportunities preparing students for success in a diverse, global society. Founded in 1868, Wayne State University offers a range of academic programs through 13 schools and colleges to nearly 28,000 students. The campus in Midtown Detroit comprises 100 buildings over 200 acres including the School of Medicine, the Eugene Applebaum College of Pharmacy and Health Sciences and the College of Nursing. The university is home to the Perinatology Research Branch of the National Institutes of Health, the Karmanos Cancer Center, a National Cancer Institute-designated comprehensive cancer center, and a National Institute of Environmental Health Sciences Core Center - Center for Urban Responses to Environmental Stressors (CURES), which demonstrates our ability to successfully manage and lead large-scale initiatives.

The infrastructure for fiduciary responsibility is already well-established within Wayne State University. All finances and related account audits are expertly managed by Sponsored Programs Administration as this division manages the University's entire research portfolio. All human and animal model research, including safety regulations, is overseen by the university's Institutional Review Board, which would also apply its oversight to this research.

The team assembled as part of this proposal is situated at two primary sites on the campus of Wayne State in the heart of midtown Detroit: Tolan Park Medical Building and the Eugene Applebaum College of Pharmacy and Health Sciences building.

The Tolan Park Medical Building is centrally located near Detroit Medical Center and the John D. Dingell VA Medical Center. Free street-level parking is available adjacent to the Tolan Park building. The main entrance is staffed by a guard and all other entrances are locked. Entrance to office suites is gained via card swipe and visitors must be accompanied by staff escort. Tolan Park houses the Department of Psychiatry's Substance Abuse Research Division which currently conducts investigations of the pharmacological, environmental, and individual difference determinants of drug seeking/use, behavioral economic approaches to substance abuse and policy, novel medication and behavioral therapy trials in substance-using populations (e.g. HIV+, nicotine and opioid dependence, pregnant women, co-occurring psychiatric problems), screening and brief intervention using technological advances, epidemiologic studies in special populations, and health services research. Several experimental chambers are equipped with a specialized ventilation system to allow for smoked marijuana administration. The **Human Pharmacology Laboratory (HPL)** laboratory occupies half of the 2nd floor at Tolan Park, covering about 4,500 sq. ft. Co-PI Dr. Lundahl and Co-Investigators Dr. Ledgerwood and Dr. Greenwald have offices in this space. The Co-Investigator (Dr. Greenwald, who is Director of the Division and Laboratory) was directly involved in designing this modern space with the architects, ensuring appropriate security (WSU Police and DEA), and working with WSU Information Technology personnel to ensure computer capabilities, Ethernet connectivity, password-protected server access, etc.The HPL has 2 screening rooms, 5 private testing rooms (equipped with specialized HVAC negative-pressure system to allow smoking on-site), and a central monitoring room with computers and audio/visual (with digital-recording) equipment. Research assistants monitor participants throughout sessions. Test rooms are equipped with Macintosh computers coupled to the monitoring room. Other equipment includes physiological monitors, automated external defibrillator and a crash cart. There is a physical examination room with ECG, exam table, weighing scale, phlebotomy, and centrifuge. There is ample office and storage space for research support staff (e.g. receptionist, research/clinical assistants). Students occupy workstations in this space. There is also a confidential file locked storage room, locked supplies storage room, copier/mail room, common day (break) room with vending machine, and toilets. A locked DEA-compliant room located in the laboratory is used for drug storage (locked safe, freezer/refrigerator, -20°C freezer for storing biological samples) and handling/preparation (Dr. Greenwald holds DEA Schedule I and Schedule II-V Researcher licenses and Michigan state licenses for the laboratory and handling controlled substances). The **WarriorCARE Center**, new space designated to conduct our current, ongoing LARA/CRA-funded cannabis trial, is housed on the first floor of Tolan Park, and consists of a reception area, small kitchen, conference room, and

two private interview rooms for testing. All screening, baseline, treatment, post-treatment, and follow-up assessments (except for fear conditioning) will occur in the WarriorCARE Center and the Human Pharmacology Laboratory (HPL) at Tolan Park.

Dr. Rabinak's laboratory totals approximately 1,000 square feet of research-dedicated space, located at Wayne State University's Department of Pharmacy Practice in the Eugene Applebaum College of Pharmacy and Health Sciences building. Dr. Rabinak's laboratory and Wayne State's shared resources infrastructure have the resources required to perform all the work proposed in the study. Dr. Rabinak's office contains a stainless-steel medical grade refrigerator with a factory-installed keypad locking system, which contains class III-controlled substances. Dr. Rabinak currently holds Schedule II-V controlled substance research licenses with the State of Michigan and the Drug Enforcement Agency. The suite to Dr. Rabinak's office is accessible by a key given only to authorized staff. Others must be admitted from the inside by the staff. The hallways entrance to the suite is only accessible by key card and the hallways and office area are monitored with continuous closed circuit security cameras. Dr. Rabinak's office has been rekeyed to take it off the master key so that custodial, maintenance, and support staff do not have access. The research laboratory maintains the necessary computer infrastructure to carry out the proposed clinical assessments, behavioral testing/training, and data collection related to fMRI and psychophysiological research. Archival storage is done via high-speed networking to an external 30TB network drive with redundant backups; another onsite RAID array is available for high-speed local processing. The laboratory has hardware and software support necessary to analyze neuroimaging (e.g.,fMRI) and psychophysiological data. The laboratory is located on the 5th floor of the Eugene Applebaum College of Pharmacy and Health Sciences building, with at least 2 rooms available for subject testing and therapy sessions. There is a parking structure across the street and the Brady Street entrance to the College is staffed by a guard and visitors without proper ID must be escorted. The Mack Ave entrance and the loading dock area are always locked from the outside. There is one full-time study coordinator, one full-time research technologist, and one part-time research assistant available to escort and run subjects.

The Wayne State University Magnetic Resonance Research Facility (MRRF) (http://www.mrc.wayne.edu/index.php?site=home) (operational since 1987) is equipped with 100% research dedicated, high-field 3 Tesla Siemens Verio whole-body human MRI scanner capable of collecting high spatial resolution anatomical MRI images, fMRI data, diffusion tensor imaging, and multi-nuclear spectroscopy or MRS data (1H and 31P) as well as echo-planar spectroscopic imaging (EPSI) data. This system also has an industry leading 32-channel head coil for superior image quality. The MRRF center is in the Harper University Hospital, Department of Radiology and is directed by E. Mark Haacke.

In addition to the world class facilities of Wayne State University, the proposed study team has a long history of national and international collaborations with academic and medical "hubs" dedicated to cannabis research, including Johns Hopkins University and McLean Hospital/Harvard Medical School, University of Calgary, the Mental Health Service and PTSD Clinic at the Ann Arbor Veteran Affairs Healthcare System, and PTSD research including the National Center for PTSD, Emory Healthcare Veterans Program, as well as with government institutions such as the Department of Veterans Affairs Team Red White and Blue (Detroit Chapter; https://about.teamrwb.org/) and the Wayne State University Student Veterans Organization (https://omvae.wayne.edu/).

(2) Current and past State of Michigan funding for INVESTIGATORS on the Current Proposal

Leslie H. Lundahl, PhD

Active State of Michigan Support

Veteran Marijuana Research Grant Program, Cannabis Regulatory Agency, State of Michigan
Leslie Lundahl (Lead PI)
Title: Wayne State Warriors Marijuana Clinical Research Program: Investigating the Impact of

Cannabinoids on Veterans' Behavioral Health
Purpose: To investigate the effects of varying doses of THC and CBD on depression, anxiety, and PTSD with the goal of reducing suicide rates and improving behavioral health in US Military Veterans.
Role in Project: Lead PI
08/30/21 – 8/29/26
Total direct costs = $6,259,037

We received funding from the VMR/CRA in August, 2021 for our project, entitled "Wayne State Warriors Marijuana Clinical Research Program: Investigating the Impact of Cannabinoids on Veterans' Behavioral Health". In this randomized, controlled clinical trial we are recruiting veterans with PTSD who report using cannabis. **We are conducting two studies that are complementary and linked via their aims and methodology**. In **Study 1**, 200 veterans are 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 are assigned into *either* a naturalistic group (n=75) and are followed as they continue to use cannabis as they normally do (observation only), *or* into a "THC reduction group" (n=75) in which veterans are asked to switch from their typical cannabis product to using a lower THC/higher CBD product; adherence to this switch is 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 also includes 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) urine, 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.

Summary of Accomplishments/Progress
Since receiving this award we have been building the infrastructure needed to support the logistical operation of study related elements including participant recruitment and study visit mechanics. A significant amount of effort was dedicated to anticipating potential obstacles and identifying solutions to these obstacles. For example, cannabis products are not approved for use within the Department of Veterans Affairs (VA) at present which requires the study team to recruit Veteran participants from Detroit-area community-based organizations. We established contact with 15 Veterans groups including the Veterans of America, Michigan Veterans Affairs Agency, Veterans of Foreign Wars (VFWs) and several others to create a recruitment network capable of reaching Veterans either for whom cannabis is an existing treatment strategy or might be an attractive intervention for them to alleviate their symptoms of PTSD, depression, and suicidality. Recruitment documents including study flyers and informational brochures have been created, approved by our IRB and printed for advertising and distribution to these and other organizations. Social media and other advertising platforms to supplement recruitment have also been identified. We created a website (Warriorcare.net) which is dedicated to the research program where veterans and their families can get information about the studies, complete initial screening for eligibility, access other resources, and contact us. The website is near completion and should be up and running by May 31, 2022.

We obtained Departmental Review Board and University Institutional Review Board (IRB) approval for both studies. The clinical staff has completed training on how to administer all of the study-related measures and conduct the diagnostic interviews. We have created online versions (Qualtrics) of all questionnaires and measures so veterans can complete them online, and we have

set up a clinical trial tracking system for both studies.

Our safety plan is finalized and our Data Safety Monitoring Board (DSMB) has been established.

We have identified a cannabis administration device that will address concerns about potential diversion or use of more than the daily allotted amount (Study 1).

Protocol details relating to secondary outcomes have been finalized and include a system for endocannabinoid collection, processing, storage, and analysis, and coordination of the genotyping analyses at the WSU Genome Sciences Core (for genotype-phenotype associations).

We started recruitment for Study 2 in mid-May. We have scheduled several "meet and greets" with veterans organizations to occur in June and July, where we will present study information and display and distribute brochures to recruit participants. We plan to start recruitment for Study 1 at the end of June, 2022.

Summary of Obstacles/Mitigation Plans
NIDA Drug Supply Program, which has supplied cannabis flower for Dr. Lundahl's cannabis studies over the past 20 years, is not able to supply the THC:CBD concentrations in the quantities we need for the trial. Thus, we reached out to the other three federally-registered DEA Schedule I growers and found that we will likely not be able to obtain all four THC:CBD concentrations in the quantities needed from one grower and will have to work with more than one, which requires the submission of additional FDA IND applications. However, we are highly experienced with both FDA and DEA regulatory processes and do not anticipate any difficulties obtaining these additional INDs or filing the protocols with the DEA. We also are in discussions with a Michigan grower who is able to supply exactly what we need, and is interested in pursuing the certifications needed to become a federally-compliant research supplier. We have set up a "pre-IND" meeting with the grower's chemists and regulatory staff at the FDA, which is scheduled in June. While we recognize this is likely a lengthy process with no guarantee of success, we anticipate this clinical trial will take several years to complete and we may be able to use this MI grower toward the later part of the study.

David Ledgerwood, PhD

Active State of Michigan Support

Veteran Marijuana Research Grant Program, Cannabis Regulatory Agency, State of Michigan
Leslie Lundahl (Co-PI)
Title: Wayne State Warriors Marijuana Clinical Research Program: Investigating the Impact of Cannabinoids on Veterans' Behavioral Health
Purpose: To investigate the effects of varying doses of THC and CBD on depression, anxiety, and PTSD with the goal of reducing suicide rates and improving behavioral health in US Military Veterans.
Role in Project: Co-PI
08/30/21 – 8/29/26
Total direct costs = $6,259,037

Completed State of Michigan Support

Dani Meier (PI), Mid-State Health Network 10/2018 – 9/2019
Title: Michigan Gambling Disorder Prevention Project – FY19 Proposal Mid-State Health Network
Study Goals: To examine the prevalence of gambling disorder among youth and among substance abuse patients in Michigan.
Amount: Direct: $33,704

State of Michigan Department of Health, Bureau of Substance Abuse and Addiction Services David Ledgerwood (PI) 10/2012 – 9/2013
Title: Evaluation of the Clinical Need for Residential Treatment Services for Problem Gambling in Michigan
Study Goals: To evaluate the clinical need for residential treatment services for problem gambling in the State of Michigan
Role in project: PI

COMPLETED PROJECT WAS UNRELATED TO THE CURRENT PROPOSAL.

Mark Greenwald, PhD

Active State of Michigan Support

Veteran Marijuana Research Grant Program, Cannabis Regulatory Agency, State of Michigan
Leslie Lundahl (Lead PI)
Title: Wayne State Warriors Marijuana Clinical Research Program: Investigating the Impact of Cannabinoids on Veterans' Behavioral Health
Purpose: To investigate the effects of varying doses of THC and CBD on depression, anxiety, and PTSD with the goal of reducing suicide rates and improving behavioral health in US Military Veterans.
Role in Project: Lead PI
08/30/21 – 8/29/26
Total direct costs = $6,259,037

Michigan State University (Mark Greenwald, 10% effort over 2 years)
"MI CARES 2" (Michigan Collaborative Addiction Resources and Education System)
Purpose: Expand our online educational training curriculum (https://micares.msu.edu, currently for board-certified physicians only) to medical students interested in pursuing addiction medicine specialization.
Source: MDHHS State Opioid Response Grant, subcontract through Spectrum Health (PI: Cara Poland)
09/01/20 – 8/31/22
Total direct costs = $60,989

Completed State of Michigan Support

Michigan State University (Mark Greenwald, content expert, 10% effort over 2 years)
"*MI CARES 1*" (Michigan Collaborative Addiction Resources and Education System)
Purpose: Collaborate with 4-member expert team to develop an online educational training curriculum for physicians interested in pursuing addiction medicine specialization; available at https://micares.msu.edu
Source: SAMHSA grant 1H79TI081712 to MDHHS (State Opioid Response Grant), subcontract through Michigan State University
3/01/19 – 2/28/21
Total direct costs = $55,000

State of Michigan Opioid Management Project Award to Kids Kicking Cancer Goldberg (PI), Greenwald (local PI)
Title: The Heroes Circle Opioid Project
Purpose: Determine whether an intervention based on martial arts, relaxation and breathing exercises can help methadone-maintained patients (with opioid use disorder)

reduce their behavioral and physical dependence on methadone without increasing substance use.
08/01/2018-07/31/2019
Amount: $90,836 (WSU subcontract)

PROJECTS ARE/WERE UNRELATED TO THE CURRENT PROPOSAL.

(3) Current and past funding for INVESTIGATORS on the Current Proposal

Christine A. Rabinak, PhD

Active Research Support:

K23 MH125315
Role: Co-Mentor (PI: Reilly Kayser, MD)
Title: *"**Multimodal Assessment of Cannabinoid Target Engagement in Adults with Obsessive-Compulsive Disorder**."* Purpose: The purpose of this research study is to test how a medication called nabilone (Cesamet) affects neurocognitive processes involved in obsessive-compulsive disorder (OCD), including threat response, processing of fear signals, and habitual behavior.
Source: NIH/NIMH
07/01/21– 06/30/26
Total Direct Costs: $795,170

Role: Co-Investigator (PI: Hilary Marusak, PhD)
Title: *"**Effects of Urban Air Pollution on Neurodevelopmental Markers of Anxiety and Risk during Adolescence**."* Purpose: To test the hypothesis that adolescents with higher (vs. lower) recent PM2.5 exposure exhibit poor fear regulation and lower frontolimbic activation, which will in turn, be associated with higher anxiety.
Source: WSU CURES Pilot Project Program
10/01/21– 03/31/23
Total Direct Costs: $65,000

F30 DA052118
Role: Co-Mentor (PI: Tabitha Moses; Primary Mentor: Mark Greenwald, PhD)
Title: *"**Neuromodulation of Stress-Induced Dysfunction and Drug-Seeking in Opioid Use Disorder: Comparison of Fronto-Cortical Targets**."* Purpose: This project will explore whether repetitive transcranial magnetic stimulation (rTMS) might improve treatment outcomes for people with opioid use disorder entering methadone treatment.
Source: NIH/NIDA
05/01/21– 04/30/25
Total Direct Costs: $250,395

R01 DE031117
Role: Co-Investigator (MPI: Laura Seligman, PhD & Andrew Geers, PhD)
Title: *"**Identifying the Mechanism of Latent Inhibition to Prevent Dental Fear.**"* Purpose: Identify the mechanism(s) underlying the latent inhibition of dental fear, allowing for more precise engagement of these target(s), and to examine whether individual differences related to ethnicity that could help account for the disparities observed in oral health and dental fear, are related to the engagement of these targets.
Source: NIH/NIDCR
07/01/21– 06/30/24
Total Direct Costs: $1,165,137

R01 MH122867
Role: Co-Investigator (PI: Ann Rasmusson, MD)
Title: *"**Facilitation of Extinction Retention and Reconsolidation Blockade by IV Allopregnanolone PTSD**."* Purpose: This study tests whether a single intravenous (IV) dose of allopregnanolone (Allo) compared to placebo (which is non-active): promotes consolidation of extinction learning (sub-study 1) or blocks reconsolidation physiological responses triggered by aversive memories (sub-study 2). The study also tests whether Allo compared to placebo affects retention of non-aversive memories.
Source: NIH/NIMH
04/01/20– 03/31/25
Total Direct Costs: $882,879

F31 MH124279
Role: Primary Mentor (PI: Nicole Zabik)
Title: *"**Neural and Behavioral Mechanisms of Avoidance Behavior and its Impact on Fear Extinction in Adults with PTSD**."* Purpose: This study will test how avoidance impacts extinction of fear and its underlying brain mechanisms in an adult population.
Source: NIH/NIMH
09/01/20– 08/31/23
Total Direct Costs: $155,709

K01 MH11924
Role: Primary Mentor (PI: Hilary Marusak, PhD)
Title: *"**Endocannabinoid Signaling and the Development of Fear Extinction Recall during Adolescence**."* Purpose: The goal of this project is to evaluate in adolescents the novel hypotheses that: (1) fear extinction recall ability increases across adolescence, (2) age-related increases in extinction recall correspond with increased activation of hippocampus (HPC)-ventromedial prefrontal cortex (vmPFC) circuitry, and (3) higher blood levels of the eCB anandamide (AEA) correspond with better extinction recall and/or higher activation within HPC-vmPFC circuitry among adolescents.
Source: NIH/NIMH
04/01/19– 03/31/24
Total Direct Costs: $806,651

1IKRX002686
Role: Co-Mentor (PI: Veronica Chui, PhD; Primary Mentor: Alana Conti, PhD)
Title: *"**Comorbidity of PTSD and Alcohol Dependence: Endocannabinoid Regulation**."*
Purpose: 1) Evaluate the effects of traumatic stress and ethanol dependence on ethanol consumption and anxiety behavior as a function of ethanol withdrawal duration. 2) Examine changes in CB signaling associated with ethanol-induced withdrawal behaviors as a factor of withdrawal duration. 3) Evaluate the efficacy of a selective CB1 agonist, methanandamide, to block stress-induced ethanol dependence and withdrawal outcomes.
Source: Veteran Affairs Career Development Program
06/01/18– 05/31/23
Total Direct Costs: $721,346

R61/33 MH11193
Role: Primary Investigator
Title: *"**Effects of THC on Retention of Memory for Fear Extinction Learning in PTSD**."*
Purpose: The goal of the current proposal is to investigate the cannabinoid system as a potential pharmacological target for improving the learning that goes on in therapy and perhaps increasing efficacy and durability of exposure therapy in treating PTSD (e.g. shortening treatment while strengthening and prolonging gains).
Source: NIH/NIMH

02/24/17– 02/23/23
Total Direct Costs: $2,629,881

Completed Research Support:

New Investigator Grant Program
Role: Co-Investigator (PI: Hilary Marusak, PhD)
Title: *"**Impact of Adolescent Cannabis Use on Endocannabinoid Signaling and Emotion Regulation Neural Circuitry**."* Purpose: The pilot project tested the novel hypotheses that adolescent cannabis use is associated with increased risk of anxiety and SUDs via reduced activation and/or coupling within emotion regulation neural circuitry and low signaling of the eCB AEA.
Source: WSU Department of Psychiatry & Behavioral Neurosciences
10/01/20– 08/31/21
Total Direct Costs: $25,000

NARSAD Young Investigator Grant
Role: Principal Investigator
Title: *"**Effects of FAAH Genotype on Fear-Related Brain Activation during Fear Extinction**."*
Purpose: The primary objective is to determine whether FAAH genotype differences are evident at behavioral and neural levels during recall of extinction learning.
Source: Brain & Behavior Research Foundation
01/15/17– 07/14/19 [NCE]
Total Direct Costs: $70,000

PF-16-057-01-PCSM
Role: Primary Mentor (PI: Hilary Marusak, PhD)
Title: *"**Neurobehavioral Correlates of Learning and Memory in Child Cancer Survivors**."*
Purpose: The fellowship project was designed to identify neurobehavioral correlates of learning and memory in young (~ages 6-9) cancer survivors.
Source: American Cancer Society
07/01/16– 06/30/19
Total Direct Costs: $163,500

Women in Health and Medical Research
Grant Role: Consultant (PI: Izelle Labuschagne, PhD)
Title: *"**Epigenetic and hormonal influences on brain mechanisms underlying sex differences in human social behavior: a pilot study**."* Purpose: To examine sex-specific and environmental modulation of the amygdala (and related subregions and neural networks) and associations with epigenetic variations in the oxytocin receptor and variations in basal levels of oxytocin.
Source: Australian Catholic University
01/02/17– 01/02/19
Total Direct Costs: $52,000

#523497
Role: Co-Investigator (PI: Hilary Marusak, PhD)
Title: *"**Martial Arts Therapy and Brain Mechanisms for Cancer-Related Pain**."* Purpose: The project tested the hypothesis that Kids Kicking Cancer, a martial arts therapy program, can reduce pain and target its underlying neural mechanisms in young cancer patients and survivors.
Source: St. Baldrick's Foundation
07/01/17– 12/31/18 [NCE]
Total Direct Costs: $50,000

K01 MH101123
Role: Principal Investigator (Primary Mentor: Mark Greenwald, PhD)
Title: *"**Cannabinoid Control of Fear Extinction Neural Circuits in Post-Traumatic Stress***

***Disorder**."* Purpose: The objective of the proposed project is to test the hypotheses that administration of THC will enhance recall of fear extinction in patients with PTSD and that these effects will be mediated via increased activation and functional connectivity of the vmPFC and HPC.
Source: NIH/NIMH
04/01/14– 12/31/18 [NCE]
Total Direct Costs: $604,569

14-238-04-IRG
Role: Principal Investigator
Title: *"**Understanding Emotional Brain Network Organization in Survivors of Childhood Cancer**."* Purpose: The goal of the project was to identify neurobiological mechanisms associated with early cancer experience.
Source: Barbara Ann Karmanos Cancer Institute
09/01/16– 08/31/17
Total Direct Costs: $30,000

MICHR T2 Translational Science Award
Role: Principal Investigator
Title: *"**Neural Mechanisms Underlying Attentional Training in Social Anxiety Disorder**."* Purpose: The aims of the proposed study are to investigate: 1) Threat processing between social anxiety disorder (SAD) and healthy controls (HC); 2) Compare threat processing from pre- to post-attentional bias modification training in SAD; and 3) Effects of attentional bias modification training directionality (toward vs. away from threat) in SAD.
Source: Michigan Institute for Clinical & Health Related Research
02/01/14– 01/31/25
Total Direct Costs: $50,000

MICHR Postdoctoral Translational Scholars Program Award
Role: Principal Investigator (Primary Mentor: K. Luan Phan, MD)
Title: *"**Behavioral and Brain Mechanisms Underlying Recall of Fear Extinction Memory in Anxiety Disorders**."* Purpose: This translational research project specifically aims to assess the behavioral and brain mechanisms of fear extinction memory recall in healthy humans volunteers and determine whether extinction of fear responses is impaired in social anxiety disorder and whether such impairment is related to dysfunctional activation of brain regions known to be involved in recall of fear extinction memory (e.g. vmPFC, HPC).
Source: Michigan Institute for Clinical & Health Related Research
07/01/11– 06/30/13
Total Direct Costs: $100,000

Leslie H. Lundahl, PhD

Active Research Support

R21 DA047662
Role: Principal Investigator
Title: *"**Human Laboratory Model to Screen Drugs with Opioid Analgesic-Sparing Effects: Cannabidiol/Morphine Combinations**."* Purpose: The objective of this study is to develop a rigorous human laboratory paradigm to evaluate potential opioid-sparing compounds that could lead to medications that reduce reliance on chronic use of high dose opioid medications for safer and more effective pain relief.
Source: NIH/NIDA
03/01/19– 02/28/23 (NCE)
Total Direct Costs: $275,000

R21 DA040150
Role: Principal Investigator
Title: *"**Effects of Stress- and Drug Cue-Exposure on Craving and Marijuana Seeking Behavior in Regular Cannabis Users**."* Purpose: To understand cue- and stress-induced cannabis abuse to effectively target these risk factors for intervention, we propose to investigate subjective, physiologic, and endocrine responses to a pharmacologic stressor combined with drug-related cues in chronic cannabis users, and examine additive effects on marijuana craving and seeking.
Source: NIH/NIDA
5/01/17 – 05/31/22 (NCE)
Total Direct Costs: $275,000

R01 DA044946-02
Role: Co-Investigator (PI: Mark Greenwald, PhD)
Title: *"**Opioid/Benzodiazepine Polydrug Abuse: Integrating Research on Mechanisms, Treatment and Policies**."* Purpose: (1) Determine from behavioral health treatment records prevalence of patients' presenting BZD/opioid PSU vs. BZD or opioid use alone, and relationships between drug use and psychiatric/physical comorbidities, medications, demographics, and treatment outcomes; (2) Among patients, characterize substance use and deficits in affective, neurocognitive, behavioral, and health function; (3) Determine whether simultaneous vs. concurrent BZD/opioid users differ in affective phenotypes, neurocognitive and behavioral measures.
Source: NIH/NIDA
Proposed funding period: 09/01/18 –08/31/23
Total direct costs = $1,684,808

Completed Research Support

R01 DA015462-09A1
Role: Co-Investigator (PI: Mark Greenwald, PhD)
Title: ***"Biobehavioral Studies of Opioid Seeking: Effects of Buprenorphine/Naloxone Dose on Experimental Stress Reactivity and Opioid Abstinence."*** Purpose: In this 3rd funding cycle, determine in volunteers with opioid use disorder whether: (1) short-term maintenance on buprenorphine/naloxone dose-dependently attenuates biobehavioral responding to an experimental pharmacological stressor (yohimbine/hydrocortisone), and (2) stressor reactivity predicts opioid abstinence during and up to 3 months after outpatient buprenorphine/naloxone dose tapering.
Source: NIH/NIDA
9/30/16 – 7/31/20 (NCE)
Total Direct Costs: $1,500,491

R21 DA040770
Role: Principal Investigator
Title: ***"Marijuana Cue-Reactivity and Seeking Behavior in Regular Cannabis Users: Pilot Test of Glutamatergic Modulation."*** Purpose: Determine whether: (1) marijuana cues increase marijuana puff-seeking behavior, and whether craving moderates this effect, (2) N-acetylcysteine, relative to placebo, attenuates marijuana cue-reactivity or drug seeking.
Source: NIH/NIDA
08/15/16 – 07/31/19 (NCE)
Total Direct Costs: $247,000

R01 DA034537
Role: Co-investigator (PI: David Ledgerwood, PhD)
Title: ***"Behavioral Treatments for Smoking Cessation in HIV."*** Purpose: This clinical trial will test the efficacy of prize-based contingency management for promoting smoking reduction and cessation, using urinary cotinine and expired carbon monoxide as behavioral targets.
Source: NIH/NIDA

9/1/13-8/31/17 (NCE)
Total Direct Costs: $1,268,634

R01 DA032678
Role: Co-investigator (PI: Mark Greenwald, PhD)
Title: ***"Behavioral Economic Analysis of Medical Marijuana Use in HIV+ Patients."*** Purpose: Remediate knowledge and policy gaps related to medical marijuana use by studying subgroups of marijuana-using HIV/AIDS patients (certified medical users, non-certified therapeutic users and recreational users) in Michigan's largest HIV primary care clinic with a prospective mixed-method approach that uses behavioral-economic simulations of marijuana demand, longitudinal health monitoring, and probability survey procedures.
Source: NIH/NIDA
9/15/11– 6/30/16
Total Direct Costs: $1,019,851

2 R01 DA015462
Role: Co-investigator (PI: Mark Greenwald, PhD)
Title: ***"Biobehavioral Studies of Opioid Drug-Seeking Behavior."*** Purpose: Determine the neurochemical mechanisms of stress-potentiated opioid-seeking and biobehavioral responses.
Source: NIH/NIDA
09/30/11– 11/30/15
Total Direct Costs: $751,403

R01 DA026761Role: Principal Investigator
Title: ***"Smoked Marijuana Discrimination and Marijuana Choice in Humans: A Laboratory Model."*** Purpose: To develop and test a laboratory model of smoked marijuana discrimination and choice to self-administer marijuana for testing medications for treatment of cannabis use disorders.
Source: NIH/NIDA
7/2009 – 6/30/12
Total Direct Costs: $500,000

1P30 NR010676-01
Role: Co-investigator (PI: Shirley Moore, PhD (School of Nursing, Case Western Reserve University)
Title: ***"Center of Excellence to Build the Science of Self-Management: A System Approach"***
Project: "Parenting of Young Children By Women in Substance Abuse Treatment" (Project PI: Linda Lewin, Wayne State University School of Nursing)
Source: NIH/National Institute of Nursing Research
1/01/10– 9/30/12
Total Direct Costs: $450,648 (for 2012)

R01 DA026861
Role: Co-investigator (PI: Mark Greenwald, PhD)
Title: ***"Human Laboratory Model of Cocaine Treatment: Behavioral Economic Analysis."*** Purpose: Determine the extent to which the magnitude and probability of non-drug positive reinforcement attenuates cocaine demand elasticity.
Source: NIH/NIDA
8/01/09 – 10/31/12
Total Direct Costs: $890,000

David Ledgerwood, PhD

Active Research Support

R61HL155793-01 NIH/NHLBI P Cunningham (MUSC, MPI), Sylvie Naar (FSU, MPI) 4/30/2021 -4/30/2023
Title: Clinical Trial of the Fit Families Multicomponent Obesity Intervention for African American American Adolescents and Their Caregivers: Next Step from the ORBIT Initiative (Co-Investigator)
Study Goals: To develop and test a behavioral intervention designed to increase physical activity, diet monitoring and weight loss among teens and their primary caregivers.
Role in project: Co-PI
Amount: Direct $535,121 – all sites

R01CA243910 NIH/NCI E.J. Edelman (MPI), S. Bernstein (Yale; MPI) 9/18/2019-8/30/2024
Title: A SMART Approach to Treating Tobacco Use Disorder in Persons Living with HIV
Study Goals: To use a tailored smart design study to examine the efficacy of combined medication (NRT, varenicline) and behavioral treatment (contingency management) for smoking cessation among people living with HIV.
Role in project: Consultant

R01MD011322 NIH/National Institute on Drug Abuse P.I.(Co): D. Ledgerwood (Co-PI) P. Cunningham (Co-PI) 8/2016 – 9/2021
Title: Behavioral Incentives to Increase Caregiver Engagement in Juvenile Drug Court
Study Goals: To assess the efficacy of adolescent and caregiver contingency management treatments for enhancing adherence to Juvenile Drug Court and substance
Role in project: Co-PI
Amount: Direct: $149,022 – Wayne State University amount

Veteran Marijuana Research Grant Program, Cannabis Regulatory Agency, State of Michigan Leslie Lundahl (Co-PI)
Title: Wayne State Warriors Marijuana Clinical Research Program: Investigating the Impact of Cannabinoids on Veterans' Behavioral Health
Purpose: To investigate the effects of varying doses of THC and CBD on depression, anxiety, and PTSD with the goal of reducing suicide rates and improving behavioral health in US Military Veterans.
Role in Project: Co-PI

Completed Research Support

MGRP-LG-15-13 Manitoba Gambling Research D. Ledgerwood (MPI), L. Najavits (Boston U; MPI)
12/2015 – 9/2021
Title: Online Coping Skills Counseling for Problem Gambling and Trauma
Role in project: MPI
Amount: Direct: $449,999 CDN

R21 CA222939-01A1 C. Kopetz (PI)
Title: Intermittent and Daily Smoking: A Comparison Between Mechanisms
Study Goals: To investigate the role of social sues compared to smoking cues on smoking-relevant outcomes in intermittent and daily smokers.
Role in project: Co-PI
Amount: Direct: $275,000

R01DA034537-01A1 NIH/National Institute on Drug Abuse David Ledgerwood (PI) 8/2013 – 7/2019
Title: Behavioral Treatments for Smoking Cessation in HIV
Study Goals: To assess the efficacy of contingency management treatments for smoking

cessation in individuals receiving treatment for HIV. We also propose evaluating a stepped care model to provide appropriate levels of care based on initial treatment response.
Role in project: PI
Amount: Direct: $1,109,615

Dani Meier (PI), Mid-State Health Network 10/2018 – 9/2019
Title: Michigan Gambling Disorder Prevention Project – FY19 Proposal Mid-State Health Network
Study Goals: To examine the prevalence of gambling disorder among youth and among substance abuse patients in Michigan.
Amount: Direct: $33,704

Level IV (Approved) Ontario Problem Gambling Research Centre David Ledgerwood (PI) 10/2011 – 9/2016
Title: Effectiveness of Cognitive-Motivational Behaviour Therapy in Community Treatment
Study Goals: To examine the effectiveness of a combined CBT/MI treatment approach for pathological gambling administered by community-based therapists.
Role in project: PI
Amount: Total Direct: $508,109

U01HL097889 NIH/NHLBI Sylvie Naar-King (PI) 9/2009 – 6/2014
Title: Intervention Procedures for Adherence to Weight Loss Recommendations in Black Adolescents
Study Goals: To develop interventions to address obesity in adolescents, and to examine the efficacy of these interventions.
Role in project: Co-PI (20% in Year 1; 5% subsequent years; Project Lead for Pilot study of Contingency Management for weight loss in obese adolescents)

State of Michigan Department of Health, Bureau of Substance Abuse and Addiction Services David Ledgerwood (PI) 10/2012 – 9/2013
Title: Evaluation of the Clinical Need for Residential Treatment Services for Problem Gambling in Michigan
Study Goals: To evaluate the clinical need for residential treatment services for problem gambling in the State of Michigan
Role in project: PI
Amount: Total Direct: $43,318

R01 DA026861 NIH/NIDA Mark Greenwald (PI) 7/2009 – 6/2012
Title: Human Laboratory Model of Cocaine Treatment: Behavioral Economic Analysis
Study Goals: Determine the extent to which non-drug alternatives (positive reinforcement and punishment), combined with novel medications, attenuate cocaine demand elasticity.
Role in project: Co-PI (10%)

R01 DA026761-01 NIH/NIDA Leslie Lundahl (PI) 7/2009 – 6/2012
Title: Smoked Marijuana Discrimination and Marijuana Choice in Humans: A Laboratory Model
Study Goals: To develop and test a laboratory model of smoked marijuana discrimination and choice to self-administer marijuana for testing medications for treatment of cannabis use disorders.
Role in project: Co- PI (10%)

Mark K. Greenwald, PhD

Active Research Support

Mark Greenwald (PI, 30% effort)

"*NET Device as a Non-Pharmacological Alternative to Medication for Promoting Opioid Abstinence*"
Purpose: This prospective, randomized, sham-controlled, quadruple-blind, superiority clinical trial will evaluate the effectiveness of NeuroElectric Therapy (NET) in treating patients with opioid use disorder.
Source: NET Recovery Corp. (contract)
Funding period: 10/01/21 – 11/30/23
Total direct costs = $353,075 (total = $466,060)

Erin Fanning Madden (Contact PI) and Mark Greenwald (Co-PI, 7% effort over 3 years)
"*Planning a Multi-Level Intervention to Reduce Substance Use Stigma in HIV Prevention and Care*"
Purpose: (1) Create a substance use educational curriculum for HIV care and prevention contexts that pilot testing demonstrates will significantly improve knowledge, attitudes and planned actions related to professional stigma toward people who use drugs; (2) Use qualitative interviews with facility administrators and personnel to identify organizational policies related to clinical interactions and referrals to substance use services that may enhance the effects of professional education on stigma reduction; (3) Develop, optimize, and finalize a trial design and protocol that will test how the multi-level stigma intervention influences intermediate professional and patient stigma outcomes (provider attitudes and actions, and patient attitudes and experiences) and principal HIV outcomes related to prevention (PrEP adherence and syringe services program use) and care (HCV screening and linkage to care, ARV adherence).
Source: NIDA R34 DA053758
Funding period: 09/30/21 – 07/31/24
Total direct costs = $469,919

Mark Greenwald (Contact PI, 22% effort) and Cynthia Arfken (Co-PI)
"*Opioid/Benzodiazepine Polydrug Abuse: Integrating Research on Mechanisms, Treatment and Policies*" (Phase 2 continuation)
Purpose: Determine in BZD/opioid PSU whether: (a) substance abuse severity among BZD/opioid users influences affective dysregulation, neurocognition, and behavioral phenotypes including more lifetime drug-use consequences, and greater price-inelasticity for opioid and BZD using behavioral economic simulation methods; (b) experimental drug administration of alprazolam/morphine vs. either drug alone or placebo, will differentially alter affective/hedonic phenotypes in three informative behavioral choice procedures.
Source: NIH/NIDA R33 DA044946
Funding period: 09/01/21 – 08/31/24
Total direct costs = $1,246,575 (total = $1,868,751)

Leslie Lundahl (PI)
Role: Co-Investigator (10% effort)
"Wayne State Warriors Marijuana Clinical Research Program: Investigating the Impact of Cannabinoids on Veterans Behavioral Health"
Purpose: Examine the use of cannabinoids (THC and CBD) for reducing PTSD and suicidality in military veterans using clinical trial and laboratory-based approaches.
Source: Michigan Department of Licensing and Regulatory Affairs (LARA) – Veteran Marijuana Research (VMR) Program
Funding period: 08/31/21–07/31/26
Total costs: $6,259,037

Michigan State University (Mark Greenwald, content expert, 5% effort over 2 years)
"*MI CARES 2*" (Michigan Collaborative Addiction Resources and Education System)
Purpose: Expand our online educational training curriculum (https://micares.msu.edu, currently for board-certified physicians only) to medical students interested in pursuing addiction medicine specialization;
Source: MDHHS State Opioid Response Grant, subcontract through MSU (PI: Cara Poland)
Funding period: 09/01/20 – 8/31/22
Total direct costs = $60,989

Mark Greenwald (PI; 2% effort)

"*Effects of Pharmacological Stress and rTMS Interventions on Executive Function in Opioid Use Disorder*"
Purpose: (1) Evaluate how stress impacts domains of behavior including (1a) executive function and (1b) opioid-seeking behavior; and (2) Determine whether rTMS stimulation attenuates (2a) executive dysfunction, (2b) stress-reactivity, and (2c) opioid-seeking in individuals with OUD.
Source: Peter F. McManus Charitable Trust
Funding period: 01/01/20 – 04/30/23
Total costs = $74,977

Mark Greenwald (Contact PI; 22% effort) and Timothy Roehrs (HFHS), Co-PIs
"*Dual Orexin Antagonism as a Mechanism for Improving Sleep and Drug Abstinence in Opioid Use Disorder*"
Purpose: Determine whether daily treatment with a dual OX-1/2 receptor antagonist, relative to placebo, can improve outpatient opioid abstinence (Aim 1), improve inpatient sleep efficiency (Aim 2), and whether improved sleep efficiency predicts increased opioid abstinence (Aim 3) among patients with opioid use disorder.
Source: NIH/NHLBI U01 HL150551
Funding period: 09/23/19 – 08/31/23
Total direct costs = $3,533,857

Christine Rabinak, PI (WSU Dept. of Pharmacy Practice)
Role: Co-Investigator, 5% effort (1% effort during NCE)
"*Effects of THC on Retention of Memory for Fear Extinction Learning in PTSD*". Purpose: (1) Assess effects of THC on extinction memory recall and brain activation, and (2) Determine whether an optimal THC dose will reduce PTSD symptom severity and increase between-session extinction during prolonged exposure therapy.
Source: NIH/NIMH R61/R33 MH111935
Funding period: 02/01/17 – 01/31/23 (NCE)
Total costs: $3,813,623

Completed Research Support

Tabitha Moses, PI (graduate student)
Role: Mentor
"Impact of rTMS of Limbic Circuitry in Stress Modulation in a Healthy Population"
Purpose: Establish the impact of repetitive transcranial magnetic stimulation (rTMS) on cognitive, behavioral and physiological measures affected by a pharmacological stressor in healthy volunteers, to plan programmatic studies focusing on populations with substance use disorder. Aims: (1) Determine during sham rTMS how pharmacological stress alone: (1a) affects performance across domains of impulsivity, (1b) alters affective state, and (1c) increases stress-related biomarkers; and (2) Determine whether active rTMS over the medial prefrontal cortex (mPFC) alters the effects of pharmacological stress-exposure on (2a) decision-making, (2b) mood, and (2c) biomarkers of stress.
Source: Departmental funding
10/01/19 – 09/30/21
Total direct costs = $23,439

Mark Greenwald (Contact PI, 10% effort in R21 years) and Cynthia Arfken (Co-PI)
"*Opioid/Benzodiazepine Polydrug Abuse: Integrating Research on Mechanisms, Treatment and Policies*".
Purpose: (1) Determine from behavioral health treatment records the prevalence of patients' presenting BZD/opioid PSU vs. BZD or opioid use alone, and relationships between drug use and psychiatric (primarily affective) and physical comorbidities, medications, demographics, and treatment outcomes; (2) Among newly admitted patients, characterize substance use pattern and assess deficits across domains (affective, neurocognitive, behavioral, health); (3) Determine in BZD/opioid PSU whether: (a) at baseline, simultaneous vs. concurrent BZD/opioid users exhibit different profiles on affective phenotypes, and on neurocognitive, and behavioral measures including more lifetime drug-use consequences, and greater

price-inelasticity for opioid and BZD using behavioral economic simulation methods; (b) experimental drug administration of alprazolam/morphine vs. either drug alone or placebo, will differentially alter affective/hedonic phenotypes in 3 different behavioral choice procedures.
Source: NIH/NIDA R21 DA044946
09/30/18 –08/31/21 (NCE)
Total direct costs = $416,454

Mark Greenwald (PI, 30% effort)
"*Biobehavioral Studies of Opioid Seeking: Effects of Buprenorphine/Naloxone Dose on Experimental Stress Reactivity and Opioid Abstinence*".
Purpose: In this 3rd funding cycle, determine in volunteers with opioid use disorder whether short-term maintenance on buprenorphine/naloxone dose-dependently attenuates biobehavioral responding to an experimental pharmacological stressor.
Source: NIH/NIDA 2 R01 DA015462-09A1
09/30/16 – 07/31/21 (NCE)
Total direct costs: $1,500,491

Leslie Lundahl, PI
Role: Co-investigator, 5% effort
"*Human Laboratory Model to Screen Drugs with Opioid Analgesic-Sparing Effects: Cannabidiol/ Morphine Combination*s"
Purpose: Develop a human experimental model to assess drugs that may enhance the analgesic effects of opioids, so that lower doses of opioids may be used for pain relief.
Source: NIH/NIDA R21 DA047662
02/01/19 – 01/31/21 (NCE)
Total direct costs = $275,000

Leslie Lundahl, PI
Role: Co-Investigator, 5% effort
"*Effects of Stress- and Drug Cue-Exposure on Marijuana Seeking Behavior in Regular Cannabis Users*".
Purpose: Determine in marijuana users whether yohimbine pretreatment and drug-related cues increase marijuana-seeking behavior.
Source: NIH/NIDA R21 DA040150
03/23/17 – 03/22/19 (NCE)
Total direct costs = $275,000

Mark Greenwald, PI, 3.5% effort
"*Heroes Circle Opioid Project*"
Purpose: Determine whether an intervention based on martial arts, relaxation and breathing exercises can help methadone-maintained patients (with opioid use disorder) reduce their behavioral and physical dependence on methadone without increasing substance use.
Source: State of Michigan award to Kids Kicking Cancer; subcontract
07/01/18 – 09/30/19
Total costs = $90,836

Christine Rabinak, PI (WSU Dept. of Pharmacy Practice)
Role: Mentor; in-kind effort
"Effects of FAAH Genotype on Fear-Related Brain Activation During Fear Extinction". Purpose: Determine whether fatty acid amide hydrolase (FAAH) genetic variability is evident at behavioral and neural levels during recall of extinction learning, and might contribute to the cause of PTSD in humans via effects on brain endocannabinoid levels.
Source: NARSAD Young Investigator Award
01/15/17 – 01/14/19
Total direct costs: $70,000

Leslie Lundahl, PI
Role: Co-investigator, 5% effort
"*Marijuana Cue-Reactivity and Seeking Behavior in Regular Cannabis Users: Pilot Test of Glutamatergic Modulation*". Purpose: Determine whether: (1) marijuana cues increase marijuana puff-seeking behavior, and whether craving moderates this effect, (2) N-acetylcysteine, relative to placebo, attenuates marijuana cue-reactivity or drug seeking.
Source: NIH/NIDA R21 DA040770
08/15/16 – 07/31/18
Total direct costs = $247,000

Mark Greenwald [in-kind effort] and Angela Tiura, Project Co-PIs
"*Physical Activity in Minority Youth: Effects on Eating, Cognition, and Metabolism*". Purpose: Determine whether exercise (vs. sedentary condition) produces intensity-dependent alterations in: (1) sympathetic, metabolic, and inflammatory biomarkers, and appetite ratings; (2) executive function; (3) palatable food choices and rate of food intake; and (4) coupling between peri-exercise measures of metabolism and appetite and post-exercise measures of cognitive function, food choice and intake.
Source: WSU Diabetes and Obesity Team Science (WSU-DOTS), funded by WSU Office of Vice President for Research
03/01/16 – 09/30/18
Total direct costs = $65,000

David Ledgerwood, PI
Role: Co-investigator, 5% effort
"*Behavioral Smoking Cessation Treatment for People Living with HIV/AIDS*". Purpose: This clinical trial will test the efficacy of prize-based contingency management for promoting smoking reduction and cessation, using urinary cotinine and expired carbon monoxide as behavioral targets.
Source: NIH/NIDA R01 DA034537
09/01/13 – 08/31/18
Total direct costs: $1,268,634

Eric Woodcock [PhD student], PI
Role: Mentor, in-kind effort
"*Neuropharmacological Investigation of Frontostriatal Network Function and Nicotine Seeking Behavior in Current Smokers*". Purpose: Determine whether a pharmacological stressor (yohimbine + hydrocortisone) relative to placebo will induce biobehavioral stress-responses, disrupt dorsolateral prefrontal cortical (dlPFC) control of reward-network regions during smoking cues, impair dlPFC-dependent memory, and increase nicotine-seeking/self-administration.
Source: NIH/NIDA F31 DA040369
04/01/16 – 03/30/18 (terminated earlier than original award end date, as Dr. Woodcock completed and left for postdoctoral fellowship at Yale starting 07/31/17).
Total direct costs: $39,988

Mark Greenwald [in-kind effort] and Sylvie Naar, Project Co-PIs
"*Relative Reinforcing Value (RRV) of Food in African American Adolescents: Behavioral Choices, Neurocognition, and BMI*. Purpose: Investigate behavioral economic determinants of overeating palatable foods by assessing: (1) parental food budgeting; (2) adolescent food choices as a function of stress; and (3) adolescent delay discounting of palatable food and brain circuitry (fMRI) involved in food choice.
Source: WSU Diabetes and Obesity Team Science (WSU-DOTS), funded by WSU Office of Vice President for Research
12/01/13 – 03/31/16
Total direct costs = $75,000

Jon-Kar Zubieta and Scott Peltier (Univ. of Michigan) and Mark Greenwald, Co-PIs, 10% effort in years 1-2 and 20% effort in years 3-5
"*Development and Use of rtfMRI for Self-Control of Nicotine Craving*". Purpose: Develop real-time

functional MRI and analytical capability to evaluate nicotine-dependent subjects' ability to control cigarette craving.
Source: NIH/NIDA R21/R33 DA026077
10/01/08 – 06/30/14
Total direct costs for R21 portion (all revenue in years 1-2) and WSU subcontract, respectively: $400,000 and $27,000; total direct costs for R33 portion (all revenue in years 3-5) and WSU subcontract, respectively: $1,200,000 and $81,000.

Mark Greenwald, PI, 15% effort
"*Biobehavioral Studies of Opioid Seeking Behavior*". Purpose: In this 2nd funding cycle, determine the neurochemical mechanisms of stress-potentiated opioid-seeking and biobehavioral responses.
Source: NIH/NIDA 2 R01 DA015462
09/30/11 – 11/30/15
Total direct costs: $751,403

Mark Greenwald, PI, 20% effort
"*Behavioral Economic Analysis of Medical Marijuana Use in HIV+ Patients".* Purpose: Remediate knowledge and policy gaps related to medical marijuana use by studying subgroups of marijuana-using HIV/AIDS patients (certified medical users, non-certified therapeutic users and recreational users) in Michigan's largest HIV primary care clinic with a prospective mixed-method approach that uses behavioral-economic simulations of marijuana demand, longitudinal health monitoring, and probability survey procedures.
Source: NIH/NIDA R01 DA032678
09/15/11 – 06/30/16
Total direct costs: $1,019,851

Jon-Kar Zubieta, PI, University of Michigan
Role: Co-investigator, 5% effort
"*Predicting Placebo Responses Across Disease States*". Purpose: Determine the contribution of specific brain regions and neurotransmitter systems, measured with a combination of functional and molecular imaging techniques, to variation in placebo responses across disease processes (major depression and nicotine dependence).
Source: NIH/NIMH R01 MH086858
09/16/09 – 06/30/13
Total direct costs overall and WSU subcontract, respectively: $820,566 and $72,000

Jon-Kar Zubieta, PI, University of Michigan
Role: Co-investigator, 10% effort
"*Interaction of Smoking and Chronic Pain at Neurochemical & Phenotypic Levels*". Purpose: Determine the effects of chronic pain and nicotine dependence on neurochemical (endogenous opioid and dopamine release) and behavioral responses to experimental pain.
Source: NIH/NIDA R01 DA027494
09/01/09 – 02/28/13
Total direct costs overall and WSU subcontract, respectively: $2,682,000 and $137,297

Mark Greenwald, PI, 35% effort
"*Human Laboratory Model of Cocaine Treatment: Behavioral Economic Analysis*". Purpose: Determine the extent to which the magnitude and probability of non-drug positive reinforcement attenuates cocaine demand elasticity.
Source: NIH/NIDA R01 DA026861 (funded under the American Recovery and Reinvestment [ARRA] Act.)
08/01/09 – 10/31/12
Total direct costs: $890,000

Leslie Lundahl, PI
Role: Co-investigator, 5% effort

"*Smoked Marijuana Discrimination and Marijuana Choice in Humans: A Laboratory Model*". Purpose: Determine whether marinol (oral THC) dose-dependently reduces the discriminative stimulus effects of smoked marijuana in cannabis abusers.
Source: NIH/NIDA R01 DA026761
07/01/09 – 06/30/12
Total direct costs: $500,000

Virginia Delaney-Black, PI
Role: Co-investigator, 5% effort
"*Teens at Risk: Prenatal Cocaine and Postnatal Challenges*". Purpose: To continue a prospective, longitudinal study to measure the impacts of prenatal cocaine exposure, socio-environmental factors and emotional regulation on late-teen (16.5–18 years old) risky behaviors of drug use, sexual activity, and delinquency.
Source: NIH/NIDA R01 DA022419
07/01/08 – 06/30/14
Total direct costs: $2,309,751

Hilary Marusak, PhD

Active Research Support:

K01 NIH MH119241 Marusak (PI) 07/01/2019-06/30/2024
Title: Endocannabinoids and the development of extinction recall neural circuitry in adolescents
This study characterizes age-related changes in extinction recall, frontolimbic activity, and endocannabinoid signaling across adolescence (ages 10-17).
Amount: $871,180 (total costs)
Role in project: Principal Investigator

R01 NIH MH111682 Jovanovic (PI) 09/23/2016-6/30/2022 NCE
Title: Impact of Trauma Exposure on Critical Periods in Brain Development and Fear Processing in Children
This longitudinal study will examine the timing and duration of trauma exposure in children ages 9-11.
Role in project: Co-Investigator
Amount: $389,424 (R01 MH111682-01); $110,599 (Supplement: R01 MH111682_03S1)

R01 NIH DE031117 Seligman and Geers (Co-PIs) 07/01/2021-06/30/2024
Title: Mechanisms of latent inhibition as a proactive interference for preventing dental anxiety.
The purpose of this project is to identify the mechanism(s) underlying the latent inhibition of dental fear, allowing for more precise engagement of these target(s).
Role in project: Site Lead and Study Co-Investigator
Amount: $76,242 (WSU Subcontract)

The Children's Foundation, Pediatric Research Grant
R1-2022-72
Marusak and Luat (MPI)
Effects of cannabidiol on anxiety and behavioral problems among children with epilepsy (year 2)
01/01/2022-12/31/2022
This prospective observational study will track seizure frequency, anxiety symptoms, and behavioral problems among pediatric epilepsy patients who are newly started on CBD (Epidiolex).
Role: Co-Principal Investigator
Amount: $65,000 (total costs)

WSU Office of the Provost Social & Behavioral Determinants of Health Research Stimulus

Program
Marusak and Barcelona (Co-PIs) 07/01/2021-06/30/2022
Title: Behind the “runner’s high”: Endocannabinoid levels as a potential mediator of the beneficial effects of exercise on cognitive performance and mental health in youth
This pilot study tests the impact of acute exercise on circulating endocannabinoid concentrations, anxiety, mood, and cognitive performance in children and adolescents.
Role in project: Co-Principal Investigator
Amount: $20,000

WSU P30ES020957 Center for Urban Responses to Environmental Stressors (CURES), Pilot Grant
Marusak (PI) 10/01/2021-03/31/2023
Title: Effects of urban air pollution on neurodevelopmental markers of anxiety risk during adolescence
This study examines the impact of particulate matter air pollution on fear extinction, frontolimbic brain circuitry, and anxiety symptoms in adolescents
Role: Principal Investigator
Amount: $65,000 (total costs)

Richard Barber Interdisciplinary Research Grant
Marusak and Barcelona (MPI) 05/01/2022-08/01/2022
Title: Mindfulness meditation: A brain booster in youth
This pilot study evaluates the impact of a brief meditation session on endocannabinoid concentrations, anxiety, mood, and cognitive performance in children and adolescents.
Amount: $20,000 (total costs)

Wayne State University P50 Center MD017351 ACHIEVE GreatER Pilot Grant
Hicks (PI) 3/1/2022-2/28/2024
Screening for social risks and health: The role of stress reduction
This pilot study will evaluate whether a community resource navigator (vs. resource pamphlet) can reduce social determinants of health and perceived stress in African Americans at high risk of cardiovascular disease.
Role: Co-Investigator
Amount: $40,000 (total costs)

Completed Research Support:

The Children’s Foundation Pediatric Research Grant R1-2021-31 Marusak (PI) 02/08/2021-12/31/2021
Title: Effects of cannabidiol on anxiety and behavioral problems among children with epilepsy
This prospective observational study will track seizure frequency, anxiety symptoms, and behavioral problems among pediatric epilepsy patients who are newly started on CBD (Epidiolex).
Role in project: Co-Principal Investigator
Amount: $57,575 (total costs)

American Public Health Association NVDRS New Investigator Award Marusak (PI) 4/23/2021-4/30/2022
Title: Youth firearm-related deaths in the United States
Role in project: Principal Investigator
Amount: $6,500

WSU Dept. of Psychiatry and Behavioral Neurosciences New Investigator Grant Marusak (PI) 10/1/2020-8/31/2021
Title: Impact of adolescent cannabis use on endocannabinoid signaling and emotion regulation neural circuitry

Role in project: Principal Investigator
Amount: $25,000

Kids Kicking Cancer Marusak (Local PI) 11/01/2019-10/31/2020
Title: The Heroes Circle – Children Healing Children
This project examines the impact of a novel martial arts-based school curriculum (vs. a standard control socioemotional development curriculum) on stress, anxiety, and behavioral problems in elementary school children (Year 2).
Role in project: Local Principal Investigator
Amount: $68,819 (WSU subcontract)

State of Michigan Opioid Management Project Award to Kids Kicking Cancer Goldberg (PI), Greenwald (local PI) 08/01/2018-07/31/2019
Title: The Heroes Circle Opioid Project 2018
This project evaluates a novel martial arts-based virtual reality intervention for individuals with opioid use disorder who are on methadone maintenance treatment.
Role in project: Co-Investigator
Amount: $90,836 (WSU subcontract)

Kids Kicking Cancer Marusak (local PI) 07/01/2018-12/31/2019
Title: The Heroes Circle – Children Healing Children
This project examines the impact of a novel martial arts-based school curriculum (vs. a standard control socioemotional development curriculum) on stress, anxiety, and behavioral problems in elementary school children (Year 1).
Role in project: Local Principal Investigator
Amount: $33,325 (WSU subcontract)

American Cancer Society Postdoctoral Fellowship PF-16-057-01-PCSM Marusak (PI) 07/01/2016-06/30/2019
Title: Neurobehavioral correlates of learning and memory in child cancer survivors
This project compares brain and behavioral responses during implicit and explicit learning and memory paradigms in child cancer survivors vs. controls.
Role in project: Principal Investigator
Amount: $163,500

St. Baldrick's Foundation Supportive Care Research Grant 523497 Marusak (PI) 07/01/2017-02/28/2019
Title: Martial arts therapy and brain mechanisms for cancer-related pain
This study examines the impact of a novel martial arts-based intervention on pain, quality of life, and neural activity in the pain neuromatrix in children with cancer.
Role in project: Principal Investigator
Amount: $45,015.93

Barbara Ann Karmanos Cancer Institute, Pilot Project Grant from the American Cancer Society 14-238-04-IRG Rabinak (PI) 09/01/2016-08/31/2017
Title: Understanding emotional brain network organization in survivors of childhood cancer
This project examines emotion processing neural circuitry in pediatric cancer survivors, and correlates with anxiety and posttraumatic stress symptoms.
Role in project: Co-Investigator
Amount: $30,000

Sheila A.M. Rauch, Ph.D.

Active Research Support:

R33 MH111935
Role: Co-Investigator
Title: *"**Effects of THC on Retention of Memory for Fear Extinction Learning in PTSD**."* Purpose: The major goals of this project are to: 1) assess the effects of THC on extinction memory recall and brain activation, and 2) determine whether an optimal THC dose will reduce PTSD symptom severity and increase between-session extinction during prolonged exposure therapy.
Source: NIH/NIMH
08/20- 07/23
Total Direct Costs: $283,009

SBIR AWD-000309-G2
Role: Co-Investigator
Title: "***Prolonged Exposure Collective Sensing System (PECSS)**."* Purpose: Dr. Rauch will work with Dr. Arriaga and colleagues at Georgia Tech's School of Computing to provide clinical insights needed to develop software that aims to enhance patient engagement in an evidence-based treatment for PTSD called Prolonged Exposure. This will include trialing new software with actual patients, during which clinical data will be collected. We will also provide a clinical perspective in the interpretation of the data and subsequent dissemination.
Source: SBIR
10/19-9/23
Total Direct Costs: $252,632.00

VA
Role: Principal-Investigator
Title: *"**Overcoming Access Barriers for PTSD Treatment in Primary Care: Demonstration and Evaluation of PE-PC in Rural PC)**."* Purpose: This Clinical Demonstration Project aims to design a facilitated implementation plan and disseminate PE-PC in 12 rural CBOCs in VA and examine the impact of reach and access to specialty PTSD treatment.
Source: Office of Rural Health
10/20-9/23
Total Direct Costs: $1,514,066

VA 101 D2625-R
Role: Principal-Investigator
Title: *"**Extending Prolonged Exposure for PTSD into VHA Primary Care**."* Purpose: The goals of this proposal are to: 1) examine the effectiveness of a brief PTSD intervention provided in a PC environment compared to standard VHA PC on functional and symptom outcomes, 2) examine changes in utilization of VA general medical (i.e., primary care, emergency department, and inpatient admissions) and MH services for 26 weeks post randomization in PE-PC compared to PCMHI-TAU, 3) assess potential mediators and moderators of improvements in functional status and PTSD symptoms, including increased self-efficacy, reduced self-stigma, or increased use of EBPs for PTSD.
Source: VA RRD
10/18-09/22
Total Direct Costs: $1,057,633

Wounded Warrior Project
Role: Co-Investigator
Title: *"**Wounded Warrior Project: Warrior Care Network**."* Purpose: This established a national Warrior Care Network to treat PTSD and TBI in post-9/11 veterans.
Source: WWP
6/15 – 5/23
Total Direct Costs: $42,000,000

Woodruff Health Science Center COVID-19 CURE Award

Role: Co-Principal-Investigator
Title: *"**Preventing a Second Pandemic among Heroes: Mental Health Resources for Frontline Healthcare Workers**."* Purpose: Develop a self-directed app for coping with trauma and stress in healthcare workers based on effective PTSD prevention and treatment.
Source: WHSC 2020 COVID-19 CURE Award
2/1/21-06/30/22
Total Direct Costs: $300,000

Completed Research Support (Past 10 Years):

Woodruff Foundation Grant
Role: Principal-Investigator
Title: "***COVID-19 Program Support for Virtual IOP**."* Purpose: Funds to assist warriors attending virtual IOP with access to care.
Source: Woodruff Foundation Grant
07/15/20-12/31/20
Total Direct Costs: $49,119

Tonix Pharmaceuticals
Role: Principal-Investigator
Title: *"**Tonix Analytic Research Support**."* Purpose: This funding supports conducting parallel analyses from the PROGRESS study data set and manuscript preparation and publication of covariate analyses.
Source: Tonix Pharmaceuticals
10/10/19- 11/30/20
Total Direct Costs: $50,900

VA/DOD CX-14-017
Role: Principal-Investigator
Title: *"**CAP-Neurobiological Predictors and Mechanisms in Exposure Therapy for PTSD**."* Purpose: The proposed project aims to add biomarkers measures to fund randomized clinical trials of prolonged exposure for PTSD. We will examine potential neuroendocrine and neurosteroid biomarkers relevant to effective treatment of PTSD among combat Veterans and service members. Specifically, direct and comprehensive analysis of candidate peripheral biomarkers that are involved in emotion processing and regulation.
Source: VA CSRD & DOD
10/01/15-09/30/19
Total Direct Costs: $1,033,003

VA CIN 14-271
Role: Co-Principal-Investigator
Title: *"**Treatment and Prevention of Opioid Use Disorder in our SATP and Empowering Veterans for Pain Programs**."* Purpose: This program evaluation focuses on evaluating Atlanta VA Healthcare System Substance Abuse Treatment Program and Empower Veterans for Pains Programs to examine the impact on patient and facility outcomes to inform best practices that can be disseminated throughout the VISN and VA System.
Source: VA HSRD
08/01/18 – 07/31/19
Total Direct Costs: $30,000

Woodruff Foundation Grant
Role: Principal-Investigator
Title: *"**Consultant Training to Support Implementation of PE**."* Purpose: Establish a PE Consultant training program and national resource center to support implementation of PE nationally for military and veteran populations with PTSD.
Source: Woodruff Foundation

04/15/17-12/31/18
Total Direct Costs: $150,000

DOD- PT110021
Role: Co-Investigator
Title: *"**In-Home Exposure for Veterans with PTSD.**"* Purpose: Randomized controlled trial of prolonged exposure psychotherapy for veterans with PTSD in three therapy delivery conditions (office-based teleconferencing; home-based teleconferencing; and in-home in person psychotherapy)
Source: DOD
04/01/13-09/29/18
Total Direct Costs: $16,897

DOD- W81XWH-08-2-0109
Role: Co-Investigator
Title: *"**Consortium to Alleviate PTSD Multidisciplinary PTSD Research Consortium.**"* Purpose: The goals of this research consortium and its projects are to examine PTSD treatment effectiveness and efficacy in OEF/OIF/OND active duty service members and biological markers related to the development and treatment of PTSD. Multiple RCTs of various PTSD treatments are proposed. Dr. Rauch is PI for an RCT examining PE for primary care in VHA.
Source: DOD
09/01/13-08/31/19
Total Direct Costs: $45,336,000

DOD- W81XWH-11-1-0073
Role: Principal-Investigator
Title: *"**Randomized controlled trial of sertraline, prolonged exposure therapy and their combination in OEF/OIF with PTSD.**"* Purpose: The major goal of this project is to examine the comparative effectiveness of prolonged exposure, sertraline, and their combination in the treatment of PTSD in OEF/OIF returnees with posttraumatic stress disorder. In addition to symptom outcomes, we will examine neurobiological predictors and mechanisms of change including genetics and genomics, brain function, and HPA axis function.
Source: DOD
12/01/10-12/31/18
Total Direct Costs: $14,539,245

VA-CDA-2-010-06F
Role: Principal-Investigator
Title: *"**Exposure Therapy for PTSD: Efficacy and Mechanisms.**"* Purpose: This project examines changes in PTSD symptoms and emotional processing and regulation, cognitive, psychophysiologic and neuroendocrine factors with PTSD treatment (exposure therapy or present centered therapy) among returning veterans from Afghanistan and Iraq.
Source: VA CSRD
07/01/07-06/30/12

VA- MHBA-002-08S
Role: Co-Investigator
Title: *"**Neurofunctional markers of SSRI response in PTSD.**"* Purpose: The goal of this project is to examine neurofunctional markers and treatment response in an open label trial of sertraline for the treatment of chronic PTSD through pre and postreatment fMRI of corticolimbic circuitry.
Source: VA CSRD
09/01/08-08/30/11

DOD- W81XWH-08-2-0208
Role: Co-Investigator
Title: *"**Mindfulness and Self-compassion Meditation for Coping with Deployment-Related***

Posttraumatic Stress Disorder: Randomized Controlled Trial for Combat. Purpose: The major goal of this project is to examine the hypothesis that practice of mindfulness and Tibetan self-compassion meditation by PTSD patients will lead to 1.) improvement in PTSD and other symptoms and quality of life 2.) improved emotional regulation, attentional control, increased 'mindfulness' and self-compassion, and 3.) strengthening of mPFC circuits during emotional provocation.
Source: DOD
09/22/08-08/31/13

END APPLICANT RESPONSE

V-G Personnel

Selected applicant(s) must be able to staff a project team that clearly possesses skill and experience in coordinating clinical trials. In the narrative, identify the authorized contact person and key personnel to be involved with this project by name and title and provide a brief summary of their experience, qualifications, and the work to be performed.

If other organizations will be playing a role in the proposed project, provide sufficient background information that will give the Issuing Office a reasonable understanding of each organization's qualifications.

Include a detailed organizational chart including names, titles, and geographic location of all individuals that will contribute to the project.

Attach a copy of your confidentiality agreement and provide a list of personnel and the date that the confidentiality agreement was signed.

BEGIN APPLICANT RESPONSE

Christine Rabinak, Ph.D. is an Associate Professor and the Director of the Translational Neuropsychopharmacology Lab within the Department of Pharmacy Practice at Wayne State University (WSU). Dr. Rabinak completed her postdoctoral training in the Mental Health Service, specifically the PTSD Clinic, at the Ann Arbor Veteran Affairs Healthcare System and the Department of Psychiatry at the University of Michigan. During her training, she was involved in a clinical trial of sertraline in veterans with PTSD returning from Operation Iraqi Freedom and Operation New Dawn and has several peer-reviewed publications from this work. Since then, Dr. Rabinak has established an internationally-recognized, productive, comprehensive and continuously funded research program in translational psychiatric neuroscience. Dr. Rabinak's expertise is in posttraumatic stress disorder (PTSD), cannabinoids, fMRI, and fear learning. Most relevant to this proposal, Dr. Rabinak is the past PI of a NIMH K01 Career Development Award and current NIMH R61/R33 Exploratory Clinical Trials of Novel Interventions for Mental Disorders to test whether pharmacological enhancement of eCB signaling (via synthetic Δ9-tetrahydrocannabinol) improves neurobehavioral mechanisms underlying extinction recall in adults with PTSD. These studies require that she maintains a DEA Schedule II-V Controlled Substance Research license and submits Investigative New Drug applications to the FDA. She is also the PI of a recently completed NARSAD grant to study genetic variation in the endocannabinoid system and neurobehavioral mechanisms of extinction recall in healthy adults. To-date, her research performance has afforded her national and emerging international recognition. Notably, Dr. Nora Volkow, the Director of the National Institutes of Drug Abuse, invited Dr. Rabinak to speak at a research summit convened by the NIH (2016), which focused on the neurological and psychiatric effects of marijuana, other cannabinoids, and the endocannabinoid system. Subsequently, in 2017, the Military Operational Medicine Research Program and U.S. Army Medical Materiel Development Activity hosted the Posttraumatic Stress Disorder State of the Science Summit (PTSD SoSS). This was an invitation-only Summit and Dr. Rabinak was one of approximately 140 subject-

matter experts and stakeholders (academia, industry, government and nonprofits) that were invited to offer information and provide insight on how to move forward in the field of PTSD treatment. In 2018, Dr. Rabinak was invited to participate in a congressional briefing in Washington D.C. and gave an oral presentation on "Cannabis and Post-Traumatic Stress Disorder: An Assessment of the Evidence." Drs. Rabinak and Greenwald have collaborated several times on different projects and Dr. Greenwald even served as her faculty mentor on her K01 award. Dr. Rabinak has also had a long-standing and successful collaboration with Dr. Rauch. Dr. Rabinak and Dr. Marusak have a fruitful and long-standing collaborative relationship. Together, they have published over 24 articles and have been awarded several federally-funded and foundation grants. Dr. Rabinak is excited to add Drs. Lundahl and Ledgerwood to her collaborative team for this innovative and timely proposal.

Leslie H. Lundahl, PhD. Dr. Lundahl is an Associate Professor in the Department of Psychiatry and Behavioral Neurosciences at Wayne State University who has been conducting clinical human behavioral pharmacology studies for over two decades. Her expertise is in developing and refining efficient and rigorous human laboratory models to study factors involved in drug seeking and drug taking, such as drug abuse liability, drug-drug interactions, effects of stress and environmental cues on choice to use drugs, and subjective and physiological responses to drugs administered in the laboratory. She has been the Principal Investigator on six federal (NIH/NIDA) cannabis-related grants and several university grants, and served as Co-Investigator on many other federal, state, and private grants examining alcohol, nicotine, cannabis, cocaine, opiates, methamphetamine, and MDMA. Dr. Lundahl holds an IND that allows cannabis and cannabinoid administration to humans. Her current projects include evaluating the potential therapeutic efficacy of cannabidiol (CBD), alone and in combination with low doses of morphine, for treating pain, investigating the effects of stress and marijuana cue exposure on marijuana craving and self-administration, and establishing the pharmacokinetic profile of CBD. Dr. Lundahl's research is funded by the National Institute on Drug Abuse (NIDA), where she serves on several grant review committees. More recently Dr. Lundahl has become interested in potential therapeutic effects of cannabinoids. She was recently awarded a grant from the Veteran Marijuana Research Grant Program, overseen by the Cannabis Regulatory Agency in the State of Michigan, to investigate the effects of varying doses of THC and CBD on PTSD symptom severity, depression, and anxiety, with the goal of reducing suicide rates and improving behavioral health in US Military Veterans. She is also a clinical psychologist with over 25 years of experience in the assessment and treatment of psychiatric and substance use disorders, and she has served as diagnostician and clinician on multiple randomized clinical trials of psychiatric and substance use disorders. In her clinical practice she specializes in depression, anxiety, and substance use issues. Thus, she has the necessary scientific, administrative, and clinical experience to lead this important work, along with Co-PI, Dr. Rabinak. Dr. Lundahl has enjoyed a long and successful history of collaboration with Drs. Ledgerwood and Greenwald, and they have worked closely with the rest of the team to develop this exciting proposal.

David Ledgerwood, PhD. Dr. Ledgerwood is a clinical psychologist and Professor studying various aspects of substance use, including cannabis, tobacco, opioids, and others. He is currently Director of the Nicotine and Tobacco Research Division in the Department of Psychiatry and Behavioral Neurosciences. He has expertise in conducting clinical trials for treatment efficacy and effectiveness. Dr. Ledgerwood has conducted research in several areas that complement the proposed work, including examining trauma, PTSD and suicidality among individuals with gambling disorder, and individuals receiving treatment for opioid use disorder. He is co-Principal Investigator of a recently completed tele-health trial examining the efficacy of Seeking Safety for co-occurring trauma and gambling problems (Najavits, Ledgerwood, & Afifi, 2022, Currently Under Review). He is currently co-Principal Investigator on the LARA-funded Veteran Marijuana Research Grant, which is exploring the use of cannabinoids (THC and CBD) for treating PTSD, suicidality and other mental health symptoms. Additionally, Dr. Ledgerwood worked on the Vietnam Era Study, a NIH-funded longitudinal cohort study at Washington University that examines PTSD, suicidality, and other co-occurring conditions among Vietnam era veterans originally recruited in 1971. Dr. Ledgerwood's research has been funded by NIH and foundation grants. He serves on several editorial and grant review boards. His funded

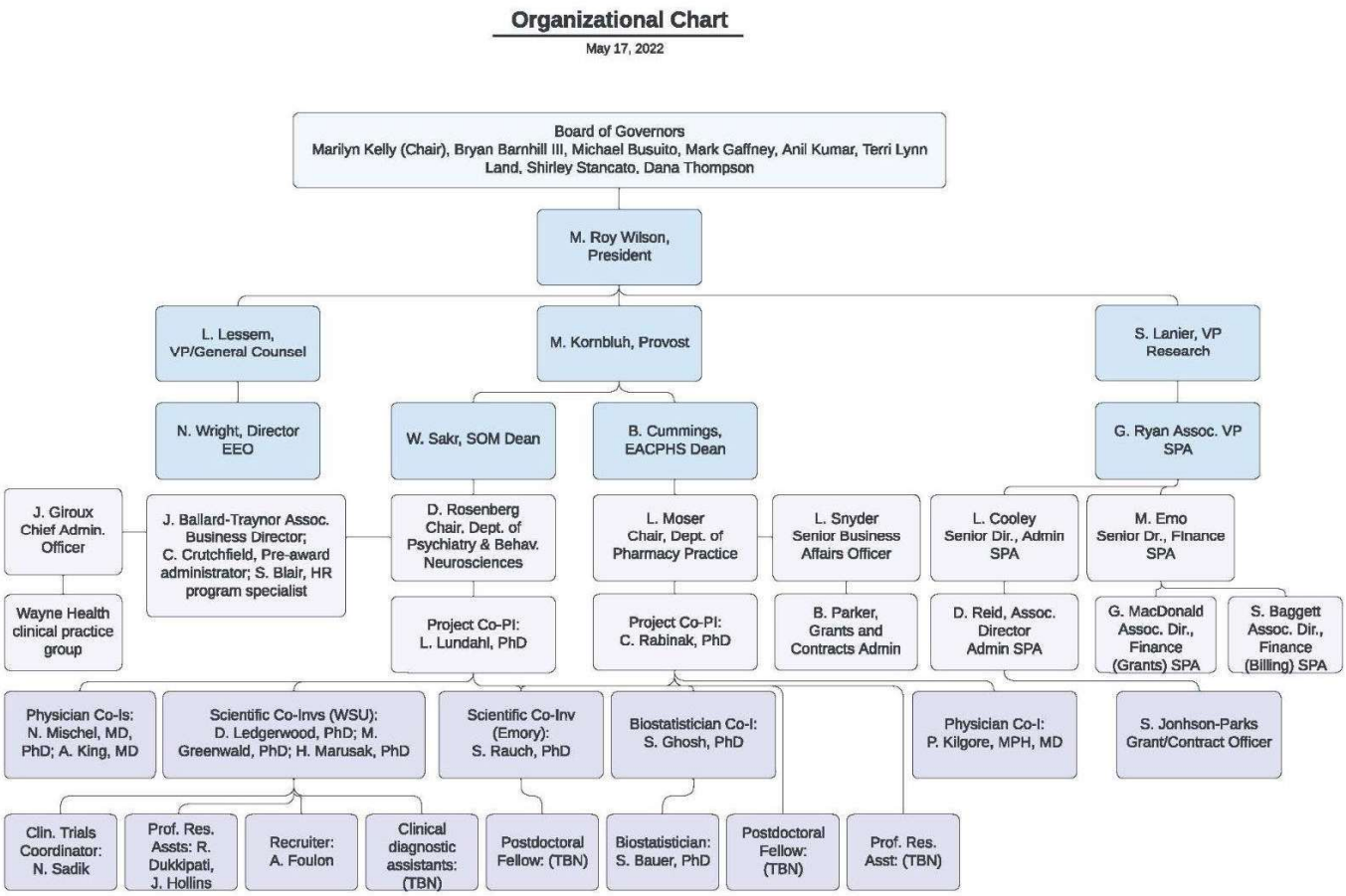
research involves primarily conducting clinical trials for behavioral interventions for individuals with nicotine use disorder, substance use disorder, and gambling disorder. Currently, Dr. Ledgerwood is conducting clinical trials and other clinical research with colleagues at several universities across North America including Medical University of South Carolina, Baylor University, University of Massachusetts Medical School, University of Windsor, and Yale University.

Mark K. Greenwald, PhD. Dr. Greenwald is Professor, the Gertrude Levin Endowed Chair in Addiction and Pain Biology, Associate Department Chair, and Director of the Substance Abuse Research Division in the Department of Psychiatry and Behavioral Neurosciences at Wayne State. His expertise is in the field of substance use disorders (SUDs), particularly opioid, cocaine and marijuana/cannabis. He conducts broad programmatic research in addiction and pain biology and therapies, directs the Human Pharmacology Laboratory (site of the proposed studies), and oversees a SUD treatment research clinic. His research foci include: (a) investigating individual-difference (e.g. genetics, affective states), environmental (e.g. cues, drug availability, response requirements), and pharmacological (PD and PK) determinants of drug seeking/use and its psychobiological consequences; (b) using behavioral, brain imaging and biomarker approaches to improve understanding of mechanisms of action; and (c) leveraging this knowledge to develop effective treatments for these conditions. Dr. Greenwald has broad training in clinical and experimental psychology, behavioral pharmacology, and neuroscience. Dr. Greenwald holds DEA Schedule I and Schedule II-V Researcher Licenses and State of Michigan Board of Pharmacy controlled substance and laboratory licenses, all of which are pivotal to performing the ongoing LARA-funded project as well as this proposed project. Dr. Greenwald has published more than 130 research papers, reviews and book chapters, and has co-authored about 300 conference research presentations. His research has received continuous funding from the NIH since 1996. He has served on multiple national and international grant review committees and formerly chaired both NIH and US Veterans Affairs grant review committees. He collaborates with several industry partners involved in developing anti-addiction pharmacotherapy and medical device treatments. He is Past-President of the American Psychological Association Division 28, has served on many national, state and local committees, and advisory boards, related to substance use disorders. He is a leader in interdisciplinary research and education, especially mentoring junior faculty, postdoctoral fellows, medical students and graduate students, on topics related to substance use disorders.

Hilary A. Marusak, PhD. Dr. Marusak is a tenure-track Assistant Professor in the Department of Psychiatry and Behavioral Neurosciences at Wayne State University, and holds an adjunct position in the Merrill Palmer Skillman Institute for Child and Family Development. Dr. Marusak directs the Trauma History Investigation of Neurodevelopment in Kids (THINK) lab at Wayne State, which incorporates neuroimaging, behavioral, and physiological approaches to understand neurodevelopmental mechanisms leading to anxiety and other fear-based disorders (e.g., posttraumatic stress disorder, PTSD) in children and adolescents. In particular, Dr. Marusak is interested in the role of the endocannabinoid system in modulating frontolimbic brain development and risk of fear-based disorders, and has developed a novel line of research to examine behavioral (e.g., exercise, meditation) or pharmacological interventions (e.g., cannabidiol, CBD) that target the endocannabinoid system for the treatment and/or prevention of anxiety and PTSD in youth. An emerging area of interest is the impact of prenatal cannabis exposure and adolescent cannabis use on neurodevelopmental and mental health outcomes. Dr. Marusak is the PI of a currently funded NIMH K01 project (MH119241) that aims to characterize age-related changes in endocannabinoid signaling across adolescence (10-17 years), and associations with fear extinction, fear extinction neural circuitry, and anxiety and PTSD symptomology. Dr. Marusak is the Co-PI on a study funded by the Children's Foundation to examine the impact of CBD on stress and anxiety in children with epilepsy, and is the Co-PI of a recently funded internal award (WSU Office of the Provost) to examine the impact of exercise on endocannabinoid levels and cognitive and mental health in youth. Dr. Marusak also works closely with the other study personnel; Dr. Marusak works closely with Drs. Lundahl, Ledgerwood, and Greenwald on their currently funded LARA/VMR study; Dr. Lundahl is a Co-I on Dr. Marusak's ongoing Children's Foundation grant award; and Dr. Rabinak mentors Dr. Marusak on her currently funded NIH K award. Drs. Rabinak and Marusak have sustained a productive, long-term

collaboration that has resulted in 5+ federal or foundation grant awards and 24+ publications.

Sheila A.M. Rauch, Ph.D., Dr. Rauch holds the Mark and Barbara Klein Distinguished Professorship and is a Professor in the Department of Psychiatry and Behavioral Science at Emory University School of Medicine. For over 20 years, her research has focused on PTSD and anxiety disorders development and treatment and psychological and biological mechanisms involved in those processes. She designed, administered, and led translational treatment outcomes studies including multi-site, trials examining outcomes and biomarkers of PTSD and effective treatment. In addition, she has led research into psychotherapy training and improving access and implementation of effective interventions for PTSD. She has been a Prolonged Exposure (PE) Trainer since 2000 and became an author of the latest version of the PE manual. She has served as Principal Investigator on several federally funded PTSD treatment grants (VA/DOD), and served as Co-Investigator on many other federal, state, and private grants. Her current projects include: examination of functional outcomes in a brief PTSD treatment compared to treatment as usual in primary care; implementation of PTSD care across civilian mental health; examination of tDCS for pain in an intensive outpatient program for PTSD; examination of THC vs placebo augmenting PE for PTSD. Dr. Rauch's research is funded by the Veterans Administration and National Institute of Health. She is a clinical psychologist with over 25 years of experience in the assessment and treatment of psychiatric and substance use disorders, and she has served as psychotherapy lead, diagnostician and clinician on multiple randomized clinical trials of PTSD treatment. In her clinical practice she specializes in PTSD, anxiety, and substance use issues. She is fully licensed in Michigan and in Georgia. She conducts PE training for research and clinical settings at least twice per year and designed a consultation program for advanced providers to train others in PE. Thus, she has the necessary scientific, administrative, and clinical experience to serve as Emory University Co-Investigator. She has enjoyed a successful history of collaboration with Dr. Rabinak and worked closely with Dr. Lundahl and Ledgerwood and the rest of the team to develop this exciting proposal. She has a split Atlanta VA Medical Center and Emory University appointment.



Confidentiality Agreement

Please see the attachment for a copy of our signed confidentiality agreement. The date that the confidentiality agreement was signed by key personnel is listed below.

Leslie Lundahl PhD	May 26, 2022
Christine Rabinak, PhD	May 26, 2022
David Ledgerwood, PhD	May 26, 2022
Mark Greenwald, PhD	May 26, 2022
Hilary Marusak, PhD	May 26, 2022
Sheila Rauch, PhD	May 26, 2022
Nicholas Mischel, MD	May 26, 2022
Paul Kilgore, MD	May 26, 2022

END APPLICANT RESPONSE

V-H Budget

To enable the Issuing Office to evaluate all project costs, **applicant(s) will submit a proposed budget and corresponding budget narrative.** Please see attachment A for the required budget format. The budget and narrative must include only VMR grant funds in the budget; do not include matching, leveraged, cost

share or any other type of supplemental funds. The budget narrative must identify the budget line item and number, provide a detailed description for each line, and include individual unit prices.

Selected applicant(s) will be required to provide supporting documentation for all grant expenditures incurred during the term of the grant. Accounting records must be supported by source documentation including, but not limited to, general ledgers, time sheets, payroll registers, invoices, check copies and bank statements, or canceled checks. Expenses will be verified based on actual expenditures incurred within the grant period that are supported by source documentation, not budgeted amounts.

(1) **Budget Changes** – Any changes to the budget must be pre-approved by the Grant Administrator. Changes in the budget of less than 5% of the total line item amount do not require a formal amendment; however, a revised budget should be submitted to the Grant Administrator for approval. The allowable transfer should be calculated as less than 5% of the total line item that the funds are being transferred from.

Cumulative changes in the budget equal to or greater than 5% of the total line item amount may be permitted only upon prior review and written approval by the Grant Administrator. A formal grant amendment must be signed by both the grantor and grantee.

(2) **Disallowed Costs** – Disallowed costs include but are not limited to the following: sick pay, vacation pay, holiday pay, bonuses, overtime, tuition reimbursement/remission, vehicle allowance, seminars, conferences, meetings, subscriptions, dues, and memberships.

(3) **Administrative Costs** – Administrative costs cover expenses related to general administrative functions and coordination of functions and oversight related to VMR administrative functions. Administrative costs should include costs of goods and services required for administrative functions of the program; travel costs incurred for official business in carrying out administrative activities or the overall management of the VMR; costs of information systems related to administrative functions; and contractual services related to sub-recipients or vendors that are solely for the performance of administrative functions. **Total administrative and indirect costs must be identified, labeled clearly, and may not exceed 10% of the overall grant.**

(4) **Budget Requirements** – the proposed budget will display three (3) headings identified as the: Line Item, Budget Category, and Total. The budget line items that need to be included, at a minimum, are listed below. The budget should reflect the best estimate of actual costs using whole numbers. Please refrain from using decimals or formulas. Refer to the budget example provided in Attachment D.

- **Personnel** – In the budget, include the name, job title, and salary for each staff position to be paid for by the grant. Time sheets and payroll registers must be submitted for each staff position, and hours worked must be grant related. Fringe benefits may not exceed 35% of each employee's salary. Fringe benefits will be reimbursed based on actual expenditures per employee up to 35%, not on budgeted amounts. Allowable benefits include: health, dental, and optical insurance, employer-paid Social Security and Medicare tax, Michigan and Federal unemployment tax, and other miscellaneous fringe benefits (life insurance, long- and short-term disability insurance, worker's compensation, and retirement program contributions up to 4%). Applicant(s) must provide details on the organization's method of calculating fringe benefit expenses that will be charged to the grant including whether fringe benefits are calculated on an annualized basis or based on the length of the grant term.

  The budget narrative must include the number of weeks the individual will work on the grant; number of hours per week a full time employee of the organization is expected to work; a description of the work to be performed by each individual; the estimated hours to be worked; actual pay rate; the fringe benefit percentage being charged to the grant for each employee; the percentage of the employee's time allocated to the grant; whether each employee is salaried-exempt, salaried-non- exempt or hourly; and any other applicable

information related to the individual's duties and responsibilities in connection with this grant.

Individuals that are not on selected applicant(s)'s payroll, e.g., independent contractors, individuals receiving a Form 1099, temporary workers, etc., must be placed under the Contractual Services budget category. Only employees on the selected applicant(s)'s payroll should be included in the Personnel budget category.

- **Supplies, Materials, & Equipment:** specify item(s) and cost. The budget narrative should include the anticipated cost of each item, a detailed explanation of the item's purpose, and how it relates to the project being funded. Be as detailed as possible.
- **Contractual Services:** these services must be competitively bid. Individuals that are not on selected applicant(s)'s payroll, e.g., independent contractors, individuals receiving a Form 1099, temporary workers, etc., must be placed under **Contractual Services**. When competitive selection is not feasible or practical, the selected applicant(s) agrees to obtain the written approval of the Grant Administrator before making a sole source selection. Selected applicant(s) must provide a copy of contracts, memoranda of understanding or agreements signed by selected applicant(s) and contractors.

  Selected applicant(s) assumes responsibility to select subcontractors on a competitive basis. A minimum of three (3) bids must be solicited and proposals must include, at a minimum: (1) name of selected applicant(s), grant number, and grant period; and (2) the type, number, and description of projects as described in the proposal.

  Selected applicant(s) must provide the Grant Administrator with the solicitation, list of vendor responses (including amounts), and name of the selected vendor. Selected applicant(s) must maintain bids on file at their place of business according to Section II-B, Records Maintenance, Inspection, Examination, Audit and Monitoring. The Grant Administrator will reserve the right to request a copy of all bids for services that are competitively bid.

  Selected applicant(s) must award the project to the lowest bid unless the Grant Administrator has given prior written approval for selection of a higher bid. Selected applicant(s) must provide a written justification for the selection of a higher bid. When awarding subcontracts, the selected applicant(s) must ensure that preference is given to products manufactured in or services offered by Michigan-based firms.
- **Travel:** in the budget include the name, job title and official workstation for each staff member that will be traveling. Selected applicant(s) must follow the State of Michigan Standardized Travel Regulations (www.michigan.gov/dtmb/0,5552,7-150- 9141_13132---,00.html). The State will reimburse for mileage, lodging, and meals, refer to the current State travel rates. Meals and lodging must be supported by itemized, legible receipts and reasons for travel. Itemized meal receipts must include a list of each item purchased; receipts for payments made by credit card that are not itemized will not be accepted.

  Mileage must be supported by travel log(s) with beginning and ending addresses, mileage total, and reason for travel. Grantees will be provided a travel log example. Out-of-state travel must be directly related to the grant project and approved by the Grant Administrator prior to travel. Travel expenses listed in the travel budget category are strictly for individuals listed on the budget under Personnel. Per Diem payments and alcoholic beverage reimbursements are not allowed.
- **Other Expenses:** This category is solely for use by organizations charging a per-case fee for work performed by subunits or internal agencies within the organization that do not require a competitive bid, i.e. contract, memorandum of understanding or any other type of signed agreement.

- **Indirect Costs:** Indirect costs are costs not directly or specifically related to the grant program. Indirect costs are costs of administering the organization and must be spread over a number of products, services, or grant programs proportionately. Examples include office supplies and equipment, utilities, rent, maintenance and repair, insurance, accounting and bookkeeping services, and legal services. Non-cash expenses like depreciation, amortization, and depletion are not allowable indirect costs under this grant. **Total administrative and indirect costs must be identified, labeled clearly, and may not exceed 10% of the overall grant.**

  Selected applicant(s) will be reimbursed for its proportional share of indirect costs. This means the MRA should be allocated a portion of the selected applicant(s)'s indirect costs and not 100% of the organization's total indirect cost.

  Indirect costs should be displayed on the face of the budget on a single line item and the indirect rate should be rounded to six (6) decimal places. The budget narrative should contain a list of indirect costs, how the selected applicant(s) determined its indirect costs, and the percentage rate calculation for reimbursable indirect costs. Selected applicant(s) is not required to provide documentation supporting indirect costs; however, documentation verifying the costs must be retained by the selected applicant(s).

(5) To ensure efficient review and approval of grant expenditures, selected applicant(s) will be provided additional guidelines to assist with calculating and determining accurate and appropriate grant expenditures.

(6) Each budget category should have a subtotal displaying the total anticipated amount to be expended, and the budget should include a subtotal for total direct project costs and a sum of total project costs.

(7) After grants are approved by the MRA, modifications of proposals and budgets may be necessary. If the MRA does not approve the total amount requested in the original proposal, selected applicant(s) will be required to submit a revised proposal, budget and budget narrative for the purpose of entering into a Grant Agreement. New line items to the revised budget are not allowed.

(8) Selected applicant(s) assumes the responsibility of ensuring all unexpended grant funds are returned to the State of Michigan at the end of the grant period. Failure to do so may render selected applicant(s) ineligible for future grant awards and/or subject to legal action.

(9) Selected applicant(s) may not commingle grant award funds with current or future grant awards. All funding sources must be managed and accounted for separately.

BEGIN APPLICANT RESPONSE

Budget Justification

Key Personnel (All personnel work 40-hr work weeks)

Christine Rabinak, Ph.D., Co-Principal Investigator (Associate Professor, tenured) directs the Translational Neuropsychopharmacology Laboratory and has over 15 years of extensive experience in designing and conducting clinical trials in individuals with PTSD using pharmacological agents, especially those related to cannabis. Dr. Rabinak is the primary person responsible for the execution and conduct of the study, including human subjects aspects, interfacing with the other participating investigators, and communicating with LARA. She has and will continue to participate in all aspects of the task design, development, and implementation for fMRI, psychophysiological, and behavioral measures, direction of study personnel, analysis, and publication of results. Collectively, the research team possesses non-overlapping, but inter-related expertise and exceptional records conducting clinical research and has a history of ongoing collaborations. She will devote 40% effort, or 16 hours per week, to the clinical trial throughout the 5-year project period.

Leslie Lundahl, Ph.D., Co-Principal Investigator (Associate Professor, tenured) is a licensed clinical psychologist and an experienced psychopharmacologist in the Human Pharmacology Laboratory within the Substance Abuse Research Division. Dr. Lundahl has over 20 years of extensive experience in designing, conducting, and publishing behavioral pharmacology clinical research studies, including the procedures proposed in this application. She will provide overall scientific direction and coordinate the design, implementation and quality control of data collected for the study in this application. She will be responsible for all communication with LARA/CRA, FDA, DEA, WSU IRB and compliance with their monitoring and reporting requirements, including filing protocols under her FDA IND for marijuana (#75,596). Dr. Lundahl will oversee all drug storage, preparation, administration, and accountability, as well as psychiatric screening and monitoring of participants in this trial. Along with Dr. Ledgerwood, she will provide prolonged exposure therapy, and train and supervise master's levels clinical students and research assistants in the conduct of clinical interviews and assessment of neurocognitive function, PTSD and suicidal ideation. She will oversee protocol and data integrity, analyses, interpretation, and publication of study results, and present these findings at scientific conferences. She will devote 40% effort, or 16 hours per week, to the clinical trial throughout the 5-year project period.

David Ledgerwood, Ph.D., Co-Investigator (Professor, tenured) a licensed clinical psychologist and experienced clinical scientist in the Substance Abuse Research Division. He is also the Director of the Nicotine and Tobacco Research Division in the Department of Psychiatry and Behavioral Neurosciences. Dr. Ledgerwood has extensive experience conducting studies that examine the efficacy and effectiveness of clinical interventions. He is skilled in clinical trial methodology and has published several behavioral trials over his career. He has also conducted and published numerous studies examining the etiology, mechanisms, treatment predictors and consequences related to substance use disorders and behavioral addictions. Dr. Ledgerwood will have several roles in this clinical trial. Specifically, he will work with Dr. Lundahl to: assist with recruitment; oversee intake assessments; review data for quality and safety; assist with data analysis; and assist with dissemination. He will provide prolonged exposure therapy and train and supervise predoctoral practicum students in the conduct of clinical interviews, and assessment of neurocognitive function, PTSD, and suicidal ideation, He will devote 30% effort, or 12 hours per week, to these clinical trials throughout the 5-year project period.

Mark Greenwald, Ph.D., (Professor, tenured) is Director of the Substance Abuse Research Division, and Chief of its Human Pharmacology Laboratory, Dept. of Psychiatry and Behavioral Neurosciences, and will serve as co-investigator for this project. Dr. Greenwald is a leading expert in the design and conduct of behavioral pharmacology studies using methods like those proposed here. He conceptualized the inclusion of anhedonia and reward processing/preference tasks that will be used in this project, and will contribute to their analysis and interpretation. Dr. Greenwald routinely collaborates with the PI on laboratory-based studies of cannabinoids, cocaine, and opioids. He will assist with study design, implementation, data analysis, interpretation of results, and will co-author publications. Dr. Greenwald will maintain his current DEA Schedule I Researcher license (he also has DEA Schedules II-V licenses). He will assist Dr. LundahlI with drug preparation and accountability. He will contribute 10% effort, or 4 hours per week, throughout this 5-year project.

Hilary Marusak, Ph.D. (Assistant Professor, tenure-track) Dr. Marusak is a tenure-track Assistant Professor in the Department of Psychiatry and Behavioral Neurosciences at Wayne State University, and holds an adjunct position in the Merrill Palmer Skillman Institute for Child and Family Development. Dr. Marusak directs the Trauma History Investigation of Neurodevelopment in Kids (THINK) lab at Wayne State, and is interested in the role of the endocannabinoid system in modulating frontolimbic brain development and risk of fear-based disorders. Given her expertise in the role of the endocannabinoid system in stress, anxiety, and PTSD, Dr. Marusak will lead all aspects of sample collection, design, analysis, and interpretation of endocannabinoid levels and will be responsible for coordinating with the WSU Lipidomics Core (Krishnarao Maddipati, Ph.D., Director) for sample collection, processing, storage, analysis, and interpretation. She will devote 15% effort to this project, or 4 hours per week throughout the 5-year project period.

Nick Mischel, M.D., Ph.D. (Assistant Professor)
Dr. Mischel provides outpatient psychiatric consultation for patients in medication-assisted treatment (MAT) with suboxone and methadone, and has also treated patients with alcohol, opiate, tobacco, cocaine, benzodiazepine, cannabis, other stimulant, and other psychedelic use disorders in both acute inpatient detoxification and rehabilitation centers. Dr. Mischel provides medical oversight on all of Dr. Lundahl's cannabis studies, and will

review EKGs, labs, and perform physicals to determine study eligibility, as well as provide medical coverage during cannabis administration sessions and oversight throughout the trial. Dr. Mischel will be involved in interpretation of findings and manuscript preparation and publication. Dr. Mischel will also oversee Liz Brunner, our Physician Assistant. He will commit 15% effort, or 6 hours per week, to this 5-year project.

Paul Kilgore, M.D. (Associate Professor tenured)
Dr. Kilgore is a board-certified physician who has provided medical oversight on Dr. Rabinak's THC clinical trials with PTSD patients. He will provide medical monitoring and oversight, and assist with interpretation of findings and manuscript preparation. He will contribute 10%, or 4 hours per week, throughout this 5-year project.

Other Personnel
Clinical Trials Coordinator, Ms. Nareen Sadik. Ms. Sadik will be responsible for managing all day-to-day project needs, helping develop and implement protocols for collecting biological, behavioral, and questionnaire data, overseeing recruiting and scheduling of screening and baseline sessions, and enrollment, and randomization procedures. She will help complete IRB paperwork, maintain agency records, oversee scheduling of phone interviews and follow-ups, and coordinate data entry and management with the research assistants. Ms. Sadik will meet regularly with the Co- PIs to assure quality control and maintenance of study records, provide summaries, and assist in preparing data for presentations and publications. She will devote 100% effort, or 40 hours per week, throughout this project.

Recruiter. Ms. Alanna Foulon is a recruiter in our laboratory. She will be responsible for creating advertisements for various print and social media, establishing contact with veterans organizations, and conducting initial telephone screens, as well as following up on screening surveys completed on our WarriorCare website. She will organize teams that will attend Veterans information fairs, health events, etc where we can set up an information booth about the study for recruitment. (We already have this structure in place for our current LARA clinical trial.) She will devote 100% time, or 40 hours per week, to this project for years 1-5.

Clinical Diagnostic Assistants, Ms. Halle Thomas, M.S. and Ms. Nicole Kouri, M.S. We request funds for two, half-time M.S.-level clinical psychology graduate practicum students (we routinely have 3-4 per year in our laboratory, who start in the Fall semester). They will have day-to-day responsibilities for conducting clinical interviews (SCID for DSM-5), PTSD and suicidal ideation assessments, and neurocognitive testing. Being half-time personnel (20 hrs/week), they will each devote 50% effort, or 10 hours per week, throughout the project, and will be supervised by Dr. Lundahl and Dr. Ledgerwood.

Rabinak Lab: Fear Conditioning and MRI
TBN, (Clinical Research Coordinator): The clinical coordinator will have extensive experience in management of clinical trials. They will also be responsible for assisting Co-PI Rabinak in the overall management of the research protocol, data management and sharing, IRB and regulatory related matters, and recruitment efforts in the Department and surrounding community. They will be responsible for scheduling and coordinating all scanning sessions. This is a 100% effort position, for 40 hours per week throughout the 5-year project period.

TBN, (Research Technologist): The research technologist will have an extensive knowledge of and experience in computer programming and will be responsible for updating and adjusting the program and coded scenarios that we utilize to deliver our task stimuli, creating digital versions of questionnaires, implementing new software systems on our server, analyzing neuroimaging data, creating analysis pipelines, installing new hardware in our lab, and has been a primary communicator with the MRI lab with which we're partnered. In general, the research technologist deals with anything concerning our lab computers, server, software implementation, data management, and coordination with IT and other technical staff. They will continue with these responsibilities on the proposed project. This is a 100% effort position, for 40 hours per week throughout the 5-year project period.

TBN, (Research Assistant): A research assistant will perform general coordination of the study including screening and scheduling of participant assessments, participant recruitment, fMRI and behavioral measures, data entry, management and the general upkeep of the study database. S/he will prepare materials, organize scheduling, follow-up with study personnel, run the reports on the data, and various other duties as needed by the study. The research assistant will also train subjects on the behavioral tasks, and collect behavioral and brain

function data related to the protocol. S/he will help prepare and submit IRB correspondence and assist in data sharing submissions under the supervision of the clinical research coordinator and the Co-PIs.

Postdoctoral Research Fellow. We request funding for one Ph.D.-level postdoc who will be trained to collect and analyze neuroimaging data along with psychophysiological data, as well as contribute to statistical analysis and manuscript preparation. The postdoctoral fellow will devote 100% effort, or 40 hrs per week, for years 1-5 of this project.

Lundahl Lab: Cannabis Administration and PE Therapy

Professional Research Assistant. Ms. Reshma Dukkipati is a Professional Research Assistant in the Human Pharmacology Laboratory. She will schedule and coordinate psychiatric/medical screening visits, provide phlebotomy services, and assist the coordinator in running experimental sessions, set up and manage the Castor questionnaire data, and conduct phone interview assessments. She will also assist Dr. Lundahl with study drug custodial record keeping. She will devote 100% effort, or 40 hours per week, throughout this project.

Professional Research Assistant. Ms. Jasmine Hollins is a Professional Research Assistant in the Human Pharmacology Laboratory. She will be responsible for collecting and processing biomarker (saliva, blood, urine) samples for this project, and will provide backup phlebotomy services for Ms. Dukkipati. Ms. Hollins will also be responsible for conducting informed consent procedures with participants, and maintaining contact tracking and follow-up calendar to make sure that all assessments are completed and on time. She will devote 75%, or 30 hours per week, to this project.

Postdoctoral Clinical Psychology Fellow. We request funding for one Ph.D.-level postdoc in Clinical Psychology who will be trained to provide PE therapy and will conduct clinical assessments, as well as contribute to statistical analysis and manuscript preparation. The postdoctoral fellow will devote 100% effort, or 40 hrs per week, for years 1-5 of this project.

Administrative Personnel

Jennifer Ballard-Traynor (Administrative Director)

Jennifer will provide financial oversight on this study. She will review all personnel charges and expenses on this study for compliance. She will monitor expenditures and report to the PI on a regular basis. Review and coordinate close out documents with the Sponsored Program Administrative Office. She will contribute 10% effort, or 4 hours per week throughout this 5-year project.

Cordell Crutchfield (Grants and Contracts Administrator)

Cordell will coordinate the pre-award aspects for this project to ensure compliance with University and sponsor. He will review budget proposals and justifications for each award period and coordinate documentation required by the granting agency. He will contribute 5% effort, or 2 hours per week, throughout this 5-year project.

Sonya Blair (HR Program Specialist)

Sonya will manage the human resource functions for this study. She will post all open TBN positions in coordination with the PI. She will oversee onboarding all new personnel for this process including gathering necessary documentation, working with HR on the hiring documents, submitting background check information, and coordinating new employee training. She will also be adding effort to the grant and reviewing effort certifications on a bi-annual basis. She will contribute 5% effort, or 2 hours per week, throughout this 5-year project.

Fringe Benefits

Fringe benefits are calculated on requested salary per the University's policy. The fringe rates are set and charged by the University based on pay classification. These amounts are subject to change on a fiscal year basis (Oct to Sep). The current rate for faculty is 27.4% (Rabinak, Lundahl, Ledgerwood, Marusak, Kilgore, Mischel), the rate for research personnel is 30.4%, and the rate for administrative personnel is 29.4% (Greenwald, Ballard-Traynor, Crutchfield, and Blair).

Consultants

Ryan Vandrey, Ph.D., Johns Hopkins School of Medicine
Dr. Vandrey brings over 20 years of experience studying the behavioral pharmacology of cannabis and conducting controlled laboratory studies with adult research volunteers, clinical trials, web-based survey research, and natural history studies with patient populations using cannabis/cannabinoids for therapeutic purposes. His work helped characterized the cannabis withdrawal syndrome, furthered our understanding on the comparative pharmacokinetics and corresponding pharmacodynamics of cannabinoids across routes of administration, examined the effects of cannabis on sleep, and evaluated risks and benefits of medicinal use of cannabis/cannabinoids for various health conditions. He will provide consultation on regulatory issues and study procedures. We would like to pay Dr. Vandrey for 15 hours of consulting in 2022-2023, 10 hours in 2024, and 5 hours each in years 2025 -2027 (total of 40 hours at $200/hr = $8,000).

Marcel Bonn-Miller, Ph.D., University of Pennsylvania
Dr. Bonn-Miller has conducted seminal work on the links between substance use and anxiety disorders, and more specifically on associations between cannabis use and PTSD. He will provide guidance on study procedures. We would like to pay Dr. Bonn-Miller for 10 hours of consultation in 2022-2023, and then 5 hours in 2024 - 2027 (total of 30 hours at $200/hr = $6,000).

Other Direct Costs

Computer Equipment
We will purchase three (3) iMac 24" desktop computers ($2258 each) for the clinical research coordinator and one Research Assistant. Two (2) MacBook Pro laptop computers ($2100 each) with 14" monitors and five (5) computing tablets ($800 each) will be purchased for day-to-day tasks and data collection in the Human Pharmacology Laboratory and testing rooms. All will be fully dedicated to this study. Cost = $2258 each x 3 desktop computers = $6774; $2100 each x 2 laptop computers = $4200; $800 each x 5 tablets = $4000; **total of $14,974**.

Two desktops, one laptop, and 3 tablets will be purchased in Year 1 ($6758), the remaining equipment will be purchased in mid-Year 3 ($8216) to replace the original ones bought in Year 1.

We will also purchase two (2) laptop computers needed to operate the lab components specific to stimulus presentation (dedicated laptop 1) and real-time psychophysiological data collection (dedicated laptop 2) for the BIOPAC MP160 system. Both computers will collect psychophysiology data pertinent to the specific aims of this proposal. ($1200/each = **$2400 tota**l, Year 1).

Data Storage and Server Management: A data server will be purchased in year 1 ($25,000) and additional storage to add on will be purchased in years 2-5 ($5,000 plus inflation).

Vitals Monitor: In Year 1 we will purchase a Welch-Allyn 300 Series Vital Signs Monitor (All States Med) to monitor participants' heart rate, blood pressure, and skin temperature during cannabis administration sessions at baseline. Vitals monitoring is both for safety and to assess physiological responses to cannabis conditions. Cost: $875

Screening Related Supplies
These items represent costs for minor medical and nursing items regularly used during study screening. They include costs for hypodermic syringes, alcohol pads, band-aids, gauze pads, thermometer probe covers, gloves, examination table paper, examination gowns, sterile saline, peroxide, ace wraps, bacitracin, and tape. These are necessary items for conducting screening evaluations (e.g., blood withdrawal, physical) with a population that can have significant associated morbidity rates. Costs for these items have been budgeted at $12 per candidate for screening and $5 per participant for the Baseline session. We estimate these costs will increase 3% per year in years 2-5.

105 participants screened in Year 1 x $12/participant = $1260 in Year 1
70 participants enrolled in Year 1x $5/participant = $350 in Year
Total = $1610 in Year 1 increasing 3% per year in Years 2-5

Research/Data Handling Supplies

Supply costs associated with daily operation of the research include notebooks to maintain records, USB drives, printer paper for hard-copy records of data and graphs, laser writer toner cartridges, fax cartridges, post-it notes, pens/pencils for data recording, staples and paper clips to organize data, notepads, and clipboards. The budget for these costs is $70 per enrollee. We estimate enrolling an average of 70 participants per year x $70/participant = $4900 in Year 1. We estimate that these costs will increase 3% per year in years 2-5.

Assessment Materials and Supplies

Costs requested include supplies needed for clinical assessments, treatment visits, computer-administered and scored assessments, such as diagnostic and rating scales, scoring sheets, binders, and assessment manuals. Costs in Year 1 are higher due to these costs also including treatment manuals for therapists and digital audio recorders for participant's *in vivo* and imaginal exposures as well as for fidelity and training purposes. Costs for assessment materials and supplies would be $7,000 in Year 1 and $4,000 in Years 2-5.

Supplies for Participants During Laboratory Sessions

When volunteers are in the laboratory for longer than 4 hours (i.e., for Baseline, PE+cannabis sessions, and Post-Treatment assessments), there are costs associated with snacks and lunches. We allow participants to select these items up to the amount of $10/day. Completers will each spend 6 such sessions in the laboratory (x $10/day = $60), whereas we estimate that non-completers will each spend 3 days in the laboratory (x $10/day = $30).

(50 completers x $60) + (20 non-completers x $30) = $3600/ Year 1. We estimate these costs will increase 3% per year in years 2-5.

HEPA filters (portable air cleaners)

The Human Pharmacology Laboratory is equipped with a negative pressure ventilation system that funnels air out of this building area to the external environment. Nonetheless, we routinely use filters to augment this system to promote the health and safety of our participants and staff members. As participants will be smoking cannabis we will need to outfit two testing rooms with HEPA filters to capture marijuana smoke so it does not filter into other rooms of the building and reduce the burden to the ventilation system. Each unit costs $300 and lasts approximately 2 years, thus we are requesting 6 units in total for $1800.

<u>Cannabis Administration Expenses</u>

Cannabis: THC and Cannabidiol (CBD)

We will purchase cannabis flower from a DEA-compliant, federally-registered supplier (e.g., GroffNA, BRC). The 5 THC:CBD combinations will be purchased: High THC:Low CBD (10 mg THC:2.5 mg CBD); High THC:High CBD (10 mg THC:10 mg CBD); Low THC:High CBD (2.5 mg THC:10 mg CBD), Low THC:Low CBD (2.5 mg THC:2.5 mg CBD), and placebo (0 mg THC: 0 mg CBD). Participants will be randomized into each of these conditions (n=70 each). At each PE+cannabis session, participants will vaporize 300mg of cannabis containing their randomized dose, which will be prepared using a digital scale with weight adjustments to measure exact doses. (For example, the High THC:High CBD dose will include 10 mg THC, 10 mg CBD, and 280 mg of placebo cannabis to make 300 mg for vaporizing).

250 completers x 4 cannabis administrations (PE Sessions 3-6) x 300 mg cannabis = 300 grams or 11 oz
100 non-completers x 2 cannabis administrations (PE Sessions 3-4) x 300 mg cannabis = 75 grams or 3 oz

Total cannabis needed: 300 g + 75 g = 375 g or 14 ounces, at $250/oz = $3500 over 5 years, or $700/year

Cannabis Vaporizers, mouthpieces, drug capsules, and capsule fillers. We will use Storz and Bickel's Mighty® Medical vaporizers to administer cannabis flower to participants. We estimate that we will need approximately 30 units ($349/each) over the course of the 5-year trial (15 in year 1 and 15 in year 3). The vaporizers will cost $349 x 30 units = $10,470 ($5235 in Years 1 and 3).

Mighty® vaporizer cooling units: The cooling unit is the removable mouthpiece on the vaporizer. We will provide a new cooling unit for each participant for sanitary purposes. We will purchase a total of 350 cooling units, at $20 each, for a total of $7000, or $1400/year.

Accessories for the Mighty® vaporizer (mouthpieces for each participant, drug capsules that are filled with cannabis flower and inserted into the vaporizer, cleaning tools, etc) will be purchased each year. The accessories will cost $1510, or $302/year.

Total cost for vaporizers is $10,470 + $7000 +$1510 = $18,980

Independent Laboratory Testing of Cannabis Flower Supply: We will have an independent lab (Midwest Analytical Services, 2905 Hilton Road, Ferndale, MI, 48220) analyze each cannabis batch and issue a Certificate of Analysis to verify cannabis concentrations issued by the federally-compliant supplier in their certificate of analysis. Samples will be tested for cannabinoids (THC THC-A Delta 8 THC-V CBD-A CBD CBN CBG-A CBG CBC), heavy metals, water activity, microbials, and solvent scan. Each analysis and report costs $600. We anticipate having 5 separate batches per year, at a cost of $3000/yr or $15,000 over 5 years.

Blood, saliva, and urine endocannabinoid and cannabinoid (THC/CBD) analysis: Blood, saliva and urine samples will be analyzed at the WSU Lipidomics Core (Krishnarao Maddipati, Ph.D., Director) using Liquid Chromatography – Mass Spectrometry (LC-MS) procedures. The Lipidomics Core has reviewed published methods and has all the necessary columns and equipment to perform the analyses. Reported detection limits are ≈1 ng/ml for most cannabinoid metabolites. State-of-the-art instrumentation at the Lipidomics Core is more sensitive than those used in most publications, so we can likely push the detection limits even lower. LC-MS analysis affords a major advantage: All analytes can be assayed in parallel for a single sample, without increasing the cost. Thus, the cost of the analysis is the same for any single class of metabolites. The cost is $93/sample and we anticipate a 3% increase over years 2-5.

1) Blood (plasma) levels: Samples from pre-PE treatment, post-PE+cannabis treatment, and post-PE treatment) will be analyzed (3 samples):

   50 completers in Year 1 x 3 samples = 150 samples x $93/sample = $13,950 in Year 1 with 3% increase anticipated in Years 2-5.

   Total blood sample analyses across 5 years: $74,062

2) Saliva samples will be analyzed pre- and post-cannabis administration during PE+cannabis sessions 3-6 (8 samples):

   50 completers in Year 1 x 8 samples = 400 samples x $93/sample = $37,200 in Year 1 (3% increase Years 2-5)
   20 non-completers in Year 1 x 4 samples = 80 samples x $93/sample = $7,440 in Year 1 (3% increase in Years 2-5

   Total saliva sample analyses across 5 years: $237,000

3) Urine samples will be analyzed at pre-PE treatment, pre- and post-cannabis administration during PE+cannabis sessions 3-6, and post-PE treatment (10 samples):

   50 completers in Year 1 x 10 samples = 500 samples x $93/sample = $46,500 in Year 1 (3% increase in Years 2-5)
   20 non-completers in Year 1 x 5 samples = 100 samples x $93/sample = $9,300 in Year 1 (3% increase in Years 2-5)

   Total urine sample analyses across 5 years: $296,250

Total blood/saliva/urine sample analyses: $74,062 + $237,000 + $296,250 = $607,312 ($114,390 in Year 1)

Salivary Genomic Collection: Salivary collection kits and storage containers will be purchased to collect samples of saliva for DNA (Oragene). Salivary kits are budgeted at $20 per unit. **Total for funding period $7,000 ($20 x 350)**

Genomic Laboratory Costs**:** These expenditures will pay for the laboratory analysis of DNA genotyping, DNA methylation, and mRNA expression in the WSU Pharmacogenomics Resource Laboratory (PGRL). Polymorphisms and mutations related to endocannabinoid receptors and associated enzymes (e.g., fatty acid amide hydrolase, FAAH) will be given priority based on the existing literature. These samples are analyzed in batches so it is difficult to estimate a cost per year but we project the **total for the funding period to be $122,500 ($350 x 350 samples).**

Phlebotomy training: Phlebotomy training and certification for Professional Research Assistants is requested (2 in Year 1, 2 in Year 3, and 1 in Year in 4) should any personnel changes occur. **Total requested is $2500.**

Psychophysiology Collection Supplies: Psychophysiology supplies include electrodes, electrode lead wires, electrolyte gel, alcohol swabs, medical tape, tissues, sanitizer, and latex gloves. **Total for all five years = $10,000 (5 X $2000).**

Biopac MP160 Nomadix System (Wireless)**: ($9,404)** As part of the proposed project, we plan to establish a dedicated startle and psychophysiology system. This system will include a Biopac MP160 psychophysiological recording system with the capacity to record multiple psychophysiological measures (electromyography (EMG), skin conductance responding (SCR), heart rate (HR) and heart rate variability (HRV) via wireless collection equipment. The wireless system will provide portability and convenience for research staff and participants.

OTHER EXPENSES

Screening Urine Testing: Urine samples will be collected during one screening visit. Each sample will be tested using multi-test cups with built-in temperature strips CLIA Waived, San Diego, CA; www.drugtesting-kits.com) for cocaine metabolites, benzodiazepines, cannabinoids, opioids, methadone, amphetamines, and barbiturates. Samples will be analyzed on-site at the rate of $10 per seven-panel test.

525 candidates screened (first urine) x $10 = $5250
Total costs = $5250/5 = $1050/year

Screening Pregnancy Testing: All female participants will have one urine pregnancy test done at screening. It is assumed that 10% of participants screened will be female. Thus, costs are for 53 females x $18/test = $955, for a yearly cost of $191.

Screening Volunteer Payments: Each candidate will earn up to $150 for the entire screening process. We anticipate that we will need to screen 525 veterans to identify 350 who are eligible to enroll (about 30% will not pass eligibility).

Total Payments for Volunteer Screenings: 525 x $150 = $78,750, for a yearly cost of $15,750.

We will be using the Clincard system to pay all research subjects. There are physical card costs of $4.95/card and a load fee of $1.15/card loaded. We will ask participants to bring back their cards to avoid additional card fees. Cards are loaded with payments as participants complete each milestone.

A total of 525 volunteers will attend 2 screening sessions:
Physical card fees: 525 x 4.95/card = $2599
Load fees: 525 x 2 sessions x $1.15/load = $1208

Total Clincard fees: $2599 + $1208 = $3807 or $761/year

Uber: Will offer Uber rides to and from study visits to all participants. Each trip one way is on average $25 per person ($50 both ways).

250 completers x 18 in-person sessions x $50 (round trip) = $225,000, or $45,000/year
100 non-completers x 5 in-person sessions x $50 (round trip) = $25,000, or $5,000/year

Total Uber costs = $250,000 or $50,000/year

Laboratory Tests: To determine that candidates are in good health and eligible, several laboratory tests are performed. These include ECG, CBC liver function test, urinalysis and electrolyte levels, the cost of which totals $80. Total costs for lab tests for candidates = 105 in Year 1 x $80 = $8400 in Year 1. We estimate that these costs will increase 3% per year in budget years 2-5.

Study Pregnancy tests for females*:* All female participants who are enrolled in the study will have urine pregnancy tests done at Baseline and prior to each study session that involves cannabis administration (PE sessions 3-6). It is assumed that 10% of participants enrolled will be female, and they will require 5 tests during the treatment phase. Thus, costs are for 35 females x 5 tests x $18/test = $3150 total or $630/year for 5 years.

Urine drug testing*:* Urine specimens will be tested on the morning of the baseline session, and prior to each of the 10 PE sessions, at $10/sample to measure cocaine metabolites, cannabinoids, benzodiazepines, opioids, methadone, amphetamines, and barbiturates.

350 enrolled x 3 samples at $10/sample = $10,500, or $2100/year
250 completers x 11 samples at $10/sample = $27,500, or $5500/year

Total urine drug testing: $10,500 + $27,500 = $38,000 or $7600/year

Participant Payments*:* Participants will be paid $100 for the Baseline assessment session; $40 for each of the 4 fear acquisition/extinction with MRI Scan sessions; $30 for each of the 5 PE sessions that do not involve cannabis administration (i.e., PE sessions 1, 2, 7-9); $60 for each of the 4 PE+cannabis sessions (PE sessions 3-6; we pay more for these sessions as they are longer because participants have to stay in the lab for 4 hours post-cannabis administration for safety reasons); $50 for PE Session 10 (this session is longer because of additional clinical assessments); $100 for the post-treatment assessment; and $50 for each of the 3 follow-up sessions. There is an additional $200 bonus for finishing the entire PE treatment and all 4 MRI scans, as well as an additional $100 bonus for completing all 3 follow-up sessions. Thus, study completers will earn a total of $1290. In addition, approximately 30% of participants who enroll in the studies will complete about 25% of the study before dropping out, thus we budget for a percentage of non-completers.

(250 completers x $1290) + (75 non-completers x $323) = $346,725 over 5 years = $69,345/year

We will be using the Clincard system to pay all research subjects. There are physical card costs of $4.95/card and a load fee of $1.15/card loaded. We will ask participants to bring back their cards to avoid additional card fees. Cards are loaded with payments as participants complete each milestone. We anticipate that half of the participants who enroll in the studies (about 175) will follow instructions to keep their cards from screening, so we anticipate having to purchase 175 additional cards.

Physical Card Fees: 350 cards needed x $4.95/card= $**1733 Total**

Completers:
19 payments (1 baseline + 4 scans + 10 PE sessions + 1 Post PE Assessment + 3 follow ups) *250 participants *1.15 card load fee = $**5463 Total**

Non-completers:
7 payments (1 baseline + 2 scans + 4 PE sessions) * 100 participants *1.15 card load fee =$**805 Total**

Total Clincard fees = $1733 + $5463 + $805 = $8001 over 5 years , or $1600/year

MRI Scans

To confirm that THC:CBD is affecting brain activation in regions that are important for treatment success we will scan a subset of veterans who meet criteria for fMRI safety. This includes scanner time, technologist time, miscellaneous supplies, usage of acquisition hardware and software, and image reconstruction by the technologist. The estimated rate is $800/hr. The scanning protocol has been estimated to last 1 hour per scan session (2 hours total Scans 1 and 2 pre-treatment and 2 hours total Scans 1 and 2 post-treatment). The total for the MRI scans is $464,000 ($92,800/year).

N = 125 completers x 4 scans x $800/scan = $400,000
N = 40 noncompleters x 2 scans x $800/scan = $64,000

Total cost for MRI Scans: $400,000+$64,000 = $464,000 or $92,800/year

Advertising/Recruiting*:* To maintain high visibility and to ensure adequate levels of screening to meet enrollment goals, we use a multi-pronged advertising strategy to recruit participants. These expenditures, although costly, are essential because recruitment is the key to completing the study successfully. We also expect to exclude approximately 30% of volunteers who will be screened. Although we also make excellent use of word-of-mouth referral, the number of calls we receive is proportional to advertising and our productivity is directly tied to the number of individuals who are scheduled for screening appointments. We will advertise the research study in local newspapers on a bi-weekly basis (alternating among different local papers). We will also use our WarriorCare website, developed for our currently ongoing veterans cannabis clinical trial, on which we post information about ongoing studies, offer contact information, resources, and conduct preliminary eligibility screening. We will also recruit via radio advertising, Facebook posts, Craig's List, and Twitter. We have established relationships with several veterans' support organizations, and will continue to work with them and to identify additional groups to recruit for the proposed study. Activities would include making presentations about the study at meetings, renting booth or table space at veterans' events where research staff would display information about the study, answer questions and conduct eligibility screenings, and other community and health outreach events.

Newspaper Ads: $200/each, we will run one biweekly each year of the study = $26,000
Radio ads: $200/each; we will run one per month each year of the study = $12,000
Table/booth space rental at Vet Fest, other events: $300/table x 4 events x 5 years = $6000
Display materials, signage for events and displays: $1000/year for 5 years = $5000
Small branding "giveaways" (pens, stress squeeze balls, etc) with our logo and phone number on them: $660 for 750 items, purchased 4x/year for 5 years = $13,200

Total advertising/recruiting: $26,000+$12,000+$6000+$5000+$13200 = $62,200 or $12,440/yr

Software fees. We will purchase yearly software upgrades for SPSS, Matlab, Presentation, Inquisit (Millisecond.com) for behavioral tasks of anhedonia, data storage, data management, and other software subscriptions.

Total software fees = $1800 per year, for a total of $9,000.

Castor: The study will utilize Castor as the electronic data capture system for recording questionnaire and screening data. The cost of Castor is paid $3,000 for study set-up during year 1 and then $1,200 for study maintenance in years 2-5.

Total cost for Castor = $3000 + $4800 = $7800 or $1560/year.

Purchased Services

Wayne Health: Liz Brunner, P.A., is a Physician Assistant employed by Wayne Health, working in the Tolan Park Medical Building (one floor below the Human Pharmacology Laboratory). She will assist with medical screenings, assist Dr. Lundahl (as she has routinely done in several past and ongoing projects) with experimental drug preparation, and she will assist Dr. Mischel (medically responsible investigator) by providing on-site monitoring of

participants' drug reactions. As a fee-for-service, we will reimburse Wayne Health for Ms. Brunner's time and effort up to $6979 each year of the study.

Biostatistics, Epidemiology and Research Design (BERD):

BERD is a core service offered at the University that is a "one-stop shop" for all quantitative and data intensive research needs. The experience and expertise of BERD is wide-ranging, with particular emphasis on intervention design, health equity and disparities, social determinants of health, and the unique demographics and epidemiology of the Detroit metropolitan area. BERD offers full service research support from inception to publication, for grants, industry collaborations, and investigator initiated studies: 1) Biostatistics (Formulation of research aims and development of plans for data collection and analysis; Statistical study design issues including experimental design, power analysis, and sample size assessment; Data cleaning and analysis, including preprocessing and shaping of data for analysis, descriptive statistics, hypothesis testing, statistical modeling, and advanced analytics; Interpretation and presentation of statistical findings. Creation of data displays and statistical tables. Production of written statistical methods and summary description); 2) Epidemiology (Content expertise in epidemiology with emphasis on measurement of health disparities and social determinants of health; Design of data collection forms, surveys and observational studies with emphasis on health equity; Collate and curate data and reports specific to health in Detroit, the region, and nationwide. Offer reports on demand for available validated data); and 3) Database (Design and development of electronic data collection instruments and study databases for a multitude of study designs including surveys, RCTs, clustered, longitudinal, and multi-center studies; Strategies for storage and management of large and complex data sets; Data archiving and cataloging; Transfer of legacy data into robust storage systems). BERD includes four Ph.D.-level faculty biostatisticians, one Ph.D.-level faculty epidemiologist, one Ph.D.-level health economist and two masters-level staff biostatisticians. Computational resources include high-end desktops (Xeon-based workstations) and access to the WSU high-performance computing grid. Statistical analyses packages include SAS, R, SPSS, STATA, and Matlab. We will utilize services at BERD to aid in data cleaning and analysis, including statistical modeling and advanced analytics, as well as interpretation and presentation of statistical findings. BERD charges $130/hr for statistical consulting. We expect to need 96 hrs/year in Years 1 - 5 to assist with database and Castor set up, database maintenance, data cleaning and analysis, and preparing findings for publication).

Total BERD Cost: 96 hrs * $130/hr = $12,480 x 5 years = $62,400

Travel

Presentations for Participant Recruitment: The Co-PIs and research staff will travel locally to 10-12 sites/year for presentations to veterans' groups, meeting with group leadership, and present at health fairs and similar community events. $300/trip (gas, mileage, food) = **$16,200 total or $3240/year.**

Miscellaneous*:* There will be costs related to writing results of this scientific study. They include poster presentation materials for years 2 – 5 ($2000), and preparation and reprint costs for publications from this research in years 3-5 ($3600). **A total of $5600 is requested.**

Occupancy Costs: All screening, baseline, PE therapy sessions, and follow-ups will be conducted at our Tolan Park Medical Building located at 3901 Chrysler Dr. Detroit, MI 48201. Participants will be seen in the WarriorCare Center on the first floor (Suite 1-B), in our reception area and interview rooms, and on our second floor in suites 2-A, specifically in rooms 238 (physical exam room) and 243 (smoking chamber). The total square footage of these rooms is 994.83 and the total cost per square footage is $35.70 which includes rent, maintenance, utilities, and property taxes. Rent is paid to Wells Fargo Bank Northwest, maintenance and utilities are paid to Colliers, our property management company, and property taxes to the City of Detroit. The interview rooms and smoking chamber will be dedicated 100% to this project, along with 50% of the reception area (the other 50% time is allocated to our current VMR trial). T**he total annual cost of these rooms is $24,041, for a total of $120,205 over the five year project.**

Data & Safety Monitoring Board (DSMB) Activities: The DSMB is made up of scientists and healthcare professionals that are not involved in the project and are appointed by the Co-PIs. The DSMB is responsible for monitoring study safety and efficacy. The DSMB is expected to meet regularly (e.g., every six to nine months). The meetings are conducted via teleconference call or may be held in-person. Funds for DSMB support and compensation for DSMB members are included. DSMB support costs include study staff time for scheduling meetings, preparing DSMB reports, traveling to DSMB meetings, and participating in the meetings. Support costs also include telecommunication costs, travel expenses for study staff and DSMB members (for in-person meetings). DSMB members are compensated for their time to review study materials and their participation in the meetings at $1,000 per year. We have 3 DSMB members, **so the total cost is $3000/yr x 5 years = $15,000.**

Subcontract to Emory University

Sheila Rauch, Ph.D., Site Lead and Co-Investigator (Professor, tenured) holds the Mark and Barbara Klein Distinguished Professorship and is a Professor in the Department of Psychiatry and Behavioral Science at Emory University School of Medicine. For over 20 years, her research has focused on PTSD and anxiety disorders development and treatment and psychological and biological mechanisms involved in those processes. She designed, administered, and led translational treatment outcomes studies including multi-site, trials examining outcomes and biomarkers of PTSD and effective treatment. In addition, she has led research into psychotherapy training and improving access and implementation of effective interventions for PTSD. She has been a Prolonged Exposure (PE) Trainer since 2000 and became an author of the latest version of the PE manual. She has served as Principal Investigator on several federally funded PTSD treatment grants (VA/DOD), and served as Co-Investigator on many other federal, state, and private grants. She is a clinical psychologist with over 25 years of experience in the assessment and treatment of psychiatric and substance use disorders, and she has served as psychotherapy lead, diagnostician and clinician on multiple randomized clinical trials of PTSD treatment. In her clinical practice she specializes in PTSD, anxiety, and substance use issues. She conducts PE training for research and clinical settings at least twice per year and designed a consultation program for advanced providers to train others in PE. Thus, she has the necessary scientific, administrative, and clinical experience to serve as Emory University site lead and Co-Investigator. She has enjoyed a successful history of collaboration with Dr. Rabinak and worked closely with Dr. Lundahl and Ledgerwood and the rest of the team to develop this exciting proposal. She is fully licensed in Michigan and Georgia. She has a split Atlanta VA Medical Center and Emory University appointment. There is a memorandum of understanding on file that details her dual appointment split between the Emory University and Atlanta Veterans Affairs Medical Center. Dr. Rauch has a 5/8 VA appointment. This proposal represents 3.6 CM of her EU effort and 0.78 of her total professional effort. She will be funded by University efforts. She will lead therapist training, consultation, ongoing supervision, and fidelity rating for the duration of the trial. In addition, she was involved in study design and will contribute to analytic planning and manuscript preparation and publication. Dr. Rauch will devote 30% effort, or 12 hours per week, for years 1-5 of this project.

Syreese Fuller, M.S., Clinical Research Coordinator: Ms. Fuller will devote 15% effort to lead the research team on regulatory and implementation of protocol to ensure all reporting and regulatory requirements are met. She will be responsible for managing all day-to-day project needs, helping develop and implement protocols for collecting biological, behavioral, and questionnaire data, overseeing recruiting and scheduling of screening and baseline sessions, and enrollment, and randomization procedures. She will lead completion of IRB paperwork, maintain agency records, oversee scheduling of phone interviews and follow-ups, and coordinate data entry and management with the research assistants. She will meet regularly with the PIs to assure quality control and maintenance of study records, provide summaries, and assist in preparing data for presentations and publications. She will devote 15% effort, or 6 hours per week, throughout this project.

TBD, Postdoctoral Fellow, Psychotherapist: We request funding for one PhD-level postdoc in Psychology who will be trained to provide PE therapy and will conduct clinical assessments, as well as contribute to statistical analysis and manuscript preparation. Effort may be split between two postdoctoral fellows to provide backup prolonged exposure to the enrolled study patients across study conditions, complete fidelity assessment of sessions, and consultation of training cases and other duties as assigned. Therapy will occur 2, 60-minute sessions per week for up to 10 sessions. Sessions will occur via telehealth under supervision of Dr. Rauch. The postdoctoral fellow will devote 100% effort, or 40 hrs per week, for years 1-5 of this project.

Telehealth Fees: Licensing fees and other costs to establish and maintain the telehealth compliance, privacy, and confidentiality. **$4000 per year for Years 1-5, for a total of $20,000.**

Travel for PE Therapist Training: Dr. Rauch and her postdoc will travel to Detroit for 3 days to provide therapist training to the Wayne State clinical therapists (postdoc, practicum students), once in Year 1 and again in Year 3, at $4000 per visit, for **a total of $8,000**.

END APPLICANT RESPONSE

V-I Additional Information and Comments

Include in this section any other information that is believed to be pertinent but not specifically requested elsewhere in this RFP.

N/A

V-J Certification of Proposal

Please sign the proposal including the following language:

I certify that all information contained in the proposal is true to the best of my knowledge and belief, and that the organization is in compliance and agreement with all sections of the Request for Proposal. Failure to comply with grant terms may result in termination.

Certified by:  Grant & Contract Officer IV 5.27.2022

Authorized Signatory and Title Date

Name of Organization

Wayne State University

NON-DISCLOSURE AGREEMENT

This Agreement is made as of the last date set forth below (the "Effective Date") by and between Wayne State University ("WSU") and State of Michigan Department of Licensing and Regulatory Affairs, Cannabis Regulatory Agency (“CRA”) with offices located at 5057 Woodward Avenue, Suite 13th floor, Detroit, MI 48202 and 2407 North Grand River Avenue, Lansing, MI 48909, respectively.

Recitals

The parties intend to discuss the 2022 Veteran Marijuana Research Grant, including information that each party regards as confidential, proprietary information of such party. The parties propose to disclose certain of such information to each other for the limited purpose(s) described on the last page of this Agreement (the "Permitted Purpose"). This Agreement sets forth the parties' understanding with respect to all such confidential information.

Agreement

The parties agree as follows:

1. The party disclosing information pursuant to this Agreement shall be referred to as the “DISCLOSING PARTY.” The party receiving such information shall be referred to as the “RECEIVING PARTY.”

2. "Confidential Information" shall mean all information disclosed to RECEIVING PARTY or its representatives by DISCLOSING PARTY (a) relating to the technology or methodologies of DISCLOSING PARTY referred to above; or (b) that relates to DISCLOSING PARTY's past, present and future research, development and business activities, including, but not limited to, confidential ideas, know-how and technical information pertaining to the Permitted Purpose.

3. The Confidential Information will be used by RECEIVING PARTY solely for the Permitted Purpose. All Confidential Information will be received and held in confidence by RECEIVING PARTY, subject to the provisions of this Agreement. RECEIVING PARTY acknowledges that it will not obtain any rights of any sort in or to the Confidential Information as a result of such disclosure and that any such rights must be the subject of separate written agreement(s) with DISCLOSING PARTY.

4. RECEIVING PARTY will restrict disclosure of Confidential Information to those of its employees to whom it is necessary to disclose such Confidential Information in connection with the Permitted Purpose. RECEIVING PARTY will not disclose Confidential Information to any third party.

5. Confidential Information shall not include the following:

   a. any information that the RECEIVING PARTY can show by documentary evidence was in its possession prior to the disclosure to it hereunder; or

   b. any information that comes into the possession of the RECEIVING PARTY, its agents or employees from another party who is under no obligation to the other to maintain confidentiality of such information; or

c. any information that becomes generally known other than through the fault of the RECEIVING PARTY, or its employees or agents;

d. any particular portion of the Confidential Information which RECEIVING PARTY can show by documentary evidence was developed by employees or agents of the RECEIVING PARTY independently of and without reference to any Confidential Information or other information that DISCLOSING PARTY has disclosed in confidence to any third party; or

e. any information which is required to be disclosed by law or legal process.

The burden of proving these exceptions to the provisions of this Agreement resides with the RECEIVING PARTY. It is understood that in the event a portion or aspect of Confidential Information becomes generally known, only that portion or aspect shall not be governed by this Agreement and that all other aspects of such Confidential Information shall remain subject to the provisions of this Agreement.

6. RECEIVING PARTY shall use its best efforts, including at least efforts fully commensurate with those employed by RECEIVING PARTY for the protection of its own confidential information, to protect the Confidential Information. The confidentiality and use provisions of this Agreement shall remain in full force and effect for a period of five (5) years from the Effective Date.

7. DISCLOSING PARTY may at any time notify the RECEIVING PARTY that RECEIVING PARTY must return to DISCLOSING PARTY the Confidential Information. RECEIVING PARTY shall within ten (10) days of such notification: (a) return all media under its control embodying the Confidential Information; and (b) return or certify (in a writing attested to by a duly authorized officer of RECEIVING PARTY) destruction of all copies, summaries, records, descriptions, modifications, or adaptations which RECEIVING PARTY or its employees or agents have made from the media referred to in Section 1.

8. If the Confidential Information is or becomes the subject of a patent application, patent, or copyright registration made or received by DISCLOSING PARTY under the laws of the United States or any foreign jurisdiction, RECEIVING PARTY hereby agrees that DISCLOSING PARTY, subject to any subsequent written agreement between the parties to the contrary, will have all the rights and remedies available to it as a result of said patent application, patent or copyright registration.

9. This Agreement shall be governed by and construed under the laws (other than the choice or conflict of laws provisions) of the State of Michigan. The provisions of this Agreement may not be amended except in a writing signed on behalf of each party. The signatory for Wayne State University is providing a signature with permission from and on behalf of all Principal- and Co-Investigators on the proposal, entitled “Wayne State Warriors Marijuana Clinical Research Program: Cannabinoid Adjunct to Prolonged Exposure & Recovery (CAPER)”.

The parties have hereinafter indicated their acceptance of this Agreement.

WAYNE STATE UNIVERSITY

By: Patty Jo Kulesza Kulaszewski
Title: Associate Director,Contract Administration

Date: May 26, 2022
Address: 5057 Woodward
13th Floor
Detroit, MI 48202
Fax: 313-577-5055

Attachment A: VMR BUDGET
Submission Date: June 1, 2022
The numbers below are actual proposed budget amounts for this proposal.

Line Item	Budget Category						
1	**Administrative Expenses**						
2	**Administrative Personnel (Grant Administration Staff)**						
3	*Salary*	**2022-2023**	**2023-2024**	**2024-2025**	**2025-2026**	**2026-2027**	**TOTAL**
4	Jennifer Ballard-Traynor, Administrative Director	$9,690	$9,981	$10,280	$10,589	$10,906	$51,446
5	Cordell Crutchfield, Grant & Contract Administrator	$3,007	$3,098	$3,190	$3,286	$3,385	$15,966
6	Sonya Blair, Program Specialist	$3,289	$3,387	$3,489	$3,594	$3,702	$17,461
7	**Total Salary**	$15,986	$16,466	$16,960	$17,468	$17,993	$84,873
8	*Fringe Benefits*						
9	Jennifer Ballard-Traynor, Administrative Director	$2,849	$2,934	$3,022	$3,113	$3,206	$15,125
10	Cordell Crutchfield, Grant & Conract Administrator	$884	$911	$938	$966	$995	$4,694
11	Sonya Blair, Program Specialist	$967	$996	$1,026	$1,057	$1,088	$5,133
12	**Total Fringe Benefits**	$4,700	$4,841	$4,986	$5,136	$5,290	$24,953
13	***Total Administrative Personnel***	$20,686	$21,307	$21,946	$22,604	$23,282	**$109,825**
14	**Administrative Supplies, Materials, and Equipment**						
15	Does not apply	$	$	$	$	$	$
16	***Total Administrative Supplies, Materials & Equipment***	$	$	$	$	$	$
17	**Administrative Contractual Services**						
18	Does not apply	$	$	$	$	$	$
19	***Total Administrative Contractual Services***	$	$	$	$	$	$
20	**Administrative Travel (Grant Administration Staff)**						
21	Does not apply	$	$	$	$	$	$
22	***Total Administrative Travel***	$	$	$	$	$	$
23	**Total Administrative Expenses**	**$20,686**	**$21,307**	**$21,946**	**$22,604**	**$23,282**	**$109,825**
24	**VMR Program Expenses**						
25	**VMR Program Staff**						
26	*Salary*						

27	Leslie Lundahl, Ph.D., Co-Principal Investigator	$87,742	$90,374	$93,085	$95,878	$98,754	$465,834
28	Christine Rabinak, Ph.D., Co-Principal Investigator	$58,120	$59,863	$61,659	$63,509	$65,414	$308,565
29	David Ledgerwood, Ph.D., Co-Investigator	$61,400	$63,242	$65,139	$67,093	$69,106	$325,980
30	Mark Greenwald, Ph.D., Co-Investigator	$24,020	$24,741	$25,483	$26,247	$27,035	$127,525
31	Hilary Marusak, Ph.D., Co-Investigator	$19,877	$20,474	$21,088	$21,721	$22,372	$105,532
32	Paul Kilgore, M.D., Co-Investigator	$16,693	$17,194	$17,710	$18,241	$18,788	$88,627
33	Nicholas Mischel, M.D., Ph.D., Co-Investigator	$21,939	$22,597	$23,275	$23,973	$24,693	$116,477
34	**Total Salary**	$289,791	$298,485	$307,439	$316,662	$326,162	$1,538,540
35	*Fringe Benefits*						
36	Leslie Lundahl, Ph.D., Co-Principal Investigator	$24,041	$24,763	$25,505	$26,271	$27,059	$127,639
37	Christine Rabinak, Ph.D., Co-Principal Investigator	$15,925	$16,403	$16,895	$17,401	$17,923	$84,547
38	David Ledgerwood, Ph.D., Co-Investigator	$16,824	$17,328	$17,848	$18,384	$18,935	$89,319
39	Mark Greenwald, Ph.D., Co-Investigator	$7,062	$7,274	$7,492	$7,717	$7,948	$37,492
40	Hilary Marusak, Ph.D., Co-Investigator	$5,446	$5,610	$5,778	$5,951	$6,130	$28,916
41	Paul Kilgore, M.D., Co-Investigator	$4,574	$4,711	$4,853	$4,998	$5,148	$24,284
42	Nicholas Mischel, M.D., Ph.D., Co-Investigator	$6,011	$6,192	$6,377	$6,569	$6,766	$31,915
43	**Total Fringe Benefits**	$79,883	$82,280	$84,748	$87,290	$89,909	$424,110
44	***Total VMR Program Staff***	$369,674	$380,764	$392,187	$403,953	$416,072	**$1,962,650**
45	**VMR Personnel Program Staff**						
46	*Salary*						
47	Nareen Sadik, Clinical Trials Coordinator	$53,045	$54,636	$56,275	$57,964	$59,703	$281,623
48	Jasmin Hollins, Professional Research Assistant	$27,476	$28,301	$29,150	$30,024	$30,925	$145,875
49	Reshma Dukkipati, Professional Research Assistant	$35,568	$36,635	$37,734	$38,866	$40,032	$188,835
50	Halle Thomas, Clinical Diagnostic Assistant	$6,000	$6,000	$6,000	$6,000	$6,000	$30,000
51	Nicole Kouri, Clinical Diagnostic Assistant	$6,000	$6,000	$6,000	$6,000	$6,000	$30,000
52	Alanna Foulon, Recruiter	$35,568	$36,635	$37,734	$38,866	$40,032	$188,835
53	TBD, Clinical Research Coordinator (Rabinak)	$50,000	$51,500	$53,045	$54,636	$56,275	$265,457
54	TBD, Postdoctoral Clinical Psychology Fellow	$54,835	$56,480	$58,174	$59,920	$61,717	$291,126

55	TBD, Postdoctoral Research Fellow (Rabinak)	$54,835	$56,480	$58,174	$59,920	$61,717	$291,126
56	TBD, Research Technologist (Rabinak)	$50,000	$51,500	$53,045	$54,636	$56,275	$265,457
57	TBD, Research Assistant (Rabinak)	$40,000	$41,200	$42,436	$43,709	$45,020	$212,365
58	**Total Salary**	$413,327	$425,367	$437,768	$450,541	$463,697	$2,190,701
59	*Fringe Benefits*						
60	Nareen Sadik, Clinical Trials Coordinator	$16,126	$16,609	$17,108	$17,621	$18,150	$85,613
61	Jasmin Hollins, Professional Research Assistant	$8,353	$8,603	$8,861	$9,127	$9,401	$44,346
62	Reshma Dukkipati, Professional Research Assistant	$10,813	$11,137	$11,471	$11,815	$12,170	$57,406
63	Halle Thomas, Clinical Diagnostic Assistant	$1,824	$1,824	$1,824	$1,824	$1,824	$9,120
64	Nicole Kouri, Clinical Diagnostic Assistant	$1,824	$1,824	$1,824	$1,824	$1,824	$9,120
65	Alanna Foulon, Recruiter	$10,813	$11,137	$11,471	$11,815	$12,170	$57,406
66	TBD, Clinical Research Coordinator (Rabinak)	$15,200	$15,656	$16,126	$16,609	$17,108	$80,699
67	TBD, Postdoctoral Clinical Psychology Fellow	$16,670	$17,170	$17,685	$18,216	$18,762	$88,502
68	TBD, Postdoctoral Research Fellow (Rabinak)	$16,670	$17,170	$17,685	$18,216	$18,762	$88,502
69	TBD, Research Technologist (Rabinak)	$15,200	$15,656	$16,126	$16,609	$17,108	$80,699
70	TBD, Research Assistant (Rabinak)	$12,160	$12,525	$12,901	$13,288	$13,686	$64,559
71	**Total Fringe Benefits**	$125,651	$129,312	$133,082	$136,965	$140,964	$665,973
72	***Total VMR Personnel Program Staff***	$538,979	$554,679	$570,850	$587,506	$604,661	**$2,856,674**
73	***VMR Supplies, Materials, & Equipment***						
74	iMac Desktop Computers	$4,516	$	$2,258	$	$	$6,774
75	MacBook Pro Laptop	$2,100	$	$2100	$	$	$4,200
76	Computing Tablets	$2,400	$	$1,600	$	$	$4,000
77	Laptops for Biopac	$2,400	$	$	$	$	$2,400
78	Psychophysiology Collection Supplies	$2,000	$2,000	$2,000	$2,000	$2,000	$10,000
79	BioPac Psychophysiology	$9,404	$	$	$	$	$9,404
80	Vitals Monitor	$875	$	$	$	$	$875
81	Screening Related Supplies	$1,610	$1,658	$1,708	$1,759	$1,812	$8,548

82	Research Data Handling Supplies	$4,900	$5,047	$5,198	$5,354	$5,515	$26,015
83	Assessment Materials and Supplies	$7,000	$4,000	$4,000	$4,000	$4,000	$23,000
84	Participant Supplies During Sessions	$3,600	$3,708	$3,819	$3,934	$4,052	$19,113
85	HEPA Filters (Portable Air Cleaners)	$1,800	$	$	$	$	$1,800
86	Cannabis	$700	$700	$700	$700	$700	$3,500
87	Mighty Medic Cannabis Vaporizer	$5,235	$	$5,235	$	$	$10,470
88	Mighty Medic Cooling Units	$1,400	$1,400	$1,400	$1,400	$1,400	$7,000
89	Mighty Medic Accessories	$302	$302	$302	$302	$302	$1,510
90	Lab Testing of Cannabis COA	$3,000	$3,000	$3,000	$3,000	$3,000	$15,000
91	Blood, Saliva, Urine THC/CBD Analyses	$114,390	$117,822	$121,356	$124,997	$128,747	$607,312
92	Salivary Genomic Kits	$7,000	$	$	$	$	$7,000
93	Genomic Lab Analysis Costs	$122,500	$	$	$	$	$122,500
94	Data Storage and Server Management	$25,000	$5,000	$5,150	$5,305	$5,464	$45,918
95	Phlebotomy Training	$1,000	$	$1,000	$500	$	$ 2,500
96	Urine Drug Testing - Screening	$1,050	$1,050	$1,050	$1,050	$1,050	$5,250
97	Pregnancy Testing - Screening	$191	$191	$191	$191	$191	$ 955
98	Volunteer Payments - Screening	$15,750	$15,750	$15,750	$15,750	$15,750	$78,750
99	Clincard Fees - Screening	$761	$761	$761	$761	$761	$3,805
100	Transportation for Research Participants	$50,000	$50,000	$50,000	$50,000	$50,000	$250,000
101	Laboratory Tests - Screening	$8,400	$8,652	$8,912	$9,179	$9,454	$44,597
102	Pregnancy Testing - During Study	$630	$630	$630	$630	$630	$3,150
103	Urine Drug Testing - Study	$7,600	$7,600	$7,600	$7,600	$7,600	$38,000
104	Participant Payments - Study	$69,345	$69,345	$69,345	$69,345	$69,345	$346,725
105	Clincard Fees - Study	$1,600	$1,600	$1,600	$1,600	$1,601	$8,001
106	MRI Scans	$92,800	$92,800	$92,800	$92,800	$92,800	$464,000
107	Advertising/Recruiting	$12,440	$12,440	$12,440	$12,440	$12,440	$62,200
108	Software Fees	$1,800	$1,800	$1,800	$1,800	$1,800	$9,000
109	Castor	$1,560	$1,560	$1,560	$1,560	$1,560	$7,800
110	Purchased Services -WH (Liz Brunner)	$6,979	$6,979	$6,979	$6,979	$6,979	$34,893

111	Biostatistics Design Services (BERD)	$12,480	$12,480	$12,480	$12,480	$12,480	$62,400
112	Presentation/Publication Costs	$0	$500	$1,700	$1,700	$1,700	$ 5,600
113	Data Safety Monitoring Board (DSMB)	$3,000	$3,000	$3,000	$3,000	$3,000	$15,000
114	Occupancy Costs	$24,041	$24,041	$24,041	$24,041	$24,041	$ 120,205
115	OnCore Fee (Clinical Trials software)	$1,532	$1,532	$1,532	$1,532	$1,532	$7,660
116	***Total VMR Supplies, Materials, & Equipment***	$635,091	$457,348	$474,997	$467,688	$471,705	**$2,506,829**
117	**VMR Contractual Services**						
118	Emory University Subcontract	$157,548	$ 155,345	$166,473	$164,537	$169,342	$813,245
119	***Total VMR Contractual Services***	$157,548	$155,345	$166,473	$ 164,537	$169,342	**$813,245**
120	**VMR Travel (VMR Staff)**						
121	Presentations for Participant Recruitment	$3,240	$3,240	$3,240	$3,240	$3,240	$16,200
123	***Total VMR Travel (VMR Staff)***	$3,240	$3,240	$3,240	$3,240	$3,240	**$16,200**
124	**VMR Other**						
125	Ryan Vandrey (Consultant)	$3,000	$2,000	$1,000	$1,000	$1,000	$8,000
126	Marcel Bonn-Miller (Consultant)	$2,000	$1,000	$1,000	$1,000	$1,000	$6,000
127	***Total EAP Other***	$5,000	$3,000	$2,000	$2,000	$2,000	**$14,000**
128	**Total VMR Program Expenses**	$1,730,218	$1,575,682	$1,631,693	$1,651,528	$1,690,303	$8,279,423
129	**Total Direct Cost**	$1,730,218	$1,575,682	$1,631,693	$1,651,528	$1,690,303	$8,279,423
130	*Indirect Cost (0.10)*	$159,767	$142,034	$146,522	$148,699	$152,096	$749,118
131	**TOTAL PROJECT COST**	$1,903,239	$1,733,250	$1,794,862	$1,816,681	$1,859,333	**$9,028,541**