FRAMEWORKS FOR FUTURE CANNABIS RESEARCH: LEGISLATIVE REPORT

Dr. Nephi Stella, Ph.D. (He/Him)

UNIVERSITY OF WASHINGTON
CENTER FOR CANNABIS RESEARCH

December 1st, 2021

Table of Contents

Introduction

►Authorizing Budget Proviso

In Washington state's 2021-23 operating budget (ESSB 5092), the University of Washington Center for Cannabis Research was directed to collaborate with the Washington State University Collaboration on Cannabis Policy, Research, and Outreach to create frameworks for future cannabis studies. The proviso included in Section 606, subsection 42 reads as follows:

(a) $100,000 of the general fund—state appropriation for fiscal year 2022 is provided solely for the center for cannabis research at the university to collaborate with the Washington State University collaboration on cannabis policy, research, and outreach to create frameworks for future studies. Each framework will include the length of time to complete, research licenses necessary, cost, literature review of national and international research, and a scope of work to be completed. The following frameworks shall be compiled in a report:
    (i) Measuring and assessing impairment due to marijuana use; and
    (ii) Correlation between age of use, dosage of use, and appearance of occurrence of cannabis induced psychosis.

(b) The report on the frameworks must be submitted to the appropriate committees of the legislature by December 1, 2021.

►About the Author

Dr. Nephi Stella is a professor at the University of Washington, School of Medicine, Department of Pharmacology and of Psychiatry and Behavioral Sciences. His is the director of the University of Washington Center for Cannabis Research (**UW-CCR**). We thank Dr. Ben Land, research assistant professor at the University of Washington, School of Medicine, Department of Pharmacology, and UW-CCR member, for help with generating this report.

►About the University of Washington Center for Cannabis Research (UW-CCR)

The UW-CCR was established in 2017 with the mission to foster cannabis research and innovation at the University and in Washington state. Key partners across the University and nation have been identified to solidify science addressing pressing cannabis questions.

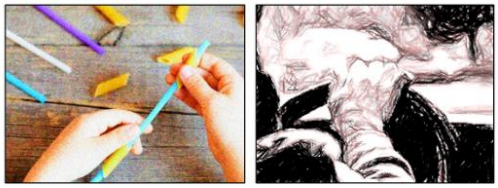
►About the Washington State University Center for Cannabis Policy, Research, and Outreach (WSU-CCPRO)

The WSU-CCPRO consists of more than 70 researchers across the WSU system. Four specific themes have been identified to establish WSU as a global leader in cannabis research, policy, and outreach: improving health and wellbeing, public policy and safety, economics, and agricultural research.

Executive Summary

Premise: There has been a recent increase in the use of *Cannabis*-based products in Washington state, including the use of products containing high levels of delta^9-tetrahydrocannabinol (**THC**), the main psychoactive compound of *Cannabis*, by both adolescents and adults. Recent evidence indicates that THC use impacts adolescent brain function during critical periods of brain development that may result in affecting select brain functions in adulthood. Cannabis use during adolescence and adulthood may increase incidence of **psychotic** episodes, suggesting that vulnerable populations to the effects of THC exist in both adolescents and adults. Cannabis use also leads to selective behavioral **impairments**, including motor, attention, sedation, and exhaustion.

Cannabis use during adolescence and adulthood may increase incidence of psychotic episodes suggesting the existence of vulnerable populations to the effects of THC.



Acute and chronic *Cannabis* use may result in behavioral impairment. The extent of motor and attention impairment, sedation and exhaustion linked to Cannabis us is unknown.

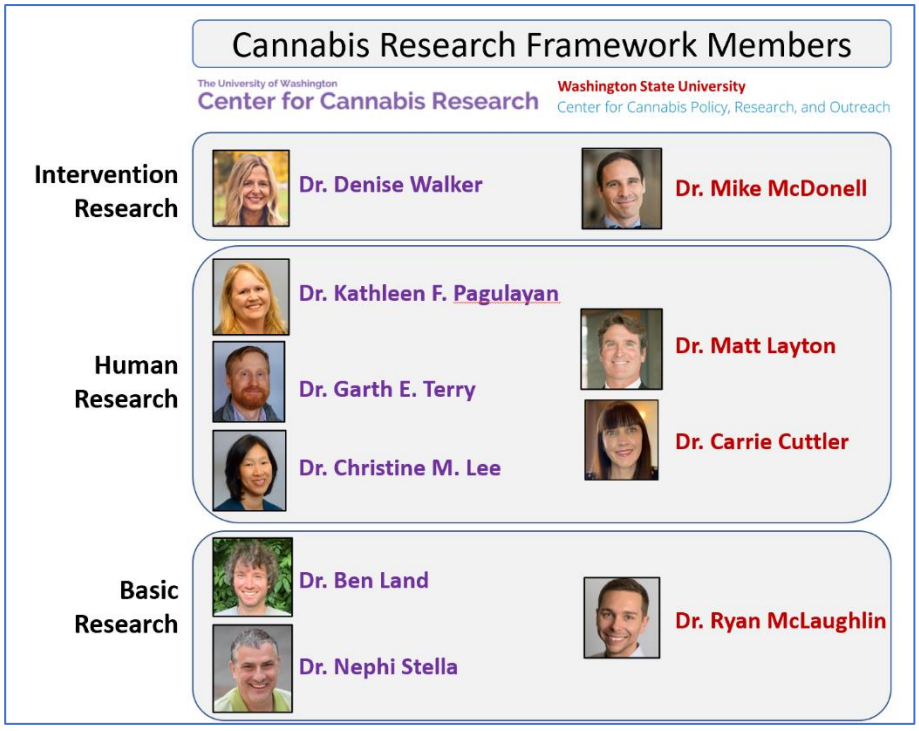
Need: To date, we lack a fundamental understanding of the amount and regimen of THC use that leads to 1] the increase incidence of psychosis in adolescents and adults, and 2] behavioral impairment in adolescents and adults. As a result, we still do not know the short- and long-term public health, social, and economic impacts of high potency THC *Cannabis* use.

Current peer-reviewed research on cannabis impacts:

This report provides the most relevant and accepted impacts associated with Cannabis use during adolescence and adulthood focusing on incidence of psychotic episodes and behavioral impairment (Annex 2).

Overview of framework for future cannabis research: The University of Washington Center for Cannabis Research (**UW-CCR**) and Washington State University Center for Cannabis Policy, Research, and Outreach (**WSU-CCPRO**) implemented a **Cannabis Research Framework (CRF)** that unites world experts studying cannabis. This platform will foster collaborations between UW and WSU and promote synergistic research.

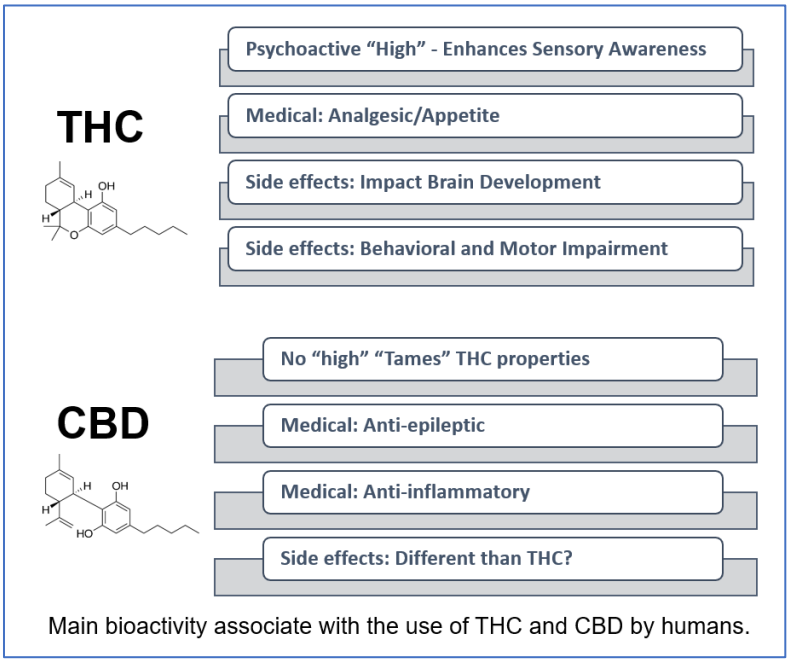
In 2022-23, the CRF aims to study the impact on brain functions of high THC potency Cannabis product use by adolescents and adults focused on the increase incidence of psychosis and on behavioral impairments. The CRF has identified 10 pressing research priorities, including intervention research, human research, and fundamental research (Annex 5). If funded, the research project findings will be shared in virtual seminars open to the public and online. CRF specifics are outlined in Annexes 3 and 4.



Background - Current Literature

►CBD and high potency THC *Cannabis* products

What is known: *Cannabis* is a dioecious plant that grows wild in many tropical parts of the world and is one of the world's oldest crops dating back about 12,000 years [1]. Δ^9-tetrahydrocannabinol (**THC**) produces psychotropic effects, typically described as enhanced sensory perception, distorted perception of space and time, and altered interpersonal relationships and thought processes [2, 3]. Cannabidiol (**CBD**) is often referred to as a non-psychotropic compound because it does not induce the euphoria and intoxication triggered by THC [4]. Of note, however, CBD does greatly influence specific brain functions and behaviors, including neuronal activity, seizure incidence, and social interactions through a different mechanism than THC [5, 6]. Thus, THC and CBD are the two most abundant phyto-cannabinoids (**phyto-CB**) produced by the *Cannabis* plant, and their effects on brain function occurs along a continuum, from beneficial effects to harm reduction properties and potential harm in vulnerable population. The continuum also occurs along the market-oriented legalization of the use of high potency Cannabis products.



Main bioactivity associate with the use of THC and CBD by humans.

The recently developed cultivation methods of the *Cannabis* plant either boost THC concentrations or boost CBD concentrations. In contrast, Hemp contains THC concentrations below 0.3%. The THC:CBD ratio in *Cannabis* has increased from 14-fold in 1995 to 80-fold in 2014, and more recent *Cannabis*-based products using *Cannabis* extracts can contain more than 90% THC [7]. Concomitantly, *Cannabis* use seems to be increasingly accepted as a safe recreational drug, as indicated by 16.4% of individuals ages 12–17 and 51.9% of individuals ages 18–25 years in the U.S. reporting the use of *Cannabis* in their lifetime (2021 NIDA). Furthermore, the age of onset of daily use of *Cannabis*-based products is rapidly shifting towards younger ages (2021 NIDA). Together, these statistics indicate that there is a shift toward increased use of high potency *Cannabis*-based products by adolescents, a scenario that may have impactful consequences on adolescent brain development and subsequent adulthood behavior. The urgency to better understand the public health impacts of Cannabis-based products is critical since thousands, if not millions, of adolescents are likely to be exposed to these chemically complex products over the coming decades.

The legalization of *Cannabis* bolstered the development of novel *Cannabis*-based products and devices. The most common are flower cigarettes (joints) and edibles (cookies and candies). Newly developed devices greatly increase THC intake and provide both faster and higher quantities of phyto-CBs delivered per use. Examples include electronic vaping devices that deliver 60-80% THC and dabbing devices that deliver high dose concentrated cannabis resin that can exceed 90% THC [8]. Unlike *Cannabis* flower cigarettes and edibles, vaping

and dabbing devices, as well as colorful candies and soft drinks, tend to be more common among adolescents who use more *Cannabis* overall. The ever-increasing landscape of devices and products that deliver high-dose THC further promotes potentially dangerous consummatory behaviors [9]. In Washington state, epidemiological data available since legalizing Cannabis use in 2012 show that *Cannabis* users are now more likely to use concentrated forms through dabbing, eating, or vaping than prior to legalization [10]. Further, it is important to better understand the diversity in THC's impact on human health, whether it varies depending on health, sex, ethnicity/race, and age. To summarize, the legalization of *Cannabis*-based products resulted in the production of new devices that rapidly deliver THC concentrates of high potency and thus may increase their psychotropic response, which raises concerns about the unknown impacts of such products on vulnerable populations, in particular adolescents.

The most common *Cannabis*-based products were flower cigarettes (joints) and edibles (cookies). The legalization of *Cannabis* use led to the development of new High potency THC Cannabis products and devices that delivery higher amounts of THC with faster onset and are appealing adolescents, including vape pens, dabbing devices, colorful candies and soft drinks, all of which are appealing to adolescents.

►*Cannabis* Use and Psychosis

What is known: Recent scientific evidence indicates regular use of high potency THC products might enhance the incidence of psychotic episodes and schizophrenia. These studies raise the possibility that high potency THC products might trigger detrimental mental health issues in select individuals that are especially vulnerable, in particular adolescents [11-14]). Indeed, more than two decades of peer-reviewed studies have demonstrated that the adolescent brain exhibits significant vulnerability to continued exposure of THC [15]. Additionally, *Cannabis* Use Disorder (**CUD**) or addiction to *Cannabis*, particularly among adolescents, was recently identified and introduced in the DSM IV as a "new" psychiatric disorder [16]. CUD impairs social functioning, memory, decision-making, school/work performance, and is more likely to be expressed by adolescent long-term users of high-dose THC compared to adults using similar amounts [17-20]. This suggests the use of high potency THC products may represent a contributing factor in adolescents transitioning from experimental use to frequent use [18]. For example, a study performed in the U.S. monitored THC potency and CUD symptom onset and found that high potency cannabis products used at *Cannabis* initiation is associated with over 4 times the risk of CUD symptom onset within the first year of initiation [19, 20]. Other studies indicate that daily use of high-potency *Cannabis* during adolescence is associated with an earlier onset (6 years earlier on average) of psychotic symptoms than non-cannabis users [12]. Scientific evidence also suggests that use of high potency THC products exacerbates negative psychotic outcomes and severity of relapse/further episodes in adult patients. Together, this evidence suggests an increased risk of experiencing CUD and other mental disorders, such as psychosis and schizophrenia, when adolescents frequently use high THC *Cannabis* products.

What is needed: There is an urgent need to determine the relationship between age of onset of high potency THC products, the frequency of use, and the ensuing impact on brain function in adolescents and adults, and whether this use enhances the incidence of psychotic episodes and schizophrenia. Such understanding will help identify the short- and long-term public health impacts of high potency THC product use in individuals vulnerable to psychosis. It will also help with the development of therapeutic interventions for the prevention and treatment of mental health issues resulting from the use of high potency THC products. Overall, additional research is necessary to inform public health and policy decisions and to help consumers make educated decisions related to *Cannabis* use.

►*Cannabis* Use and Impairment

What is known: In addition to the "high" (i.e., psychotropic effects), THC also produces significant behavioral changes, including sedation, attention deficits, and impairment of select motor behaviors. As a result, use of high potency THC products impacts psychomotor and cognitive processes critical to daily functions, including driving and working [21-26]. Considering this effect, the impact of using high potency THC products may have significant economic and public safety consequences. However, research on impairment resulting from high potency THC products is limited to date.

1) Driving Impairment: A recent study in Washington state indicates increases in both the prevalence of drivers with high THC concentrations compared to pre-legalization and risk of car accident after *Cannabis* use at higher THC blood concentrations.

2) Workplace Impairment: To date, few studies have analyzed the relationship between use of high potency THC products and workplace impairment, possibly due to complications in study design. Remarkably, one study showed no relationship between *Cannabis* use and worksite injury, although the study design did not consider use of high potency THC products or the operation of heavy machinery.

3) Psychomotor impairments: Basic research conducted in rodents (i.e., mice and rats) demonstrate that THC triggers characteristic motor impairment behaviors, including reduced locomotion, impaired motor coordination, altered perception, short term memory and spatial memory, all of which are critical components of accurate motor behaviors.

What is needed: There is an urgent need to better understand how acute and chronic use of high potency THC products leads to behavioral changes, including sedation, attention deficits, and impairment of select locomotor behaviors, all of which may affect driving skills and rate of car accidents, as well as workplace performance and safety. Importantly, we currently lack reliable measurements in real-world environments on how the use of high potency THC products affects brain functions, making behavioral change assessments difficult. Basic research can help identify fundamental locomotor behaviors impairments, which can be utilized to improve public and workplace safety.

UW-WSU Cannabis Research Framework

Overarching Goal: In 2022-23, the UW-WSU Cannabis Research Framework (CRF) aims to study the impact of high THC potency *Cannabis* product on brain functions when used by adolescents and adults, focusing on both the increased incidence of psychosis and on behavioral impairments. This research is needed to solidify our current understanding of the short- and long-term impacts of Cannabis use, identify vulnerable populations, and inform public health officials and public policy.

Cannabis Research Framework: The University of Washington Center for Cannabis Research (UW-CCR) and Washington State University Center for Cannabis Policy, Research, and Outreach (WSU-CCPRO) implemented the CRF to foster collaborative and synergistic Cannabis research in Washington state. UW-CCR and WSU-CCPRO identified 11 faculty members with expertise and ongoing research projects in Cannabis use and psychosis and Cannabis use and impairment to participate in the CRF. In total, 10 research topics were identified as directly relevant to the overarching goal. Each CRF member contributed a research proposal for 2022-2023 directly addressing the most pressing and relevant questions associated with Cannabis use and psychosis and Cannabis use and impairment. The research proposals are outlined in Annex 4 and will need to be funded through public and/or private dollars. They will also need to receive the appropriate federal and state research licenses. The research projects will be highlighted on a UW-CCR website, and their findings will be shared in virtual seminars open to the public and online for the benefit of Washingtonians and society.

The UW and WSU CRF researchers and research topics include:

CRF Members	The University of Washington Center for Cannabis Research	
Cannabis Use and Psychosis:		Research Topics
Intervention Research	 Dr. Denise Walker	Developing an intervention approach for Cannabis use and Psychosis by adolescents.
Human Research	 Dr. Kathleen F. Pagulayan  Dr. Garth E. Terry	Early risk factors for development of psychotic disorders following cannabis use
Basic Research	 Dr. Benjamin Land	Preclinical measurement of THC's impact on cognitive behavior in mice
Cannabis Use and Impairment:		Research Topics
Human Research	 Dr. Christine M. Lee	Passive sensing via mobilephone to identify acute cannabis impairment among young adults
Basic Research	 Dr. Nephi Stella	Preclinical measurement of THC's impact on locomotor impairment in mice

Framework Members

Washington State University
Center for Cannabis Policy, Research, and Outreach

Cannabis Use and Psychosis:		Research Topics
Intervention Research	 Dr. Mike McDonnell	Promoting Research Initiatives in Substance Use and Mental Health (PRISM) Collaborative.
Basic Research	 Dr. Ryan McLaughlin	Preclinical measurement of THC's impact on cognitive behavior in mice

Cannabis Use and Impairment:		Research Topics
Human Research	 Dr. Matt Layton	Training rural primary care doctors, physician assistants and nurses to work with patients who have psychiatric disorders and drug addictions
Human Research	 Dr. Carrie Cuttler	Elucidating the potentially beneficial and detrimental effects of chronic cannabis use and acute cannabis intoxication

Framework operation: The virtual framework will unite UW and WSU Cannabis researchers in several endeavors.

■ **Early 2022:** Implement a Virtual Workshop for UW and WSU members of the CRF to share research progress and successes and troubleshoot challenges, as well as determine future research priorities at each level of investigation: Intervention Research, Human Research and Basic Research.

■ **Early 2022:** Implement a UW-CCR website using existing proviso funding, a platform that will include CRF research findings, provide regular information on the *Cannabis* research findings, workshops, seminars and symposia, and grant opportunities, all of which will be coordinated with WSU-CCPRO.

■ **Throughout 2022:** Virtual townhall seminars will be given by CRF researchers open to the public with a focus on Cannabis use and psychosis and *Cannabis* use and impairment.

■ **Late 2022:** Execute symposia open to the public and focused on *Cannabis* use and psychosis and Cannabis use and Impairment, and that will allow CRF researchers to provide updates on their Cannabis use and psychosis and Cannabis use and impairment research results and future research priorities.

Projects for 2022-23

Outlined below are potential research projects that were developed by the CRF. In order to be completed, they would need to be funded through public and/or private dollars.

Faculty at the University of Washington

►Intervention Research

Project 1

Principal Investigator: **Dr. Denise D. Walker, Ph.D.**
Research Associate Professor – School of Social Work.

Title: Developing an intervention approach for Cannabis use and Psychosis by adolescents

Summary: For young adults experiencing first episode psychosis (**FEP**), continued use of high THC potency *Cannabis*-products is associated with worse psychosis treatment outcomes and dire consequences. Our work has demonstrated a clear need for science-based resources specific to the impacts *Cannabis* has on psychosis. This pilot study will develop resources for providers and for parents that can assist in having strategic conversations with FEP patients who use of high THC potency *Cannabis*-products to promote reductions in their use and improve FEP treatment outcomes. Resources will be iteratively developed and evaluated for acceptability and feasibility and can be promptly incorporated in existing ongoing FEP programs and tested for efficacy in future studies.

■ **Personal Statement:** A main area of focus over my career has been on the development and evaluation of interventions for marijuana disorders for both adults and adolescents, utilizing brief interventions (Motivational Enhancement Therapy, MET), longer courses of treatment (MET+CBT), and more recently aftercare. In addition, I have been a Co-Investigator on several trials to develop computerized treatments, treatment for co-users of marijuana and tobacco, and brief interventions for marijuana focused on marijuana dependent adults and heavy using college students. I have also been the PI of six RO1 or DoD-funded RCTs, three of which focused specifically on marijuana interventions. In addition to the development and evaluation of MET based interventions, I have largely been responsible for the clinical training, supervision and monitoring of the intervention fidelity in 10 randomized clinical trials (all having a MET focus or main component). I have provided trainings in Motivational Interviewing across the country and have been a member of the Motivational Interviewing Network of Trainers since 2001 and am the Director of the UW Innovative Programs Research Group.

■ **Scientific Contributions:** 1] Development and evaluation of the Teen Marijuana Check-Up, 2] Marijuana treatment and intervention, 3] Etiology of marijuana and alcohol use and 4] Documenting normative misperceptions.

■ **Funding History**: 1] Grant from the Department of Defense "Improving Voluntary Engagement for PTSD Treatment Among Soldiers" (W81XWH-17-1-0002, Walker & Kaysen (PIs), 11/15/2016-11/14/2020), 2] Grant from National Institute of Health "Community-based participatory partnership for randomized comparative effectiveness trial" (RO1MD011574, Walker (Co-I), 09/27/2016-06/30/2021) and 3] Grant from National Institute of Health (RO1DA040650); Hartzler & Walker (PIs), 05/15/2016-02/28/2021, "Hybrid Effectiveness-Implementation Trial of A School-Based Teen Marijuana Checkup"

►Human Research

Project 2

Co-Investigator: **Dr. Kathleen Pagulayan, Ph.D.**
Associate Professor – Psychiatry and Behavioral Sciences.

Co-Investigator: **Dr. Terry, Garth E. Ph.D.**
Acting Assistant Professor – Psychiatry and Behavioral Sciences.

Title: Early risk factors for development of psychotic disorders following cannabis use

Summary: Cannabis use can contribute to psychosis onset that can lead to psychiatric hospitalization and, in some cases, progress toward chronic schizophrenia. Declines of cognitive and social performance in adolescence/early adulthood often precede development of schizophrenia and contribute to impairment in adult vocational functioning. It is unclear if the risk of developing a psychotic disorder following cannabis use and during or following declining cognitive and/or social performance is independent or synergistic. We propose a retrospective study to examine the temporal relationship of cannabis use and prodromal cognitive/social functioning in individuals with early-stage psychotic disorders through interview and medical chart review.

■ **Personal Statement Dr. Pagulayan:** I am a clinical neuropsychologist at the VA Puget Sound and an investigator in the VA Northwest Network Mental Illness Research, Education, and Clinical Center with expertise in the assessment of cognitive and emotional functioning and neurobehavioral outcomes among individuals with psychiatric disorders and neurologic injury/illness. Particularly relevant to this proposal, I have investigated substance use patterns following TBI in Veteran and civilian populations, as well as the effects of cannabis use on cerebellar integrity. My research is currently focused on developing and evaluating novel interventions to address persistent cognitive difficulties in Veterans with a history of TBI and *Cannabis* Use.

■ **Scientific Contributions:** 1] Relationship between sleep and functional outcome following mTBI and 2] Clinical Trials to Improve Cognitive and Emotional Functioning Post-TBI.

■ **Funding History**: 1] Grant from the Dept of Defense "Development of a Brief Version of Compensatory Cognitive Training for Veterans with Mild Traumatic Brain Injury" (W81XWH1910531; Pagulayan (PI); 2019-2021) and 2} Grant from the UW ADAI "Relationship Between Cannabis Use and Persisting Post-concussive Symptoms in Veterans with a History of mTBI" (Pagulayan (PI); 2018-2019).

■ **Personal Statement Dr. Terry:** My career has focused on using positron emission tomography (PET) in neuropsychopharmacology research, and cannabinoid pharmacology. My doctoral work focused on the development and validation of one the first highly selective, highly specific radioligands for the cannabinoid CB1 receptor. As a clinical-research psychiatrist I have provided scientific and medical support to multiple clinical trials through the National Institute of Drug Abuse (NIDA) Clinical Trial Network (CTN) sponsored site at UCLA and the VA Northwest Network Mental Illness Research, Education, and Clinical Center (MIRECC) at VA Puget Sound, where I am currently a Physician/Research Associate. To date I have 19 peer reviewed publications (6 as first or last author) with over 600 citations and yielding an h-index of 11, in addition to 5 book chapters, the majority of which are related to PET neuroimaging and/or cannabinoid pharmacology. Expanding upon this background, my current VA Career Development Award seeks to image a biomarker of neuroinflammation, translocator protein 18 kDa (TSPO), in both a mouse model of repetitive mild traumatic brain injury (mTBI) and in Veterans with a history of blast mTBI and post-concussive symptoms. Of relevance to this project, I was a

study clinician in the NIDA sponsored CTN study assessing the efficacy of N-acetylcysteine for cannabis use disorder in adults (ACCENT). I have also been awarded a grant from the Alcohol, Drug, and Addiction Institute and am currently the principal investigator of a study to assess the feasibility of prazosin for treatment of cannabis use disorder. I will be a study site Co-Investigator (Co-I) for two upcoming multi-site studies on: 1) the use of □9-tetrahydrocannabinol (THC) and/or cannabidiol (CBD) for chronic diabetic neuropathic pain, and 2) the use of THC/CBD for end stage dementia. I regularly provide educational seminars to health care providers of all levels on the topics of potential benefits and risks of cannabis, cannabinoid pharmacology, and cannabis use disorder and comorbidities, reaching >750 attendees in 2021 alone.

■ **Scientific Contributions:** 1] PET imaging and quantification of cannabinoid CB1 receptors in rodents, non-human primates, and humans, 2] PET imaging CB1 receptors in substance abuse and 3] Characterization of neuroimaging and neurodegenerative markers in a mouse model of repetitive blast mild traumatic brain injury (mTBI) and Veterans with history of blast TBI.

■ **Funding History**: 1] Grant from the VA "Molecular Imaging of Neuroinflammation in Repetitive Mild Traumatic Brain Injury" (2019 – 2024), 2] Grant from ADAI-UW "Assess the Feasibility of Prazosin for Cannabis Use Disorder in Individuals with or without Post-Traumatic Stress Disorder (12/2019 – 12/2021) and 3] Development of F-18-Labeled Radiotracers for PET Imaging of Brain Alpha1A Adrenoceptor: A Tool for Precision Medicine in PTSD.

►Human Research

Project 3

Principal Investigator: **Dr. Christine M. Lee. Ph.D.**
Research Professor – Psychiatry and Behavioral Sciences.

Title: Using passive sensing via mobile phones to identify acute cannabis impairment among young adults.

Summary: Our prior work documents acute and longer-term harms from cannabis use among young adults; however, better assessment and understanding of acute impairment as it occurs in real-time is needed. Research suggests that alcohol impairment can be accurately determined by passive sensing (e.g., gait movements, texting behavior) via mobile phones. Using similar methods, this proof-of-concept study will integrate ecological momentary assessment of cannabis use (including timing, THC levels of products used, mode of use, etc.) with passive data collection and machine learning techniques to develop methods for identifying acute cannabis impairment, which can be used in future studies and real-time interventions.

■ **Personal Statement:** My background and expertise are in etiology and prevention/intervention of young adult alcohol and marijuana use and consequences. I have published over 160 peer-reviewed manuscripts on these topics and have been the PI of nine longitudinal federally funded (NIAAA and NIDA) research projects (6 R01s, 2 R21s, 1 R34). Across this portfolio of research, I have incorporated developmental theory and perspectives to my research questions and methodological approach, including the utilization of novel methods for assessment and intervention. Most relevant to the present application, I have PI'd studies utilizing web-based daily diaries and intensive measurement-burst ecological momentary assessment (EMA) designs using interactive voice response (automated telephone interviews, R01AA016979), web-based surveys (R01AA025037), and mobile applications (2R01AA016979) to assess behavior and cognitions multiple times a day for up to six bursts across two years. I have developed several brief feedback interventions for high-risk alcohol use, including several web-based interventions. My work has also demonstrated success in recruiting a diverse sample of young adults in the community with excellent retention, including for intensive longitudinal and daily designs (R01AA022087,

R01AA016979). As Associate Director of the Center for the Study of Health and Risk Behaviors and Research Professor in Psychiatry and Behavioral Sciences, I have been mentoring early career investigators and junior faculty in the development of brief interventions for alcohol and marijuana, design and implementation of daily EMA designs, development of useful tracking databases to synthesize real-time data, development of reliable and valid measures for daily use, and data analysis with complex research designs including multiple surveys per day. I have successfully mentored several early career scientists as they transitioned to their own PI's grants/labs.

■ **Scientific Contributions:** 1] Intervention of high-risk alcohol and marijuana use, 2] Motivations for and consequences of alcohol and marijuana use and 3] EMA Studies of Alcohol and Marijuana Use with Young Adults

■ **Funding History**: 1] Grant from Grant from National Institute of Health "Intensive Daily Measurement of Simultaneous Alcohol and Marijuana Use in a High-Risk Community Sample of Young Adults: Impacts on Acute and Longer-Term Use and Consequences" (R01AA025037; Lee/Patrick (MPI); 8/1/16-7/31/21), 2] Grant from Grant from National Institute of Health "Personalized mobile app intervention: Challenging alcohol expectancies to reduce high-risk alcohol use and consequences" (R01AA016979; Lee (PI); 9/10/17-8/31/22), 3] Grant from Grant from National Institute of Health "Predictors and consequences of young adult marijuana use and concurrent and simultaneous alcohol use: Month to month variation across 24 consecutive months" (R01AA027496; Lee (PI); 9/15/19-8/31/22) and 4] Grant from Grant from National Institute of Health "COVID-19 pandemic-related impacts on longitudinal trajectories of alcohol, marijuana, and simultaneous use and mental health among young adults" (R01AA027496; Lee (PI); 9/1/20-8/31/22).

►Basic Research

Project 4

Principal Investigator: **Dr. Benjamin Land. Ph.D.**
Research Assistant Professor – Pharmacology.

Title: Preclinical measurement of adolescent THC/CBD on adulthood cognitive behaviors.

Summary: Prior work has shown that in adult rodents, THC is associated with cognitive impairment that can be partially blocked by treatment of CBD. However, the relationship between adolescence, THC/CBD consumption, and later cognitive dysfunction is unknown. Using our voluntary gelatin self-administration model of cannabinoid intake, we will allow free access to THC and CBD during a critical developmental window in adolescent mice. In adulthood, we will then assess select cognitive and social behaviors that reliably models schizophrenia-like behavior. The results of this study will shed light on the role of cannabinoid combinations in the context of adolescence and schizophrenia.

■ **Personal Statement:** For almost 20 years, I have studied neurobiology across domains of stress, drug addiction, depression, food intake, and pain. My graduate work demonstrated that the kappa opioid receptor was responsible for the negative feelings of stress, and my postdoctoral work integrated optogenetics into models of hyperphagia and depression. As research faculty, one of my primary research interests has been the treatment of pain using cannabinoids, with the hope that efficacious cannabinoids can provide opioid-sparing and help mitigate the current opioid crisis in the US. Further, I have developed novel models of cannabinoid consumption using gelatin and look forward to applying them in the larger context of *Cannabis* and cognitive dysfunction. While my lab is nascent, I have been awarded several small grants to study cannabinoids in the context of pain and plan to expand my group in the coming year. I also assist in research projects of 4 other faculty at the University.

■ **Scientific Contributions:** 1] Demonstration that cannabinoids provide long-term benefit in chronic pain models (at least 3 weeks), in contrast to morphine. 2] Demonstration of variety of mouse behavioral models for

dysphoria, depression, drug reward, and cognition via several seminal papers on the kappa opioid receptor system. 3] Optogenetic advances including free feeding behavior and internal light generation.

■ **Funding History**: 1] Pending R01, NCCIH "Cannabidiol and terpenoid interactions in amygdala regulation of pain states" 2] R21, NIDA "Impact on adult mouse brain of oral THC and CBD consumption during adolescence" (DA051558; Stella (PI) and Land (Co-I); 07/01/20 – 06/30/22).

►Basic Research

Project 5

Principal Investigator: **Dr. Nephi Stella. Ph.D.**
Professor – Pharmacology.

Title: Preclinical measurement of THC's impact on locomotor impairment in mice.

Summary: It is well known that treatment of rodents with THC is associated with impairment of motor behaviors characterized by reduced locomotion, yet recent results show a more complex impairments that might include impaired motor coordination, altered stimuli perception, and defective short-term memory and spatial memory, all of which are critical components of accurate motor behaviors. Using our voluntary gelatin self-administration model of THC intake, we will study the impact of free access to gelatin THC on these characteristic psychomotor in both adolescent and adult mice. This study will unravel how use of impairs fundamental and critical psychomotor behaviors.

■ **Personal Statement:** For over 25 years, I have studied the molecular mechanism and therapeutic value of cannabinoid-based molecules and targeting the endocannabinoid (eCB) signaling system. My work led to the discovery and validation of the prominent endocannabinoid, 2-arachidonylglycerol (2-AG), in the brain, and one of its degrading enzymes, ABHD6, that controls 2-AG's levels and activity at cannabinoid receptors, including cannabinoid 1 receptors (CB_1R). My interests have focused on optimizing the therapeutic value of cannabinoid-based drugs by better understand their efficacy at treating of devastating neurological diseases, including multiple sclerosis, Huntington's' disease and epilepsy, and their impairing activity on select behaviors, including locomotor and addictive behaviors. To understand both the mechanism of action of cannabinoid-based drugs and the biological function of eCB signaling under healthy and disease states, my laboratory leverages pharmacological and genetics approaches applied at the molecular, cellular, and preclinical (rodents) level, and is always excited to adopt novel technological approaches. Through my work, I have developed scientific expertise in neuroscience, drug target identification and validation, as well as drug development and preclinical studies. I have also developed expertise in pharmacokinetics, and experimental toxicology and behavior analyses (spontaneous locomotion, motor coordination and motivated behaviors). Since starting my laboratory at the University of Washington (UW) in 1999, I have trained 10 graduate students and 9 post-doctoral fellows and served on multiple NIH study sections. I greatly value the importance of career development and developing skills such as clear communication and effective leadership and have over the years implemented such training in my laboratory.

■ **Scientific Contributions:** 1] 2-arachydonoyl glycerol (2-AG): Identification and validation of the most abundant endocannabinoids in brain, 2] Cannabinoids and behavioral impairments in adolescence and adulthood: Molecular interactions between cannabinoids, locomotion, and dopamine-dependent behaviors and 3] Targeting endocannabinoid signaling as therapy for neurological diseases, including brain cancer and epilepsy and 4] Technologies to study the impact of cannabinoids on brain: Delivery systems and devices, and in vivo cannabinoid receptor imaging.

■ **Funding History**: 1] Grant from National Institute of Health ‘’ ABHD6 and amphetamine stimulated locomotion” (DA047626; Stella (PI); 07/01/19 – 06/30/21), 2] Grant from National Institute of Health “Impact on adult mouse brain of oral THC and CBD consumption during adolescence” (DA051558; Stella (PI) and Land (Co-I); 07/01/20 – 06/30/22) and 3] Grant from National Institute of Health “Role of ABHD6 in 2-AG Signaling” (R01DA026430; Stella (PI); 9/30/09 – 7/31/20)

Faculty at the Washington State University

►Intervention Research

Project 6

Principal Investigator: **Dr. Michael McDonell, Ph.D.**
Professor – Medical Education and Clinical Sciences

Title: Effect of Cannabis Use and Psychosis.

Project Summary: Evidence suggests increased incidence of Psychosis. We are currently studying the potential association between Cannabis use and psychosis in several venues, and will implement a study to specifically assess if and how Cannabis use by vulnerable populations might increase the incidence of psychosis and schizophrenia.

■ **Personal Statement:** I have extensive expertise in developing and testing the effectiveness of treatments for co-occurring substance use disorders and mental illness. I also partners with American Indian and Alaska Native communities to develop, test, and implement new treatment approaches for addictions. Many of his studies utilize novel biomarkers. Most of my work focuses on the use of contingency management to improve addiction treatment. I am passionate about partnering with communities to conduct research that improves the lives community members, as well as mentoring graduate students, staff, and faculty who identify as members of groups under-represented in science.

■ **Scientific Contributions:** 1] Director of the Promoting Research Initiatives in Substance Use and Mental Health (PRISM) Collaborative and 2] Co-Director of the Rural Center for Opioid Prevention, Treatment and Recovery.

►Human Research

Project 7

Principal Investigator: **Dr. Matt Layton, M.D., Ph.D.**
Professor – Translational Medicine and Physiology

Title: Effect of Cannabis Use on Impairment in Humans.

Project Summary: Evidence suggests an effect of Cannabis use on sleep and resulting human impairment. We are currently working on the effects of cannabis use, sleep deprivation and resulting impact on motor impairment using an innovative simulation platform for humans and are actively working on obtaining a Schedule 1 license to administer cannabinoids in humans. In an interprofessional collaboration, we are also working closely with the WSU schools of Pharmacy and Nursing school to study the possible pharmacological interactions of Cannabis use with other bioactive ingredients (including opioids) for treatment of neuropathic pain. Funds would allow development of these projects to establish a high degree of precision on how THC affects motor impairment.

■ **Personal Statement:** I am the physician of record and co-investigator in the WSU Sleep and Performance Research Center. My current research focuses on the psychological and physiological changes in smokers during the first few days after they quit smoking. I am also involved in collaborative efforts in other addictions and pain.
■ **Scientific Contributions:** 1] Medical director of the College of Nursing Program of Excellence in Addictions Research and 2] Medical director of the Spokane Regional Health District Opioid Treatment Program.
■ **Funding History**: 1] Grant from National Institute of Health ''National Drug Abuse Treatment Clinical Trials Network: Pacific Northwest Node" (U10DA013714 NIDA (Layton, Donovan & Roll): 2010-2015) and 2] Grant from Department of Defense 'Enabling the Identification of Biomarkers for Individual Susceptibility to Fatigue: Scaling Up from Attentional Processes to Operational Performance" (N000141310302 (Layton and Dongen, H): 2012-2015).

►Human Research

Project 8

Principal Investigator: **Carrie Cuttler, Ph.D.**
Assistant Professor – Psychology

Title: Acute impairing effects of high potency cannabis on everyday life memory.

Summary: One of the most robust detrimental effects of *Cannabis* is on memory. However, most prior studies have focused on examining verbal memory using list-learning tasks. Few studies have investigated the effects of *Cannabis* on more naturalistic memory tests such as prospective memory (the ability to remember to execute tasks in the future), temporal order memory (the ability to recall the sequence of previously experienced events), source memory (the ability to recall the source of previously learned information), autobiographical memory (the ability to recall events in one's life), or false memory (the recollection of events that did not previously occur). This is problematic because these domains of memory better map onto the types of events and experiences that we must remember in everyday life. Further, most previous studies of the acute effects of *Cannabis* on memory have relied on rather low potency products and almost few studies have examined the effects of high potency cannabis flower or concentrates on memory. We will work with Biopharmaceutical Research Company (BRC) which recently acquired DEA approval to provide researchers with *Cannabis* products with higher potencies than those available through the traditional NIDA drug supply. This will allow us to examine the effects of high potency *Cannabis* flower and extremely high potency *Cannabis* concentrates on each of these aspects of everyday life memory. This study will provide further insights into domains of memory impacted by acute *Cannabis* intoxication and whether *Cannabis* concentrates are more impairing than *Cannabis* flower.

■ **Personal Statement:** Research in The Health & Cognition (THC) I direct at WSU focuses on elucidating the potentially detrimental and beneficial effects of acute and chronic cannabis exposure on stress, mental health, mood, and cognition. While most of my work is conducted in humans, I also conduct translational research with Dr. McLaughlin using his novel vapor chamber model of cannabis self-administration with rodents. I have a background in psychology, with specific training and expertise in cannabis use, neuropsychological assessment, survey research, naturalistic research, and secondary data analysis of big app data. I have over 15 years of experience designing studies, managing and analyzing large datasets, presenting at conferences, and writing manuscripts. Most of the studies I have completed involved recruiting and testing large samples (n > 100) of cannabis users and non-users from the local community. These studies have resulted in nearly 60 published manuscripts (h-index = 23). I am also adept at training others in conducting research and analyzing data. I have trained over 60 undergraduate students in the various stages of research and have had 3 Ph.D. students and 5

M.S. students successfully defend their theses in my THC Lab. Moreover, I have a great deal of expertise in research methods and statistics. I have taught courses in research methods for over a decade, published multiple books on these topics, and presently teach two graduate level statistics courses. In summary, I have the training, experience, expertise, and motivation necessary to successfully carry out the proposed research project.

■ **Scientific Contributions:** 1] Developed the Daily Sessions, Frequency, Age of Onset, and Quantity of Cannabis Use Inventory (DFAQ-CU) which is the only psychometrically sound comprehensive measure of cannabis use patterns, 2] Discovered a blunted stress response in chronic cannabis users that was subsequently back-translated using a rodent model to demonstrate that cannabis causes a blunted cortisol response to acute stressors, 3] Assessments of aspects of cognition impaired by chronic cannabis use and acute cannabis intoxication, and 4] Investigations of the acute effects of cannabis with varying concentrations of THC and CBD on various mental health (OCD, PTSD, Depression, Anxiety) and medical (Headache, Migraine, Nerve Pain, Joint Pain, Muscle Pain) conditions using naturalistic big app data.

■ **Funding History**: 1] External grant from National Institute of Drug Abuse ''Effects of chronic cannabis use on the neuroendocrine stress response (DA051740-01-A1; McLaughlin PI, Cuttler Co-I; 07/2021-06/2023), 2] Internal faculty pilot grant from the Alcohol and Drug Abuse Research Program "Acute and Chronic Effects of Cannabis on Cognition in Adult Attention-Deficit/Hyperactivity Disorder" (137843; Cuttler (PI); 12/2019 – 12/2021) and 3] Internal faculty pilot grant from Alcohol and Drug Abuse Research Program "Acute Effects of High Potency Cannabis on Everyday Life Cognition" (133959; Cuttler (PI); 07/2018 – 07/2022)

►Basic Research

Project 9

Principal Investigator: **Dr. Ryan J. McLaughlin, Ph.D.**
Associate Professor – Department of Integrative Physiology and Neuroscience

Title: Effects of developmental cannabis exposure on cognitive functioning and the corticostriatal pathway in rats.

Summary: *Cannabis* is the most used illicit drug among pregnant mothers. As the number of states with legal cannabis continues to increase, there has been a concomitant rise in the rate of maternal cannabis use. This is particularly troubling given that prenatal cannabis exposure could interfere with neurodevelopment and increase the risk for cognitive dysfunction later in life. Preclinical animal models are advantageous in that they provide fine control over potentially confounding variables. However, current models of cannabis use have been plagued by methodological concerns that limit the translatability of these data to human populations. Our laboratory has generated important new data using a novel, translationally relevant model of cannabis vapor exposure in rats. This new method of administration delivers discrete 'puffs' of vaporized, plant-derived *Cannabis* extracts. Using this approach, we have shown that prenatal cannabis vapor exposure produces marked deficits in behavioral flexibility in male and female offspring. Behavioral flexibility, a symptom associated with psychosis, requires coordinated release of dopamine within, and communication between, the medial prefrontal cortex and nucleus accumbens. However, the long-term effects of prenatal *Cannabis* exposure on the structure and function of this corticostriatal circuit, and implications for behavioral flexibility, remain unknown. To address this gap, we propose to use multiple complementary approaches to identify long-term alterations in the corticostriatal circuit that give rise to flexibility deficits in cannabis-exposed offspring using our model of maternal cannabis vapor self-administration.

■ **Personal Statement:** Since the beginning of my research career, I have been devoted to the study of cannabinoids and their influence on the brain and behavior. Of the 44 manuscripts that I have published, 33 of those have focused on cannabis or endocannabinoids. I have attended the annual symposium for the International Cannabinoid Research Society 13 of the past 15 years and have been invited to speak about our cannabinoid research at numerous national and international meetings, including the Gordon Cannabinoid Meeting on 3 separate occasions, as well as the Canadian Consortium for the Investigation of Cannabinoids on 2 separate occasions. Locally, I have participated in the UW-WSU joint symposium as a speaker in each of the 3 years that it has been offered. My laboratory's research has been featured in The Seattle Times, The Scientist, Scientific American, WSU Insider, Washington State magazine, and most recently, we were a primary focus of an MTV Documentary on myths of cannabis use.

■ **Scientific Contributions:** 1) Development of a more translationally relevant preclinical model of cannabis use. 2) Role of corticolimbic endocannabinoid signaling in stress coping and emotional behavior, 3) Endocannabinoid mechanisms of stress adaptation

►Timelines and Budgets

Included below are research proposal timelines and budgets that were developed by the CRF. They would need to be funded through public and/or private dollars.

What will be addressed in Y1 of this Framework (7/1/2022–6/30/2023):

1) For Intervention Research, the team of Dr. Walker will develop and iterate science-backed resources so that providers and parents can provide optimal behavioral approaches to minimize *Cannabis* use in psychosis-vulnerable adolescents.

2) For Human Research, the team of Drs. Pagulayan and Terry will use interview and medical charting-based methodology to understand the relationship between adolescent cognitive decline and cannabis use and psychosis risk. The team of Dr. Lee will use passive sensing *via* mobile phones to identify acute cannabis impairment among young adults.

3) For Basic Research, the team of Dr. Land will leverage preclinical mouse models of THC/CBD use in adolescents to assess the incidence of schizophrenia-like behaviors using gelatin-based self-administration of THC and CBD experimental methods and measure cognitive and social behavior in adulthood. The team of Dr. Stella will leverage preclinical mouse models of THC use by adolescent and adult mice to assess the incidence of psychomotor impairment using gelatin-based self-administration of THC experimental method.

►Budget

Projects	Research	UW Faculty	Effort	Program Cost	Total
1	Intervention	Dr. Walker	$85,000	$15,000	$100,000
2	Human	Drs. Pagulayan and Terry	$85,000	$15,000	$100,000
3	Human	Dr. Lee	$70,000	$30,000	$100,000
4	Basic	Dr. Land	$80,000	$20,000	$100,000
5	Basic	Dr. Stella	$80,000	$20,000	$100,000
UW-CCR Operations			$80,000	$20,000	$100,000
Budget for 2022-2023 Research			*$480,000*	*$120,000*	$600,000

Projects	Research	WSU Faculty	Effort	Program Cost	Total
6	Intervention	Dr. McDonell	$85,000	$15,000	$100,000
7	Human	Dr. Layton	$85,000	$15,000	$100,000
8	Human	Dr. Cuttler	$80,000	$20,000	$100,000
9	Basic	Dr. McLaughlen	$80,000	$20,000	$100,000
WSU-CCPRO Operations			$80,000	$20,000	$100,000
Budget for 2022-2023 Research			*$410,000*	*$90,000*	$500,000

►Research Licenses

All research projects will need to receive the necessary federal and state research licenses, including but not limited to:

■ **Drug Enforcement Administration (DEA) Schedule 1 License:** Research using THC will be carried using DEA Schedule 1 licenses and include Projects 2, 4, 5, 7 and 9. The research projects will obtain THC products through the National Institute of Health Drug Supply.

■ **Institutional Review Boards (IRB):** Research in humans will be carried in accordance with the IRB and include Projects 1, 2, 3, 6, 7 and 8.

■ **Institutional Animal Care and Use Committee (IACUC)**: Research in humans will be carried in accordance with the IRB and include Projects 4,5 and 9.

The CRF is determining any additional licenses necessary, as well as potential roadblocks and steps forward.

►Experimental designs, measures, and methods

Measuring Psychosis Episodes and Schizophrenia symptoms:

■ **Human Research**: Psychotic episodes and Schizophrenia are typically defined via criteria from the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). This includes both positive symptoms like mania, and negative symptoms such as affective flattening and catatonia.

■ **Basic Research:** Modeling psychosis in animals has historically been challenging, but there are recently developed tests that hold excellent face/predictive validity. A primary test, named prepulse inhibition, measures the phenomenon that a startling stimulus (like a loud noise) will be less startling when a weaker stimulus is presented just prior. Both animals and humans show deficits in this behavior in schizophrenic models. Decreased social interaction and locomotor impairments are also used to assess schizophrenia-like behavior in rodents.

Behavioral and Pharmacological intervention to moderate psychosis:

■ **Behavioral Interventions**: Effective knowledge of the role that *Cannabis* plays in Psychosis will allow providers a preventative approach when dealing with adolescent use and psychosis risk. Unfortunately, a lack of concrete information related to the above factors makes recommendations difficult. The research outlined here will help refine the risk factors to make intervention more accessible.

■ **Pharmacological**: Recent peer-reviewed studies provided convincing evidence that CBD can blunt features of psychosis in both animal and human models. Therefore, Cannabis products that also contain significant amounts of CBD may help prevent development of psychosis. This is especially relevant in the context of increased-potency THC products, which often minimize CBD content.

Measuring Impairment:

■ **Animal Models**: Cannabis impairment can be measured using tasks that monitor animal movement. Two models typically used are simply measuring how much an animal moves in a given time after *Cannabis* treatment (locomotor activity) and measuring catalepsy (bar test). While this does not address decision making, it has high face validity for human locomotor impairment.

■ **Human Models**: In controlled settings, Cannabis impairment can be measured using computer-based psychomotor/cognitive tests (DRUID, Karoly et al, 2020, Spindle et al, 2021). However, this does not capture the

reality of human usage and behavior. A group at the UW is addressing this issue by using passive smartphone sensing coupled with real-time self-reports, to measure physical aspects of movement and correlating with intoxication state. This has been used successfully in the context of alcohol consumption.

► ***THC/CBD combinations for moderating impairment***

Evidence that a second, non-psychoactive component of *Cannabis*, cannabidiol (CBD), may be able to alleviate some of the deleterious effects of *Cannabis* (eg. Murphy et al, 2017). In models using injection of these two compounds, CBD did not significantly affect locomotor activity. However, this route of administration does not closely model human intake patterns, and thus may not provide direct translational evidence. Researchers at both the UW and WSU are actively pursuing relevant intake measures (i.e., vape and oral route) to model this more accurately.

► ***What will be addressed in Y1 of this Framework:***

1) A proactive, preventative strategy for impairment would be real-time feedback that can alert an individual that they may be impaired. Individuals could then take action to prevent their impairment from the above issues. Lee and colleagues will determine whether use of mobile phones can adequately detect *Cannabis* impairment, as they have already shown for alcohol.

2) As stated above, there is a lack of preclinically relevant models for *Cannabis* administration, which limits our ability to accurate assess impairment, and a preventative role of CBD. Stella and McLaughlin will each determine whether CBD can ameliorate impairment features of THC when co-administered via gelatin or vapor, respectively.

Bibliography referecences:

1. Ryz, N.R., D.J. Remillard, and E.B. Russo, *Cannabis roots: a traditional therapy with future potential for treating inflammation and pain.* Cannabis and cannabinoid research, 2017. **2**(1): p. 210-216.
2. Tart, C.T., *Marijuana intoxication: common experiences.* Nature, 1970. **226**(5247): p. 701-704.
3. Hollister, L.E. and H. Gillespie, *Delta-8-and delta-9-tetrahydrocannabinol; Comparison in man by oral and intravenous administration.* Clinical Pharmacology & Therapeutics, 1973. **14**(3): p. 353-357.
4. Grotenhermen, F., E. Russo, and A.W. Zuardi, *Even high doses of oral cannabidiol do not cause THC-like effects in humans: Comment on Merrick et al. Cannabis and Cannabinoid Research 2016; 1 (1): 102–112; DOI: 10.1089/can. 2015.0004.* Cannabis and Cannabinoid Research, 2017. **2**(1): p. 1-4.
5. Todd, S. and J. Arnold, *Neural correlates of interactions between cannabidiol and Δ9-tetrahydrocannabinol in mice: implications for medical cannabis.* British journal of pharmacology, 2016. **173**(1): p. 53-65.
6. Renard, J., et al., *Adolescent cannabinoid exposure induces a persistent sub-cortical hyper-dopaminergic state and associated molecular adaptations in the prefrontal cortex.* Cerebral Cortex, 2017. **27**(2): p. 1297-1310.
7. Smart, R., et al., *Variation in cannabis potency and prices in a newly legal market: evidence from 30 million cannabis sales in Washington state.* Addiction, 2017. **112**(12): p. 2167-2177.
8. Sagar, K.A., et al., *Made from concentrate? A national web survey assessing dab use in the United States.* Drug and alcohol dependence, 2018. **190**: p. 133-142.
9. Sagar, K.A. and S.A. Gruber, *Marijuana matters: reviewing the impact of marijuana on cognition, brain structure and function, & exploring policy implications and barriers to research.* International Review of Psychiatry, 2018. **30**(3): p. 251-267.
10. Firth, C.L., et al., *How high: differences in the developments of cannabis markets in two legalized states.* The International journal on drug policy, 2020. **75**: p. 102611.
11. Van der Steur, S.J., A. Batalla, and M.G. Bossong, *Factors moderating the association between cannabis use and psychosis risk: a systematic review.* Brain sciences, 2020. **10**(2): p. 97.
12. Di Forti, M., et al., *Daily use, especially of high-potency cannabis, drives the earlier onset of psychosis in cannabis users.* Schizophrenia bulletin, 2014. **40**(6): p. 1509-1517.
13. Di Forti, M., et al., *The contribution of cannabis use to variation in the incidence of psychotic disorder across Europe (EU-GEI): a multicentre case-control study.* The Lancet Psychiatry, 2019. **6**(5): p. 427-436.
14. Pierre, J.M., M. Gandal, and M. Son, *Cannabis-induced psychosis associated with high potency "wax dabs".* Schizophrenia research, 2016. **172**(1-3): p. 211-212.
15. Hurd, Y.L., et al., *Cannabis and the developing brain: insights into its long-lasting effects.* Journal of Neuroscience, 2019. **39**(42): p. 8250-8258.
16. Mennis, J., G.J. Stahler, and T.P. McKeon, *Young adult cannabis use disorder treatment admissions declined as past month cannabis use increased in the US: An analysis of states by year, 2008–2017.* Addictive behaviors, 2021. **123**: p. 107049.
17. Freeman, T. and A. Winstock, *Examining the profile of high-potency cannabis and its association with severity of cannabis dependence.* Psychological medicine, 2015. **45**(15): p. 3181-3189.
18. Barrington-Trimis, J.L., et al., *Risk of persistence and progression of use of 5 cannabis products after experimentation among adolescents.* JAMA network open, 2020. **3**(1): p. e1919792-e1919792.
19. Arterberry, B.J., et al., *Higher average potency across the United States is associated with progression to first cannabis use disorder symptom.* Drug and alcohol dependence, 2019. **195**: p. 186-192.
20. Gunn, R.L., et al., *Complex cannabis use patterns: Associations with cannabis consequences and cannabis use disorder symptomatology.* Addictive behaviors, 2020. **105**: p. 106329.
21. Tournier, B.B. and N. Ginovart, *Repeated but not acute treatment withΔ 9-tetrahydrocannabinol disrupts prepulse inhibition of the acoustic startle: Reversal by the dopamine D2/3 receptor antagonist haloperidol.* European Neuropsychopharmacology, 2014. **24**(8): p. 1415-1423.
22. Dar, M.S., *Cerebellar CB1 receptor mediation of Δ9-THC-induced motor incoordination and its potentiation by ethanol and modulation by the cerebellar adenosinergic A1 receptor in the mouse.* Brain research, 2000. **864**(2): p. 186-194.

23. Saravia, R., et al., *Concomitant THC and stress adolescent exposure induces impaired fear extinction and related neurobiological changes in adulthood.* Neuropharmacology, 2019. **144**: p. 345-357.
24. Calabrese, E.J. and A. Rubio-Casillas, *Biphasic effects of THC in memory and cognition.* European journal of clinical investigation, 2018. **48**(5): p. e12920.
25. Metna-Laurent, M., et al., *Cannabinoid-induced tetrad in mice.* Current protocols in neuroscience, 2017. **80**(1): p. 9.59. 1-9.59. 10.
26. Wiley, J.L. and B.R. Martin, *Cannabinoid pharmacological properties common to other centrally acting drugs.* European journal of pharmacology, 2003. **471**(3): p. 185-193.