Brown University COBRE Center for Addiction and Disease Risk Exacerbation

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ABSTRACT

The Center for Addiction and Disease Risk Exacerbation (CADRE) is a COBRE establishing a thematically linked, state-of-the-art, multidisciplinary Center investigating mechanisms where-by substance use (SU) increases the risk for or exacerbates chronic disease. It does so by employing a combination of behavioral and physiological laboratory-based approaches across several substances and across several diseases. COBRE projects investigate mechanisms underlying effects of opioids, cannabis, tobacco, and alcohol on risks for and progression of SU-related disease. Though linkages between SU and disease are well documented, physiological mechanisms underlying such associations are poorly understood, mainly because published studies use cross-sectional designs that do not allow for causal interpretations. Mechanisms studied in CADRE projects include systemic inflammation, immune system dysregulation, high blood pressure, pulmonary effects, and carcinogen exposure. A Clinical Laboratory Core provides infrastructure, resources, and scientific expertise and a center-wide database of risk factors associated with the development of SU and chronic disease.

KEYWORDS: substance use, chronic disease, mechanisms, interdisciplinary, early career faculty

INTRODUCTION

The Brown University Center for Alcohol and Addiction Studies has established the Center for Addiction and Disease Risk Exacerbation (CADRE), a COBRE funded by the National Institute of General Medical Sciences (NIGMS) in August 2019. The CADRE is led by Peter M. Monti, PhD, Director of the Brown University Center for Alcohol and Addiction Studies and Professor of Behavioral and Social Sciences (BSS), by Jasjit S. Ahluwalia, MD, Professor of BSS and Professor of Medicine, and by Jennifer W. Tidey, PhD, Professor of BSS and Associate Dean for Research at the Brown School of Public Health. Together these three constitute the CADRE's Executive Committee, which has the formal charge of internal governance of the Center.

The primary goal of this Center is to establish a thematically linked, state-of-the-art, multi-disciplinary center to investigate the mechanisms by which substance use increases the risk for or exacerbates chronic disease. More specifically, our CADRE investigates the biobehavioral mechanisms whereby substance use impacts disease. It does so by employing a combination of behavioral and physiological laboratory-based approaches and across several substances of abuse and several chronic diseases. Our overarching goal in establishing this Center is to create a vehicle that will support the emerging careers of promising early-career interdisciplinary faculty, and in so doing, enhance their competitiveness for external independent funding. The ultimate goal is to improve the lives of those living with substance use disorders (SUDs).

ASSOCIATIONS BETWEEN SUBSTANCE USE AND MAJOR MEDICAL ILLNESSES

Substance use negatively affects the risk, management, progression, and outcomes of chronic disease and contributes to socio-economic and racial/ethnic disparities. Prevalence rates of medical conditions among patients with versus those without SUDs support this thesis. Furthermore, risks of disease or disease progression are exacerbated among those otherwise at risk or who already have chronic medical conditions, such as people living with HIV (PLWH) and people living with chronic pain.[1-3] For example, among sexual minority men who have sex with men, alcohol contributes to the fact that they are more severely affected by HIV than any other group in the United States. Further, among HIV-positive smokers, tobacco accounts for more deaths than HIV.

Though linkages between substance use and disease are well documented, physiological mechanisms underlying such associations are poorly understood and underappreciated, mainly because the literature is based on studies that use cross-sectional designs that do not allow for causal interpretations. For example, as pointed out by Bahorik and colleagues,[4] documented relationships between pain and illicit opioid use may evolve because patients who are prescribed pain medication later migrate to illicit opioid use, or patients misuse illicit opioids instead of using pain medications, or both. Studies using experimental designs are needed to understand the biobehavioral mechanisms that link substance use and chronic disease and inform the development of

targeted prevention and intervention efforts to reduce risks.

Unfortunately, experimental research in this area is relatively nascent. A review by Bachi et al[5] characterizes the effects of SUDs on the organism as "accelerated aging", which occurs when biological aging (i.e., wear and tear on one's organs) outpaces chronological age. Factors by which SUDs contribute to accelerated aging include effects of drugs on the brain (brain dopamine, cerebrovascular pathology, neuroinflammation, enhanced stress sensitivity), other physiological effects of drugs (on cardiovascular, pulmonary, metabolic, immune, and circadian health), and effects of drugs on behavior and social functioning (poor nutrition, poor sleep patterns, lack of physical activity, stigmatization, impaired access to healthcare, low family/community support, poverty, infectious diseases and involvement in the criminal justice system).[5]

Clearly, this is a vast area of research. Fortunately, pathophysiological processes underlying these factors are beginning to be identified. One major pathway is the promotion of oxidative stress by drugs and alcohol, leading to cellular damage, tissue injury, and inflammation. Exposure to toxic substances promotes inflammation in the gut, liver, brain, and other organs. Inflammation in combination with increased oxidation may be especially damaging.[6] Oxidation, inflammation and stress hormone exposure also accelerate telomere shortening[7] and stem cell decline,[8] diminishing resilience and regeneration capacity. When chronically present, oxidative stress and inflammation lead to pathologies such as diabetes, cancer, cardiovascular disease, and neurodegenerative diseases.[9]

A basic tenant of the CADRE is that investigating systems and pathways involved in associations between substance use and chronic disease, and intervening to prevent these associations, requires multidisciplinary, multilevel approaches, which bring together behavioral scientists, clinical researchers, physicians, and basic scientists who conduct basic biology, prevention and intervention studies, as well as lab-based human behavioral studies. CADRE studies are especially attentive to the many biological and socio-environmental factors that contribute to racial and ethnic disparities. Our interdisciplinary multilevel approach, focused on related questions using shared resources and learning experiences, not only is poised to contribute new knowledge but importantly serves as the nexus and path toward independence for the next generation of CADRE scientists. The research projects and pilot studies comprising our CADRE investigate mechanisms underlying the effects of opioids, cannabis, tobacco, and alcohol on risks for SUD-related disease progression. Mechanisms studied in the initially funded four CADRE research projects include systemic inflammation, immune system dysregulation, high blood pressure, pulmonary effects, and carcinogen exposure. CADRE studies are serviced by an Administrative Core and a Clinical Laboratory Core.

ADMINISTRATIVE CORE

Peter M. Monti, PhD, CADRE PI, is Brown University's Distinguished Professor of Alcohol and Addiction Studies and Director of the Center for Alcohol and Addiction Studies (CAAS). He founded and is currently Deputy Director of Brown University's Alcohol Research Center on HIV and is PI of CAAS's Alcohol T32 Postdoctoral Training Program. His research interests span understanding the biobehavioral mechanisms involved in behavior change and addiction treatment intervention, and he is particularly interested in the relationship between alcohol and HIV. Jasjit S. Ahluwalia, MD, MPH, MS, Deputy Director, and Core Leader, is a physician and population health/public health scientist. He has been a practicing physician, faculty member, department chair, and Associate Dean. He has served as PI of an NIH Center of Excellence on Minority Health and Health Disparities and as Associate Director of the University of Minnesota's CTSA grant, directing education, training, and career development. He most recently served as a School of Public Health Dean. His primary research has focused on nicotine addiction and smoking cessation in African-American smokers.

The Administrative Core provides an organizational structure for the CADRE, state-of-the-art mentoring for CADRE Project Leaders (PLs) and Pilot PLs, a Pilot Project Program, supports diversity and health disparities work, and leads CADRE's evaluation effort. The Core creates an environment that promotes and encourages scientific exchange and innovation in the realm of substance use and chronic disease. Core personnel work with PLs to prepare competitive grant proposals and peer-reviewed manuscripts emanating from CADRE-sponsored research. The Core brings nationally-known distinguished scholars to the Brown campus each year to present to the extended academic community.

By its nature, COBRE's operate such that once a PL obtains an independent research grant, e.g., an R01, she/he "rotates off" salary funding from the COBRE grant. Thus, an important task of the Executive Committee is to solicit and organize the selection of replacement PLs. This is done in consultation with a distinguished External Advisory Committee.

CLINICAL LABORATORY CORE

Jennifer W. Tidey, PhD, lead, the Clinical Laboratory Core, Associate Dean for Research at the Brown School of Public Health, Associate Director of CAAS's Drug Abuse T32 Training Program, and Director of the CAAS Laboratory. Dr. Tidey is a translational addictions scientist who focuses on developing and testing interactive models of biological, social, and environmental variables to understand the etiology and persistence of SUDs. Her work has assessed the behavioral, subjective, and physiological effects of opioids, psychomotor stimulants, alcohol, and nicotine/tobacco,

in studies based on conditioning and behavioral economic theories of addiction. Her work spans multiple intervention development stages – from basic science, to intervention generation, and pilot testing, to traditional efficacy testing, to policy-informed research.

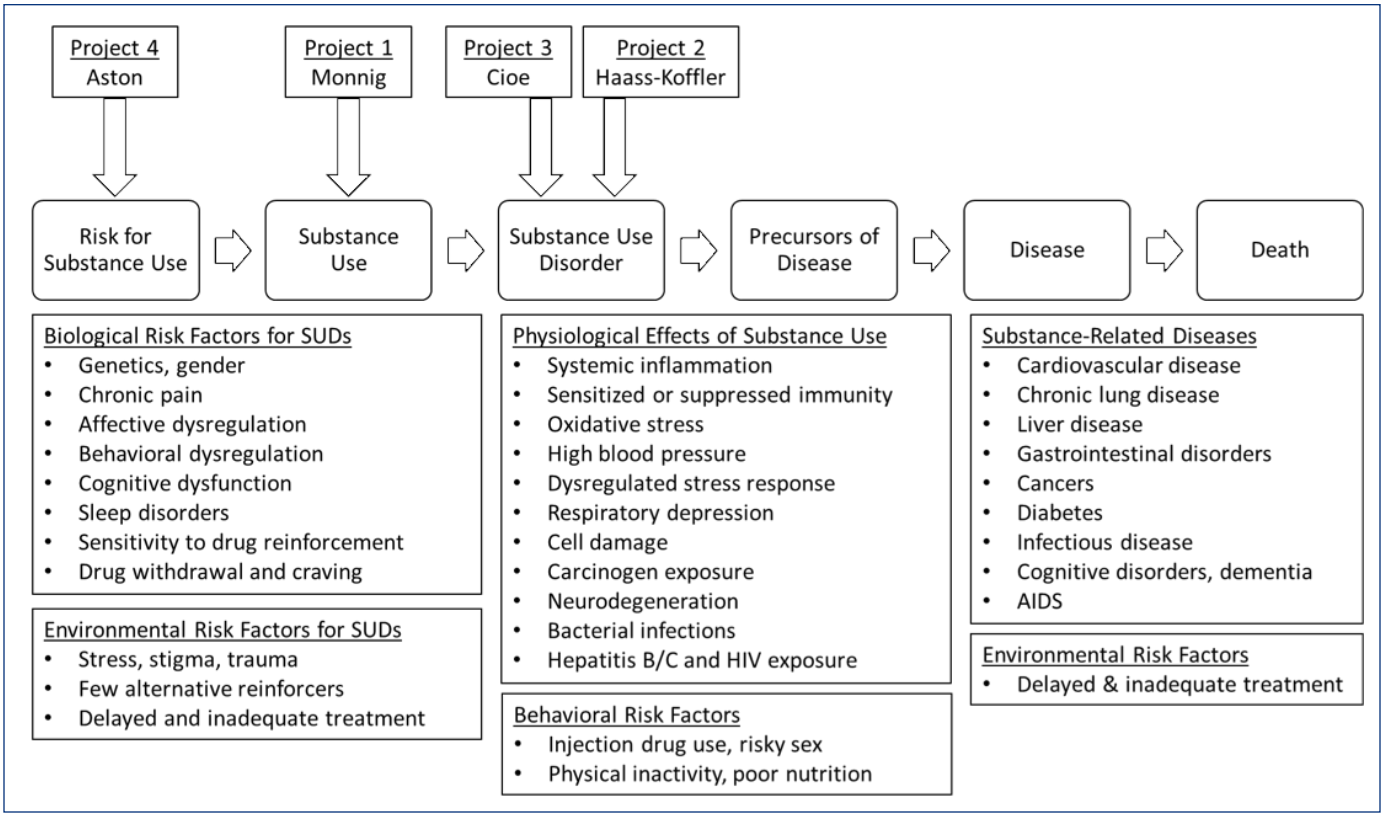
The Clinical Laboratory Core facilitates the goals of the major projects and pilot projects and benefits the broader Brown community, by providing infrastructure, resources, and scientific expertise, in the service of developing and sustaining a multi-disciplinary center. It maximizes CADRE's efficiency and cost-effectiveness by creating linkages between CADRE's Research Projects and other COBREs. Additionally, it is creating a center-wide data base of risk factors associated with development and progression of SUDs and chronic disease available to CADRE PLs and others engaged in research consistent with CADRE's mission. This center-wide database consists of biopsychosocial assessments collected across projects to allow for the formulation and testing of multi-causal models of relationships between SUDs and chronic disease. Further, through NIGMS funding, supplemented by institutional funds, we have made significant renovations to the CAAS Laboratory and purchased major state-of-the-science equipment to meet the ever-growing needs and technical capability of the CADRE.

CADRE RESEARCH PROJECTS

CADRE originally consisted of four thematically and technically linked research projects (RPs) led by an interdisciplinary group of early-career faculty. These RPs and their relationship to biological risk factors, physiological effects, and substance-related diseases are depicted in **Figure 1.**

Mollie Monnig, PhD, Research PL, is a clinical psychologist and Assistant Professor of BSS at CAAS. Dr. Monnig's primary research objective is to advance understanding of alcohol's effects on the gut-brain axis in the context of HIV. In her CADRE project, Dr. Monnig is examining acute neural and immune effects of alcohol in PLWH. Given the dearth of experimental research on alcohol use in PLWH, it is not known whether alcohol exacerbates immune dysfunction in this population. Monnig examines whether alcohol stimulates acute inflammatory responses along the gut-brain axis and compares alcohol's effects on immune biomarkers and neurobiological outcomes in PLWH and healthy controls. This multidisciplinary framework will enable the detection of temporally related changes through measurement of plasma biomarkers of microbial translocation and immune activation and MRI measures of neurometabolic, white matter diffusivity, and extracellular water, consistent with alcohol-induced inflammation in the peripheral immune system and brain.

Figure 1. CADRE conceptual model indicating biopsychosocial mechanisms underlying the linkages between substance use and chronic disease, and where the aims of the initial CADRE research and pilot projects fit on this continuum.



Elizabeth Aston, PhD, Research PL, received a PhD in Neuroscience from Wake Forest School of Medicine and is currently an Assistant Professor of BSS at CAAS. Dr. Aston's primary research objective is to examine predictors of cannabis use disorder severity among regular marijuana users and the relative reinforcing value of marijuana using a behavioral economic marijuana purchase task. In her CADRE project, Dr. Aston examines the effects of cannabis on rheumatoid arthritis pain, affect, and inflammation and investigates whether the effects of cannabis on pain and affect are mediated via the effects of cannabis on inflammatory biomarkers. As such, her study is motivated by a looming concern that some analgesic pharmacotherapy classes have limited efficacy in pain treatment and, in the case of opioids, have significant abuse liability.

Patricia Cioe, PhD, an Assistant Professor of BSS at CAAS with a background in nursing research, was part of the original CADRE application and had proposed in her CADRE project to examine the effects of electronic nicotine delivery systems (ENDS) in PLWH, who are not motivated to quit smoking. PLWH have increased cardiovascular disease rates, pulmonary disease, infection and lung cancer relative to the general population. Outcomes were to include smoking as well as effects on biomarkers of cardiac disease, pulmonary disease, and carcinogen exposure. Dr. Cioe rotated off the CADRE once her U01 was funded to conduct a similar (though more extensive) study to that proposed for the CADRE.

Carolina Haass-Koffler, PharmD, is an Assistant Professor of Psychiatry and Human Behavior and BSS at CAAS and came to CADRE with a strong background in pharmacology and neuroscience. Dr. Haass-Koffler is a translational investigator who integrates preclinical and clinical research to examine the biobehavioral mechanisms of addiction toward developing novel medications. For her CADRE project, Dr. Haass-Koffler proposed translating a validated preclinical paradigm (yohimbine-induced stress) to human laboratory research and pairing it with a human laboratory paradigm (cue reactivity) to investigate whether the anti-stress hormone, oxytocin, reduces opioid craving during stress induction. Dr. Haass-Koffler rotated off the CADRE as a PL once an R01 was recently awarded to her by NIAAA. However, as described below, CADRE has funded a pilot study of reduced scope to the initially proposed research.

Hayley Treloar Padovano, PhD, pending PL, is a clinical psychologist and Assistant Professor of Psychiatry and Human Behavior and BSS at CAAS. Dr. Treloar Padovano's research program's long-term goal is to develop more effective interventions to promote alcohol abstinence and prevent relapse in AALD patients. For her CADRE project, Dr. Treloar has recently proposed to examine alcohol-associated liver disease (AALD) and drinking in patients suffering from AALD. She proposes a prospective, two-arm intervention study comparing patients with AALD/AUD vs. those with AUD only. Ecological momentary assessment and a human laboratory paradigm will assess biomarkers of inflammation and immune response and behavioral AUD endophenotypes in the setting of a brief motivational intervention targeting drinking. This project has received approval from CADRE's External Advisory Board and is in the final stages of NIGMS approval.

CADRE PILOT PROJECTS

Carolina Haass-Koffler, PharmD, is examining the initial efficacy of oxytocin as a potential pharmacotherapy for opioid use disorder, as described above.

Mollie Monnig, PhD, is examining participants' experiences and substance use behavior during the Coronavirus pandemic in the context of a community/longitudinal survey. As Dr. Monnig is a CADRE PL, her pilot study is funded with institutional funds rather than by NIGMS.

A third pending pilot project has been approved internally and is awaiting final approval from NIGMS.

SUMMARY

As shown in the above-listed projects, our CADRE has been very productive during its initial 18 months. Indeed, we have published 22 manuscripts to date. We are fortunate to have excellent, interdisciplinary PLs and an impressive pipeline for future potential early career applicants. Two of our original PLs have "graduated," and the remaining PLs have R01s in various stages of submission. We have two replacement PL's pending NIGMS approval. Through our Laboratory Core, the provision of resources and expertise is a highly sought-after feature of CADRE, one which already is in high demand by non-CADRE faculty. Given the innovative theme of the CADRE, biopsychosocial mechanisms linking SUDs and chronic illness, and the prevalence of substance use and chronic disease, scientific contributions emanating from CADRE should be of high public health significance and therefore should accelerate the careers of our faculty. We anxiously await our initial studies' results and look forward to sharing them with the scientific community.

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