Medical University of South Carolina
Theme: Role of sex and gender differences in substance abuse relapse

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Center Abstract

Over the last four years, the Medical University of South Carolina's (MUSC) Specialized Center of Research (SCOR) on Sex and Gender Factors Affecting Women's Health has functioned as a productive interdisciplinary research center focused on treatment and relapse in substance use disorders in women. When the MUSC SCOR was established in 2002, it filled an important gap. While MUSC had significant depth and strength in translational, interdisciplinary research in the area of substance use disorders, there was no gender-specific focus. Furthermore, the MUSC SCOR was the first women's health research initiative to be undertaken on the MUSC campus. The active, campus-wide collaborations of SCOR investigators, combined with the SCOR pilot project program have encouraged and impacted gender-based research campus-wide.

During the renewal period, we propose to more closely link our scientific projects and follow up on intriguing findings from the previous funding period. Each core research project will involve the investigation of the biological basis of sex differences in drug abuse reinstatement, craving and/or relapse, and treatment implications. The overarching goals of the center will focus not only on supporting and maximizing the translational scientific collaborations of the core and pilot research projects, but also on continuing to catalyze the growth of gender-based research throughout the MUSC campus.

The Specific Aims for the years 6-10 of the MUSC SCOR are:
Specific Aim #1: To continue the well-established, multidisciplinary, translational program of research focused on gender-related issues in substance use disorders at MUSC.

Specific Aim #2: To provide common resources through the Administrative Core to assist investigators in increasing efficiency, maximizing scientific rigor and productivity, and collecting pilot data.

Specific Aim #3: To encourage and support the growth of gender-based research throughout the MUSC campus.

Specific Aim #4: To attract and mentor young investigators and new faculty in the area of research, particularly patient-oriented research, in women's health issues.

Specific Aim #5: To provide a regional education and training resource for research in women's health research.

Center funding through the P50 funding mechanism has allowed us to 1) carve out a unique identity on campus, bringing energy and visibility to the importance of gender-specific research, 2) bring together institutional and scientific leadership to form a single operational unit, 3) establish critical infrastructure support to allow for efficient operations, integration, and stability of resources, 4) coalesce a group of senior investigators to integrate their scientific expertise and research skills and advance gender-specific research in the substance abuse area, 5) attract and train new and junior investigators in gender-specific research, 6) support the development and testing of innovative ideas through pilot project funding, and 7) provide an impressive and supportive training environment for future basic and clinical researchers interested in gender based research. The next funding period will allow us to build on these accomplishments, expand our research program into new areas utilizing innovative techniques, enhance our outreach and dissemination efforts, and attract new investigators through the Pilot Core. Our SCOR, with a truly interdisciplinary focus on gender issues in substance use disorders, is a ready resource for inter-ORWH Center collaborations and, as such, is an asset to the ORWH program.

Project 1: Sex and Estrous Cycle-Dependent Differences in Cocaine-Seeking Behavior
Type: Basic

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Project Abstract

Relapse to drug abuse following abstinence is a significant impediment in the treatment of cocaine dependence. Although various factors (stress, conditioned cues, drugs) that contribute to relapse have been studied in males, the impact in females has been less explored. We have

recently shown sex differences for conditioned cue-induced and drug-primed reinstatement of cocaine-seeking in an animal model of relapse. Moreover, the differences seen in females are closely linked to the estrus phase of the estrous cycle. Building on these previous studies, this SCOR project will provide a comprehensive approach to examine sex and estrous cycle dependent differences in reinstatement of cocaine-seeking produced by various trigger factors. Using direct pharmacological activation of the neural pathways that mediate stress responses (e.g., ascending noradrenergic pathways and corticotropin-releasing factor receptors) we predict that female rats (particularly during the estrus phase) will show greater reinstatement of cocaine-seeking than male rats exposed to the same stressor. The use of the exact same stressors and cue reactivity approaches in both the animal model and the human clinical laboratory (SCOR Project #2), will provide a high degree of homology and integration. Following characterization of stress and stress+cue induced reinstatement in males and females, we will examine sex and estrous cycle dependent pharmacotherapy interventions that will attenuate relapse, specifically: a) clonidine, a noradrenergic receptor agonist that may selectively block stress-induced reinstatement; b) progesterone, an ovarian hormone that we have recently found to be inversely related to cocaine-seeking in females; and c) aripiprazole, a novel dopamine receptor partial agonist that blocks cue and drug-primed reinstatement in males, but has never been tested in females. The information gained from these studies will integrate with the clinical SCOR projects that will focus on gender differences and relapse in cocaine (Project #2) and nicotine (Project #3) dependent women and men, including the relationship of ovarian hormones to drug-seeking.

This preclinical animal model of relapse will characterize fundamental sex and estrous cycle dependent differences in cocaine-seeking behavior produced by known risk factors for relapse in humans (i.e., stress, cues, drugs). Furthermore, we will assess pharmacotherapies that may be generalized across males and females, as well as interventions that may be gender-specific. The results from these studies will help identify promising pharmacotherapeutic agents for future testing in the human laboratory setting.

Project 2: Stress-Induced Craving: The Impact of Sex and Ovarian Hormones
Type: Clinical

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There are likely to be gender differences in relapse to drug use following abstinence in cocaine-dependent individuals. In our current SCOR human laboratory study, gender differences in the response to a social stressor and cocaine cues in cocaine-dependent individuals has been demonstrated. Additionally, work from another current MUSC SCOR project has demonstrated

sex differences in response to cocaine-conditioned cue and cocaine-primed reinstatement in animal models which was correlated with reduced plasma progesterone levels. Although gender differences in factors such as stress and conditioned cues that contribute to relapse in cocaine-dependent individuals have been studied independently, the interaction of stress and cues and the effect of hormonal status on response has not been directly explored. The proposed study will build on the work done during the last funding period by studying the role of hormonal status on the response to cocaine-related cues with or without stress in cocaine-dependent women and men. This project will also be important in extending an animal model of pharmacologically-induced stress (yohimbine-induced stress) to a human laboratory setting. As such, this project will use the exact same stressor as the proposed synergistic basic science project (Project 1), providing a high degree of homology and integration. This project will further the ability to directly translate findings from an animal model of relapse to an ecologically valid test of relapse in cocaine-dependent humans and explore the impact of hormonal status on response in this model. As a further integration of the research focus between SCOR projects, both this study and Project 4 will explore the relationship between impulsivity and craving.

The specific aims of this project are: 1. To determine the interaction of a pharmacological stressor with exposure to cocaine-related cues and the impact of ovarian hormone status on this response in women; 2. To explore the relationship between impulsivity, stress, and cocaine craving in cocaine-dependent men and women; and 3. To explore the relationship between the DHEA/cortisol ratio and response to a pharmacologic stressor in control and cocaine-dependent men and women.

The interaction of stress and cues has not been systematically investigated although this paradigm closely mirrors real-life situations. Animal studies suggest that gonadal hormones play a role in the subjective and reinforcing effects of stimulants, but their role in cue or stress-induced craving has not been explored. In addition, there are important sex differences in the impact of stress on cognition that appear to be related to gonadal hormones. Sex differences in the cognitive response to stress, including increased impulsivity, may be important in the relationship between stress, cocaine cues and craving.

Project 3: Gender, Menstrual Cycle and Smoking Cue Reactivity
Type: Clinical
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Project Abstract

Nicotine addiction, in the form of cigarette smoking, is the leading preventable cause of morbidity and mortality in the US. Although the prevalence of smoking has decreased substantially in the last few decades, it remains the single most prevalent form of addictive behavior. A growing body of research has shown that stimuli associated with nicotine administration (e.g., sight and odor of a cigarette) gradually acquire the capacity to elicit craving (urge to smoke) and other physiological responses (e.g., heart rate changes) that are presumed to contribute to the maintenance of smoking behavior. Recent research suggests that gender and intra-gender factors, such as menstrual cycle phase in women, may modulate the craving and physiological reactions elicited by smoking cues. Relatedly, the findings of our on-going SCOR protocol suggest that men and women may differ in their craving and physiological reactions to smoking and stress cues, and that these same reactions may differ among women smokers who are in different phases of their menstrual cycle. Additionally, a SCOR-funded pilot protocol has permitted us to establish procedures for, and determine the feasibility of, a study to manipulate the timing of quit attempts relative to menstrual cycle phase and to determine the impact on smoking cessation outcome.

Building on our previous work, this application proposes a two-part research design, in which we first randomize 226 nicotine-dependent women aged 18-40 to receive a single-session, cue reactivity/impulsivity assessment in either the follicular or luteal phase of their menstrual cycle. In this session, standardized measures of cue reactivity and impulsivity will be obtained. Cue reactivity procedures will involve exposure to robust in vivo smoking cues and take place under conditions of nicotine deprivation. The second part of the study, using the same study sample, proposes a 2x2 randomized clinical trial, in which tinning of quit attempts (follicular vs. luteal menstrual cycle phase) is crossed with pharmacotherapy (transdermal nicotine patch vs. varenicline). Thus, our study represents a programmatic extension of our prior research on menstrual-related effects on smoking behavior, integrates a human laboratory cue-reactivity paradigm with a treatment outcome study, tests whether pre-treatment responses to smoking cues predict measures of treatment outcome, and examines potential interactions between timing of menstrual phase and type of treatment. This application fits well within the scope of the overall SCOR and specifically interdigitates with Component 2, which examines cue-induced craving to cocaine in a clinical population. Results of this study may inform treatment-optimizing decision-making among women smokers.

CORE

Administrative Core

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Administrative Core Abstract

The Administrative Core (AC) is the hub of the MUSC SCOR. It serves as the central coordinating point for all SCOR activities. It influences each research component and brings the various components together to form a cohesive, functioning unit. The AC is active in coordinating all of the outreach activities across the MUSC campus, as well as nationwide with the SCOR advisory board and ongoing collaborations with other SCOR centers The AC provides: (1) defined physical space, (2) unambiguous leadership, (3) a clear management and committee structure, (4) administrative and fiscal services, (5) a means for ongoing communication, integration and quality control, (6) a structure for training and outreach activities, and (7) coordination and supervision of the pilot research program. In the previous funding period, the Administrative Core (AC) served as the backbone of the MUSC SCOR operations. The AC facilitated the work of the SCOR investigators by providing for integration, coordination, and evaluation of the various components and the pilot project program. The AC provided the organizational framework for addressing emergent issues, budgetary concerns, and daily operational issues of the SCOR. The AC insured the integration of the SCOR within MUSC, in general, with the Center for Drug and Alcohol Programs, the Department of Neurosciences, and the Department of Psychiatry and Behavioral Sciences at MUSC, and with local and statewide officials and community treatment centers. Additionally, the AC developed and implemented internal and external quality control mechanisms to insure that the MUSC SCOR and the AC are accomplishing their goals. The AC will continue in these roles in the proposed funding period.

Assays
Project 1:
Plasma estradiol, progesterone, corticosterone, and ACTH concentrations will be determined using radioimmunoassay (Diagnostic Systems Laboratories, DSL-81100, Webster, TX, USA)

Project 2:
Laboratory specimens collected during the testing procedures will be processed through the General Clinical Research Center.