

EVALUATION OF RESEARCH APPLICATION TO NATIONAL INSTITUTE OF HEALTH/DRUG ABUSE (NIH/NIDA) BY 3 REVIEWERS

Getwele Natureceuticals' Summary of Innovation

Persistent craving that drives relapse is a recalcitrant problem of drug abuse. While current treatment focuses on pharmaceutical and cognitive-behavior therapy, which still results in multiple relapses in 40-60% of cases, Getwele is focusing on anti-relapse intervention. Reasons for craving result from both external cues (recall of reward experience and stress and internal cues (depletion in brain chemistry, nutrient deficiencies and metabolite accumulations). Getwele has manufactured a family of 3 functional foods, SMAASH-C (Cocaine), [SMAASH-A (Alcohol), and SMAASH-H (Heroin) that can replenish and balance the biochemical depletions, improve brain function and reduce/eliminate drug desire/seeking behaviors.

Getwele's Achievements

Through its CEO, Getwele pioneered and proved a correlation between biochemical balance (restoration) and reduction in drug desire/seeking in 2014. Concept was accepted in 2017 by a Maryland Family Advocacy group that included us into a Guide to Alternative Therapies that they will submit to the Federal Senate Committee of Maryland General Assembly. Current collaboration with University of Virginia (UVA) confirmed less drug seeking.

3 students were given a PhD & MSc (Biochemistry) and 1 MSc (Physiology) scholarships to study the concept by the University of West Indies, Jamaica.

Summary of Study Proposal Application to NIH/NIDA:

Relapse to drug seeking after abstinence is a major challenge in treating substance use disorder. Abstinent drug users remain at risk of relapse even after extended drug-free periods. Exposure to drug-associated cues or stress during abstinence can trigger intense craving and precipitate relapse. New and more effective anti-relapse interventions are critically needed, particularly for cocaine use disorder since no effective pharmacological intervention is available. We discovered that a nutritional supplement we developed for clinical use, as part of a nutritional approach for managing substance use disorder, had the benefit of being a potentially robust anti-relapse approach. This supplement, SMAASH-C, contains a combination of vitamins, omega-3 fatty acids, and minerals, as well as tyrosine and other amino acids that are known to be depleted by chronic cocaine exposure. We originally learned of its potential therapeutic value through anecdotal reports from our patients of reduced drug desire and seeking. As a follow-up, we screened SMAASH-C in a rat model of relapse, and confirmed its potential efficacy as a support for abstinence intervention. Specifically, we found that 15-days of SMAASH-C treatment during abstinence, via a clinically relevant oral route (mixed in food), resulted in a 50% reduction in extinction and cue-induced cocaine-seeking as compared to control treatment (non-supplemented food). Notably, SMAASH-C did not affect body weight, food intake, or non-specific responding during the cocaine seeking tests indicating its potential as a safe and selective intervention. In fact, results from toxicology analyses of a 12-week SMAASH-C treatment regime in saline and cocaine-withdrawn rats suggests that it offsets markers of cocaine-induced toxicity (e.g., oxidative stress, hepatic injury). The overall objective of this R21 application is to validate the use of SMAASH-C as an efficacious and selective intervention for

cocaine relapse. To do so, we will determine its efficacy at reducing cocaine-seeking following extended access self-administration and protracted abstinence, and in response to two of the most common triggers of craving and relapse in humans: drug-associated cues and stress. Selectivity will be assessed by comparing effects on cocaine- versus sucrose-seeking. Both males and females will be included given literature highlighting the need for sex-specific interventions. Our overall hypothesis is that SMAASH-C will robustly (>50%), selectively (no effect on sucrose-seeking), and dose-dependently (larger doses will produce greater decreases) decrease cocaine-seeking in both males and females). We anticipate that at the conclusion of these studies we will validate SMAASH-C as an effective and selective abstinence support intervention. These findings will then be used to help guide the development of SMAASH-C for use in humans as support for abstinence.

Public Health Relevance: We discovered that a nutritional supplement we developed for clinical use, SMAASH-C, had the benefit of being a potentially robust support for abstinence; our pilot data in rats are consistent with patient reports, and show that it markedly decreases cocaine-seeking without affecting food intake or body weight. The overall objective of this R21 application is to validate the efficacy and selectivity of this novel nutraceutical at reducing cocaine-seeking in males and females in response to common triggers of craving/relapse (drug-associated cues and stress). These findings will help guide the development of this novel nutraceutical as a support for abstinence for women and men with cocaine use disorders. It is our plan to study FENTANYL and ALCOHOL with their own products after we are done with cocaine study.

SUMMARY OF DISCUSSION OF THE NIH/NIDA REVIEWERS:

This project aims to characterize the efficacy of a nutritional supplement, SMAASH-C, at reducing cocaine seeking—in the context of drug-associated cues or stress, both of which are strong relapse triggers in humans—in a rat model of cocaine addiction followed by abstinence. This has the potential impact of identifying a means of facilitating recovery in cocaine abusers. The investigative team and research environment are exceptionally well suited for the conduct of this work, the premise of which is supported by preliminary data and some reports of efficacy in humans. This systematic behavioral efficacy trial of SMAASH-C is rigorously designed, and includes appropriate dose-response curves as well as evaluation of both sexes. The committee concluded that this is a well-designed study that is likely to be carried out successfully.

Reviewers' comments

Overall Impact:

- This exploratory/developmental (R21) grant application aims to determine the efficacy of using a nutritional supplement SMAASH-C for reducing relapse to cocaine self-administration with conditioned cues and stress-induced reinstatement. The studies are straightforward tests of efficacy of a treatment to reduce relapse under two common triggers for relapse, conditioned cues and stress. The methods of study are the classic procedures of intravenous (IV) self-administration in the rat model. These are well designed and should provide interpretable outcomes.
- This is a project testing the scientific premise that, in a rodent model of addiction, a novel compound, SMAASH-C, will be effective at reducing relapse vulnerability in response to cocaine associated cues and stress. Further, SMAASH-C has the added benefit of alleviating

cocaine-induced toxicity. The premise is supported by preliminary data from the Principal Investigator's laboratory. This is a strong application for testing a novel compound. Strengths include the quality, productivity, and experience of the Principal Investigator, the environment, the comprehensive approach to addiction treatment, testing multiple reinstatement modalities, use of both sexes, and using an addiction model that results in an addiction phenotype combined with an incubation model of drug craving. These strengths override the minor weaknesses in the innovation and approach, making this project likely to have a high impact in the field of addiction treatment.

- This project uses state-of-the-art animal models to study cocaine addiction and a nutritional intervention thereon about the quality controls for SMAASH-C formulation.

Significance

- Cocaine addiction continues to be a substantial health problem without very effective treatments to prevent relapse. It is a growing societal problem with great morbidity and mortality and it has no truly successful treatments. The examination of a nutritional approach is innovative and has the potential to be very accessible, if successful.
- In light of the current opioid epidemic, stimulant addiction has received less attention than opioid use disorder. However, as the application points out, cocaine use has also increased in the past decade and is still increasing at an alarming rate. More comprehensive treatment options are needed to address the multifaceted problem of addiction. Treatment approaches like those proposed in this application provide a comprehensive, affordable approach rather than a targeted focus on one particular neurotransmitter system or molecule.
- The proposed compound SMAASH-C has an added benefit to offset measures of cocaine toxicity.

Investigators

- The Principal Investigator has extensive experience in studying rat models of cocaine addiction and its treatment. The Co-Investigator is an experienced dietary-supplement developer.

Innovation

- The approach of using a dietary supplement to improve successful cocaine abstinence could be an innovative approach.
- The use of SMAASH-C as an anti-relapse medication is novel, as is the concept of testing nutritional supplements as medication.
- There are several innovations that are remarkable in that the project is using a nutrition-based intervention, that the addiction model is an established phenotype, and the intervention is being carefully tested in both sexes.

Approach

- The methods of study of cocaine self-administration, and relapse with cues and stress are classic and well validated. The studies are generally well designed.
- The long-access discrete trial model results in an addictive phenotype in both males and females. The experiments are straightforward and consist of dose-response studies for SMAASH-C in both males and females.
- The application presents preliminary data in Figures 2 through 5 with promising evidence that SMAASH-C treatment does not impact weight or elements of physical health in rats.

They also show that treatment enhances extinction of cocaine self-administration and reduces cue induced cocaine seeking.

- The studies are carefully designed to examine significant sex and estrous cycle phase differences.
- There is a thoughtfully considered rationale for the use of yohimbine, a noradrenergic alpha-2 receptor antagonist because it is a commonly used pharmacological stressor, and has been shown to reliably induce stress-like responses in both humans and animals.
- The study design thoughtfully examines cue- and stress-induced cocaine craving responses
- There is an appropriate control trial using sucrose self-administration to test if SMAASH-C specifically reduces cocaine craving and not natural reward self-administration.
- The inclusion of a sucrose group will determine specificity to cocaine. Scientific rigor is well described, as is the inclusion of sex as a biological variable.
- Preliminary data generated by the Principal Investigator support the scientific premise for the proposed efficacy of SMAASH-C to reduce cocaine seeking.
- Testing two different precipitators, stress and drug associated cues, to a relapse event is a strength

Reviewers' Recommendations for moving forward

We are recommended to carry out the followings for the completeness of our study

- Mechanism of Action
- Human study
- Quality Control Protocol
- Characterization of SMAASH-C
- Coordination of study