U.S. Department of Health and Human Services
National Institutes of Health

Minutes of the Seventh Joint Meeting of the National Advisory Council on Alcohol Abuse and Alcoholism, National Advisory Council on Drug Abuse, and National Cancer Advisory Board

May 15, 2019
Bethesda, Maryland

Members of the National Advisory Council on Alcohol Abuse and Alcoholism (NIAAA), National Advisory Council on Drug Abuse (NIDA), and the National Cancer Advisory Board of the National Cancer Institute (NCI) convened for their seventh joint meeting on May 15, 2019, in Bethesda, Maryland. Chaired by George Koob, Ph.D., Director of NIAAA, and Nora Volkow, M.D., Director of NIDA, this open session convened at 9:01 a.m.

National Advisory Council on Alcohol Abuse and Alcoholism Members Present:
Carmen E. Albizu-Garcia, M.D.
Louis E. Baxter, Sr., M.D.
Howard C. Becker, Ph.D.
Jill B. Becker, Ph.D. (by telephone)
Daniel J. Calac, M.D.
Tom B. Donaldson
Alex M. Dopico, M.D., Ph.D.
Karen G. Drexler, M.D. ex-officio
Tatiana M. Foroud, Ph.D.
Robert J. Hitzemann, Ph.D.
Constance M. Horgan, Sc.D.
Joe L. Martinez, Jr., Ph.D. (by telephone)
Charles S. Milliken, M.D., ex-officio
Scott J. Russo, Ph.D.
Arun J. Sanyal, M.D.
Vijay H. Shah, M.D.
Frank A. Sloan, Ph.D.
Susan M. Smith, Ph.D.
Edith Vioni Sullivan, Ph.D.
Constance M. Weisner, D.R.P.H.

National Advisory Council on Drug Abuse Members Present:
Judith D. Auerbach, Ph.D.
Julie Ann Blendy, Ph.D.
Linda Chang, M.D.
H. Westley Clark, M.D., J.D.
Arthur T. Dean, M.A.
Lakshmi A. Devi, Ph.D.
Gail D'Onofrio, M.D.
Jay N. Giedd, M.D.

Christian A. Heidbreder, Ph.D.
Kenneth P. Mackie, M.D.
Lisa A. Marsch, Ph.D.
Edward V. Nunes, M.D.
Robert G. Rancourt, J.D.
Steffanie A. Strathdee, Ph.D.

National Cancer Advisory Board Members Present:
Lawrence O. Gostin, J.D. (by telephone)
Margaret R. Spitz, M.D. (by webcast)

Chairs: George Koob, Ph.D., and Nora Volkow, M.D.

National Institute of Alcohol Abuse and Alcoholism (NIAAA) Director: George Koob, Ph.D.

National Institute on Drug Abuse (NIDA) Director: Nora D. Volkow, M.D.

National Cancer Institute/Division of Cancer Control and Population Sciences (NCI/DCCPS) Director: Yvonne Prutzman, designee of Robert T. Croyle, Ph.D.

NIAAA Deputy Director: Patricia Powell, Ph.D.

NIDA Deputy Director: Wilson Compton, M.P.E., M.D.

NIAAA, Director, Office of Extramural Activities: Abraham P. Bautista, Ph.D.

NIDA, Director, Division of Extramural Research: Susan B. Weiss, Ph.D.

NCI, Director, Division of Extramural Activities: Wlodek Lopaczynski, M.D., Ph.D., designee of Paulette S. Gray, Ph.D.

NIDA Senior Staff: Carlos Blanco, Ph.D.; Bethany Deeds, Ph.D.; Gaya Dowling, Ph.D.; Katia Howlett, Ph.D., M.B.A.; Roger Little, Ph.D.; Michele Rankin, Ph.D.; Rita Valentino, Ph.D.; and Tracy Waldeck, Ph.D.

NIAAA Senior Staff: Ralph Hingson, D. Sc.; Kathy Jung, Ph.D.; and Bridget Williams-Simmons, Ph.D.

NCI Senior Staff: Wlodek Lopaczynski, M.D., Ph.D.; Yvonne Prutzman, Ph.D.

Additional Participants
Approximately 35 observers joined the meeting, including representatives of constituent groups, liaison organizations, and members of the general public.

Call to Order and Introductions
Dr. Koob called to order the seventh joint meeting of the National Advisory Councils of NIAAA, NIDA, and NCI in open session at 9:01 a.m. on Wednesday, May 15, 2019. Council members and Institute leaders introduced themselves.

NIAAA Director's Presentation

Dr. Koob highlighted data published by Drs. Anne Case and Angus Deaton showing the rising morbidity and mortality in midlife among white non-Hispanic Americans due in large part to poisonings, suicide, and chronic liver disease. He pointed out the relationship between these conditions and alcohol and other substance misuse, including the opioid crisis, and depression. Dr. Koob, Dr. Volkow, and Joshua Gordon, M.D., Ph.D., Director of the National Institute of Mental Health (NIMH), have been discussing this issue. NIAAA has focused efforts on the underlying issues that contribute to these "deaths of despair." Data also demonstrates that alcohol use contributes to opioid overdoses. Between 2006-2014, there has been a significant increase in emergency room (ER) visits due to opioids (110 percent increase) and alcohol (135 percent increase); alcohol contributes to approximately 15 percent of ER visits. Alcohol alone kills nearly 90,000 people per year; about half of these deaths are due to acute alcohol-related causes. While less attention has been paid to alcohol in the midst of the opioid crisis, ongoing efforts to address opioid misuse are having the benefit of increasing focus on substance use disorder (SUD) treatment overall.

A Heuristic Framework of Addiction: Dr. Koob presented a heuristic conceptual framework for studying the neurobiological bases that drive SUDs. The framework posits an iterative three-phase cycle with each phase corresponding with distinct regions of the brain. The cycle begins with the binge/intoxication stage, associated with incentive salience, and involving the basal ganglia of the brain. The withdrawal/negative affect stage, is characterized by loss of reward (reward deficit) and an increase in the brain's stress system (stress surfeit) and is associated with the brain's extended amygdala. The preoccupation/anticipation stage is characterized by executive function deficits and is associated with the prefrontal cortex of the brain. Laura Kwako, Ph.D., NIAAA, and colleagues developed an Addictions Neuroclinical Assessment organized around the domains of the addiction cycle and evaluated the relevance of this conceptual framework in a study with 500 patients at the NIH Clinical Center. They confirmed the three key neurobiological domains critical to the addiction cycle (incentive salience, negative emotionality, and executive function) using measures of addiction, personality, cognition, behavior, and exposure to early-life stress, employing a multiple indicators, multiple causes approach.

NIAAA is applying the framework to other areas, such as pain. Alcohol is an effective pain reliever, but its analgesic effects only occur at the binge/intoxication level (0.08 blood alcohol concentration [BAC]). Chronic alcohol use and withdrawal produce hyperalgesia (increased pain sensitivity). Another use of the framework is in understanding the role of the negative affect stage in the differences between males and females in their reactions to stress, particularly chronic stress. In males, stress and chronic ethanol exposure each activate distinct neuronal populations in the central nucleus of the amygdala (CeA) in preclinical models. In females, more similar distributions of CeA neurons are activated in response to stress or chronic ethanol exposure. In the locus coeruleus (LC), stress alters the corticotropin releasing factor receptor (CRFr) function in a sex-specific manner. In females, stress enhances cellular signaling and compromises internalization of CRFrs, which renders females more sensitive to low levels of CRF and less adaptable to high levels of CRF.

Emerging Issues: One emerging issue is the relationship between alcohol use disorder (AUD) and sleep disturbance, an area that has long been neglected in the alcohol field despite the fact that it is rare for someone with AUD to not report a sleep disturbance. Dr. Koob recently submitted a review of the literature about this issue. Another emerging issue to which NIAAA is responding is the relationship between AUD and post-traumatic stress disorder (PTSD). AUD frequently co-occurs with other SUDs and mental health conditions. AUD patients with co-occurring conditions tend to have a poorer prognosis.

NIAAA previously issued a Funding Opportunity Announcement (FOA) on Alcohol-PTSD Comorbidity: Preclinical Studies of Models and Mechanisms in collaboration with Cohen Veterans Bioscience to develop, validate, or apply animal models for mechanistic studies of comorbid PTSD and AUD**.**

Alcohol and the Brain: Dr. Koob presented findings from the longitudinal National Consortium on Alcohol and Neurodevelopment in Adolescence (N-CANDA) study that shows that the frontal cortex changes during adolescence. During normal adolescence, gray matter decreases and white matter increases, while the overall size stays about the same. Heavy drinking adolescents have steeper reductions in gray matter volume than no/low drinking adolescents. Such findings hint at what the much larger Adolescent Brain Cognitive Development (ABCD) study may find.

Medications Development: The three-stage conceptual framework is being used to energize NIAAA's Division of Medications Development that supports human laboratory screening studies to bridge the gap between preclinical and clinical trials. The NIAAA Clinical Investigations Group (NCIG) (also within the Division of Medications Development) conducts "fast success/fast fail" Phase II clinical trials with an 18 month turn-around time, while the intramural program conducts clinical studies on novel compounds with AUD treatment potential. A successful clinical trial has been completed on a Vasopressin receptor [AVPR1B] antagonist by NCIG and one is underway now with a glucocorticoid receptor [NR3C1]) antagonist via extramural funding. These studies target the second stage of the framework, i.e., the negative emotional stage associated with the amygdala. Industry has yet to pursue the AVPR1B antagonist for further clinical trials. The Division of Medications Development also supports a Small Business Innovation Research (SBIR)/Small Business Technology Transfer (STRR) program to facilitate studies leading to Investigational New Drug (IND) applications to the Food and Drug Administration (FDA). The SBIR/STTR programs use the U44/UT2 mechanism, a cooperative agreement, to facilitate working closely with NIAAA Medication's Development staff.

Resource Development: A priority for both NIAAA and NIDA is closing the treatment gap by improving physician training in substance abuse prevention and treatment at all levels, and Integrating prevention, early intervention, and treatment into routine health care. In the United States, fewer than 10 percent of people with AUD receive any form of treatment. Many health care providers do not perform alcohol screening, are not aware of evidence-based treatments, and do not know where to refer patients for treatment. To that end, NIAAA has developed the Alcohol Treatment Navigator, and is updating it to include a Clinician's Navigator. In addition, NIAAA is developing the NIAAA Clinician's Core Resource, designed for any healthcare provider who sees patients. Its goals are to provide a core base of knowledge on topics such as alcohol's presentation in primary care; its role in common co-occurring conditions; neuroscience; alcohol misuse across the lifespan; diagnostic criteria, recommended drinking limits; alcohol withdrawal syndrome; evidence-based therapies/medications; addressing stigma; and interactions with commonly used medications. The Core Resource will also include practice suggestions, such as how to start a conversation about alcohol, and available resources, e.g., screening tools.

Discussion: Charles Milliken, M.D., inquired if providers can earn continuing medical education (CME) credits for using the resource materials that NIAAA is developing. Bridget Williams-Simmons, Ph.D., reported that NIAAA is exploring that possibility. Steffanie A. Strathdee, Ph.D., asked if Dr. Koob had uncovered any relationship between sleep apnea and alcohol in his literature review. Dr. Koob responded that there is a relationship between sleep apnea and excessive alcohol use; it was not included in the review article due to length limitations. Arun Sanyal, M.D., suggested that incorporating NIAAA's Clinician's Core Resource into the curriculum of the Accreditation Council for Graduate Medical Education (ACGME) would provide a good return on investment. Dr. Koob commented that multiple

organizations have a core curriculum that is generally ignored. Therefore, NIAAA has adopted the strategy of consolidating the information into one place for anyone to use, as well as providing it to the American Society for Addiction Medicine (ASAM), which is drawing up a protocol for treating alcohol withdrawal. Daniel Calac, M.D., asked if there were efforts underway to add health warnings to containers of alcoholic beverages, analogous to those on cigarette packages. Dr. Koob responded that he was unaware of any such efforts and believes instead that alcohol is becoming ever more ubiquitous.

NIDA Director's Presentation

Dr. Volkow noted that people continue to die from alcohol and tobacco, but these substances are often overlooked because they've been around for so long. With the opioid crisis, there is the opportunity to shift the addiction field to where it should have been a long time ago. There are pharmacological differences among different substances, but the concept of addiction is consistent across all of them.

NIDA's Budget: The Fiscal Year 2019 NIDA budget is $1,158,216,000. There is also $250 million allocated for opioid use disorder (OUD) as part of the Helping End Addiction Long-Term℠ (HEAL) initiative.

2018 Monitoring the Future Results: The most recent survey of 8th, 10th, and 12th graders revealed a significant drop in binge drinking across all age groups in the past five years. Illicit drug use, other than marijuana, is at its lowest point in the past 20 years. Heroin use (0.4 percent) is at its lowest rate ever. Teens are more likely to use marijuana than to smoke cigarettes; five-year trends in daily marijuana use remain steady among 10th (3.4 percent) and 12th (5.8 percent) graders but is declining among 8th graders (0.7 percent). Actual rates among youth may be higher because students who use marijuana regularly are more likely to drop out of school and would not be picked up in this school-based survey. The strength of tetrahydrocannabinol (THC) has tripled since 2000, making it much more harmful to the developing brain. Marijuana users are also more likely to be consuming alcohol and tobacco. Prescription drug use also declined, although benzodiazepines (tranquilizers) (5.0 percent) and Adderall use (4.6 percent) declined less than other drugs. Past-year use of Vicodin and OxyContin among 12th graders significantly declined in the past 15 years to less than 1.7 percent and 2.3 percent respectively. And although cigarette smoking has continued to decline among youth—only 7 percent said they smoked cigarettes in the past month-- their use of vaping devices dramatically increased, with 37.3 percent of 12th graders, 32.3 percent of 10th graders, and 17.6 percent of 8th graders reporting that they vaped. In previous years, teens reported vaping for the flavors; in 2018, 12th graders were more likely to report that they vaped for nicotine, making them more vulnerable to becoming addicted to combustible cigarettes. Nicotine can be a gateway drug that enhances the reinforcing effects of other drugs. Thus, decreasing the use of vaping needs to be a priority for the field.

The HEAL Initiative: Opioid deaths have increased dramatically in the United States during the past five years. Starting in New Mexico and Appalachia in 2003, the opioid epidemic has now spread across the country and overdoses are as likely in urban centers as in rural areas. The emergence of synthetic opioids and fentanyl has accelerated the overdose rates. Thus, the nation is facing an extremely complex epidemic that is changing rapidly. In response, the NIH HEAL initiative targets 1) the enhancement of pain management by advancing effective treatments for pain through clinical research and accelerating discovery and development of pain treatments; and 2) improving treatments for misuse and addiction by expanding therapeutic options, developing new and improved prevention and treatment strategies, optimizing effective treatments, and enhancing treatments for infants with Neonatal Abstinence Syndrome (NAS)/Neonatal Opioid Withdrawal Syndrome (NOWS).

Advancing the fundamental science to improve pain management includes discovering and validating novel targets for pain treatment, with a focus on non-opioid alternatives; engineering preclinical screening platforms and novel drug development, such as tissue chips, 3D-printed organoids, and stem cell-derived neurons; and improving understanding of the transition from acute to chronic pain, i.e., finding acute-to-chronic pain signatures. Advancing effective treatments for pain includes the establishment of an unprecedented clinical trials network to test a wide range of strategies for the management of multiple different pain syndromes. Industry has agreed to make available dozens of promising pain treatments; and to help develop ways to make pain management data more widely accessible to speed clinical translation and to encourage innovative partnerships.

NIDA has received $250 million to invest in research to address opioid misuse and use disorders (OUD), and overdose. Priority research areas under HEAL are expanding therapeutic options; optimizing effective treatment strategies; developing new and improved prevention and treatment strategies; and enhancing treatments for infants with NAS/NOWS. The addiction cycle framework provides a basis for expanding therapeutic options for OUD, including the development of non-invasive stimulation technologies, e.g., transcranial magnetic stimulation, that target neurocircuits associated with each phase of the cycle. Advancing effective treatments includes the expansion of the NIDA Clinical Trials Network to increase the number of places where existing effective treatment for OUD may be obtained, as well as treating patients in places other than the medical setting, e.g., in the criminal justice system through a new Justice and Community Opioid Network (JCOIN). Further, NIDA, in partnership with Substance Abuse and Mental Health Services Administration (SAMHSA), is supporting the HEALing Communities Study, in which evidence-based interventions will be integrated across health care, the criminal justice system, and communities (e.g., schools, faith-based organizations, etc.) in four states. Outcomes will be compared across communities with and without integrated systems. Among the goals to be achieved through this initiative is a decrease in opioid-related fatalities by 40 percent.

The Healthy Brain Child Development Center (HBCD), a large multi-site longitudinal study, will examine the brain, cognitive, behavioral, emotional, and social development prenatally through childhood to understand how the opioid and other drug exposures during fetal development, along with adverse/protective environmental experiences affect the brain. HBCD is an outgrowth of both the ABCD and N-CANDA studies. The project will start with an 18-month pilot supported by multiple NIH Institutes; grant applications will be reviewed this summer.

Discussion: Dr. Milliken suggested offering CME credit for information/training that NIDA provides. He also noted that the Centers for Disease Control and Prevention (CDC) might decide to send small teams to underserved locales for short periods to help address the opioid crisis; this would be more effective if there were a telemedicine component. Dr. Volkow responded that NIDA requires all projects to demonstrate sustainability, and telehealth is one potential solution. She said that one challenge in the provision of training materials about opioid prescribing is that most were developed by pharmaceutical companies. And, even if the health care field is successful in addressing opioids, there are new drugs emerging, such as illicit fentanyl that need to be targeted. Karen Drexler, M.D., commented that the challenge is to change the culture from one in which SUDs are considered medically non-urgent to one in which treatment is important. She asked if the goal of HEALing Communities is to initiate treatment. Dr. Volkow commented that clinics are beginning to emerge to address opioids, but some use methods that are not evidence-based. It's also important for patients to evaluate their treatment so that prospective patients have information on expected outcomes. Dr. Calac inquired about why Alaska appeared to have rapidly increased levels of opioid use. He also noted that American Indians are at high risk and encouraged their inclusion in the HBCD study. Dr. Volkow reported it is difficult to recruit

American Indians to participate in research studies because of trust issues; but NIDA is working with tribal communities/nations to improve the situation.

FDA's Comprehensive Plan for Tobacco and Nicotine Regulation

Dr. Volkow introduced Mitch Zeller, J.D., Director of the FDA's Center for Tobacco Products, who described the agency's comprehensive plan for tobacco and nicotine regulation, including regulatory policies on addiction, appeal, and cessation; youth tobacco prevention plan; and science-based review of tobacco products. The focus of the plan is primarily on cigarettes, which account for 480,000 preventable deaths each year. Driving the comprehensive plan is FDA's vision of a world where cigarettes would no longer create or sustain addiction, and where adults who still seek nicotine could get i**t** from alternative and less harmful sources.

Regulatory Policies on Addiction, Appeal, and Cessation: On March 15, 2018, FDA issued an advance notice of proposed rulemaking (ANPRM) titled the *Tobacco Product Standard for Nicotine Level of Combusted Cigarettes,* seeking public comment for consideration in developing a potential product standard to lower nicotine to a minimally or non-addictive level in cigarettes. Newly published estimates of the outcomes of one possible policy scenario on this approach predicted that by 2100, 33+ million people won't become regular smokers; the smoking rate will decline from its present 15 percent to 1.4 percent; and 8 million deaths would be avoided. A single rule-making, however, is insufficient. A national dialogue on nicotine, one component of FDA's comprehensive plan, focuses on educating the public to discuss the core of the problem and the solution to addiction.

The FDA's Nicotine Steering Committee was formed in September 2017 and charged with re-evaluating and modernizing FDA's approach to the development and regulation of nicotine replacement therapy (NRT) products. Since then, FDA has held public hearings on the topic; issued "Nonclinical Testing of Orally Inhaled Nicotine-Containing Drug Products" Draft Guidance; and issued "Smoking Cessation and Related Indications: Developing Nicotine Replacement Therapy Drug Products" Draft Guidance. It has also held a public hearing and a scientific workshop on treatment strategies for youth tobacco use, including vaping. On March 20, 2018, the FDA issued an ANPRM on the *Regulation of Flavors in Tobacco Products.* Another ANPRM was issued on March 23, 2018, regarding *Regulation of Premium Cigars*, and public comment sought on adolescent and young adult patterns of cigar use and associated health risks.

Youth Tobacco Prevention Plan: FDA's Youth Tobacco Prevention plan has three main strategies: Preventing youth access; curbing the marketing of tobacco products aimed at youth; and educating teens and their families. A major concern is the popularity of products that closely resemble a USB flash drive, have high levels of nicotine, and have emissions that are hard to see. These characteristics may facilitate youth use by making products more attractive to youth. Youth may unaware that these products contain nicotine. FDA's enforcement actions in the youth tobacco access and marketing domain include the largest coordinated enforcement effort in FDA's history, in which the agency issued more than 1,100 warning letters and 131 civil money penalty complaints to retailers who illegally sold e-cigarettes to minors. The FDA also issued 17 warning letters for selling e-liquids with labeling and/or advertising causing them to resemble kid-friendly food products such as juice boxes, candy and cookies, some with cartoon imagery. FDA also conducted a large-scale, undercover nationwide "blitz" of brick-and-mortar & online retailers for selling vaping products to underage youth, among other enforcement actions.

FDA's policy actions to address youth tobacco access and marketing respond to finding from the 2018 National Youth Tobacco Survey data that revealed an alarming surge in youth e-cigarette use, with 3.6 million teens using these products making them the most commonly used tobacco product among youth.

In September 2018, FDA announced that the agency would be reconsidering all policy options with respect to e-cigarette products. In March 2019, FDA released a "Modifications to Compliance Policy for Certain Deemed Tobacco Products" Draft Guidance that outlines policy changes and prioritization of enforcement resources. Under the new policy, certain flavored electronic nicotine delivery systems (ENDS) products (other than tobacco-, mint-, and menthol-flavored ones, which are popular with adults), and ENDS products that are targeted to minors or likely to promote use of ENDS by minors, will be subject to enforcement beginning 30 days after guidance is finalized. Also, any new flavored cigars (other than tobacco-flavored) on the market as of August 2016 –and that meet the definition of a new tobacco product –would be subject to enforcement beginning 30 days after the guidance is finalized. FDA also plans to move forward with a proposed rule to ban all characterizing flavors in cigars.

FDA is coupling its enforcement and policy actions regarding youth tobacco access and marketing with "The Real Cost" Youth E-Cigarette Prevention Campaign targeted to youth aged 12-17 who have used e-cigarettes or are open to trying them. Launched in September 2018, the Campaign messages focus on educating youth that using e-cigarettes, just like cigarettes, puts them at risk for addiction and other health consequences. The Campaign includes online ads and location-targeted advertising around high schools nationwide, such as posters in school bathrooms where students are most likely to use e-cigarettes. This summer, FDA plans to extend the campaign to include television ads.

Science-based Review of Tobacco Products: In April 2019, FDA authorized the marketing of new tobacco products for Phillip Morris Products S.A's IQOS "Tobacco Heating System" electronic device that heats tobacco-filled sticks wrapped in paper to generate a nicotine-containing aerosol. Referred to as "heat-not-burn" or "heated" tobacco products, these products may be less harmful than combustible cigarettes as fewer toxins are released. Stringent marketing restrictions are imposed on the products to prevent youth access, use, and exposure, and market dynamics, such as potential youth uptake, will be monitored. Since December 2016, FDA has filed applications for scientific review for 15 modified risk tobacco products. No product has yet received approval.

Discussion: Carmen Albizu-Garcia, M.D., inquired about harm reduction strategies about vaping in the presence of non-smokers. Mr. Zeller replied that there is no federal clean air legislation, but some jurisdictions have worked to pass local clean indoor air laws to limit vaping. What is currently unknown, however, is to what toxins bystanders are actually being exposed. Louis Baxter, M.D., recommended targeting younger children with the anti-vaping message, as they may influence other family members. Mr. Zeller responded that "The Real Cost" campaign targets middle school and high school students, but that posters and other materials are available at no cost for community and faith-based organizations and could be used to reach younger audiences. H. Westley Clark, M.D., J.D., asked if FDA was going to be monitoring the African American population among whom menthol flavor is popular. Mr. Zeller replied affirmatively but asked what advice should be offered to an African American smoker who is concerned about his health and is offered the availability of a menthol cigarette that heats but doesn't burn. Dr. Clark responded his advice would be "don't smoke," but pointed out that research is needed to determine if these potentially less harmful products actually achieve harm reduction. Constance Weisner, D.R.P.H., noted that there are reports from clinicians that pregnant women think vaping is harmless. Mr. Zeller responded that there are no currently approved cessation products for pregnant

women. Vijay Shah, M.D., inquired about FDA's relationship with tobacco manufacturers. Ms. Zeller described the FDA as wearing two hats: Cops on the beat on the one hand, reviewers who encourage manufacturers to discuss questions to facilitate the chances that their application will have a successful scientific review on the other. Susan Smith, Ph.D., said she preferred the language "a world where kids cannot become addicted to nicotine," to the FDA's "a world where kids cannot become addicted to cigarettes." She hopes the findings of the ABCD study will provide a scientific basis for the FDA to make this change. Mr. Zeller commented that combustible cigarettes are the primary driver in the FDA vision, but that the agency is taking multiple other steps to discourage young people from initiating any nicotine use. Most adult cigarette smokers began smoking as adolescents, so the FDA has adopted cigarettes in its vision; but this is not meant to imply that the use of any nicotine is acceptable.

Adolescent Brain and Cognitive Development (ABCD) Study Update

Dr. Volkow introduced Gaya Dowling, Ph.D., Director of the ABCD study, who updated Council members on the status of the study.

Enrollment: With a total of 11,878 participants, enrollment is now complete. Sample targets were set to reflect the nation's demographics reported by the American Community Survey (ACS). Among singleton and sibling enrollees, the racial/ethnic demographics match nicely with the ACS. It has been more challenging to match racial/ethnic demographics for the twins/multiple births cohort of the study where there is an overrepresentation of white enrollees, but also a good representation of African Americans. In addition to racial/ethnic demographics, there was also an attempt to match the socio-economic status (SES) demographics of the ACS. While there is greater representation of higher education categories among ABCD enrollees than in the ACS, the number of enrollees in each cohort is large enough for reliable findings.

Follow-up Assessments: Dr. Dowling reviewed the timeline of assessments in the study. For the one-year follow-up assessment, some items were added that had been deleted from the baseline assessment due to time limitations. These new items include a gender identity questionnaire, a delinquency scale, life events scale (to assess traumatic events), substance use expectancies questions, a delay discounting task, an emotional faces Stroop task, and a new urine test (NicAlert). There are also new additions to the two-year follow-up assessment. ABCD has partnered with the National Heart, Lung, and Blood Institute (NHLBI), and added items of interest to this Institute: Blood pressure recording, a nutrition screener, and an extra tube of blood to assess A1C, cholesterol, CBC, anemia, and genetic and epigenetic factors. There are also additional items in the areas of mental health, substance use, neurocognition, and culture and environment. In addition, there is a broadened screen time survey and Fitbits will be deployed cohort-wide to assess sleep and activity.

Retention: ABCD is using a results-based monitoring framework to track where each research site is in completing each data collection phase. Thus far, the study has retained 99.4 percent of enrollees. ABCD is closely examining the characteristics of those who miss a visit, finding that minority enrollees are more likely to do so. Metrics being examined for this purpose include sex, race/ethnicity, household income, parental education, Spanish language, parental employment status, distance to the study center, and sub-study participation. If study administrators can understand why visits are missed (e.g., lack of child care), then they can find ways to intervene to correct the problem. Study administrators have also developed tools, such as email alerts, to assist sites with retention.

Imaging completion at baseline was 94 percent, rising to 97 percent at the two-year follow-up. For motion-free rsfMRI, the completion rate at baseline was 82 percent, rising to 92 percent at two-year follow-up.

ABCD Phase II: The project is nearing completion of its original five-year timeline. Requests for Applications (RFAs) have been released for renewal awards.

Data Sharing and Use: ABCD adopted an open science model to make data available to the entire scientific community as quickly as possible. Raw images are released to the NIMH database on an ongoing basis. Full baseline curated data on 11,875 participants was released in April 2019 based on data collection completed in October 2018. It included basic demographics; assessment of physical and mental health, substance use, culture and environment, and neurocognition; tabulated structural and functional neuroimaging data; minimally process brain images; biological data (e.g., pubertal hormone analyses); genotypic data from the Smokescreen array; and residential history derived data (e.g., crime, area deprivation index). There is also a Data Exploration and Analysis Portal (DEAP) for scientists to find measures of interest from more than 40,000 shared observations available for each ABCD participant in order to test hypotheses using a multi-level regression model suitable for the ABCD study and to run novel multi-level statistical analysis directly from the DEAP interface.

The scientific community has expressed interest in the data, with a dramatic increase in unique user data downloads following release of the full baseline data. The fast track images and clinical files have been popular since their initial release. There have also been four grants awarded across three Institutes/Centers (ICs) that are based on ABCD data. Two FOAs for using the data are now available: PAR-18-062 —Accelerating the Pace of Drug Abuse Research Using Existing Data (R01), funded by NIDA, NIAAA, and NCI; and PAR-19-163 –Accelerating the Pace of Child Health Research Using Existing Data from the ABCD Study (R21), funded by NIDA, the National Institute of Neurological Disorders and Stroke (NINDS), National Institute on Minority Health and Health Disparities (NIMHD), NIMH, NCI, the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), and the Office for Research on Women's Health (ORWH).

To date, 11 journal articles based on ABCD data have been published, four of them from non-ABCD investigators. Elizabeth Hoffman, Ph.D., and Kim Le Blanc, Ph.D., both from the ABCD office, reviewed two of these papers to illustrate the potential of ABCD data. Dr. Hoffman's presentation focused on an article entitled "Resting-State Functional Connectivity and Psychotic-like Experiences in Childhood: Results from the ABCD Study" published in *Biological Psychiatry* (2019) by N. Karcher, K. O'Brien, S. Kandala, and D. Barch from the Washington University in St. Louis study site. This report was based on data from the February 2019 release of data on about one-half of the cohort. It examined the role of three major cortical networks—the cingulo-opercular network (CON), default mode network (DMN), and frontoparietal network— in psychotic-like experiences (PLEs) among participants; these networks are consistently implicated in psychosis and PLEs in adults. The researchers found that decreased CON and DMN connectivity, as well as cinguloparietal (CPAR) network connectivity, was associated with greater PLEs among participants, even after accounting for a family history of psychotic disorder, cognitive functioning, and internalizing symptoms. The investigators are currently replicating these findings in the full cohort and hoping to examine longitudinal changes. A potential future implication of this study is implementation of a general population screening effort. Dr. Le Blanc reviewed a study published in *JAMA Psychiatry* (2019) entitled "Association of Prenatal Cannabis Exposure with Psychosis Proneness among Children in the Adolescent Brain Cognitive Development (ABCD) Study" led by Jeremy Fine and other researchers at Washington University in St. Louis. Cannabis has been shown to increase the risk of

psychosis in adults, but less studied is the impact of prenatal cannabis use on psychosis. Of particular concern are the findings of a 2018 study that found past-month marijuana use among pregnant mothers in the United States increased by 75 percent between 2002 (2.85 percent) and 2016 (4.98 percent). Among the 4,361 children (ages 9 to 10.9 years) sampled in the first release of the ABCD data, 201 (4.61 percent) were reported to have been exposed to marijuana before birth. Of these, 138 were exposed before the mothers knew they were pregnant; two were exposed after the mother knew she was pregnant. Risk of psychosis was measured with the Prodromal Questionnaire—Brief Child Version. Findings indicated that prenatal cannabis exposure might be one factor that contributes to psychosis proneness. Other factors, such as family history of mental illness, likely carry more weight. The new HBCD study may be an opportunity to study this relationship more directly.

Discussion: Jill Becker, Ph.D., commented that there was no mention of sex as a biological variable (SABV) in the presentation, e.g., percentage of males and females recruited. SABV is important because males and females develop at different rates. Dr. Dowling responded that the study cohort is about 52 percent male and 48 percent female but acknowledged Dr. Becker's point was well-taken. SABV is stressed in NIH's discussions with investigators; for example, ORWH gave a presentation on it at the last investigators' meeting. Dr. Clark asked if study sites had adopted NIH's suggestions for retention. Dr. Dowling responded that ABCD has a retention workgroup to monitor the numbers. She didn't show site specific numbers in this presentation, but some sites face greater challenges in maintaining minority and low SES participants; these sites are taking advantage of NIH's suggestions for outreach. She asked Linda Chang, M.D., to comment about what the University of Maryland at Baltimore study site, which enrolls a large percentage of minority and low SES participants, is doing to retain participants. Dr. Chang said the site makes frequent phone calls to families, reschedules appointments as needed, and is offering transportation and child care to make it easier for participants and families to come to the center. Nonetheless, retention remains challenging. Dr. Shah inquired about the open source data policy, wondering how ABCD avoids redundancy of studies and if it prioritizes data use in studies by those who collected the data. Dr. Dowling replied that the study is leaving those issues up to the scientific community to resolve. Dr. Volkow commented that this open source policy has been used in genetic and other studies and has not proved to be problematic. NIH made the policy clear to all ABCD Principal Investigators at the outset. She also commented that it is difficult in general to recruit American Indians for studies and asked how ABCD has handled American Indian recruitment and retention. Dr. Dowling responded that the Tulsa site has been the primary focus one recruiting American Indians. It has relationships with native organizations in the area and is hoping these will be beneficial. ABCD asked the Tulsa site to include a tribal member on its local community advisory council to help with the retention efforts. She noted that it's going to take a lot of proactive work to retain all participants, especially those from subgroups that are underrepresented in research. Dr. Chang commented that a data-sharing and use agreement has been signed between the Navajo Nation and NIH grantees of the Environmental influences on Child Health Outcomes (ECHO) Program. Dr. Dowling noted that the agreement extended only to sharing data within the ECHO project, not with the full scientific community. Alex Dopico, M.D., Ph.D., requested clarification of distress in psychotic ideation. Dr. Hoffman explained that the only question asked in the ABCD study about psychotic proneness was how much such an idea bothered the participant. It was associated with internalizing symptoms, suggesting there was a correlation with distress.

NCI's Smokefree.gov Initiative: Using Digital Technology to Help Smokers Quit

Yvonne Prutzman, Ph.D., M.P.H., introduced NCI's use of digital technology to help smokers quit smoking.

Background: Tobacco remains the leading preventable cause of death in the United States, contributing to 40 percent of all cancer diagnoses and one in three cancer deaths. Evidence-based cessation treatments include both counseling and pharmacotherapy. Historically, cessation programs have been delivered via self-help, face-to-face counseling, and telephone quitline services. These treatments are effective, but only a small percentage of smokers use them. Internet and mobile technologies can be leveraged to reach and engage smokers in assisted cessation efforts because of their broad reach. Ninety percent of adult Americans use the Internet and 95 percent of adult Americans own a cell phone (77 percent have smartphones). Further, these technologies offer the potential to reach groups that are traditionally underserved, such as rural residents, low-SES individuals, and young adults. These digital technologies offer reduced structural barriers to treatment, low cost, and are scalable as well as confidential/anonymous. Digital-based treatment is available on-demand and can be highly tailored based on user data. Common digital platforms include mobile optimized websites, text message-based interventions, smartphone applications (mobile apps), and social media. There is sufficient research evidence to support use of the first two platforms. ~~Furthermore,~~

Overview of Smokefree.gov Initiative: Smokefree.gov is a suite of web-and mobile-based smoking cessation resources that provide evidence-based information and tools to support to smokers who want to quit smoking. The Initiative is managed by NCI's Tobacco Control Research Branch. Its content follows U.S. Clinical Practice Guidelines and is freely available to the public in both English and Spanish. Started in 2003 as a website, today it encompasses two smartphone apps and multiple social media platforms, allowing smokers to choose the tool that is best for them. In 2018, Smokefree.gov reached about six million people. The main driver of reach is the Smokefree.gov website, which had 3,618,942 unique visitors in 2018. Smokefree.gov also supports its federal partners' public information campaigns that point smokers to the Smokefree website where there are landing pages for those campaigns. Partners and their campaigns include FDA's "Every Try Counts" (repeat quitters), "The Real Cost" (teens), and "This Free Life" (LGBT people), as well as CDC's "Tips from Former Smokers."

SmokefreeTXT is a text-messaging intervention designed for people who are prepared to set a quit date and make a long-term quit attempt. It provides tips, encouragement, and support to smokers who are trying to quit via 3-5 messages per day over a six to eight-week program. There have been over 200,000 subscriptions to date. Smokefree mobile applications include two apps for iPhone and Android: The QuitGuide launched in December 2010, and quitSTART launched January 2012. These provide real-time cessation resources, such as on-demand craving and mood support, tracking and monitoring, geolocation-based and time-based messaging, and distractions and challenges. Both apps are meta-tagged to allow tracking of user behavior; there have been 205,014 total downloads to date. Social media is used to raise awareness of Smokefree resources, enable targeted outreach to hard-to-reach populations, provide access to a community of other smokers trying to quit, and build the Smokefree brand.

Future directions for Smokefree.gov include data-driven program optimizations based on user data; integration of SmokefreeTXT with Electronic Health Records, including a closed loop electronic referral, and a digital "toolkit;" increased personalization of mobile apps, ~~such as an~~ using features such as ecological momentary assessment and "just in time" interventions; and the use of chatbots and natural language processing to create a sophisticated, automated resource.

Discussion: Dr. Koob asked if NCI contracts out development of the Smokefree apps and if FDA clearance is required. Dr. Prutzman replied that FDA approval is not required. NCI subject matter experts

curate the content, as well as treatment and therapeutic uses. These are provided to a contractor that develops the actual apps. NCI recognizes that it is competing in a crowded digital marketplace and relies on smokers finding its apps organically. The contract team puts a lot of work into making the apps easy to find through search engine optimization. Partnerships and outreach on social media are also used to reach out to smokers. Lisa Marsch, Ph.D., asked how interested NCI would be in developing data that could be submitted to FDA to get market authorization as part of its research portfolio. Dr. Prutzman responded that NCI is supporting a number of efficacy studies of mobile health, including an FOA for the past five years soliciting studies on mobile health interventions for cessation. One of the challenges in such trials is how to verify outcomes. Dr. Clark noted that Dr. Prutzman's presentation didn't mention SAMHSA or the Health Resources and Services Administration (HRSA), both of which are trying to reach low-income smokers. He asked if NCI had reached out to them. Dr. Prutzman responded that conversations with HRSA had occurred. The broader question is to what extent NCI can build partnerships with those serving underserved populations. NCI is currently working with the Veterans Administration to reach veterans and with the Centers for Medicare and Medicaid Services (~~D~~CMS) to reach pregnant smokers. It would like to do more in this area. Dr. Clark suggested focusing on those with substance use and mental health disorders because they have high rates of tobacco use. Judith Auerbach, Ph.D., inquired if NCI was using the SBIR mechanism, suggesting it could provide an avenue for getting ahead of the competition in a crowded digital marketplace. Dr. Prutzman responded that the SBIR program is not being used for Smokefree.gov, which is funded internally as a service that NCI offers to smokers because it fits within the Institute's mission. Wlodek Lopaczynski, M.D., Ph.D., clarified that there is communication between the Tobacco Control Branch and the SBIR office at NCI, but that they are totally separate operations. Scott Russo, Ph.D., asked about sharing the data from the Smokefree.gov technologies with the research community. Dr. Prutzman responded that NCI collects data from these technologies, all of which is meta-tagged, and which is used to improve the user experience, rather than for research. NCI has collaborated on a case-by-case basis with about 30 researchers with whom it has shared data.

Concept Clearance: Integrative Research on Polysubstance Abuse and Addiction

Dr. Volkow introduced Shelley Su, Ph.D., who reported that the NIDA Council had already had a robust discussion of this proposed research.

Background: Polysubstance use (PSU) is common: 20 to 30 percent of youth and young adults are polysubstance users. Compared to single drug users, polysubstance users exhibit worse health and societal outcomes, including mental health problems, drug overdose, and adverse social outcomes. However, this "real world context" is rarely incorporated into basic and clinical research studies because of inherent complications, including complex data interpretation, the need for additional control groups, and the challenges of modeling "real world" phenomena within a laboratory setting. However, translational approaches can advance PSU research efforts. In June 2016, CRAN issued PAR-18-084 with these goals: 1) characterize how neurobiological alterations, associated behaviors, and public health consequences are affected by polysubstance use vs. single drug use; and 2) facilitate and accelerate integrative polysubstance research along a translational pipeline of population, clinical, and basic research. The second goal was accomplished using an R21/R33 phased mechanism where the investigator can study one drug combination in one translational stage under an R21 grant, then, if successful, move on to an R33 to study the same drug combination in another translational phase. To date, six projects have been funded. Most of the funded projects initiated their research in population science, with equal proposed translation to both clinical and basic science. There was a slight emphasis on tobacco and cannabis, but psychostimulants and opioids are also well-represented. Most studies

have focused on behavioral outcomes; one addresses neurobiological mechanisms and one focuses on polygenic risk scores and epigenetic modifications.

This Program Announcement needs to be approved for renewal. There are three areas of growth that are being considered: 1) to encourage more neurobiological applications to understand the impact of PSU on the brain; 2) to create a pipeline connecting treatment and services research; and 3) to encourage NIAAA to solicit more alcohol-related applications.

Discussion: Howard Becker, Ph.D., inquired if applications under this program announcement would be reviewed in a dedicated study section. Dr. Su responded that applications were historically reviewed by a special emphasis panel, which contributed to the success of the program. Susan Weiss, Ph.D., interjected that NIDA cannot guarantee that will be the case in the future; the Institute can only ask. Dr. Becker said that a dedicated study section is important because, in his experience on an early CRAN project, review panels think one drug is important but not the either. Dr. Volkow commented that these studies should also be promoting the study of physiological responses to different drugs and not only how they affect the brain, in order to provide a knowledge base about how to intervene. She emphasized the need to study the effects of drug combinations on toxicity. Dr. Koob concurred. Dr. Marsch recommended integrating mental health issues and NIMH into this and future CRAN considerations given the high rate of co-occurring disorders.

Round Table Discussion

Dr. Volkow responded to Dr. Calac's earlier question about why Alaska appeared to show a sharp increase in the incidence of opioid overdoses. She explained that the data are normalized by population segments of 100,000, so that a small increase will show up as a large response. In terms of absolute numbers, the incidence is small, but the rate of change is worrisome. Synthetic opioids are beginning to appear in Alaska. NIDA is trying to develop a more accurate picture of the impact of these drugs on American Indian populations. Dr. Dopico asked why most medical schools do not include more hours on addiction education. Dr. Koob responded the NIH has tried on numerous occasions to stimulate interest and some schools have inserted addiction into their neuroscience curricula. Addiction Medicine fellowships are stimulating interest from others. But if the content is not on the exams, it's generally not in the curriculum. NIAAA's solution is to get the Core Alcohol Resource out to providers. Dr. Volkow commented that with the help of the scientific community, a couple of questions about addiction have been added to the exams. NIDA created Centers of Excellence for Physician Information to develop materials that medical schools can incorporate into their curricula; the opioid crisis provides an incentive to do so. There is also a need to improve training in specialty care. Multiple professional associations and agencies are working on this issue and, although the field is still far behind, there is beginning to be some traction. Gail D'Onofrio, M.D., described efforts at Yale University School of Medicine where faculty from addiction medicine and addiction psychiatry collaborated on developing materials about substance use, from basic science to case studies, that have been incorporated at all levels of the curriculum. Dr. Baxter emphasized the need for Congressional action and appropriation of funding to promote addiction education. Dr. Volkow invited ideas from Council members to accelerate the trend to include addiction in medical curricula and elsewhere. Dr. Chang suggested that one way to create change is to work with the billing system in health care organizations. For example, tobacco screening increased when the Centers for Medicare and Medicaid (CMS) changed the billing codes such that providers who screened could bill for higher reimbursement. She commented that that's a more realistic way to get practices out to providers than teaching them in medical school. Dr. Howard Becker noted that some medical schools are cutting their programs from four to three years to reduce the cost of a

medical education, by truncating the curriculum. On another matter, he raised a concern about the shortened eligibility time limits for K99/R00 applicants. Some faculty are discouraging post docs from applying for F32s and encouraging them to wait for a K99 which would increase the chances of employment for an academic position. The fear is that these young people may drop out of science. He asked if NIAAA or NIDA had statistics on these applications. Dr. Koob responded that NIH is considering a return to five years of eligibility. In the meantime, there are exceptions that can be made under appropriate circumstances. At NIAAA, there is not a dearth of F32s, but many more F31s pre-doctoral applications are received. Dr. Weiss commented that NIDA has not seen K99 applications declining in numbers. NIDA is in favor of the five-year eligibility for the K99/R00 mechanism. She noted that there's a BRAIN K99/R00 program to increase diversity that allows for five years, and NIH does make exceptions if there are good reasons for doing so. Dr. Clark encouraged NIAAA and NIDA to meet with the Federation of State Medical Boards that deals with impaired or misbehaving providers. The Federation is not interested in reducing the number of providers with SUD expertise, so it may be one place to focus on addiction education, rather than with education institutions.

Adjournment
Dr. Volkow adjourned the meeting at 1:00 p.m.

CERTIFICATION

I hereby certify that, to the best of my knowledge, the foregoing minutes are accurate and complete.

For NIAAA:

/s/

George Koob, Ph.D.
Director
National Institute on Alcohol Abuse and Alcoholism
and
Chairperson
National Advisory Council on Alcohol Abuse and Alcoholism

/s/

Abraham P. Bautista, Ph.D.
Executive Secretary
National Advisory Council on Alcohol Abuse and Alcoholism
National Institute on Alcohol Abuse and Alcoholism

For NIDA:

/s/

Nora Volkow, M.D.
Director
National Institute on Drug Abuse
and
Chairperson
National Advisory Council on Drug Abuse

/s/

Susan Weiss, Ph.D.
Executive Secretary
National Advisory Council on Alcohol Abuse
National Institute on Drug Abuse

For NCI:

/s/

Margaret R. Spitz, M.D.
Acting Chair
National Cancer Advisory Board
National Cancer Institute

/s/

Paulette S. Gray, Ph.D.
Executive Secretary
National Cancer Advisory Board
National Cancer Institute