College on Problems of Drug Dependence
Policy on Administering Drugs with Abuse Potential in Human Research

I. Definition of Abuse Potential

The United States Department of Health and Human Services Food and Drug Administration's Center for Drug Evaluation and Research defines drugs with abuse potential as "substances that have central nervous system (CNS) activity and produce euphoria or other changes in mood, hallucinations, and effects consistent with CNS depressants or stimulants." Abuse potential of a drug is determined by studies assessing the drug's chemistry, pharmacology, pharmacokinetics, and behavioral effects in animals and humans.

II. History of Research on Drugs with Abuse Potential

Research involving the administration of drugs with abuse potential has a long and scientifically productive history with significant impact on public health and regulatory policy. At the basic science level, it has enhanced our understanding of behavioral, pharmacological, and physiological mechanisms that underlie substance use disorders, including drug intoxication, tolerance, reinforcement, physiological dependence, and withdrawal. It has contributed significantly to discovery of specific brain areas that mediate drug euphoria and craving, and to identification of risk factors associated with individual differences in drug use vulnerability. At the prevention level, this research has been instrumental in assessing the abuse liability of new medications and in assuring that medications with significant risk are not introduced without proper regulatory control and health care provider education. At the therapeutic level, research involving the administration of drugs with abuse potential has played a major role in the development of new medications for the treatment of substance use disorders, including methadone and buprenorphine for treatment of opioid use disorders, naltrexone for treatment of opioid and alcohol use disorders, and nicotine-replacement medications and varenicline for treatment of tobacco use disorders, as well as the advancement of non-pharmacological treatments such as motivational enhancement and cognitive behavioral therapy. It has also contributed significantly to the development of drug antagonists such as naloxone, which by reversing opiate overdose, has saved hundreds of thousands of lives. Collectively, these efforts have significantly reduced morbidity and mortality associated with substance use via a decrease in use initiation as well as more effective methods for harm reduction, cessation, and treatment.

III. Application of Research on Abuse Potential in Other Areas

Research involving the administration of drugs with abuse potential to human participants is not limited to the prevention and treatment of addiction. It also occurs in other areas of biomedical research to better understand a wide range of disorders. For example, drugs with abuse liability are administered to humans to understand basic neurophysiological processes and mechanisms underlying pain, attention, memory, sleep, appetite, obesity, intestinal functioning, sexual behavior, anxiety, and depressive disorders. This research, in turn, has contributed significantly to the development of several important new medications, particularly for mental health conditions such as depression (e.g., ketamine), anxiety (e.g., benzodiazepines), and conditions such as Attention-Deficit/Hyperactivity Disorder (amphetamine salts and methylphenidate) and multiple sclerosis (cannabinoids). Other applications include new analgesics with lower abuse potential, antitussives, hypnotics, antidiarrheals, anorectics, as well as medications to treat a variety of other medical conditions.

IV. Importance of Knowledge to be Gained

The high morbidity and mortality associated with substance use disorders underscores the need for research to develop better prevention, treatment, and harm reduction methods. From an economic perspective, substance use has been estimated to cost the U.S. over $740 billion each year in crime, property destruction, law enforcement, lost productivity, premature death, and treatment, with 74% of the cost carried by alcohol and tobacco (www.drugabuse.gov). These financial costs do not include the unmeasurable personal and family suffering associated with substance use disorders, or the extent to which they contribute to social and

interpersonal problems.

There is an urgent need to know more about the effects of drugs with abuse potential, particularly the features that lead to the transition from initial use to regular use or poly-substance use. As part of this research effort, drugs with abuse potential are sometimes administered to human participants to learn more about the causes and consequences of drug use. Through this research, investigators can bring drug-related phenomena into the laboratory so they may be studied in a controlled environment using rigorous scientific protocols. This research contributes significantly to our efforts to prevent and treat substance use disorders. Such research may be conducted safely and ethically, provided careful attention is paid to protecting the human participants who volunteer for these studies. Enumerated below are some recommended guidelines that can enhance the protection of participants in such research. These factors were discussed more thoroughly in a special report by the College on "Human Subject Issues in Drug Abuse Research" that was published in *Drug and Alcohol Dependence* (1995) and have been further updated by the National Institute on Drug Abuse's (NIDA) National Advisory Council on Drug Abuse (NACDA) in 2006 (https://www.drugabuse.gov/funding/clinical-research/nacda-guidelines-administration-drugs-to-human-subjects).

V. Protections and Guidelines to Safeguard Human Participants

Research with human participants, including individuals who are considered vulnerable populations, begins with an assessment of the risk-benefit ratio conducted by the study investigators and evaluated by an Institutional or Ethics Review Board (see below). Investigators must consider each of the following:

- Importance and validity of scientific data to be gained
- Degree of risk to human participants
- Procedures to minimize risk
- Availability of alternative research methods (e.g., laboratory and animal testing), and information sources.

- Data Safety Monitoring Plans (DSMPs) and Data Safety Monitoring Boards (DSMBs) serve an important function by overseeing a study's risk-benefit ratio and tracking adverse events/side effects and-related safety issues during the course of study, particularly in large clinical trials. All studies with human participants are required to have a written DSMP to outline specific procedures to ensure data quality and safety. Additional monitoring by a DSMB may also be required. Studies conducted in the US may also need approval by the Food and Drug Administration (FDA) via an Investigational New Drug Application.

- As with all research employing human participants, studies involving the administration of drugs with abuse potential should be conducted under the review and approval of local Institutional Review Boards (IRBs) or equivalent research ethics boards. Members of the IRB should include scientists, lay community members, and others with the necessary expertise to review the following:
  - Potential for human subject issues
  - Adequacy of the informed consent process
  - The risk-benefit ratio, ethical considerations, and the fairness of distribution of burdens and benefits within the population being studied.

- Participants should be volunteers. Prior to being enrolled in a study, they should be given all relevant information necessary about the study drug and the study procedures to make an informed assessment of the risks and benefits of study participation. Consent should only be attempted with individuals who are competent and/or authorized to give such consent.

- Participants should be carefully screened before study participation to eliminate any individuals likely to be harmed by drug administration. In addition, they should be appropriately monitored throughout the study. Since drugs with abuse potential differ regarding their medical risks, the intensity of medical supervision should be proportionate to the risks involved. If serious consequences are possible, facilities should be available to provide immediate emergency medical care.

- Both biological sexes should be represented in the participant population, and the results analyzed for sex

differences. If only one sex is utilized in a study, the investigators should provide adequate justification for including only one sex. The potential for pregnancy among women should not automatically exclude them from participation in research, but the potential risk to the fetus should be assessed and necessary protections put in place. Contraception and pregnancy tests may be required for some studies.

- Participants should be selected with backgrounds relevant to the issue being addressed by the study. Whenever possible, participants should be experienced with the drug being studied or similar pharmacological agents. Such participants might include those with recreational drug use experience but no history of a substance use disorder or treatment . However, at times it may be necessary to recruit individuals with less drug-using experience to address particular research questions.

- Participation in studies involving drugs with abuse potential is unlikely to either create or worsen the severity of substance use disorders in participants, because the amount of the drugs administered is limited and because the setting in which they are given is a safe and controlled environment. Studies have shown that participation in drug administration trials is not associated with increased alcohol or other drug use (Bacio, et al., 2014; Kalapatapu et al., 2012; Sommer et al., 2015). Nevertheless, this risk should be minimized whenever possible by exposing participants to the least amount of drug necessary to achieve the purpose of the study. It may also be appropriate to limit the extent of exposure to new drugs or new routes of drug administration with potentially greater abuse liability. Furthermore, it may be appropriate in some studies to limit inclusion based on history and/or severity of previous or ongoing substance use disorders.

- If payment is provided for research participation, compensation should be appropriate to the time and effort involved. The goal of compensation should be to achieve a level of payment that is acceptable and fair to volunteers, and is not coercive, unduly influencing, nor exploitive.

- Participants with substance use disorders should be routinely encouraged to enter treatment and/or provided with resources on how to minimize drug harms and risks, including those involving the administration of drugs with abuse potential. Information on treatment referrals should be provided to all participants with substance use disorders.

It should be recognized that there are benefits as well as risks to individuals for participating in research. One important benefit of research participation is that it brings individuals into contact with the health system, where they may find counseling and treatment. As one example, participants often receive free medical and psychological evaluation, as well as HIV/AIDS testing and counseling to reduce the risk of contracting HIV/AIDS infection or of transmitting the infection to others.

The College on Problems of Drug Dependence (CPDD) recognizes the value and importance of research involving the administration of drugs with abuse potential to human participants and endorses research in this area that has an acceptable risk-benefit ratio. Such research plays a vital role in the acquisition of new knowledge needed to understand and reduce substance use disorders and associated problems.

Revised by the CPDD Human Research Committee (November 20, 2018)

SUGGESTED READINGS

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