

A Progress Report on Marijuana Research and Dissemination Efforts From the National Institute on Drug Abuse

Marijuana is the most commonly abused illegal drug in the United States. NIDA is committed to reducing the use of this drug and disseminating new findings to a variety of audiences.

A Renewed Emphasis on Supporting Marijuana Research—Numerous New RFA's And PA's On Marijuana

Under Dr. Volkow's leadership, NIDA has initiated a number of activities to encourage researchers to more rapidly bring new preventions and treatments for cannabis-related disorders to fruition.

1. NIDA has initiated three new Requests for Applications (RFA's) in FY2004 to stimulate research on marijuana. These RFA's will solicit proposals to answer specific scientific questions related to the consequences of marijuana use on the developing brain, medications development, and screening and intervention methodologies.

Three New FY 2004 RFA's

RFA-DA-04-016 Consequences of Marijuana Use on the Developing Brain [Receipt Date: April 16, 2004]: The purpose of this RFA is to support investigations of the effects of exposure to marijuana, the most commonly used illicit drug among teenagers in the United States, on the developing brain. This RFA intends to encourage research on effects of marijuana exposure on the developing brain, at points along a continuum of development from the prenatal period through the transition to adulthood. The focus is on influences on brain biochemical, physiological, morphological, and functional parameters, and/or on cognitive, behavioral, and social outcomes resulting from such influences.

RFA-DA-04-014 Medications Development for Cannabis-Related Disorder [Receipt Date: March 23, 2004]: The National Institute on Drug Abuse (NIDA) is seeking grant applications focusing on the identification, evaluation and development of safe and effective pharmacological treatments for cannabis-related disorders (CRDs), such as cannabis abuse or dependence, and cannabis-induced disorders (e.g., intoxication, delirium, psychotic disorder, and anxiety disorder), and their comorbidity with other medical and psychiatric disorders (e.g., depression), with special interest in the treatment of children and adolescents. Cannabis use includes marijuana, hashish, and other tetrahydrocannabinol (THC) containing substances.

RFA-DA-04-006 Screening and Intervention for Youth in Primary Care Settings [Receipt Date: February 19, 2004]: National Institute on Drug Abuse (NIDA) invites grant applications for the conduct of health services research to

expand the role of primary care in the prevention and treatment of problem drug use, abuse, and related health problems among youth in the pre-dependency phase of drug abuse, **with specific emphasis on marijuana use** (alone or in combination with nicotine, alcohol, and other drugs of abuse). This request for applications (RFA) seeks to build on recent efforts to address problematic alcohol and nicotine use in primary care settings in order to similarly expand the availability and delivery of efficacious drug abuse interventions.

Relevant FY 2003 RFA's

RFA: DA-03-003 **Improving Behavioral Health Services And Treatment For Adolescent Drug Abuse**: Applications were encouraged that (1) investigated ways to broaden youth access to treatment services; (2) examined improvements in treatment delivery, including breadth, integration, and targeting of services for adolescents at different developmental stages in both their own maturation and their drug use and treatment careers; (3) developed, modified, or tested behavioral treatments, or combined behavioral and pharmacological treatments, targeting adolescent drug abusers; and (4) analyzed strategies for translating efficacious clinical treatments into effective community interventions. It was noted that treatments for adolescents would differ from those developed for adults given that the groups utilize different types of drugs. For example, **marijuana** use is more commonly observed among adolescents than adults.

2. To further stimulate new marijuana research, all existing and new Program Announcements (PA's) include specific requests for studies on marijuana and/or cannabis, when appropriate.

New Program Announcements

PA-03-175 **Fine Mapping Genes And Gene Variants For Drug Addiction Susceptibility**: This PA seeks investigator-initiated applications for research that builds on the initial goals of the RFA DA-99-003 and PA-00-115, "Genetics of Drug Addiction Vulnerability," which were to identify chromosomal regions involved in addiction and addiction vulnerability (including addiction to, or dependence on, stimulants, narcotics, nicotine, benzodiazepines, barbiturates, **cannabis**, hallucinogens and/or poly drug abuse). Once chromosomal regions are identified, the natural progression of the research is to identify the gene and gene variants responsible for the initial localization of the chromosomal region. The objectives of this PA, then, are to build on, encourage and support innovative research from investigators who have, or can obtain access to data and resources to conduct fine mapping of chromosomal regions and quantitative trait loci (QTL) involved in addiction vulnerability and/or can uncover genetic variants within those regions to assess their association with addiction vulnerability.

PA -03-155 **Molecular Genetics Of Drug Addiction Vulnerability**: This PA seeks investigator-initiated applications for research projects that identify chromosomal loci and genetic variation in genes and haplotypes that are

associated with increased vulnerability to addiction or dependence on stimulants (e.g., cocaine and amphetamine), narcotics (e.g., opiates), nicotine, benzodiazepines, barbiturates, **cannabis**, hallucinogens, and/or multiple drugs of abuse in human beings.

PA-03-126 **Behavioral Therapies Development Program**: NIDA and the National Institute on Alcohol Abuse and Alcoholism are seeking research grant applications on the development of behavioral treatments for drug and alcohol abuse and dependence. Research regarding treatments for **marijuana** abuse and/or addiction is listed as a specific area of interest under this PA.

PA-02-095 **Chemistry, Pharmacology, and Toxicology of Smoked Drugs of Abuse**: NIDA encourages research that will further the understanding of the chemical composition of smoked drugs of abuse, and the resulting pharmacological and toxicological effects associated with such exposure. This PA solicits non-clinical basic research efforts aimed at chemical isolation/identification, metabolic studies, pharmacokinetics, and in vitro cellular and in vivo animal pharmacology/ toxicology studies of condensates or extracts of volatile materials and particulates produced in a smoking process. The drugs of abuse of interest include **marijuana**, tobacco, crack cocaine, heroin, PCP, and methamphetamine hydrochloride.

3. The National Drug Abuse Treatment Clinical Trials Network, a cooperative undertaking of NIDA, university drug abuse scientists, and community treatment providers, in which research-based treatments are tested in community settings, will be encouraged to increase their focus on cannabis-related disorders.

4. The NIDA Medications Development Program will shift its emphasis to concentrate more efforts on identifying treatments for marijuana abuse and addiction.

Highlights from NIDA's Marijuana Dissemination Efforts

A primary goal of the National Institute on Drug Abuse (NIDA) is to disseminate the results of research on preventing and treating drug abuse and addiction, so that these findings can be implemented as soon as possible into clinical application and contribute to policy making decisions. Sharing scientifically based information on marijuana has been a major area of emphasis for NIDA for years. Examples of recent efforts are presented here.

Briefings on the State of the Science

In February 2003, the former Acting NIDA Director, Dr. Glen Hanson, briefed the ONDCP Director and staff on NIDA's marijuana research portfolio and on new findings.

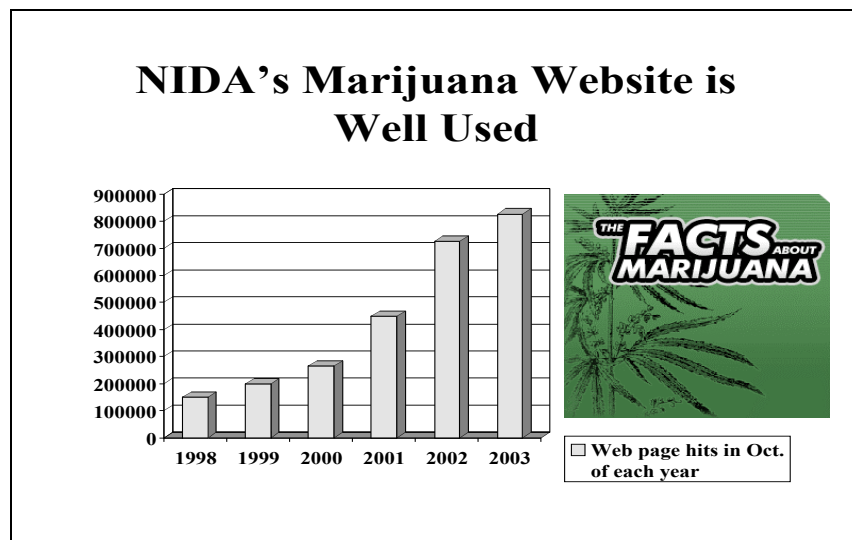
In October 2003, the NIDA Director, Dr. Nora Volkow, NIDA staff and NIDA-supported researchers briefed ONDCP officials on the latest research regarding marijuana use. Presenters included Alan Budney on “Marijuana Dependence: Studies of Withdrawal and Treatment Outcome,” Daniele Piomeli on “The Endogenous Cannabinoid System and the Treatment of Addiction,” and Harrison Pope on “Cognitive Effects of Cannabis Use: An Update.”

At the request of ONDCP, NIDA continues to review much of the anti-drug advertising materials developed by the Partnership for a Drug Free America to ensure scientific accuracy. NIDA reviews and comments on materials on a fast turn-around basis.

Dissemination Efforts for the General Public

Developing a Dedicated Website on Marijuana - NIDA developed and launched a dedicated website <http://www.marijuana-info.org> on June 7, 2002. It has had 435,095 visitors since its launch. It was created to allow NIDA to have a page that would rank higher when the word “marijuana” was entered into web search engines.

The marijuana pages are (and have been for some time) the most popular information pages on the site. For example, last month of the top 25 most requested pages, 10 were marijuana information pages. The marijuana brochures are one of the top three directories having been viewed 826,000 times in October 2003.



NIDA’s Website also maintains all NIDA publications about all drugs of abuse at www.drugabuse.com.

Publications Focusing on Marijuana

NIDA’s Marijuana Research Report (updated May 2003). This series of reports simplifies the science of research findings for the educated lay public, legislators,

educational groups, and practitioners; and covers topics such as how many people in the United States abuse marijuana and the health effects of marijuana abuse.

NIDA InfoFacts on Marijuana (updated in June 2003). Concise fact sheets on marijuana that are available in English and Spanish. Available by mail or online.

Marijuana: Facts Parents Should Know (updated in March 2003) Provides valuable information from research on the dangers of marijuana. Gives parents explanations of the latest scientific information about the drug and suggestions on how to talk to teenagers about this drug. Over 3 million have been distributed. The publication is available in English and Spanish.

NIDA NOTES: In July of 2003 NIDA issued a special edition of NIDA Notes that contained more than 30 articles regarding marijuana abuse that have been published since 1995. In addition, in December 2003 NIDA Notes issued an article titled “Cognitive Deficits in Marijuana Smokers Persist After Use Stops” and in November 2003 NIDA Notes issued an article titled “Twins Study Links Early Marijuana Use to Increased Risk of Abuse or Dependence.”

Dissemination Efforts for Targeted Audiences

Media

In addition to news releases, NewsScan informs the media of research findings related to drug abuse and addiction being published in medical and scientific journals as well as NIDA research funding opportunities and awards.

NewsScan: In May 2003 NIDA issued a summary article titled “Starting Marijuana Use in Mid-Teens or Younger May Result in Cognitive Impairment Later in Life But Reasons are Unclear.” Researchers showed that there is evidence that individuals who start to smoke marijuana at an early age—while the brain is still developing—show deficits in cognition which are not seen in individuals who begin use of the drug when they are older. The reasons for this difference are unclear. [H. Pope et al., March 2003, *Drug and Alcohol Dependence*.]

NewsScan: In April 2003 NIDA issued a summary article titled “Concurrent Use of Tobacco and Marijuana May Hamper Cigarette Smoking Cessation Efforts.” Participants who reported recent use of marijuana during the study were about twice as likely to continue to smoke tobacco 13 years later compared those who did not use marijuana within the preceding 30 days. Those who reported daily marijuana use were over three times more likely to still smoke tobacco. About 66 percent of recent marijuana users reported trying to quit tobacco during the following 13 years compared to 80 percent of those who had never used marijuana. These findings suggest that marijuana use may interfere with tobacco cessation attempts. However, there is no evidence that marijuana use can substitute for tobacco use. [Toomey et al., Aug. 2002, *Drug and Alcohol Dependence*.]

NewsScan: In January 2003 NIDA issued a summary article titled “Teen Drug Use Associated with Psychiatric Disorders Later in Life.” The study highlighted in this article found that children who start to use alcohol, marijuana or other illicit drugs in their early teen years are more likely to experience psychiatric disorders, especially depression, in their late 20s. [Brook et al., Nov. 2002, *Archives of General Psychiatry*].

NewsScan: In January 2002 NIDA issued a summary article titled “Alcohol Use Prior to Smoking Marijuana Results in Increased THC Absorption” in which investigators concluded that alcohol might increase the absorption of THC, the active ingredient of marijuana, into the body, resulting in a higher high than is experienced when using marijuana alone. Marijuana and alcohol are often used together, but little is known about why they are combined. The results of this experiment suggest that these two drugs are used to maximize the desired effects of the drug experience and so may explain the popularity of this combination. [Lukas et al., Oct. 2001, *Drug and Alcohol Dependence*]

Educational System – Teachers and Students

NIDA Goes Back to School

NIDA is committed to developing dynamic educational pieces for both teachers and students. Recently NIDA reissued the popular *NIDA Goes Back to School* packet to schools across the country. This mailing consisted of science-based information on drugs of abuse, which can be used in science classrooms and drug abuse prevention programs at the middle and high school levels. Many of the materials mentioned in this section were repackaged and redistributed as a part of this effort, including NIDA’s newly revised “Preventing Drug Use among Children and Adolescents: A Research-Based Guide for Parents, Educators, and Community Leaders” (also known as the “Red Book”).

Preventing Drug Use Among Children and Adolescents: A Research-Based Guide for Parents, Educators, and Community Leaders (updated in September 2003)

This book, and its smaller companion pieces, reflects NIDA’s expanded prevention research program and knowledge base, and includes updated principles, new questions and answers, new program information, as well as expanded references and resources.

Marijuana: Facts for Teens (updated in March 2003)

Explains the current knowledge about marijuana and the latest scientific information on its effects. Provides teens with answers to frequently asked questions about marijuana, including what it is, who uses it, how it affects a person physically and mentally after short- and long-term use. Over 2.5 million have been distributed. Available in English and Spanish.

Mind Over Matter: The Brain's Response to Marijuana (1996 first printed, 2000 updated, currently initiating update and reprint process): An educational series for middle school students. This popular magazine format and teachers guide has been distributed to more than 6.7 million since 1996. The series encourages young teens to reject drug use by helping them understand the effects of drugs on the brain. There are eight topics in the series. The one focused on marijuana explains how THC – the active

ingredient in marijuana – affects memory, emotions, balance and judgment. (Poster – THC Receptors in the Hippocampus) Over 1 million have been distributed.

Slide Teaching Packets—CD ROMs. Developed in 2001. This CD Rom contains popular educational slide series “The Brain and the Actions of Cocaine, Opiates and Marijuana,” and the Neurobiology of Drug Addiction,” as well as two new teaching packets.

Science Education Materials. In 2001 and 2002 comprehensive curricula for high school and elementary schools were released, which have some discussion of marijuana in them.

- *The Brain: Understanding Neurobiology Through the Study of Addiction.* This extensive high school curriculum was developed in collaboration with the National Institutes of Health (NIH) Office of Science Education (OSE) and released in 2001. NIH OSE has been conducting teacher training for the materials at science teacher meetings, and is conducting training sessions with various school districts.
- *Brain Power! NIDA Junior Scientists.* This curriculum provides lessons and activities designed to teach elementary school students about the brain and the effects of drugs on the brain. The first portion of the curriculum (released in 2002) is designed for grades 2-3. During the next few years, NIDA will be adding materials for additional grades. When the entire project is completed, the materials will span kindergarten through middle school. NIDA plans to conduct teacher training at teachers meetings appropriate for each grade level.

Community Providers

Practical Theorist (August 2003): NIDA continues to collaborate with **Community Anti-Drug Coalitions of America (CADCA)** on the production of *Practical Theorist*, a series of technical assistance publications. The latest publication, on marijuana, was released in August 2003 and includes research on marijuana abuse in a concise, convenient format and offers strategies on how to use the data to mobilize communities, affect policy, and support local anti-drug coalition efforts to build drug-free communities.

Special Populations

A number of NIDA publications have also been printed in Spanish, including “NIDA InfoFacts on Marijuana,” “Marijuana: Facts for Teens,” and “Marijuana: Facts Parents Should Know.”

Research Scientists

Journal Supplement: On August 13-14, 2001, the Center on AIDS and Other Medical Consequences of Drug Abuse collaborated with the Division of Neuroscience and

Behavioral Research to organize and conduct a workshop on the clinical consequences of marijuana. A group of nationally and internationally known clinician/scientists reviewed and presented state-of-the-art information on the health effects of marijuana and made recommendations for future research. Results from this meeting were published in the November 2002 issue of the Journal of Clinical Pharmacology.

Congress

NIDA is responsive to the needs of Congress and provides information about our marijuana research when requested. NIDA's FY 2005 Congressional Justification highlighted several exciting new marijuana research findings.

Selected Highlights From NIDA's Research Portfolio

NIDA supports a comprehensive research portfolio that addresses all drugs of abuse, both legal and illegal, with the exception of a primary focus on alcohol. The ultimate aim of our Nation's investment in drug abuse research is to enable society to prevent drug abuse and addiction, and to reduce the adverse individual, social, health, and economic consequences associated with drugs, particularly marijuana.

Epidemiological and Prevention Research:

NIDA funds epidemiological research to better understand the factors contributing to use, characteristics of current users, as well as the effects of marijuana use in various populations.

NIDA's Monitoring the Future Study is a valuable source of data on the illicit drug use patterns and attitudes of our Nation's 8th, 10th, and 12th grade students. The study found that in 2003 46% of 12th graders had tried marijuana and that 21% were current users (i.e., had used within the past thirty days). This makes it the most commonly abused illicit drug among high school students. The study also reported that the use of marijuana was significantly decreased in eighth graders, although the numbers were lower (non-significantly) in tenth graders as well. Notably, perceptions of the dangers of marijuana use increased. Such changes in perception often predict future decreases in drug use, and suggest that educational efforts on the dangers of marijuana may be working.

Another NIDA-funded epidemiological study has shown that long-term cannabis use results in a lower college completion rate and lower household incomes in addition to subjective perceptions of impaired cognitive abilities, social life, physical and mental health.

Attributes of Long-Term Cannabis Users - In this study, current and former long-term heavy users of marijuana were compared on a number of measures of life achievement and satisfaction to a control group of subjects who reported smoking cannabis at least once in their life, but not more than 50 times. Heavy cannabis users (both current and former) differed markedly on various measures of life accomplishment from controls. For example, despite similar education and incomes in their families of origin, the subjects themselves differed significantly on education and income: fewer of the cannabis users than controls completed college and more had household incomes of less than \$30,000. When asked how marijuana affected their cognitive abilities, career achievement, social life, physical and mental health, the overwhelming majority of heavy cannabis users reported a deleterious effect of the drug on all of these measures. Given the continuing widespread use of marijuana, it is imperative to prioritize efforts to prevent and treat cannabis dependence. (Gruber AJ, Pope HG, Hudson JI, and Yurgelun-Todd D (2003) Attributes of long-term heavy cannabis users: a case-control study. *Psychological Medicine* 33: 1415-1422).

Fried P, Watkinson B, and Gray R (2003) Differential effects on cognitive functioning in 13- to 16-year-olds prenatally exposed to cigarettes and marijuana. *Neurotoxicology and Teratology* 25: 427-436 - Scientists have long debated the longitudinal effects of prenatal exposure to nicotine and marijuana on the neurobehavioral development of children and adolescents. An ongoing longitudinal study that was initiated in 1978 examined the cognitive performance of 145 youth from birth through adolescence for whom prenatal exposure to marijuana and nicotine had been ascertained. This particular aspect of the study focused on thirteen- to sixteen-year-old adolescents and tested general intelligence, achievement, memory, and aspects of executive functioning. Results suggested that prenatal maternal cigarette smoking was associated with an impairment in general intelligence and aspects of auditory functioning. Furthermore, prenatal maternal exposure to marijuana was negatively associated with cognitive tasks that required visual memory, analysis, and integration. Although previous studies in this cohort show that prenatal maternal nicotine and cannabis exposure does not appear to substantially impact birth weight or childhood behavior, this research and several additional studies have found statistically significant cognitive deficits among the adolescents of mothers who used marijuana and nicotine during pregnancy.

Slater MD (2003) Sensation-seeking as a moderator of the effects of peer influences, consistency with personal aspirations, and perceived harm on marijuana and cigarette use among younger adolescents. *Substance Use and Misuse* 38: 865-80 - Current statistics indicate that adolescents continue to use tobacco and marijuana at alarmingly high rates, starting in the middle school years. Research from the drug abuse field demonstrates that contacts with peers serve many significant functions in adolescents' lives and development. Peers can either encourage or discourage drug use

behaviors. Peer relationships may play an even more important role today than in past generations, given that children participate frequently in various after-school and summer activities (e.g., clubs, sports, camps) which allow them to spend considerably more time with similar-age peers. By examining over 3000 8th grade students in 20 middle schools, this study expanded on previous research that hinted at the significance of sensation-seeking adolescents leading to involvement with drug-using peer groups. Findings suggest that "low sensation-seekers," or individuals who are risk-averse, are more likely to resist the pressures from risk-taking peers, whereas "high sensation-seekers" would be inclined to experiment with drugs. Similarly, perceived negative consequences (such as harm) tend to influence the behavior of risk-averse low sensation-seekers more so than high sensation-seekers. This discovery indicates that moderate and high sensation-seekers should be one of the primary target audiences for substance abuse prevention efforts directed toward younger adolescents. Curbing cigarette and marijuana use among these high-risk, sensation-seeking youth when they are in middle school may prevent the emergence of more serious problems later on.

Hopfer CJ, Stallings MC, Hewitt JK and Crowley TJ (2003) Family Transmission of marijuana use, abuse and dependence. *Journal of the American Academy of Child and Adolescent Psychiatry* 42: 834-841 - Researchers in the program project of Thomas Crowley, University of Colorado, have shown family transmission of three levels of marijuana use, abuse, and dependence in a clinic-referred sample of adolescents. This study expands the literature that had previously only focused on use in adolescents or abuse and dependence in adults. Risk ratios ranged from 1.5 to 3.3; spousal correlations ranged from .33 to .70; parent-offspring correlations ranged from .17 to .30, and sibling correlations ranged from .34 to .44. The proportion of variance attributed to parent transmission ranged between 25% and 44%. These results document the not surprising observation of significant risk of transmission from parents, environmental influence from siblings, and assertive mating for all levels of marijuana use.

Yzer MC, Cappella JN, Fishbein M, Hornik R (2004) The Role of Distal Variables in Behavior Change: The Effects of Adolescents' Risk for Marijuana Use on Intention to Use Marijuana. *Journal of Applied Social Psychology* (in press) - Adolescents at low and high risk differed in outcome and normative beliefs, particularly those concerning social costs and costs to self-esteem. In general, at-risk adolescents were far more positive toward regular marijuana use than low risk adolescents. These findings suggest that very different interventions are needed for high-risk and low-risk adolescents. The latter do not intend to use marijuana so interventions should help maintain this intention. Interventions that target high-risk youth need to try to change intentions and this might be done by changing beliefs about regular marijuana use, particularly messages that increase their beliefs that marijuana use yields social and self-esteem costs.

Research on communication strategies has been investigating the characteristics of drug prevention messages that will have the greatest impact on the subjective perceptions of adolescents and youth.

Characteristics of drug prevention messages - An experimental study was designed to investigate the influence of message strategies on cognitive processing and changes in attitudes, behavioral intentions, and behavior in relation to marijuana use. Researchers evaluated anti-marijuana messages designed to vary on cognition value as well as sensation value. There was partial support for a main effect of message sensation value on changes in attitude, intention and behavior. Additionally, high cognition value messages led to greater recall than low cognition messages. Cognitive processing and message cognition value did not affect attitude, behavioral intentions or behavior regarding marijuana use. (Harrington NG, Lane DR, Donohew L, Zimmerman RS, Norling GR, An JH, Cheah WH, McClure L, Buckingham T, Garofalo E, and Bevins CC (2003) Persuasive Strategies for Effective Anti-Drug Messages. *Communication Monographs* 70: 16-38).

Yzer MC, Cappella JN, Fishbein M, Hornik R, and Ahern RK The Effectiveness of Gateway Communications in Anti-Marijuana Campaigns. *Journal of Health Communication* 8: 129-143 - This study examined different sets of anti-drug advertisements for persuasion and priming effects focusing on the effectiveness of the gateway argument in anti-marijuana interventions. Results did not support the use of the gateway belief in anti-marijuana interventions. No clear persuasion or priming effects were found for any of the ad sequences. Adolescents who watched the explicit gateway message tended to agree less with the gateway message and showed weaker correlations between anti-marijuana beliefs and their attitude toward marijuana use than youth in the control condition. This finding suggests that the gateway message should not be used in anti-drug interventions.

Basic Research:

Basic research on cannabinoids has led to advances in our understanding of the neurobiology of addiction. By studying how marijuana produces its mood-altering effects, we have gained insight into a novel brain modulatory system that is not only involved in addiction, but also learning and memory, pain regulation, appetite, immunological function, reproduction and psychomotor control. Basic research to understand the mechanisms of action and the resulting effects provide the foundation necessary to develop treatment and prevention strategies for marijuana abuse.

New Relief for Chronic Pain That May Lack Addictive Liability - Basic research on the mechanisms of marijuana's effects on the brain led to the discovery of cannabinoid receptors, which bind delta-9-tetrahydrocannabinol (THC), the active ingredient in marijuana. At least two types of cannabinoid (CB) receptors have been identified: CB₁ and CB₂. The latter are found almost exclusively outside of the brain and central nervous system. Based on earlier studies, the authors hypothesized that the CB₂ receptors were involved in certain types of pain, and therefore could be useful targets for developing medications to alleviate pain. A new compound, AM1241, was designed to selectively affect CB₂, but not CB₁ receptors; that is, it does not affect the brain. In a model of neuropathic pain, when AM1241 was given to animals, they did not appear to feel the effects of the painful stimulation. This work opens up a new avenue of medications development for the treatment of neuropathic pain, a disabling condition affecting millions of people within the United States alone. Importantly, medications that act at the CB₂ receptor site are unlikely to have many of the adverse side effects associated with other drugs that are currently used in the treatment of pain or with cannabinoids (like THC) that act in the central nervous system. (Ibrahim MM, Deng H, Zvonok A, Cockayne DA, Kwan J, Mata HP, Vanderah TW, Lai J, Porreca F, Makriyannis A, Malan Jr. TP (2003) Activation of CB2 cannabinoid receptors by AM1241 inhibits experimental neuropathic pain: Pain inhibition by receptors not present in the CNS. *Proc Natl Acad Sci* 100:10529-10533.)

Basic Research: Learning and Memory

Hampson RE, Simeral JD, Kelly EJ, Deadwyler SA (2003) Tolerance to the memory disruptive effects of cannabinoids involves adaptation by hippocampal neurons.

***Hippocampus* 13: 543-56** - Previous research has shown that cannabinoids disrupt short-term memory, but animals develop tolerance to this effect after chronic exposure. Recent studies have now shown that both the memory-disruption from acute cannabinoid administration, and tolerance with repeated administration occur at the level of synaptic processes in the hippocampus thus modifying memory-related neural firing patterns.

Hoffman AF, Oz M, Caulder T and Lupica CR (2003) Functional tolerance and blockade of long-term depression at synapses in the nucleus accumbens after chronic cannabinoid exposure. *Journal of Neuroscience* 23: 4815-4820 - The present study demonstrates that chronic Δ^9 -THC exposure caused marked tolerance to the presynaptic effects of cannabinoids. This finding represents the first time that physiological tolerance to cannabinoids at defined synapses in the CNS has been described. Another consequence of long-term exposure to Δ^9 -THC was that a specific form of synaptic plasticity, known as long-term depression (LTD) of glutamatergic synaptic transmission, was completely blocked in the nucleus accumbens of rats chronically treated with Δ^9 -THC, but not in vehicle controls. Since LTD is critically dependent on endogenous cannabinoids in the nucleus accumbens, these data suggest that chronic treatment with Δ^9 -THC can alter the sensitivity of synapses to endogenous cannabinoids, and that tolerance to Δ^9 -THC is associated with a deficit in synaptic plasticity.

Hoffman AF, Riegel AC and Lupica CR (2003) Functional localization of cannabinoid receptors and endogenous cannabinoid production in distinct neuron populations of the hippocampus. *European Journal of Neuroscience* 18: 524-534 - In order to determine whether synaptic inputs to hippocampal interneurons are regulated by cannabinoids, whole-cell electrophysiological recordings in distinct interneuron populations were performed. In this study, authors found that, whereas glutamatergic inputs to pyramidal cells were presynaptically inhibited by the cannabinoid agonist WIN55, 212-2, glutamatergic inputs to interneurons were unaffected by this agonist. In contrast, GABAergic inputs to the interneurons were inhibited by WIN55, 212-2, and this effect was reversed by the CB1 receptor antagonist SR141716A. Also, using a sensitive electrophysiological bioassay for endogenous cannabinoid release, they found that pyramidal cells, but not interneurons, released endogenous cannabinoids. The localization of endogenous cannabinoid release to pyramidal neurons suggests that the role of these molecules may be limited to the regulation of specific synapses. This work identifies a novel neuronal pathway for consideration when examining the substrates responsible for the disruption of memory by marijuana.

Basic Research: Immunological Function

Kaplan BLF, Rockwell CD and Kaminski NE (2003) Evidence for cannabinoid receptor-dependent and independent mechanisms of action in leukocytes. *Journal of Pharmacology and Experimental Therapeutics* 306: 1077-1085 - Cannabinoids exhibit immunosuppressive actions that include inhibition of interleukin-2 production in response to a variety of T cell activation stimuli. Using CB1 and CB2 antagonists, this study demonstrated that cannabinoid-induced inhibition of phorbol ester plus calcium ionophore (PMA/Io)-stimulated interleukin-2 was not mediated via CB1 or CB2. It was, however, demonstrated that cannabinoids elevated intracellular calcium concentration in resting splenocytes and that the cannabinol-induced elevation in intracellular calcium concentration was attenuated by treatment with both SR144528 and SR141716A. Interestingly, pretreatment of splenocytes with agents that elevate intracellular calcium concentration inhibited PMA/Io-stimulated interleukin-2 production, suggesting that an elevation in intracellular calcium concentration might be involved in the mechanism of interleukin-2 inhibition. These studies suggest that immune modulation produced by cannabinoids involves multiple mechanisms, which might be both cannabinoid receptor-dependent and-independent.

Basic Research: Reproduction

Wang H, Matsumoto H, Guo Y, Paria BC, Roberts RL and Dey SK (2003) Differential G-protein coupled cannabinoid receptor signaling by anandamide directs blastocyst activation for implantation. *Proceedings of the National Academy of Sciences* 100: 14914-14919 - These studies utilized genetic, pharmacological and physiological approaches to uncovering a potentially important regulatory mechanism for synchronizing blastocyst and uterine competency to implantation. This observation in addition to advancing our basic knowledge has high clinical relevance as elevated levels of anandamide could induce spontaneous early pregnancy losses in women who smoke marijuana.

Clinical Research:

Clinical studies have demonstrated that marijuana use can produce physical withdrawal symptoms similar to other drugs of abuse. One might, therefore, hypothesize that such withdrawal could contribute to increased rates of relapse.

Withdrawal after marijuana use - Dr. Budney of Vermont University reports that withdrawal symptoms following cannabis cessation are comparable to tobacco and other withdrawal syndromes. An outpatient study assessed 18 marijuana users during a 5-day Smoking-as-usual Phase followed by a 45-day Abstinence Phase with a parallel assessment of 12 ex-users. A withdrawal pattern was observed for aggression, anger, anxiety, appetite, decreased body weight, irritability, restlessness, shakiness, sleep problems, and stomach pain. Onset occurred between Days 1-3, peak effects between Days 2-6, and most effects lasted 4-14 days. The magnitude and timecourse of these effects appeared comparable to tobacco and other withdrawal syndromes. These effects likely contribute to the development of dependence and difficulty stopping use. Budney AJ, Moore BA, Vandrey RG, and Hughes JR (2003) The Time course and Significance of Cannabis Withdrawal. *Journal of Abnormal Psychology* 112: 393-402)

Haney M, Bisaga A, and Foltin RW (2003) Interaction between naltrexone and oral THC in heavy marijuana smokers. *Psychopharmacology* 166: 77 – 85 - Results from preclinical studies suggest that opioid antagonists block the reinforcing effects of cannabinoids. In this study, marijuana smokers received the opiate antagonist naltrexone followed one-half hr later by 30 mg of the active ingredient in marijuana, THC. Contrary to predictions, pretreatment with naltrexone significantly increased many of the "positive" subjective effects of oral THC (30 mg), that is, ratings of "Good Drug Effect" and "Liking", while producing no change in plasma THC levels. Thus, naltrexone tended to increase the reinforcing effects of oral THC (30 mg), as indicated by performance in a drug choice test.

Research About Consequences of Marijuana Use:

The consequences of marijuana use range from physiology and behavioral effects to the impact of early exposure on the subsequent use of other drugs of abuse.

Relationship between early cannabis use and progression to other drugs of abuse - Studies have examined whether the association between early cannabis use and subsequent progression to use of other drugs and drug abuse/dependence persists after controlling for genetic, shared environmental influences, and other risk factors. Data come from a cross-sectional survey of young adult monozygotic and dizygotic same-sex twin pairs discordant for early cannabis use. Findings indicate early cannabis use is associated with increased risk of other drug use, alcohol dependence, and drug abuse/dependence. The authors interpret these results as being consistent with the "gateway theory" of drug use. (Lynskey MT, Heath AC, Bucholz KK, Slutske WS, Madden PAF, Nelson EC, Statham DJ, and Martin NG (2003) Escalation of Drug Use in Early Onset Cannabis Users vs. Co-twin Controls. *JAMA* 289: 427-433)

McDonald J, Schleifer L, Richards JB and de Wit H (2003) Effects of THC on Behavioral Measures of Impulsivity in Humans. *Neuropsychopharmacology* 28: 1356-1365 - Healthy men and women received capsules containing placebo, 7.5, or 15 mg THC in randomized order under double-blind conditions. Subjects were tested on tasks of impulsivity which measure the ability to inhibit a pre-potent motor response, on a go-no go task, on a delay discounting task which measures the value of delayed or uncertain reinforcers, and on a time estimation task which measures alterations in time perception. THC increased impulsive responding on the first task but did not affect performance on the remaining three. Thus, THC may increase certain forms of impulsive behavior while not affecting others.

Liguori A, Gatto CP, Jarrett DB, McCall WV, Brown TW (2003) Behavioral and subjective effects of marijuana following partial sleep deprivation. *Drug and Alcohol Dependence* 70: 233-240 - This study tested whether performance on a driving simulator task would be more impaired when marijuana use followed partial sleep deprivation (PSD). Approximately 6.5 h after waking, marijuana-experienced subjects smoked marijuana in a laboratory and were tested at 2, 62, and 122 min. High-potency marijuana increased body sway similarly across sleep conditions. PSD increased the dose-dependence of THC effects on heart rate and subjective impairment, but did not enhance the effects of marijuana on standing balance and brake latency in a driving simulation task.

Zimmerman MA and Schmeelk-Cone KH (2003) A Longitudinal Analysis of Adolescent Substance Use and School Motivation Among African American Youth. *J Res Adolesc* 13: 185-210 - The current study examined the link between adolescent substance use and educational motivation in a longitudinal sample of African American youth. School motivation did not affect graduation status, but marijuana use early in high school was related to a lower likelihood of graduating from high school. The findings support a systems model where school experiences can affect substance use, which, in turn, can affect the completion of high school.

Treatment Research:

NIDA is currently concentrating efforts to promote research on the development of therapeutics for marijuana abuse for FY04 and FY05.

Haney M, Hart CL, Vosburg SK, Nasser J, Bennett A, Zubarán C and Foltin RW (2004) Marijuana Withdrawal in Humans: Effects of Oral THC or Divalproex. *Neuropsychopharmacology* 29: 158-170 - Abstinence following daily marijuana use can produce a withdrawal syndrome characterized by negative mood. Two studies evaluated effects of delta-9-THC and a mood stabilizer and anti-convulsant, Divalproex (which increases GABA levels in the brain), on symptoms of marijuana withdrawal. Oral THC decreased marijuana craving and withdrawal symptoms at a dose that was subjectively indistinguishable from placebo. Divalproex worsened mood and cognitive performance during marijuana abstinence.

Moore BA and Budney AJ (2003) Relapse in outpatient treatment for marijuana dependence. *Journal of Substance Abuse Treatment* 25: 85-89 - This study examined lapse and relapse to marijuana use in individuals who achieved at least 2 weeks of abstinence during outpatient treatment. Early lapses were more strongly associated with consequent relapse.

Sinha R, Easton C, Aubin L, and Carroll KM (2003) Engaging young probation-referred marijuana abusing individuals in treatment: A pilot study. *American Journal on Addictions* 12: 314-323 - To evaluate treatment engagement strategies in young marijuana abusers, 65 probation-referred abusers were randomly assigned to either three-session motivation enhancement therapy (MET alone) or three sessions MET plus contingency management (MET/CM), with vouchers for treatment attendance. A significantly higher number of participants in the MET/CM condition completed the three-session intervention as compared with MET alone. Participants in both conditions reported significant reductions in marijuana use and improvement in legal problems. These findings suggest that young marijuana abusers benefit from scientifically validated treatments.

NEWLY FUNDED MARIJUANA-FOCUSED GRANTS

The grants presented below were funded in FY 2003/2004. Therefore, no data from these projects is currently available. These grants are listed to provide information on anticipated research for the next few years.

Basic Research:

Effects of Drug Abuse on Human Neurodevelopment

This study will characterize specific regional alterations of dopamine and opioid peptide related genes in the striatum and amygdala of midgestation human fetuses exposed prenatally to cannabis. An experimental prenatal cannabis rat model will be developed to mimic the neural alterations evident in the human fetal brain to study long-term behavioral and neurochemical alterations in adult offspring.

Marijuana and Cytokine Actions on Rat Brain Mitogenesis

This study seeks to examine the effects of delta-tetrahydrocannabinol on cell proliferation, the first phase of neurogenesis, in the dentate gyrus of adult rats, a region associated with learning and memory.

Endocannabinoid Sites as Therapeutic Targets

This investigator proposes to develop novel chemical probes that act as substrates or inhibitors for enzymes that breakdown endogenous cannabinoids. These compounds may be useful tools in future molecular studies of these enzymes and will set the stage for the development of novel therapeutics for the treatment of neuropsychiatric and substance abuse disorders.

Drug Discrimination and THC Withdrawal in Monkeys

This pilot study seeks to establish a drug discrimination model in rhesus monkeys to investigate withdrawal and determine whether it can be used to define pharmacological mechanisms underlying delta9-THC dependence.

Cannabinoid-Induced Apoptosis in T Cell Regulation

This study will investigate the role of apoptosis (programmed cell death) in cannabinoid-induced immunomodulation following prenatal and postnatal exposure.

Clinical Research:

Frontal Neural Mechanisms and Risk for Substance Abuse

This study will examine the integrity of the anterior cingulate cortex and dorsolateral prefrontal cortex, regions shown to be a part of the neural network underlying executive functioning, in marijuana abusers using functional magnetic resonance imaging and diffusion tensor imaging.

Acute Marijuana Effects on Regional Cerebral Blood Flow

The current study seeks to explore the effects of acute and chronic marijuana use on regional cerebral blood flow and cognitive function, specifically cerebellar function, cerebellar-cortical and reward circuitry.

fMRI and Cognition in Adolescent MDMA and Cannabis Users

The goal of this exploratory project is to use functional magnetic resonance imaging and neuropsychological tests to better understand the degree to which use of MDMA and cannabis during late adolescence affect brain functioning.

Motivation and Attention in Marijuana Use and Withdrawal

This study will quantify marijuana withdrawal effects on memory and attention in marijuana-dependent adults with a heavy use history both before and during withdrawal from chronic marijuana use.

Clinical Significance of Marijuana Withdrawal This project seeks to determine the clinical significance of marijuana withdrawal in adults and adolescents. Such information will be critical to determining the dependence potential of marijuana and to help decide whether pharmacological treatments for dependence focused on relieving withdrawal should be pursued.

Sleep Disturbance in Marijuana Withdrawal

This study seeks to determine if heavy marijuana use is associated with objective sleep abnormalities as measured by polysomnographic procedures. Such findings could lead to new treatments for alleviating the unpleasant symptoms of marijuana withdrawal.

Treatment Research:

Marijuana Dependence and Depression: Venlafaxine Treatment

Given the co-morbidity of depression and marijuana dependence, this investigator will conduct a placebo-controlled trial of the antidepressant venlafaxine extended release in

marijuana-dependent patients with current major depression to determine whether depressive symptoms are reduced and sustained abstinence is achieved.

NEWLY FUNDED GRANTS – NOT MARIJUANA-SPECIFIC

These grants investigate marijuana use/abuse as part of their research, in addition to other drugs of abuse. Their main focus is not specific to marijuana use. These grants were also funded in FY2003/2004 and thus have no data currently available.

Epidemiological Research:

Substance Use Disorders in Women with Anorexia/Bulimia

Using a unique data set gathered from a longitudinal study of eating disorders (EDs) this proposal seeks to examine the co-occurrence of SUDs (especially marijuana) through a series of secondary analyses. We will examine differences between women with and without SUDs in ED symptomatology, rates of ED recovery and relapse, comorbid psychopathology, suicidality, treatment participation and psychosocial functioning. Weekly assessments of ED symptoms, comorbid psychopathology and treatment participation as well as monthly ratings of psychosocial functioning were collected.

Opportunities and Actual Drug Use Among Hispanics

The project studies the exposure to opportunities to use drugs among American Hispanics and the transition to first drug use as well as progression from use of one drug to others (i.e. alcohol and tobacco use to marijuana use to cocaine use). The study includes the organization and re-analysis of data from the National Household Survey on Drug Abuse as well as the development of a pilot study using quanti-qualitative methods to explore the meanings of opportunities to use drugs among Hispanics as well as some potential new items for surveys in this area. This project will consider clustering in neighborhoods and acculturation.

Prevention Research:

Almost the entire Prevention Research Portfolio includes information about marijuana usage in its research. Below is a selection of the research grants, which include investigation into marijuana usage, along with other drugs.

Drug Resistance Strategies Minority Project

This study will build upon the existing Drug Resistance Strategies Project, a culturally appropriate, school based prevention program, and test the effectiveness of 5th grade and 7th grade multicultural and enculturation enhanced versions of program.

Diffusion of Prevention Science in Communities

Data collected from 41 communities in 7 states included in the original grant are examined to determine how risk and protective profiles operate within communities, change over time, and interact with and affect provision of prevention services.

NIDA Strengthening Washington, DC Families Grant

This project will test the effectiveness of a substance abuse prevention program entitled strengthening families program (SFP). Each component (parent training, children's skills, training & family skills training) will be tested with high-risk inner city African American & white children.

Long Term Results of ALERT PLUS

Project ALERT is an exemplary school-based curriculum designed to prevent or delay adolescents' use of alcohol, tobacco and other drugs including marijuana during middle school. The primary aim of this five-year project is to determine by means of a randomized field trial whether ALERT's middle-school effects can be sustained in the high-school years by adding booster lessons for 9th and 10th grade students. Consistent with the strong links between drug use and behaviors affecting public health and productivity, we propose to expand our assessment of outcomes to include violent behavior, dropping out of high school, post-secondary educational attainment and emotional distress. We will also assess the program's cost-effectiveness and cost benefit ratio over time.

Interactive Training for Parents of At-Risk Adolescents

This project will produce an interactive multimedia program to teach behavioral parenting skills to parents of at risk adolescents. The program focuses on replacing parenting techniques such as yelling or threatening with more prosocial behaviors such as listening.

Clinical Processes in Drug Abuse Prevention

This study will examine group processes in a family-based drug abuse prevention program for low-income families in high-risk neighborhoods and link these processes to attendance and attrition. The goal is to identify predictors of participation for this population.

Diffusion of Project Towards No Drug Abuse (TND)

This study will evaluate a comprehensive training and consultation approach to increase implementation and maintenance of Project Towards No Drug Use (TND), an evidence-based drug abuse prevention program for high school students. A sample of schools that have recently adopted Project TND will be randomly assigned to one of three conditions: (1) standard TND training; (2) comprehensive Implementation Support; and (3) delayed intervention control. We will determine the relative effectiveness of the two interventions on fidelity of program implementation and program maintenance. We will also examine the effects of the two intervention groups relative to the control group on student use of tobacco, alcohol, marijuana and other drugs.

Keepin' It Real: An Interactive CD-ROM for Teachers This company will develop a prototype of a skills-based teacher training CD-ROM to implement Keepin' It Real, a culturally-based substance use prevention curricula which has demonstrated effectiveness in reducing tobacco, alcohol and marijuana use in middle school youth.

Services Research:

Drug Outcome Monitoring Study (DOMS) Early Reintervention (ERI) Experiment

This study will determine the relative effectiveness of a low cost early re-intervention protocol in

terms of its ability to reduce the time to re-admission, increase the rate of early treatment readmission, & consequently improve long-term outcomes by bringing relapsed clients earlier into treatment.

Employment Dynamics in Response to Welfare Reform

The study will monitor how drug using welfare recipients respond to two new welfare reform requirements (compulsory employment after 2 years on welfare; and loss of benefits after 5 years). An attitudes, behaviors, and skills assessment instrument will be developed & administered at 4-month intervals.

Causal Effects of Community-Based Treatments for Youths

This research program will study the use of propensity scores, an innovative statistical method, to estimate the comparative effectiveness of community-based drug abuse services for adolescents using data from NIDA's Drug Abuse Treatment Outcome Studies for Adolescents (DATOS-A).

Adoption and Implementation of Adolescent EBT State-Wide

This study will compare statewide adoption and implementation of an evidence-based treatment for adolescent substance abuse (contingency management) among practitioners in the state substance abuse treatment system vs. those in the state mental health system of South Carolina. The focus of the present study is to provide substance abuse treatment through the existing and more extensive network of mental health providers.

Do Changes in the Economy Affect Teenage Drug Use?

This small study will examine how teenage marijuana use changes with the economy and variations in state unemployment rates. It will also explore whether drug use behavior of subgroups (race, ethnicity, and gender) respond differently. With this research evaluators could parse out the effects of the economy to obtain more accurate estimates of how effective anti-drug campaigns have been.

The Role of Judicial Status Hearings in Drug Court

This study will conduct a randomized evaluation of different approaches to the use of judicial status hearings in a misdemeanor drug court in Delaware. Clients will be randomly assigned to either attend bi-weekly status hearings or they will be monitored by a case manager at the treatment program.

Training – NIDA supports the development of young scientists interested in pursuing marijuana research through a variety of fellowships and career development awards.

NIDA INTRAMURAL RESEARCH PROGRAM (IRP)

The majority of NIDA-funded research is conducted in the extramural scientific community. However, NIDA has a very active intramural research program that conducts research relevant to marijuana abuse as well. Highlighted below are two such studies investigating the effects of long-term cannabis use.

Pope Jr., HG, Gruber AJ, Hudson JI, Huestis MA, and Yurgelun-Todd D (2002) Cognitive

Measures in Long-term Cannabis Users. *Journal of Clinical Pharmacology* 42: 41S-47S - In collaboration with Dr. Harrison Pope, Biological Psychiatry Laboratory, McLean Hospital and the Department of Psychiatry, Harvard Medical School, the NIDA IRP has recently studied the neuropsychological performance in long-term cannabis users. Current daily users who had smoked cannabis at least 5000 times in their lives, former heavy users and control subjects, who had smoked marijuana no more than 50 times in their lives, participated in a study assessing general intellectual function, abstraction ability, sustained attention, verbal fluency, and the ability to learn and recall new verbal and visuospatial information. On days 1 and 7 of abstinence, current heavy users scored significantly below control subjects on recall of word lists. However, by day 28, there were virtually no significant associations between cumulative lifetime cannabis use and test scores. Some cognitive deficits were detected for at least seven days after heavy cannabis use but appeared to be reversible and related to recent cannabis exposure, rather than irreversible and related to cumulative lifetime use.

Pope HG, Jr., Gruber AJ, Hudson JI, Cohane G, Huestis MA, and Yurgelun-Todd D. (2003) Early-onset cannabis use and cognitive deficits: what is the nature of the association? *Drug and Alcohol Dependence* 69: 303-310 - Hypothesizing that individuals who initiated cannabis use at an earlier age might be more vulnerable to lasting neuropsychological deficits than individuals who started later in life, the previous study was extended to include 122 long-term heavy cannabis users and 87 comparison subjects with minimal cannabis exposure. Cognitive performance on days 1, 7 and 28 of abstinence were evaluated for early (initiation of cannabis use before 17 years) and late onset (initiation of use at 17 years or later) cannabis users, controlling for age, sex, ethnicity, and family attributes. The early-onset users differed significantly from both the late onset users and from the controls on several measures, most notably verbal intelligence. Few differences were found between the late-onset users and controls on the cognitive test battery. These results may be due to innate differences in cognitive abilities between early- and late-onset cannabis users prior to any cannabis use, an actual neurotoxic effect of cannabis on the developing brain, or poorer learning of cognitive skills by young cannabis users.

FY 05 Efforts: NIDA Will Continue to Build on the Research It Has Encouraged Under the FY 04 RFA's and to Disseminate New Findings.

In FY 05, NIDA will place greater emphasis on encouraging researchers to support efforts to develop treatments for marijuana addiction and abuse.

As part of its Primary Care Initiative, NIDA will also work to educate physicians about the consequences of marijuana and how to advise their patients about drugs of abuse.

NIDA will continue to disseminate new findings and information about marijuana to a variety of audiences. This includes the attendees of the more than 40 conferences at which NIDA exhibits annually.