

A Collection of

NIDA NOTES

NATIONAL INSTITUTE
ON DRUG ABUSE

Articles That Address



RESEARCH
ON MARIJUANA

U.S. Department of Health and Human Services
National Institutes of Health
National Institute on Drug Abuse

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Introduction

The National Institute on Drug Abuse (NIDA) supports most of the world's research on drug abuse and addiction. NIDA-funded research enables scientists to apply the most advanced techniques available to the study of every aspect of drug abuse, including:

- genetic and social determinants of vulnerability and response to drugs;
- short- and long-term effects of drugs on the brain, including addiction;
- other health and social impacts of drug abuse, including infectious diseases and economic costs;
- development and testing of medication and behavioral treatments for abuse and addiction; and
- development and evaluation of effective messages to deter young people, in particular, from abusing drugs.

Included in this document are selections of topic-specific articles reprinted from NIDA's research newsletter, *NIDA NOTES*. Six times per year, *NIDA NOTES* reports on important highlights from NIDA-sponsored research, in a format that specialists and lay readers alike can read and put to use. Selections like the current one are intended to remind regular *NIDA NOTES* readers and inform other readers of important research discoveries during the periods they cover.

We hope the information contained here answers your needs and interests. To subscribe to *NIDA NOTES* and for further information on NIDA's drug abuse and addiction research, please visit our Web site at www.drugabuse.gov.

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Marijuana Smoking Is Associated With a Spectrum of Respiratory Disorders

Two NIDA-funded studies identify health risks that underscore the importance of curbing marijuana abuse.

By Patrick Zickler, *NIDA NOTES* Contributing Writer

A large new epidemiological study suggests that marijuana smoke can cause the same types of respiratory damage as tobacco smoke. Significant associations between marijuana smoking and a variety of respiratory diseases also have been confirmed by an extensive review of clinical literature.

Monitoring the Effects of Tobacco and Marijuana

Dr. Brent Moore and colleagues at Yale University, the National Cancer Institute, and the University of Vermont evaluated data from a nationally representative sample of 6,728 adults. Their analysis indicated that a history of more than 100 lifetime episodes of smoking marijuana, with at least one episode in the past month, increased an individual's risk of chronic bronchitis, coughing on most days, wheezing, chest sounds without a cold, and increased phlegm.

"The most significant difference between tobacco smoke and marijuana smoke is their principal active ingredients—nicotine in tobacco and delta-9-tetrahydrocannabinol (THC) in marijuana. Beyond that, marijuana contains at least as much tar and half again as many carcinogens as smoke from conventional tobacco," says Dr. Moore. "Quitting marijuana smoking may benefit respiratory health as much as quitting cigarettes, in addition to the clear and considerable health, psychological, and social benefits of no longer abusing an illicit drug."

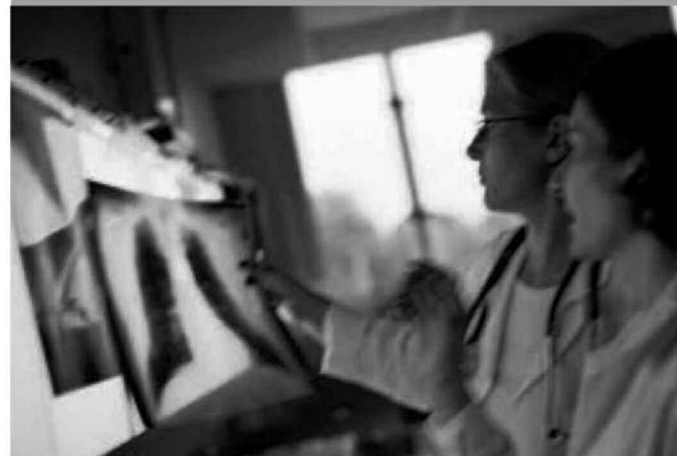
The information Dr. Moore and his colleagues analyzed was gathered through the third National Health and Nutrition Examination Survey (NHANES III), conducted between 1988 and 1994. Participants included 4,789 non-smokers of either tobacco or marijuana; 1,525 smokers of tobacco but not marijuana; 320 smokers of both marijuana and tobacco; and 94 who smoked marijuana only. On average, marijuana abusers had smoked the drug on 10 of the preceding 30 days, with 16 percent reporting daily or almost daily smoking. Tobacco smokers consumed roughly the same number of cigarettes—averaging 19.2 per day—whether or not they also smoked marijuana. Survey participants answered questions about their experiences of a range of respiratory symptoms and were examined for signs of respiratory abnormalities.

The researchers concluded that tobacco smokers who also smoked marijuana had a higher prevalence of most respiratory symptoms than tobacco-only smokers. Compared with tobacco-only smokers, however, those who also smoked marijuana were less likely to have had pneumonia during the previous year or to show spirometric evidence of obstructive pulmonary disorder. Commenting on this finding, Dr. Moore says that it is important to note that the marijuana smokers in the sample were significantly younger (average age 31.2 years) than the tobacco smokers (average age 41.5 years). "The marijuana-related respiratory effects correspond to a relatively young population, and NHANES III did not ask participants older than age 59 about drug use," he adds. "It is likely that respiratory effects will be higher in older marijuana smokers, and, because of the high prevalence of tobacco use among marijuana smokers, there appears to be an increased risk for illness due to cumulative effects of smoking both drugs."

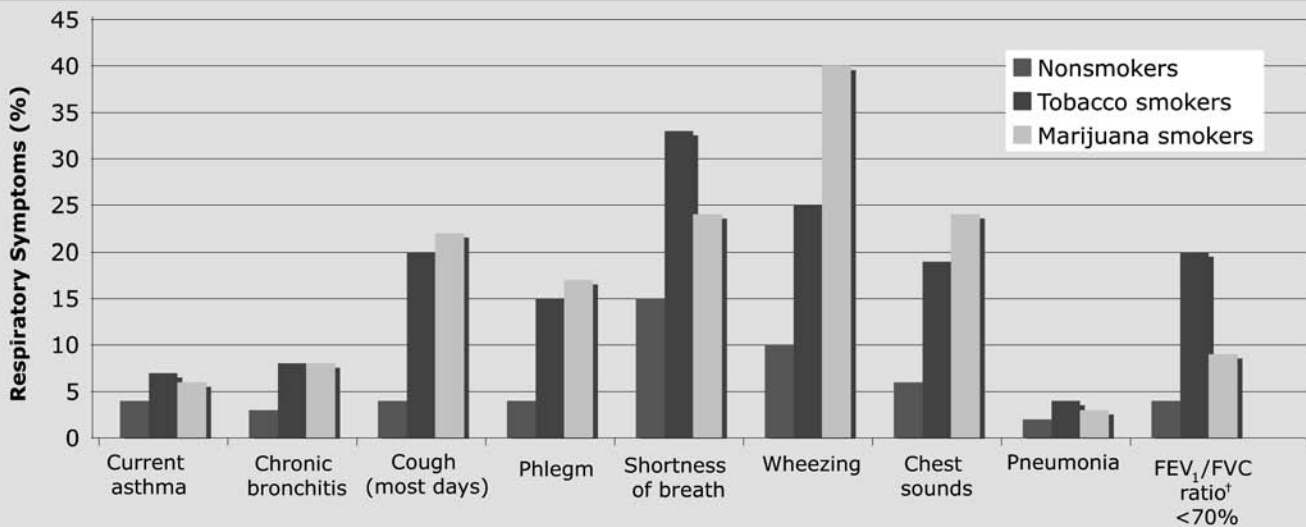
Marijuana's Long-Term Pulmonary Effects

Further evidence of marijuana's respiratory toxicity emerged from a study conducted by Dr. Donald Tashkin at the University of California, Los Angeles. Dr. Tashkin conducted an extensive review of clinical and epidemio-

RESEARCHERS CITE PUBLIC HEALTH IMPACT More than 2 million adult Americans are heavy marijuana smokers, and increased efforts to prevent marijuana use may have significant public health benefits.



SURVEY TIES MARIJUANA ABUSE AND RESPIRATORY SYMPTOMS In a nationally representative sample of 6,728 U.S. adults, self-reported marijuana use was associated with chronic bronchitis, coughing on most days, phlegm production, wheezing, and chest sounds without a cold. Medical examinations provided overall chest findings and measures of pulmonary function.



SOURCE: National Health and Nutrition Examination Survey (NHANES III)
[†]FEV₁/FVC ratio measures lung obstruction or restriction.

logical research to determine the extent to which chronic marijuana smoking might lead to long-term pulmonary effects and diseases similar to those caused by tobacco. Unlike the NHANES III data examined by Dr. Moore, the studies evaluated by Dr. Tashkin made it possible to assess a possible association between marijuana smoking and respiratory cancers.

The results of animal and cell culture studies are mixed with respect to the carcinogenic effects of THC, some studies showing that THC promotes lung cancer growth and others showing an anti-tumoral effect on a variety of malignancies. Although the results of epidemiological studies are also mixed, a large, recently completed case-control study has failed to find a direct link between marijuana use (including heavy use) and lung, throat, or other head and neck cancers. “Nevertheless, there is evidence that suggests precarcinogenic effects in respiratory tissue,” Dr. Tashkin says. “Biopsies of bronchial tissue provide evidence that regular marijuana smoking injures airway epithelial cells, leading to dysregulation of bronchial epithelial cell growth and eventually to possible malignant changes.” Moreover, he adds, because marijuana smokers typically hold their breath four times as long as tobacco smokers after inhaling, marijuana smoking deposits significantly more tar and known carcinogens within the tar, such as polycyclic aromatic hydrocarbons, in the airways. In addition to precancerous changes, Dr. Tashkin found that marijuana smoking is associated with a range of damaging pulmonary effects, including inhibition of the tumor-killing and bactericidal activity of alveolar macrophages, the primary immune cells within the lung.

Taken together, Dr. Tashkin’s survey of clinical and epidemiological studies and Dr. Moore’s assessment of self-reported and clinically observed effects provide an extensive catalog of respiratory and pulmonary damage associated with marijuana smoking. Smokers are subject to:

- Coughing and phlegm production on most days;
- Wheezing and other chest sounds;
- Acute and chronic bronchitis;
- Injury to airway tissue, including edema (swelling), increased vascularity, and increased mucus secretion; and
- Impaired function of immune system components (alveolar macrophages) in the lungs.

Sources

- Moore, B.A., et al. Respiratory effects of marijuana and tobacco use in a U.S. sample. *Journal of General Internal Medicine* 20(1):33-37, 2005.
- Tashkin, D.P. Smoked marijuana as a cause of lung injury. *Monaldi Archives for Chest Disease* 63(2):93-100, 2005.
- Hashibe, M., et al. Marijuana use and the risk of lung and aerodigestive tract cancers: results of a population-based case-control study. *Cancer Epidemiology, Biomarkers & Prevention* 15(10):1829-1834, 2006.



MTF Survey Finds Overall Decline in Teen Substance Abuse

Substance abuse among teenagers in the United States declined 19 percent over the past 4 years, with 15.8 percent reporting past-month abuse in 2005, compared with 19.4 percent in 2001, according to the latest Monitoring the Future Survey. The nationwide survey of 8th-, 10th-, and 12th-graders found that the overall decline was tempered by increases or unchanged rates of abuse of some prescription drugs, inhalants, and other substances.

The 4-year decline has been driven largely by decreasing rates of marijuana abuse. For example, since 2001, past-month abuse of marijuana fell by 28 percent among 8th-graders and by 23 percent among 10th-graders. Although most year-to-year changes in the annual survey are not statistically significant, teen abuse of five substances—GHB, LSD, MDMA/Ecstasy, methamphetamine, and steroids—showed significant declines from 2004 to 2005.

The survey findings are encouraging because teenagers are most vulnerable to the effects of drugs and youths who abstain in their teen years are less likely to abuse drugs later in life, NIDA Director Nora D. Volkow, M.D., says. She notes, however, that teens' abuse of prescription medications and inhalants has continued unabated in the past few years. NIDA is particularly concerned about the non-prescribed use of opioid painkillers, such as OxyContin and Vicodin. In 2005, 9.5 percent of 12th-graders reported abusing Vicodin in the past year, and 5.5 percent reported OxyContin abuse, which has increased more than one-third since 2002. "Using these drugs without a

prescription is dangerous. It's imperative that teens get this message," Dr. Volkow stresses.

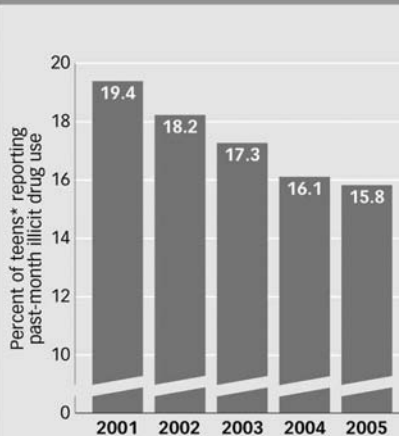
Abuse of inhalants, which are found in common household substances such as nail polish remover, glue, and cleaning fluids and are very toxic, also has been rising in recent years. Abuse among eighth-grade students has increased significantly since 2002, Dr. Volkow says.

Smoking Decline May Be Tapering Off

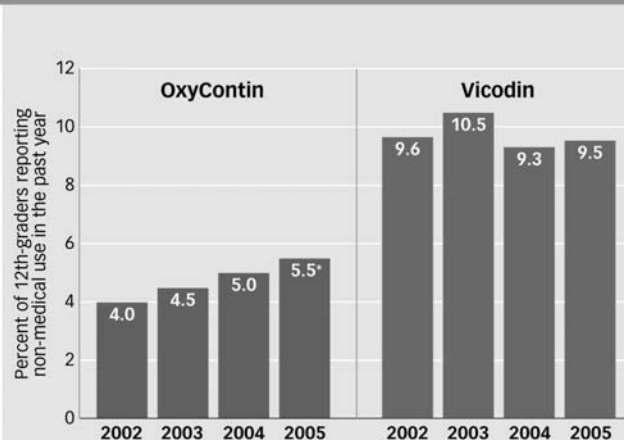
Dr. Lloyd Johnston of the University of Michigan, the principal investigator of the study, notes a worrisome signal that the decline in smoking may be tapering off: The smoking rate among eighth-graders held steady in the latest survey, following a long-term decline over the past several years. Eighth-graders are considered an important bellwether of drug-related trends among teenagers. Moreover, smoking declines in the upper grades also slowed in 2005. Survey data do not indicate long-term declines in the abuse of marijuana and other illicit drugs among 8th-graders, and declines among 10th- and 12th-grade students were very modest, Dr. Johnston notes.

On the positive side, cigarette smoking is at its lowest rate in the 30-year history of the survey. Also, the proportion of eighth-graders reporting that they have ever tried to smoke cigarettes declined in the latest survey, which could reflect shifts in behaviors and intentions that occurred several years earlier.

ILLICIT DRUG USE DROPS AMONG TEENS, BUT NONPRESCRIPTION USE OF PAINKILLERS REMAINS A CONCERN While overall substance abuse among teenagers in the United States declined 19 percent over the past 4 years, abuse of prescription opioid painkillers such as OxyContin and Vicodin has continued unabated.



* 8th, 10th, and 12th grades combined.
SOURCE: University of Michigan, 2005 Monitoring the Future Survey.



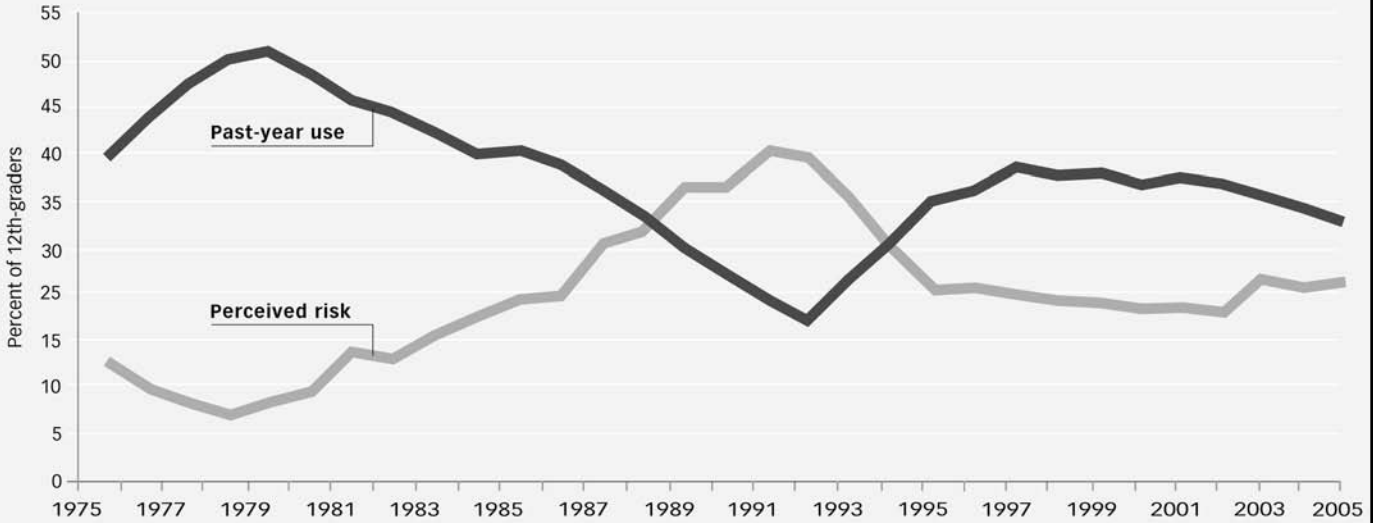
* Increase in the abuse of OxyContin by 12th-graders between 2002 and 2005 was significant.
SOURCE: University of Michigan, 2005 Monitoring the Future Survey.

The survey covered about 50,000 students in more than 400 public and private schools. The University of Michigan conducted the survey under a grant from NIDA, the National Institutes of Health, and the Department of Health and Human Services. Further details on the survey are available at www.drugabuse.gov/DrugPages/MTF.html and at monitoringthefuture.org. **NN**

WHAT THE NUMBERS SAY

Abuse Drops When High School Seniors View Marijuana as Dangerous

The graphic shows the relationship between two trends identified in the annual Monitoring the Future Survey of 12th-graders. The annual prevalence of marijuana abuse by high school seniors falls when the perceived harmfulness of marijuana use rises, and vice versa.



SOURCE: University of Michigan, 2005 Monitoring the Future Survey.

Twin Study Links Marijuana Abuse, Suicide, And Depression

By Patrick Zickler, NIDA NOTES Staff Writer

Men and women who smoked marijuana before age 17 are 3.5 times as likely to attempt suicide as those who started later. Individuals who are dependent on marijuana have a higher risk than nondependent individuals of experiencing major depressive disorder and suicidal thoughts and behaviors. The researchers who discovered these relationships, in a recent NIDA-funded large-scale epidemiological study, say that although the causes are not clear, their findings demonstrate the importance of considering associated mental health issues in the treatment and prevention of marijuana abuse.

Dr. Michael Lynskey and colleagues at the Washington University School of Medicine in St. Louis, Missouri, gathered data from four groups of same-sex twin pairs (508 identical, 493 fraternal; 518 female, 483 male) enrolled in the Australian Twin Registry. The groups and findings were:

- Among the 277 pairs who were discordant for marijuana dependence (that is, one twin but not the other met the criteria for a diagnosis of marijuana dependence), the dependent twins were 2.9 times as likely as their nondependent co-twins to think about suicide without attempting it, and 2.5 times as likely to make a suicide attempt;
- Among the 311 pairs discordant for early marijuana initiation (just one twin in each pair smoked marijuana before age 17), the early initiators were 3.5 times as likely as their twins to attempt suicide, but no more likely to suffer a major depressive disorder (MDD);
- Among the 156 pairs discordant for diagnosis of MDD before age 17, fraternal but not identical twins with early diagnosis of MDD were 9.5 times as likely to develop marijuana dependence; and
- Among the 257 pairs discordant for having suicidal thoughts before age 17, fraternal but not identical twins with early suicidal thoughts were 5.5 times as likely as their twins to become dependent on marijuana.

“Overall, the associations between marijuana abuse and depressive disorders suggest a relationship that is contributory but not necessarily causal. Depressive disorders in and of themselves do not cause people to abuse marijuana, and marijuana abuse and dependence do not of themselves cause depression or suicidal behavior,” Dr. Lynskey says.

Marijuana Abuse and Depressive Disorders In Twin Pairs					
		Major Depressive Disorder		Suicidal Thoughts	Attempted Suicide
		Identical Twins	Fraternal Twins		
Pairs in which one twin	Developed dependence on marijuana	1.16	3.40	2.89	2.53
	First smoked marijuana before age 17	0.86	1.14	1.10	3.49
Marijuana Dependence					
Pairs in which one twin		Identical Twins		Fraternal Twins	
	Had suicidal thoughts before age 17	1.78		5.50	

The study identified relationships between twins' histories of marijuana abuse and mental health problems.

“Nevertheless, clinicians treating patients for one disorder should take the other into account at initial assessment and throughout treatment. In the context of treatment, both need to be addressed, because it is not necessarily the case that eliminating one disorder will get rid of the other.” The fact that two of the relationships were observed in fraternal but not identical twins suggests that the experiences related in each—marijuana dependence and MDD, and marijuana dependence and suicidal thoughts—may share a common underlying genetic basis, notes Dr. Lynskey.

The associations identified in this study are complex, but point to a simple policy implication, observes Dr. Lynskey. “It is important to see that prevention efforts aimed at one disorder may well have the additional benefit of preventing or reducing the other,” he says.

“Drug abuse and depression co-occur at rates much greater than chance and constitute a serious public health concern,” says Dr. Naimah Weinberg of NIDA’s Division of Epidemiology, Services and Prevention Research. “Understanding how each disorder may contribute to the development and course of the other, and what factors may underlie their co-occurrence, has important implications for prevention and treatment of these disabling conditions. Genetic epidemiologic approaches, such as those applied by Dr. Lynskey and his colleagues, are very powerful tools to help parse out the etiologic relationships between co-occurring disorders.”

Source

- Lynskey, M.T., et al. Major depressive disorder, suicidal ideation, and suicide attempt in twins discordant for cannabis dependence and early-onset cannabis use. *Archives of General Psychiatry* 61(10):1026-1032, 2004. **NN**

NIDA Intensifies Focus on Marijuana Abuse

By NIDA Director Nora D. Volkow, M.D.

More than 96 million Americans have smoked marijuana at least once. Marijuana abuse is particularly prevalent among adolescents: Of the more than 2 million people who abuse the drug for the first time every year, two-thirds are between 12 and 17 years of age.

The damaging effects of marijuana fall heavily on adolescents and young adults. Half of all patients admitted to treatment for marijuana abuse are younger than 21. Cognitive impairments caused by marijuana linger a month or more after an individual's last exposure, and the damage is dose dependent—the more a person smoked prior to abstinence, the more marked are the deleterious effects on visual perception, verbal and visual memory, executive function, and manual dexterity, among other mental capabilities (see "Cognitive Deficits in Marijuana Smokers Persist After Use Stops," *NIDA NOTES*, Vol. 18, No. 5, p. 8). Loss of social and intellectual growth because of these impairments may have a life-long impact on a person's experience and achievement. As well, compared with teens who never smoke marijuana, a boy or girl who smokes marijuana before age 17 is more than twice as likely to abuse opioids, three times as likely to abuse cocaine or other stimulants, and nearly four times as likely to abuse hallucinogens later in life (see "Twins Study Links Early Marijuana Use to Increased Risk of Abuse or Dependence," *NIDA NOTES*, Vol. 18, No. 4, p. 11).


NIDA is intensifying efforts to fully understand the effects of marijuana exposure from the earliest ages through adolescence and young adulthood. This research (see RFA DA-04-016, "Consequences of Marijuana Use on the Developing Brain," at <http://grants2.nih.gov/grants/guide/rfa-files/RFA-DA-04-016.html>) will provide new insight into the mechanisms by which marijuana affects brain development, a continuum that begins before birth and lasts into early adulthood. We are encouraging research



projects that focus on the effect of marijuana during all phases of neurological development, from the neurogenesis and cell differentiation that takes place in the womb to the refinement of connections among cells that continues past adolescence. Our research initiative will produce a fuller understanding of normative brain development. It also will illuminate the importance of family and social contexts in adolescence as well as the differing biological and environmental factors that precede marijuana use or nonuse.

NIDA also is expanding support of research to develop treatments for marijuana abuse (see RFA DA-04-014, "Medications Development for Cannabis-Related

Disorder," at <http://grants2.nih.gov/grants/guide/rfa-files/RFA-DA-04-014.html>). There is a clear public health need for interventions to alleviate withdrawal symptoms and to help chronic abusers deal with social and other factors that make stopping marijuana abuse difficult. NIDA's expanded research agenda will encourage development of medications to counter marijuana dependence through animal studies as well as Phase I and Phase II clinical trials with humans. Some medications will be aimed at marijuana-associated disorders such as intoxication, delirium, psychosis, and anxiety. Other medications may address specific aspects of addiction recovery, such as withdrawal, craving, relapse, and complications such as cognitive impairment, sleep disorders, and depression and other mood disorders that often accompany marijuana abuse.

Successful comprehensive treatment of marijuana-related disorders will require a multidisciplinary approach. Therefore, NIDA's marijuana medications development initiative will encourage investigation of treatments that include behavioral intervention. This broad focus, building on the insights to be gained through increased understanding of marijuana's developmental impact, will help reduce the health costs and alleviate the damage inflicted by widespread abuse of this dangerous drug. 

Marijuana-Related Disorders, But Not Prevalence of Use, Rise Over Past Decade

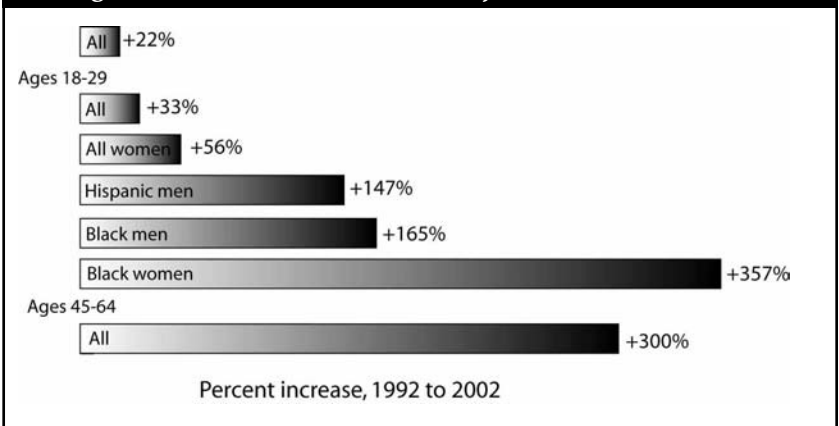
By Patrick Zickler, *NIDA NOTES* Staff Writer

More Americans suffer from marijuana-related mental health disorders now than a decade ago, even though the prevalence of marijuana smoking has not increased. Survey results from 2002, compared with data from a decade earlier, showed that overall, rates of marijuana consumption in adults 18 and older held relatively steady at 4 percent of respondents. However, rates of marijuana-related disorders—discrete conditions defined according to criteria established by the American Psychiatric Association—increased from 1.2 percent to 1.5 percent of respondents; this means that 37.5 percent of marijuana smokers were affected. The increase was particularly sharp among young adult black men and women aged 18-29, among whom marijuana consumption rose only modestly while the incidence of disorders tripled. Rates of marijuana-related disorders among Hispanic men in the same age span also increased sharply despite only a moderate increase in their rate of marijuana smoking.

“The rise in marijuana-related disorders means that there were approximately 800,000 more adults in the United States with marijuana abuse disorder or dependence in 2002 than a decade earlier,” says Dr. Wilson Compton of NIDA’s Division of Epidemiology, Services and Prevention Research. “In the 1992 survey, these problems were more common among Whites than among minorities, but in 2002 the differences in rates among the different ethnic groups had narrowed, in large part because of increases that nearly tripled the rate among young African American men and women and more than doubled the rate among young Hispanic men.”

Dr. Compton and colleagues at NIDA, and Dr. Bridget Grant and colleagues at the National Institute on Alcohol Abuse and Alcoholism (NIAAA), evaluated data from two large, national epidemiologic surveys—the National Longitudinal Alcohol Epidemiologic Survey (NLAES), conducted in 1991-1992, and the National Epidemiological Survey on Alcohol and Related Conditions (NESARC), conducted in 2001-2002. Both studies define abuse and dependence using criteria that match the diagnostic standards found in the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV); see “Defining Marijuana-Related Disorders.”

Older Americans, Young Blacks, and Hispanic Men Show Largest Increases in Rates of Marijuana-Related Disorders



Survey data collected 1991-1992 and 2001-2002 show little increase over the decade in rates of marijuana smoking, but overall prevalence of marijuana-related disorders increased by 22 percent. Increases in a few demographic groups accounted for most of this increase.

The study also reveals a shift in marijuana use and its associated problems among older adults, Dr. Compton says. “Marijuana smoking increased by 167 percent and the prevalence of marijuana-related disorders quadrupled among men and women aged 45 to 64,” he observes. “Given this shift, the possibility that marijuana may contribute to health problems among the aging population deserves research attention.”

The surveys do not explain why disorders increased in some groups and not in others. However, increased potency of marijuana in the last decade may be partly responsible for the overall upward trend of marijuana-related disorders, the researchers speculate. Regardless of the causes, the sharp increases among minority groups merit further investigation, Dr. Compton says. “We see what could be described as a minor epidemic of marijuana-related disorders going on among young adult minorities. It probably has been going on undetected for years, and points to the need for specifically targeted prevention and intervention efforts.”

Source

- Compton, W.M., et al. Increases in the prevalence of marijuana use disorders in the United States 1991-1992 and 2001-2002. *JAMA* 291(17):2114-2121, 2004. **NN**

Teen Drug Abuse Continues Its Three-Year Decline

Illicit drug abuse among the Nation's youth declined by almost 7 percent from 2003 to 2004, continuing an encouraging trend that began in 2001. At the same time, the latest report from the Monitoring the Future (MTF) survey shows a recent increase in the abuse of inhalants among eighth graders and the painkiller OxyContin among all students surveyed.

Overall, the trends in the past 3 years have been positive, with a decline in past-month drug abuse among 8th, 10th, and 12th graders combined from 19.4 to 16.1 percent. This reduction translates into roughly 600,000 fewer adolescent drug abusers than in 2001, advancing the goal President George W. Bush set in February 2002 to reduce drug use among youth by 25 percent in 5 years. The 2004 findings emerged from responses provided by nearly 50,000 students in 406 public and private schools across the country. In addition to declines in past-month use, students' past-year use fell from 31.8 to 27.5 percent; their lifetime use dropped from 41.0 to 36.4 percent between 2001 and 2004.

"Drug use is preventable. The overall reduction in drug abuse by America's young people shows the power of partnership among all working to address the problem—from scientists developing basic knowledge to people implementing services in the community to those making policy at all levels," said NIDA Director Dr. Nora D. Volkow. "Our concerted effort to provide students, teachers, and families with accurate information about addiction and drug abuse have had an impact, but we must sustain and advance this work to realize further reductions in drug abuse."

The MTF survey, launched in 1975, measures drug, alcohol, and cigarette abuse and attitudes about use among 8th, 10th, and 12th graders nationwide. Funded by NIDA, the survey has been conducted annually since its inception by the University of Michigan's Institute for Social Research. Now in its 30th year, MTF questions and analyses have changed with informational needs—for example, expanding the list of drugs, analyzing data for all three grades combined, tracking students' attitudes toward drug abuse, and examining the impact of anti-drug



advertising. Although generally positive, this year's MTF results for two drugs raise concerns and bear close monitoring.

Lifetime abuse of inhalants among eighth graders increased from 15.8 to 17.3 percent between 2003 and 2004. The survey showed that 8th and 10th graders' perceptions of the risks associated with abusing inhalants has declined in the past 3

years, suggesting a need to increase awareness of the potentially dangerous consequences of abusing these often inexpensive and easily obtainable intoxicants. The number of high school students using the painkiller OxyContin without medical supervision increased from 2002 to 2004. Past-year abuse of this drug—an opioid with a high potential for addiction—was disturbingly common at 1.7, 3.5, and 5.0 percent for grades 8, 10, and 12, respectively.

Key substance abuse patterns that emerged between 2001 and 2004 are:

- **Cigarettes.** Smoking among teenagers continues to decline from peak levels in the mid-1990s, although more slowly than in the past 8 years. Lifetime and current abuse of cigarettes declined among 8th, 10th, and 12th graders. Lifetime cigarette abuse dropped 19.5 percent, from 49.1 to 39.5 percent, and current abuse fell 20.3 percent, from 20.3 to 16.1 percent.
- **Marijuana.** Abuse of marijuana declined significantly. Current abuse declined 18.1 percent, from 16.6 to 13.6 percent; past-year abuse also declined 13.7 percent, from 27.5 to 23.7 percent; and lifetime abuse declined 11.2 percent, from 35.3 to 31.3 percent. In the past 2 years, students' perceived risk of abusing marijuana increased markedly; the proportion of teens reporting that it would be easy for them to get the drug also declined in recent years.
- **Amphetamines.** Abuse of this class of drug without medical supervision has been widespread among youth in the past, but has been gradually declining. Lifetime abuse fell 19.6 percent—from 13.9 to 11.2 percent. Both past-year and current abuse fell as well, from 9.6 to 7.6 percent and from 4.7 to 3.6 percent, respectively.

- **LSD and MDMA (Ecstasy).** Students' abuse of the hallucinogens LSD and MDMA plummeted between 2001 and 2004. Lifetime abuse of LSD fell 55 percent, from 6.6 to 3.0 percent, and past-year and current abuse both dropped by approximately 60 percent. Lifetime use of MDMA dropped 40.7 percent, with past-year and current abuse falling by more than

half, from 5.5 to 2.5 percent and 2.3 to 0.9 percent, respectively. In the late 1990s and until 2001, the sharp increase in the abuse of MDMA among teens was a concern. Increases in students' perceived risk of abusing the drug preceded the decreases in abuse seen since 2001. **NN**

Marijuana Abuse: Age of Initiation, Pleasure of Response Foreshadow Young Adult Outcomes

By Robin Eisner, *NIDA NOTES* Contributing Writer

A boy or girl who is smoking marijuana at 13 is likely to earn less money as a young adult than peers who aren't abusing the drug. An adolescent who smokes less marijuana than a friend but enjoys the experience more is likelier to be addicted to the drug at 21. These are findings from two recent studies that looked at adult outcomes associated with marijuana abuse in adolescence.

Dr. Phyllis L. Ellickson and colleagues at the RAND Corporation in Santa Monica, California, surveyed 5,800 adolescents from 30 schools in California and Oregon about their marijuana use between ages 13 and 23. A statistical analysis of the responses revealed four distinct patterns related to marijuana abuse.

Approximately 45 percent did not smoke marijuana. The researchers called these youths Abstainers. Of those who did smoke marijuana:

- Some 5 percent were considered *Early High Users*—teens who smoked marijuana from once a week to monthly at age 13, decreased their abuse by age 18, and as young adults smoked 3 to 10 times a year.
- About 17 percent were *Stable Light Users*—teens who smoked infrequently at age 13 and never abused the drug more than 10 times a year, on average.
- *Occasional Light Users* made up 53 percent of the marijuana-abusing population. They were similar to Stable Light Users but started after age 13 and abused lower amounts than Stable Light Users throughout the study period.
- *Steady Increasers*, approximately 25 percent of the abusers, started after age 13 and increased their usage during the study period.

The researchers found that the Early High Users lagged behind all other groups in earnings and education when resurveyed at age 29. Their average yearly earnings were \$20,940, compared with about \$32,000 for the Occasional Light Users and Abstainers and \$28,140 for the Steady Increasers. Both groups that initiated marijuana abuse by age 13 reported less schooling than Abstainers and those who first smoked after age 13: Early High Users and Stable Light Users did not usually go to college, while Steady Increasers completed on average one year of college, Occasional Light Users almost two years of college, and Abstainers, almost three years of college.

Relationship Between Number of Positive Responses to Marijuana and Later Addiction

Positive Responses	Marijuana-Addicted Subjects
0	5.2%
1	8.5%
2	13.3%
3	19.9%
4	28.7%
5	39.1%

Source: Fergusson, D.M.; Horwood, L.J.; Lynskey, M.T.; and Madden, P.A.F. (2003).

Researchers examined whether teens' positive responses to marijuana were related to later marijuana addiction. Positive responses noted by participants included "got really high," "felt happy," "felt relaxed," "did silly things," and "laughed a lot." Almost 40 percent of teens with five positive responses were addicted to marijuana between ages 16 and 21 compared with 5.2 percent of those who had no positive response.

"The bad news is that if you start marijuana use by age 13, even if you eventually decrease your usage, you are likely to have a lower income and lower level of schooling by age 29," Dr. Ellickson says. "The good news is that 45 percent of the youths in our sample did not use marijuana between adolescence and emerging adulthood. We need to understand what helped those kids abstain over time." Dr. Ellickson says although her findings show an association between marijuana abuse and reduced income and educational performance, they do not prove that marijuana contributes causally to those outcomes, which result from multiple factors. The results also suggest that delaying initiation of marijuana abuse does not necessarily guarantee better outcomes, especially if the late starters escalate abuse. Youths who started after age 13, but steadily increased their marijuana use during and after high school, abused marijuana more than any other group as young adults, smoking 3 to 10 times during the past month on average. In young adulthood, the late starters who intensified their use of marijuana also abused other illegal drugs at rates similar to those of the early starters, with 32 percent admitting to past-year abuse of illegal drugs besides marijuana.

The patterns of abuse revealed by the study suggest that interventions against marijuana abuse may be important from primary school through to high school graduation, says Dr. Kathleen Etz, of NIDA's Division of Epidemiology, Services and Prevention Research.

"At each stage, the goal will be to prevent children who are at risk from initiating use, and to persuade any who have already started to reduce or quit," Dr. Etz says. "The counseling ideally would educate children about the potential problems of marijuana abuse and address the broad goal of self-awareness leading to healthy life choices."

Positive Initial Response Linked to Later Dependence

In the second study, led by Dr. David Fergusson of the Christchurch School of Medicine and Health Sciences in Christchurch, New Zealand, researchers found that positive emotional responses to initial marijuana abuse pre-

dicted later addiction to the drug better than did the amount of marijuana smoked. The researchers worked with data from the Christchurch Health and Development study, a 21-year longitudinal project that followed a group of children born in the city from birth through adolescence. Dr. Fergusson's analysis included 1,011 of these youths.

When the study participants were 15 or 16, they answered a series of interview questions about their cannabis exposure in the preceding year. These included their frequency of abuse as well as feelings about their most recent experience: Did they get "really high," feel happy, feel relaxed, do silly things, laugh a lot, feel ill or dizzy or frightened, or pass out?

In this first interview, 20 percent of those later included in Dr. Fergusson's study had abused marijuana. Study participants were interviewed again at ages 18 and 21. By then, approximately 9 percent reported signs of being addicted to marijuana; the prevalence among those who started before age 16 was 21.7 percent. Almost half (46.7 percent) of those who had reported five or more pleasurable responses to the drug in the first interview reported being addicted by age 21, compared with 3.9 percent of those reporting no positive responses.

The results indicate that the pleasure of early use, not how much marijuana is used, determines the likelihood of later addiction. "There are people smoking a lot of marijuana who aren't addicted to it," Dr. Fergusson explains. "Others are smoking less but are addicted or headed for addiction."

Dr. Fergusson says his findings parallel those of studies on cigarette smoking and alcohol use

"At each stage, the goal will be to prevent children who are at risk from initiating use."

Marijuana Abstainers Enter Adulthood Ahead

Outcomes of Five Marijuana User Groups at Age 29

	Early High Users n=37	Steady Increases n=336	Stable Light Users n=171	Occasional Light Users n=753	Abstainers n=1,229
Overall Health ¹	3.53 ^c	3.82 ^b	3.86 ^b	3.89 ^b	4.03 ^a
Mental Health ¹	3.64 ^{ab}	3.67 ^b	3.82 ^{ab}	3.72 ^b	3.84 ^a
Life Satisfaction ¹	3.88 ^b	3.99 ^b	4.03 ^b	4.10 ^b	4.27 ^a
Educational Attainment ²	5.56 ^d	6.48 ^c	5.99 ^d	6.89 ^b	7.43 ^a
Yearly Earnings (\$ in thousands)	20.94 ^c	28.14 ^b	27.71 ^b	32.29 ^a	31.93 ^a
"Yes" to Past-Year Other Drug Use	27.4% ^c	31.9% ^c	30.3% ^c	18.3% ^b	8.5% ^a
Frequency of Past-Month Marijuana Use ³	.90 ^c	2.17 ^e	1.32 ^d	.53 ^b	.14 ^a

Source: Ellickson, P.L.; Martino, S.C.; and Collins, R.L. (2004).

Note: Means/percentages are adjusted for sex, race/ethnicity, parental education, and nuclear family. A result marked by *a* represents a significantly more favorable outcome such that *a* > *b* > *c* > *d* > *e*. Same-letter superscripts in each row indicate no statistically significant differences between those entries.

¹Averages based on a scale of 1 to 5, with 1 indicating poor and 5, excellent.

²Values ranged from 1 indicating 8th grade or less, to 11 indicating an advanced professional degree.

³Based on a five-category index: 0 indicates no use; 1, < 3 times; 2, 3-10 times; 3, 11 times; and 4, > 11 times and 6 or more days in the past month.

among adolescents, which suggest that initial subjective response to a drug might be a behavioral marker for biological addiction-vulnerability. This growing body of research indicates that vulnerable individuals seem to experience enhanced sensitivity to a drug's positive effects, diminished sensitivity to its negative effects, or a combination of the two responses.

Dr. Wilson Compton, director of the Division of Epidemiology, Services and Prevention Research at the National Institute on Drug Abuse, says that research in animals has revealed genetic differences between those that prefer alcohol and those that do not. Similar research might identify the neurobiological factors underlying differences in the response to marijuana, perhaps eventually leading to risk-reduction treatments, says Dr. Compton.

Sources

- Ellickson, P.L.; Martino, S.C.; and Collins, R.L. Marijuana use from adolescence to young adulthood: Multiple developmental trajectories and their associated outcomes. *Health Psychology* 23(3):299-307, 2004.
- Fergusson, D.M.; Horwood, L.J.; Lyndskey, M.T.; and Madden, P.A.F. Early reactions to cannabis predict later dependence. *Archives of General Psychiatry* 60(10):1033-1039, 2003. **NN**

Early Use of Drugs May Lead to Later Psychiatric Disorders

By Jill Schlabig Williams, NIDA NOTES Contributing Writer

One of the challenges of research into comorbidity—the co-occurrence of substance abuse and mental disorders—is determining the order in which these disorders occur and the factors that they share. Recent findings from a longitudinal study that followed more than 700 individuals from early childhood into their late twenties now confirms one sequence of events in the comorbidity conundrum.

Dr. Judith S. Brook and Dr. David W. Brook of New York's Mount Sinai School of Medicine and Dr. Patricia Cohen of Columbia University, also in New York, provide evidence that substance abuse significantly predicts the later occurrence of psychiatric disorders, including major depressive disorder (MDD), alcohol dependence, and substance use disorders (SUDs). Moreover, their findings suggest that there are common risk factors for both substance abuse and MDD and that once abuse begins, it becomes an additional risk factor for MDD.

“Most studies obtain data on psychiatric disorders and drug abuse simultaneously, so it's almost impossible to determine which came first,” says Dr. Judith Brook. “This longitudinal data set is unique because it follows one group of people through their lives, collecting data roughly every 5 years on drug abuse patterns, psychiatric disorders, and other factors. This approach allows us to study the progression of drug abuse, how it affects a person's functioning, and how it relates to subsequent psychiatric disorders.”

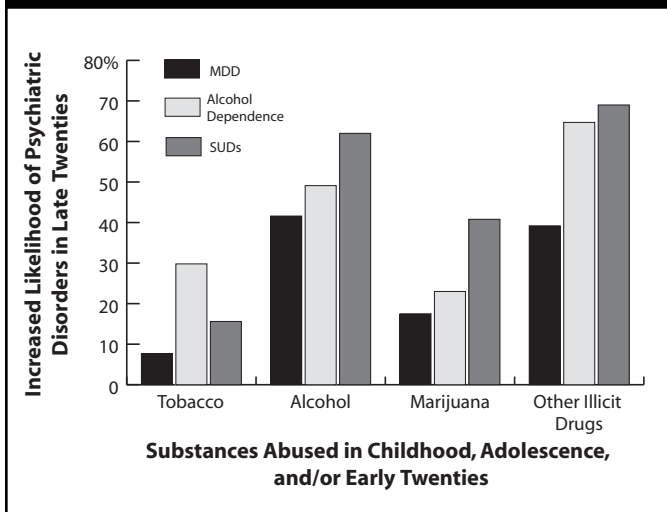
Researchers from the City University of New York randomly selected 736 survey participants in 1975 as part of an effort to identify the health needs of children in Albany and Saratoga, New York. The ratio of boys to girls in the study reflected that of the population of children in both cities, as did the level of family intactness, family income, and parents' education level. The children were, on average, 6 years old when the study began.

Eight years later, Dr. Judith S. Brook and Dr. Cohen acquired the original data set and study population with support from NIDA and the National Institute of Mental Health (NIMH). Subsequent interviews were completed at approximately 5-year intervals. Participants were asked about tobacco, alcohol, marijuana, and other illicit drug abuse during each set of interviews, and psychiatric disorders were measured.

“Overall, alcohol and substance abuse during the early years was significantly related to later psychiatric disorders, even after we statistically controlled for age, sex, parents' education level, family income, and episodes of prior psychiatric symptoms,” says Dr. Brook. “The cumulative frequency of substance abuse from childhood through early adulthood is strongly associated with episodes of MDD, alcohol dependence, and SUDs in the late twenties.”

Earlier marijuana and tobacco use were each more strongly related to participants' development of MDD in their late twenties than more recent use of these substances. However, the opposite was true for alcohol use and other illicit drug use—recent use was more strongly related to development of MDD in the late twenties. The relationship between earlier use of all four substances—tobacco, alcohol, marijuana, and other illicit drug use—was more

Early Substance Abuse Increases Likelihood of Developing Psychiatric Disorders in Late Twenties



Longitudinal study participants who abused tobacco, alcohol, marijuana, and other illicit substances in earlier years were more likely to have diagnoses of major depressive disorder (MDD), alcohol dependence, or substance use disorders (SUDs) in their late twenties.

strongly related in every case to later alcohol dependence or SUDs than to later episodes of MDD.

Dr. Brook cites results related to marijuana use as a particularly key finding. Earlier marijuana use showed substantial effects on later incidence of MDD, alcohol dependence, and SUDs—17, 23, and 40 percent more likely, respectively. “Use of marijuana during childhood and adolescence should not be treated as benign, but rather may signal the later development of MDD, alcohol dependence, and SUDs,” she says.


Treatment providers may benefit by considering the relationship between early substance abuse and later psychiatric disorders. “Well-coordinated interventions against the earliest use of drugs may alleviate the physiological and psychosocial problems that are related to adult psychiatric disorders,” says Dr. David W. Brook.

Dr. Leslie Cooper of NIDA’s Division of Epidemiology, Services and Prevention Research agrees that the findings in this study are significant. She cautions, however, that results must be interpreted carefully because the study sample is 92 percent white, with 93 percent of the participants having received at least a 12th-grade education.

Although the sample is not representative of the general population, it was representative of the Northeast’s population when the data were originally collected, she notes. “This longitudinal data set is extremely valuable because it allows us to track the relationship between early drug abuse and later psychiatric disorders,” Dr. Cooper says. “But we can’t generalize these results to other populations. We need to build on this study and gather information on other populations.”

Dr. Brook will continue collecting data on this cohort every 5 years. “We will be able to watch these individuals as they move into their thirties and forties and see how earlier substance use affects their functioning at that age. We can also look at transmission across generations: How will the children of participants fare?”

Source

- Brook, D.W.; Brook, J.S.; et al. Drug use and the risk of major depressive disorder, alcohol dependence, and substance use disorders. *Archives of General Psychiatry* 59(11):1039-1044, 2002. 

Cognitive Deficits in Marijuana Smokers Persist After Use Stops

By Jill Schlabig Williams, NIDA NOTES Contributing Writer

NIDA-funded scientists have found that cognitive impairments resulting from smoking marijuana can last up to at least 28 days after an individual last smoked the drug. The more a person had smoked prior to abstinence, the more profound this impairment, with marijuana smokers with lower IQs faring worse than their higher IQ peers, even if the latter had routinely smoked more of the drug.

NIDA-funded researchers Dr. Karen Bolla from the Johns Hopkins University School of Medicine in Baltimore and Dr. Jean Lud Cadet from NIDA's Intramural Research Program (IRP) admitted marijuana smokers to IRP's Clinical Inpatient Research Unit on Hopkins' Bayview campus, tested them to ensure they abstained from marijuana use throughout their 4-week stay, and gave them a battery of neurocognitive tests at the end of the study.

Twenty-two individuals participated. Their average age was 22, 86 percent were male, and all reported consuming fewer than 14 alcoholic drinks a week. The researchers estimated that the group had been smoking marijuana for an average of 4.8 years. Based on participants' reports of their current levels of marijuana use, the researchers grouped them as light, medium, or heavy smokers. "Determining an exposure index—how many joints participants smoked per week—and looking at the range of use in the study population strengthened our ability to make causal inferences," says Dr. Bolla.

Very heavy abusers smoked an average of 94 joints a week and scored worse than light abusers (average 11 joints per week) on 24 of the 35 neurocognitive tests, even after 28 days of abstinence. The measures on which the heavy abusers had comparative deficits included verbal and visual memory, executive functioning, visual perception, psychomotor speed, and manual dexterity. On some tests, quantity of marijuana use accounted for more than half the variance in test scores. "We found a dose-response relationship," says Dr. Bolla. "The more marijuana people used, the worse they performed on the tests, especially those for memory."

"We know a lot about the acute effects of marijuana use, but researchers are just now beginning to look at the long-term effects," says Dr. Jag Khalsa of NIDA's Center on AIDS and Other Medical Consequences of Drug Abuse. "This study demonstrates that marijuana smoking has chronic, dose-related effects on cognitive impairments up to 28 days after last use. But how long do these effects

persist beyond that point? That's something we have to examine."

"We have shown that marijuana use is associated with persistent detrimental cognitive effects," explains Dr. Bolla. "These results are not attributable to use of other drugs, because participants were excluded for current or past history of significant use of other substances, including alcohol. Marijuana appears to be harmful when smoked in very large quantities."

The study results also suggested that some people are at higher cognitive risk from smoking marijuana than others. Cognitive performance in individuals with lower IQ scores decreased as the number of joints smoked per week increased, while those with higher IQ scores had fewer decrements even as marijuana use increased. "This finding demonstrates the concept of cognitive reserve," says Dr. Bolla. "People with higher IQs do better than those with lower IQs; the fewer cognitive reserves you have, the more impact you will see from a slight change in brain function."

The results of this study are consistent with study findings obtained by Dr. Harrison Pope, Jr., at Harvard University McLean Hospital in Belmont, Massachusetts (see "Studies Show Cognitive Impairments Linger in Heavy Marijuana Users," *NIDA NOTES*, Vol. 11, No. 3). Dr. Pope and his colleagues found that memory and learning problems caused by heavy marijuana smoking lasted for at least a week after use stopped, although the problems disappeared within a month. "Since marijuana has a half-life of 4 days, the neurocognitive effects seen in Dr. Pope's study after 7 days indicate that marijuana does have residual effects," says Dr. Khalsa. "Study differences in longer term effects could be explained by differences in the study population."

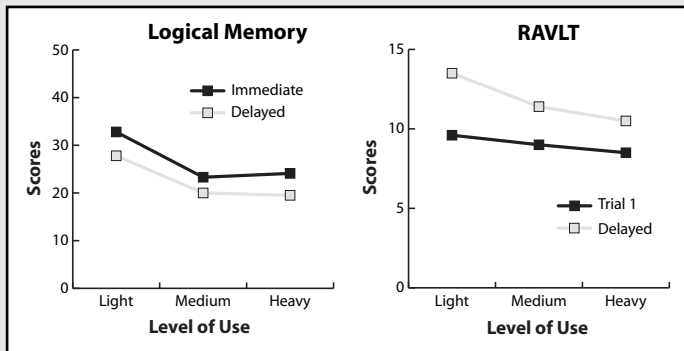
In the Harvard study," Dr. Bolla notes, "participants were older, ranging from age 30 to 55; had higher IQs; were more affluent; and were more likely to be employed. Our inpatient study was conducted in the inner city with a younger, poorer population that used marijuana more heavily. Plus, Dr. Pope measured lifetime episodes of smoking marijuana, not the current number of joints smoked per week." In Dr. Bolla's study, duration of use was associated with a decrease in performance on just one neurocognitive test, which measured participants' ability to copy a complex figure.

Source

- Bolla, K.I., et al. Dose-related neurocognitive effects of marijuana use. *Neurology* 59(9):1337-1343, 2002. **NN**

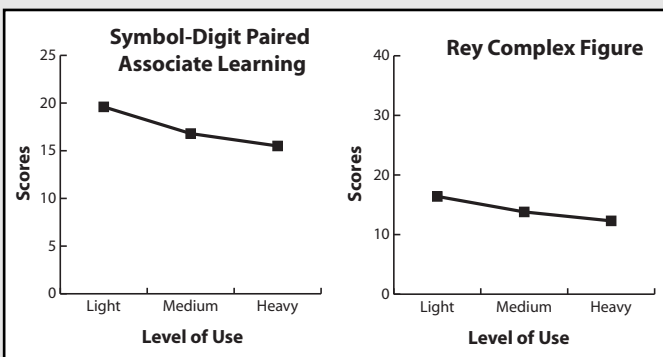
Severity of Cognitive Deficits Varies by Level of Marijuana Use

Verbal Memory. In tests of logical memory, participants were read a paragraph and then asked questions about it immediately and again after 30 minutes. The Rey Auditory Verbal Learning Test (RAVLT) involved listening to 15 words and then repeating them either immediately (Trial 1) or after 30 minutes. The response patterns suggest difficulty with information recall, not with the acquisition or retention of information, according to the researchers.



Heavy marijuana users scored below light users on all measures of verbal memory, although they had no problems recognizing previously learned material.

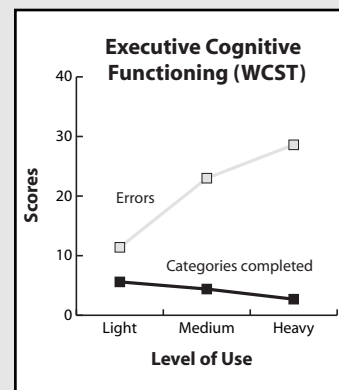
Visual Memory. In the Symbol-Digit Paired Associate Learning test, seven flash cards featuring a symbol and a number were displayed; test subjects were then shown only the symbol and asked to supply the number that originally accompanied that symbol. In the Rey Complex Figure tests, participants were shown a complex figure and asked to draw it from memory.



Heavy marijuana use affected visual learning and memory.

Executive Cognitive Functioning.

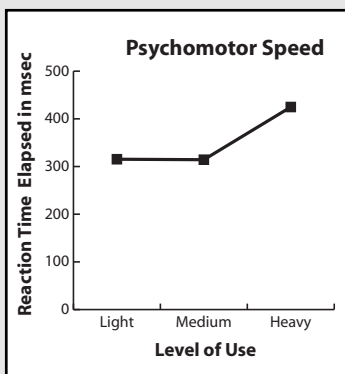
In the Wisconsin Card Sorting Test (WCST), participants are asked to sort cards by three different concepts that the tester changes. This exercise tests the subject's ability to switch cognitive sets based on feedback. Poor performance indicates difficulty incorporating feedback to guide and change incorrect response selection.



Greater marijuana use was associated with lesser executive cognitive functioning.

Psychomotor Speed.

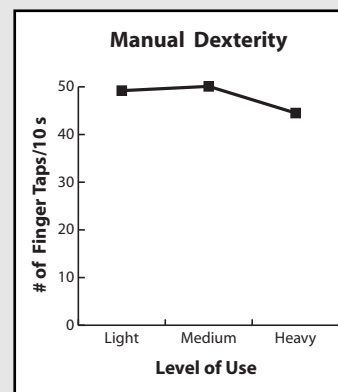
Participants were given the California Computerized Assessment Package (CALCAP) to measure their psychomotor speed. In this test, they were asked to hit a button when they saw a light flash. Reaction time measured the milliseconds that elapsed between the light flashing and the participant hitting the button.



Heavy marijuana users showed slower reaction times on a test of simple reaction time.

Manual Dexterity.

For this test, participants were asked to tap a finger on their left hand. Manual dexterity was determined by the number of taps made in 10 seconds.



Heavy marijuana use was associated with lower performance on manual dexterity measures.

Twins Study Links Early Marijuana Use to Increased Risk of Abuse or Dependence

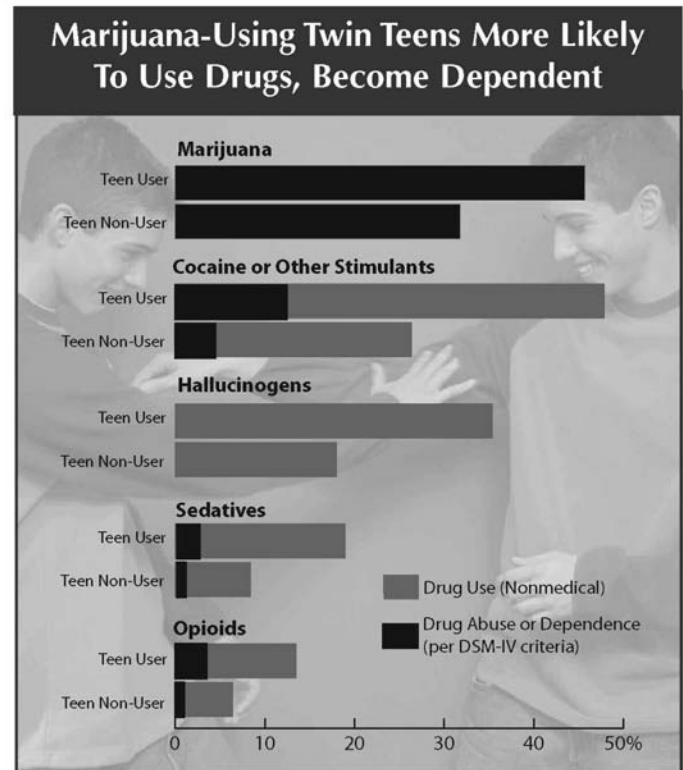
By Patrick Zickler, NIDA NOTES Staff Writer

Many genetic, biological, and environmental factors can influence whether and when an individual initiates drug abuse or develops drug dependence or addiction. One tool that helps scientists isolate and evaluate the effect of different factors is research on twins, who share many inherited biological traits and environmental influences. In a study of more than 300 pairs of same-sex twins, NIDA-supported investigators found that smoking marijuana before age 17 is linked to a greater likelihood of proceeding to serious problems with marijuana or other drugs.

“This finding underlines the significance of early drug initiation,” says Dr. Wilson Compton, director of NIDA’s Division of Epidemiology, Services and Prevention Research. “Identical twins had the same inherited biological characteristics, and fraternal twins shared half their genes. All the twins had common family influences and social environments. Even though they had so much in common, something influenced one twin to take drugs earlier than the other, and that difference had a profound impact on later experience with drugs.”

The same-sex twin pairs grew up in the same households and attended the same schools. In each pair, one twin smoked marijuana before his or her 17th birthday and the other did not. “When we interviewed the twins as adults, the early users were more than twice as likely to have taken other illicit drugs. They also were from two to five times more likely to move on to abuse or dependence on alcohol, marijuana, stimulants, opioids, or sedatives,” says Dr. Michael Lynskey, who conducted the study with colleagues at the Washington University School of Medicine in St. Louis, Missouri; the Queensland Institute of Medical Research in Brisbane, Australia; and the University of Missouri in Columbia.

The researchers asked both members of 2,765 twin pairs included in the Australian Twin Register if they had ever smoked marijuana and, if so, how old they were when they smoked it for the first time. The researchers identified 311 pairs of same-sex twins (average age 30) in which one twin first smoked marijuana before age 17 and the other twin had either never smoked the drug (77 pairs) or did so for the first time at age 17 or older (234 pairs). Of the 311 twin pairs, 136 (74 female, 62 male) were identical and 175 (84 female, 91 male) were fraternal. The



Researchers investigated the drug use patterns of same sex twin pairs in which one twin first smoked marijuana before age 17 and the other either never smoked marijuana or first smoked the drug at age 17 or older. As adults (average age 30), those who had smoked before age 17 were more likely than their siblings to have used other illicit drugs and to develop symptoms of abuse or dependence on marijuana, cocaine or other stimulants, opioids, or sedatives.

interviews were conducted by phone in Australia and the data analyzed by scientists at Washington University and the University of Missouri.

The investigators defined “use” as drug taking on one or more occasions for a nonmedical reason. The researchers defined “abuse” and “dependence” according to criteria adapted from the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*. Abuse was understood to involve taking the drug in physically hazardous situations or circumstances that interfered with major obligations. According to the DSM-IV criteria, twins described as drug- or alcohol-dependent had two or

more of the following symptoms: needing increasingly larger amounts to achieve drug effect, using for longer periods or more frequently than intended, and continuing to use despite associated emotional problems or recurrent desire to cut down use.

Overall, the researchers found, twins who smoked marijuana before age 17 were more than twice as likely as their sibling to use opioids, three times as likely to use sedatives, three times as likely to use cocaine or other stimulants, and nearly four times as likely to use hallucinogens. Those who smoked marijuana before age 17 also were from 1.6 to 6 times as likely to have reported abuse or dependence on alcohol or an illicit drug. Nonetheless, Dr. Lynskey points out, the majority (52 percent) of twins who smoked marijuana before age 17 did not go on to develop abuse or dependence. The increased odds of using other drugs or for developing abuse or dependence were not greater for identical than for fraternal twins, nor for males or females.

“While these study findings indicate that early marijuana use is associated with increased risk of progression to other illicit drug use and possibly to drug abuse or dependence, it is not possible to draw strong causal conclusions solely on the basis of these associations,” Dr. Lynskey cautions. Additional research in other cultures, using a range of research designs, will be needed to determine the causes of the association, he says.

“Given that early initiation of marijuana smoking appears to be associated with increased risks,” says Dr. Lynskey, “there is a need for greater physician awareness of those risks. Focused interventions also are needed to prevent escalation to use of other drugs among young people identified as being at risk.”

Source

Lynskey, M.T., et al. Escalation of drug use in early-onset cannabis users vs. co-twin controls. *Journal of the American Medical Association* 289(4):427-433, 2003. **NN**

Gender and Ethnic Patterns in Drug Use Among High School Seniors

Although rates of marijuana, alcohol, and tobacco use by 12th-grade boys and girls declined over the 25-year period ending in 2000, the “gender gap” in use of these drugs remained largely unchanged. According to data compiled by the annual Monitoring the Future (MTF) survey, senior girls were 77 percent as likely as boys (compared with 78 percent in 1976) to have reported using marijuana in the past month. Girls in the 12th-grade class of 2000 were 64 percent as likely (up from 54 percent in 1976) to have had five or more drinks in a row during the past 2 weeks, and girls and boys were equally likely to be daily smokers.

Ethnic differences in drug use—for boys as well as girls—are much wider than are gender differences. A recently published review of MTF data reveals that these ethnic differences are significant and have persisted since MTF began collecting drug use data in 1976. Key substance use patterns among ethnic groups and gender differences within those groups are presented below.

Smoking

Daily smoking declined among all ethnic groups between 1976 and 1990, then leveled off before beginning to increase modestly between 1996 and 2000. Among ethnic groups, Native Americans were most likely to smoke and African Americans least likely. Within ethnic groups, African-American girls were less likely than boys to be daily smokers.

Alcohol

Girls were less likely than boys to report heavy alcohol use (five or more drinks in a row within the past 2 weeks), and the prevalence for girls and boys over the 25-year period ending in 2000 generally decreased. Among ethnic groups, Native Americans were most likely to report heavy drinking; Asian-American and African-American 12th-graders reported the lowest prevalence. No significant gender differences in alcohol use emerged within ethnic groups.

Substance Use Among High School Seniors, 1976-2000*

	12th-Grade Females					12th-Grade Males				
	'76-'80	'81-'85	'86-'90	'91-'95	'96-'00	'76-'80	'81-'85	'86-'90	'91-'95	'96-'00
Daily Cigarette Smoking										
White	28.8	23.6	22.6	22.2	27.2	24.4	18.6	19.2	22.3	26.3
Black	20.8	12.2	5.8	3.4	5.1	21.9	10.8	7.7	6.5	10.9
Mexican American	15.6	13.2	8.4	9.3	11.0	19.1	13.2	11.8	12.6	15.1
Puerto Rican/**	18.0	15.0	12.4	15.2	17.9	18.7	13.7	12.4	22.5	23.4
Other Latin American				10.8	9.8				8.9	15.3
Asian American	13.3	10.2	8.0	8.6	10.1	14.5	11.5	10.8	12.9	14.3
Native American	49.8	39.8	30.5	34.2	34.2	38.7	30.8	25.7	32.4	24.7
Heavy Alcohol Use Within Past 2 Weeks										
White	32.1	34.1	30.8	24.6	28.0	53.4	52.9	46.8	39.7	42.4
Black	12.1	11.1	8.6	7.6	8.3	27.5	24.8	22.9	19.9	18.0
Mexican American	25.0	26.8	21.4	19.6	23.4	52.0	48.3	44.1	38.8	40.6
Puerto Rican/**	21.9	18.5	13.0	16.2	18.0	36.6	34.6	30.3	34.2	27.0
Other Latin American				15.5	19.4				26.7	32.6
Asian American	14.7	11.4	9.0	8.2	11.1	28.4	22.4	19.4	15.2	18.9
Native American	40.9	38.3	30.8	26.9	32.5	62.8	57.6	46.8	46.2	41.5
Marijuana Use Within Past 30 Days										
White	30.8	24.6	17.9	15.0	20.8	40.4	31.6	22.5	19.7	26.0
Black	22.1	20.1	7.2	6.8	12.7	36.6	29.2	14.6	15.9	26.6
Mexican American	25.9	21.2	11.7	10.5	18.7	39.8	36.9	19.5	19.9	29.3
Puerto Rican/**	19.5	14.4	8.7	10.8	20.7	34.7	22.7	17.2	26.4	26.7
Other Latin American				11.0	12.9				13.7	19.6
Asian American	18.3	13.8	5.2	5.1	9.1	31.2	13.0	9.8	9.0	16.0
Native American	44.7	30.3	19.7	21.5	32.0	50.9	36.1	26.6	25.5	27.2

*Percentage prevalence shown as the mean for each 5-year span.

**Beginning in 1990, the data distinguish between Puerto Rican and Other Latin American.

Marijuana

Overall, 12th-grade boys in all ethnic groups were somewhat more likely than girls to have used marijuana within the past 30 days. Prevalence rates for girls and boys declined between 1976 and 1990, held steady until 1995, and increased between 1996 and 2000. Among ethnic groups, Native Americans were most likely and Asian Americans least likely to have used marijuana within the past month.

Source

- Wallace, J.M., et al. Gender and ethnic differences in smoking, drinking and illicit drug use among American 8th, 10th and 12th grade students, 1976-2000. *Addiction* 98(2):225-234, 2003. **NN**

Youths' Opportunities To Experiment Influence Later Use of Illegal Drugs

By Kimberly R. Martin, *NIDA NOTES* Contributing Writer

NIDA-supported researchers have reported new epidemiological evidence about the associations linking earlier alcohol or tobacco use with later use of marijuana, and the link from earlier marijuana use to later use of other illegal drugs such as cocaine and hallucinogens. This study builds on the many prior NIDA-supported studies of the "gateway" theory of youthful drug involvement: Once use of tobacco or alcohol begins, there is greater likelihood of marijuana use, and once marijuana use begins, there is greater likelihood of other illegal drug use.

"This research increases our understanding of the complex relationship between the different stages of drug use and raises concerns about factors that promote the transition from opportunities to initiate drug use to patterned use," says Dr. Kathleen Etz of NIDA's Division of Epidemiology, Services and Prevention Research. "We know that earlier drug use is associated with later, more advanced use; however, this research identifies a previously overlooked aspect of this transition, opportunities to use."

Using annual data from the 1991 through 1994 National Household Survey on Drug Abuse (NHSDA), the research team, led by Dr. James C.

Anthony from Johns Hopkins University Bloomberg School of Public Health in Baltimore, analyzed the responses of 26,015 individuals aged 12 to 18 who answered questions regarding marijuana use and the responses of 44,624 individuals aged 12 to 25 who answered questions regarding cocaine use. The research focused on a concept called "drug exposure opportunities." This concept takes into account that some young people actively seek out opportunities to try marijuana or cocaine, whereas others are more passive recipients of drug exposure opportunities.

The researchers found that alcohol and tobacco users were more likely than nonusers to have an opportunity to try marijuana and were also more likely to try the drug when the opportunity arose. About 75 percent of alcohol or tobacco users reported an opportunity to try marijuana by

age 18, and more than 85 percent of them made the transition to marijuana use. Only about 25 percent of non-smokers and nondrinkers were given an opportunity to try marijuana by the same age. Of these, fewer than 25 percent began smoking marijuana within 6 years after they were first given the opportunity. Overall, alcohol or tobacco users were seven times more likely to start using marijuana than individuals who had used neither alcohol nor tobacco.

Prior marijuana use was closely associated with the opportunity to try cocaine and the likelihood of young people's starting to use cocaine once given the opportunity. Among the young people who were given the chance to try cocaine, those who were already using marijuana were 15 times more likely to use cocaine than those who did not use marijuana.

About 50 percent of marijuana users used cocaine within 2 years of their first opportunity to do so. However, among young people who never used marijuana, fewer than 10 percent initiated cocaine use.

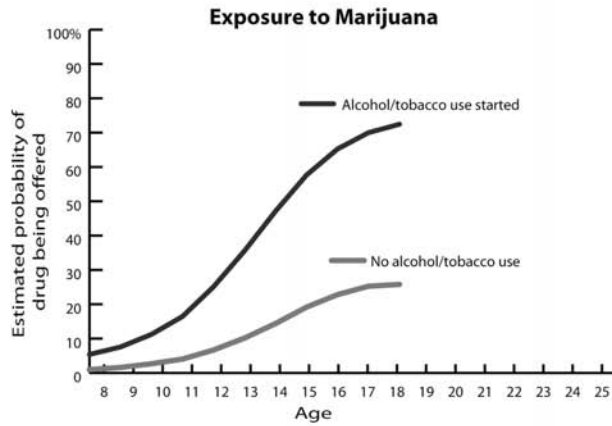
In a separate but related study, the researchers analyzed data from 41,271 young people who participated in the 1991 through 1994 NHSDA, investigating the relationship between the use of marijuana and

Prior marijuana use was closely associated with the opportunity to try cocaine and the likelihood of young people's starting to use cocaine once given the opportunity.

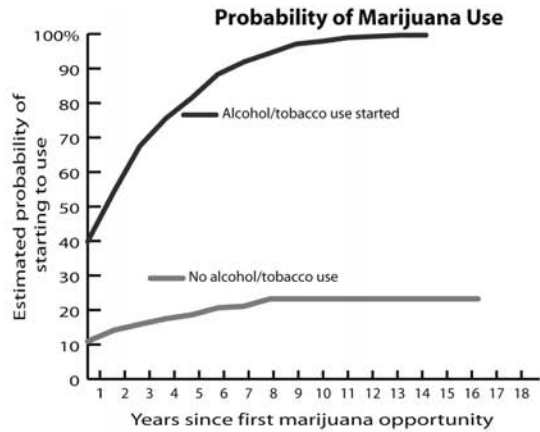
use of hallucinogens. The results showed that marijuana users are more likely than nonusers to be offered an opportunity to use LSD, mescaline, mixed stimulant-hallucinogens, and PCP and more likely than nonusers to try these hallucinogenic drugs when they're offered. By age 21, nearly one-half of the teenagers who had smoked marijuana were presented with the opportunity to try hallucinogens, compared to only one-sixteenth of those who had not used marijuana. Once given the opportunity to use hallucinogens, marijuana smokers were about 12 times more likely to use hallucinogens than those who did not use marijuana.

"These studies are the first to support the idea of two separate mechanisms linking the use of alcohol, tobacco, marijuana, cocaine, and hallucinogens—one mechanism

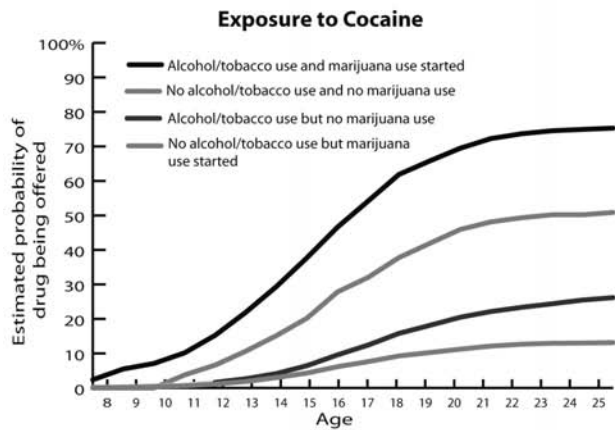
Drug Use Associated With More Opportunities To Use, Higher Rates of Acceptance



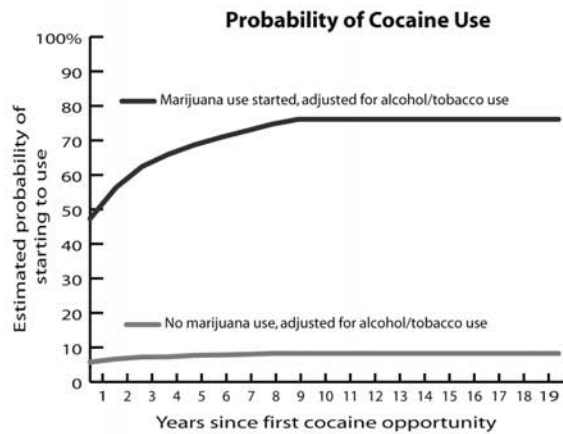
The likelihood that a non-smoking, nondrinking 14-year old will be exposed to marijuana is only 14 percent, but the odds jump to 47 percent for a user of alcohol or tobacco.



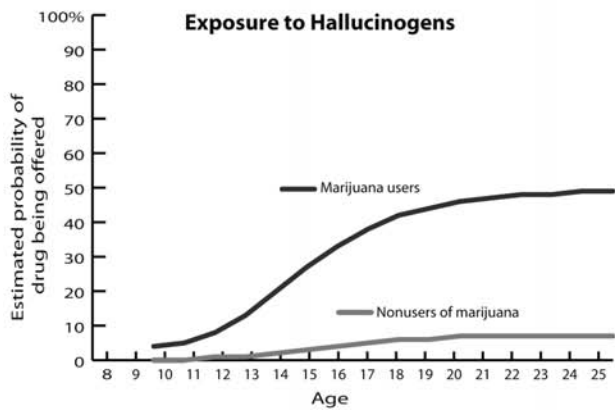
Among nonsmoking, nondrinking youth, 11 percent will be marijuana users 1 year after their first exposure to marijuana, compared to 40 percent of alcohol/tobacco users. Over time, the likelihood of marijuana use for the alcohol/tobacco users climbs to greater than 95 percent.



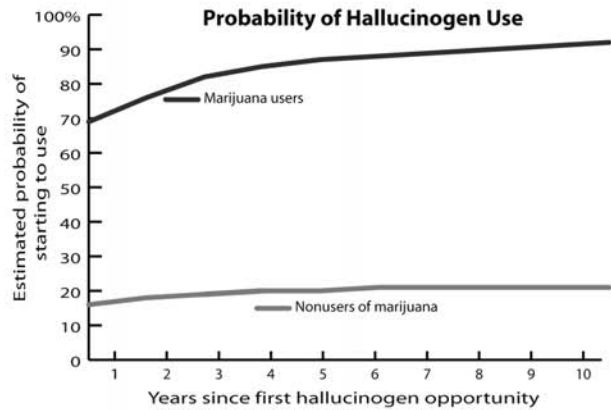
A 14-year-old user of tobacco or alcohol and marijuana is 10 times more likely to be exposed to cocaine than a nonsmoking nondrinker.



Having been exposed to cocaine, fewer than 1 in 10 nonusers of marijuana will use cocaine, compared to 50 to 75 percent for marijuana users.



Although fewer than 5 percent of nonusers of marijuana are exposed to hallucinogens, the likelihood jumps to nearly 50 percent for marijuana users over time.



Fewer than one in five nonusers of marijuana who are exposed to hallucinogens will use hallucinogens, but 70 to 90 percent of marijuana users will try hallucinogens.

Sources: Wagner and Anthony, American Journal of Epidemiology, 2001; Wilcox et al., Drug and Alcohol Dependence, 2002.

involving increased drug exposure opportunity, and a separate mechanism involving increased likelihood to use once the opportunity occurs,” says Dr. Anthony. “Even if there is an underlying common vulnerability or predisposition that accounts for the observed sequencing of drug exposure opportunities and actual drug use, these observations may have implications for the design and evaluation of drug prevention activities. Drug users often are members of social circles where drug use and experimentation are more common and friends are likely to share drugs. In addition to trying to persuade young people not to use drugs, it may be worthwhile for us to persuade users not to share their drugs with friends.” Previous research has also shown that although males are more likely than females to have opportunities to use drugs, both are equally likely to make a transition into drug use once an opportunity to try a drug has occurred. Dr. Anthony and his colleague, Dr. Fernando Wagner, also from Johns Hopkins University Bloomberg School of Public Health, have made similar observations in ongoing research studies.

Dr. Anthony believes that his research carries a strong message for parents and pediatricians, who often neglect the opportunity to ask children and adolescents about whether they have had chances to try illegal drugs. As Dr.

Anthony notes, “Kids will talk to us about their chances to try illegal drugs even when they are unwilling to talk about actual drug use. Once the chance to try marijuana or cocaine occurs, it is a red flag, and we need to be paying close attention to what happens next.”

“Future research in this area will be a great asset to the development of effective drug prevention programs,” says Dr. Etz. “It will assist us in understanding the process through which the use of one drug is related to use of another and help us to target prevention programs to individuals more likely to progress to advanced substance use.”

Sources

- Wagner, F.A., and Anthony, J.C. Into the world of illegal drug use: Exposure opportunity and other mechanisms linking the use of alcohol, tobacco, marijuana, and cocaine. *American Journal of Epidemiology* 155(10):918–925, 2001.
- Wilcox, H.C.; Wagner, F.A.; and Anthony, J.C. Exposure opportunity as a mechanism linking youth marijuana use to hallucinogen use. *Drug and Alcohol Dependence* 66(2):127–135, 2002. **NN**

Teen Drug Use Declined in 2002, Report Shows

By Patrick Zickler *NIDA NOTES* Staff Writer

Drug use by American teenagers declined in a broad range of categories during 2002, according to the latest Monitoring the Future survey. Use of MDMA (ecstasy) dropped for the first time since it was added to the annual survey in 1996, and marijuana use declined to its lowest level in 8 years. The numbers of 8th-10th- and 12th-graders who said they had smoked cigarettes in the month preceding the survey fell by 12 percent, 17 percent, and 10 percent, respectively.

“Our science-based education and prevention efforts are paying off,” said NIDA Acting Director Dr. Glen Hanson at a press conference announcing the 2002 survey findings. “Teenagers are considering the information in the messages before deciding whether or not to use drugs, and they are making better decisions. In this survey we see that teenagers are increasingly choosing not to use marijuana, not to use ecstasy and other club drugs, not to begin

smoking or using alcohol. They should be congratulated.”

The Monitoring the Future survey (MTF) is conducted annually by the University of Michigan’s Institute for Social Research and has

been supported by NIDA throughout its 27-year history. The survey tracks illicit drug use and attitudes toward drugs among 8th-, 10th-, and 12th-grade students. The 2002 study surveyed a representative sample of more than 43,000 students in 394 schools across the Nation. Students are asked about their attitudes toward drugs (Do they perceive a risk associated with trying the drug? Do they approve or disapprove of someone’s trying the drug?) and about lifetime, past-year, and past-month drug use. (“Lifetime” refers to use at least once during a respondent’s lifetime. “Past year” refers to an individual’s drug

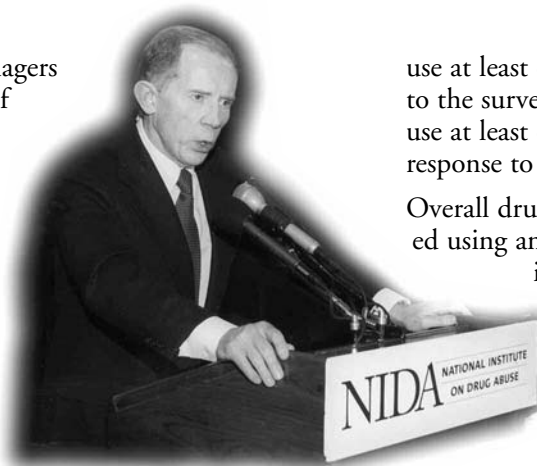
use at least once during the year preceding their response to the survey. “Past month” refers to an individual’s drug use at least once during the month preceding their response to the survey.)

Overall drug use—the proportion of students who reported using any illicit drug in the preceding year—declined in grades 8 and 10. “This is the first time since 1998 that we have seen a significant decline in overall illicit drug use among 10th-graders,” said Dr. Lloyd Johnston, MTF principal investigator.

MTF results for 2002 show that teenagers’ attitudes about drugs are changing. Compared with 2001, this year more students in grades 10 and 12 said they believed use of MDMA once or twice is harmful, and the proportion of students who said they disapproved of trying MDMA increased in all three grades. “We are gratified, but not satisfied. NIDA will continue to generate and disseminate science-based information that leads to increases in understanding of the harm that comes from drug use,” said Dr. Hanson.


“These changes in perceived risk and disapproval are encouraging indicators of future downturns in drug use,” Dr. Johnston observed. “This has proven to be the case with ecstasy. In 2000, only 38 percent of seniors said there was great risk of harm associated with trying ecstasy. That jumped to 48 percent in 2001 and increased again to 52 percent in 2002. These unusually rapid changes no doubt reflect the effects of media coverage of adverse events as well as NIDA’s efforts to document and disseminate information about the adverse consequences of using ecstasy.”

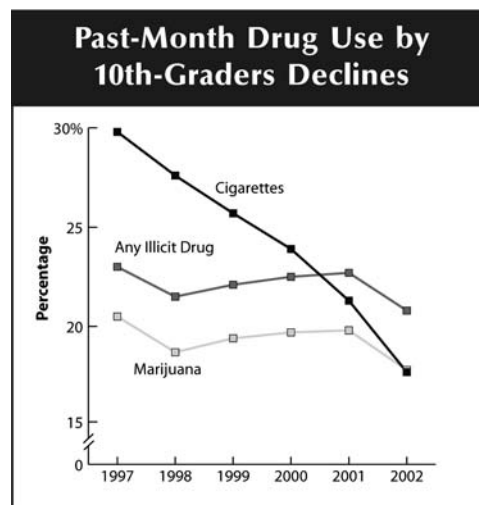
Similarly, the decreases in smoking reported for 2002 follow increases in the proportion of students who perceived a negative image of smoking. Roughly half of students in all three grades said they strongly agree with the statement “I dislike being near people who are smoking.” Perhaps more important to teens, Dr. Johnston noted, is the social implication of changing attitudes toward smoking. “Roughly three-quarters of boys and girls in all three grades said they prefer to date nonsmokers. It now appears that taking up smoking makes a youngster less attractive, just the opposite of what cigarette advertising has been promising.”



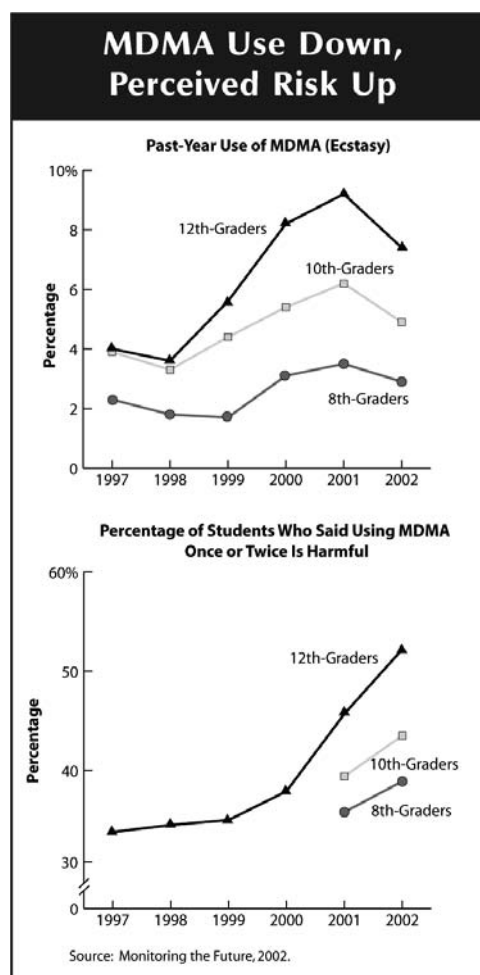
Significant changes reported in the 2002 MTF survey include the following:

- **Marijuana**—Among 10th-graders, marijuana use in the past year and past month decreased, and daily use in the past month was down. Past-year use decreased from 32.7 percent to 30.3 percent; past-month use went from 19.8 percent to 17.8 percent; and daily use in the past month declined from 4.5 percent to 3.9 percent.
- **Cocaine**—Crack use showed a significant increase in past-year use among 10th-graders, returning to around its 2000 level following a decline in 2001. For 2002, 2.3 percent of 10th-graders reported past-year use of crack cocaine, compared with 1.8 percent in 2001 and 2.2 percent in 2000.
- **Opiates**—For the first time, MTF asked students about nonmedical use of the prescription painkillers OxyContin and Vicodin. Past-year use of OxyContin without a doctor's order was reported by 1.3 percent of 8th-graders, 3.0 percent of 10th-graders, and 4.0 percent of 12th-graders. Nonmedical use of Vicodin in the past year was reported by 2.5 percent of 8th-graders, 6.9 percent of 10th-graders, and 9.6 percent of 12th-graders.
- **Inhalants**—Lifetime, past-year, and past-month use of inhalants decreased among 8th-graders, and lifetime use decreased among 10th-graders. Lifetime use went from 17.1 percent in 2001 to 15.2 percent in 2002 among 8th-graders and from 15.2 percent to 13.5 percent among 10th-graders.
- **LSD**—LSD showed major changes from 2001 to 2002. Rates of use decreased markedly in each grade and reporting period. Past-year use, for example, declined from 6.6 percent to 3.5 percent among 12th-graders, from 4.1 percent to 2.6 percent among 10th-graders, and from 2.2 percent to 1.5 percent among 8th-graders. These are the lowest rates of LSD use in the history of the survey for each grade.
- **Club Drugs**—Rates of MDMA (ecstasy) use decreased significantly among 10th-graders. Their past-year use declined from 6.2 percent to 4.9 percent, and past-month use went from 2.6 percent to 1.8 percent.

Findings from the 2002 MTF report are available through NIDA's Web site, www.drugabuse.gov, and at the MTF Web site, <http://monitoringthefuture.org>. 



Monitoring the Future survey results show that teen drug use declined in 2002. Tenth-grade students reported significant reductions in overall drug use and in use of marijuana and cigarettes.



Use of MDMA (ecstasy) declined sharply among all teenagers in 2002, reversing 3 years of increased use. The decrease in use follows increased perception among teens that MDMA use has harmful consequences.

Study Demonstrates That Marijuana Smokers Experience Significant Withdrawal

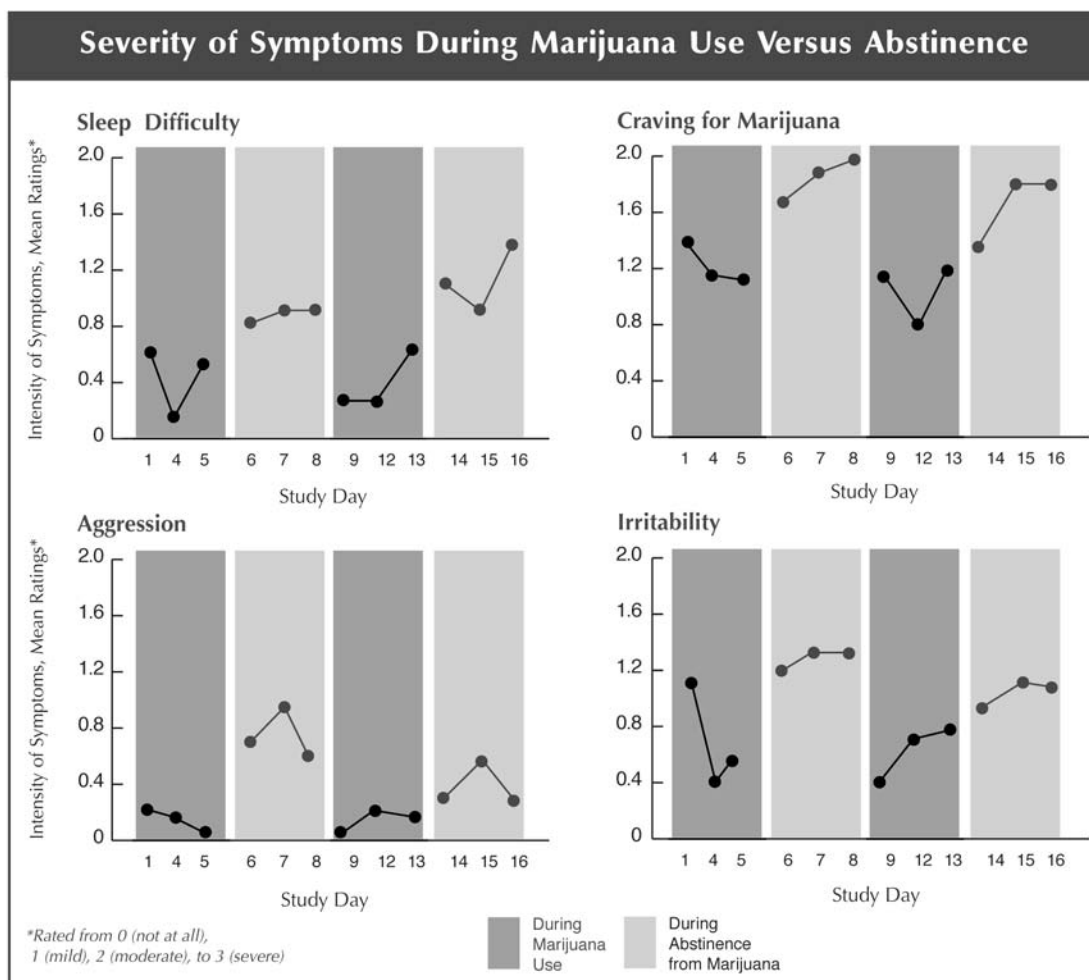
By Patrick Zickler, NIDA NOTES Staff Writer

Animal research and controlled studies of marijuana smokers during inpatient treatment suggest that marijuana dependence, like dependence on other addictive drugs, is associated with withdrawal symptoms—such as irritability, anger, depressed mood, headaches, restlessness, lack of appetite, and craving—that can make it difficult to stop using the drug.

Now, NIDA-supported research conducted by Dr. Alan Budney and colleagues at the University of Vermont in

Burlington has found that marijuana smokers who stop using the drug while in their home environment suffer withdrawal symptoms that appear as severe as those associated with tobacco-smoking.

“These findings represent a significant step toward general acceptance of withdrawal as a key aspect of chronic marijuana use,” says Dr. Jag Khalsa of NIDA’s Center on AIDS and Other Medical Consequences of Drug Abuse. Treatment providers may not address the problem of



Marijuana smokers living at home reported “clinically significant” withdrawal symptoms—such as sleep difficulty, marijuana craving, aggression, and irritability—during periods of abstinence from the drug. The participants’ self-reports were confirmed, in part, by observers who reported increased restlessness and irritability among the marijuana users when they were not smoking.

marijuana withdrawal because the condition is not currently included in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*, the standard reference published by the American Psychiatric Association.

Dr. Budney and his colleagues evaluated withdrawal symptoms in 12 adult marijuana smokers (7 male, 5 female, average age 30 years) over 3-day abstinence periods that followed 5-day periods when participants could smoke marijuana at will. “We found consistent emotional and behavioral symptoms that increased during abstinence and dramatically decreased when marijuana smoking resumed, suggesting that these types of symptoms are the hallmark of acute marijuana withdrawal,” Dr. Budney says. “The symptoms most closely resembled many of those observed during nicotine withdrawal.”

During the study, participants lived at home and made daily records rating the intensity of withdrawal symptoms (on a scale from 0, “not at all,” to 3, “severe”) over the preceding 24 hours. In addition, each participant designated an observer—a friend or family member who spent at least 2 hours each day with the participant—to provide an independent rating of the participant’s withdrawal symptoms. The participants made daily laboratory visits during which their abstinence was confirmed by urine tests.

During the abstinence periods, participants reported increases in the severity of craving and sleep difficulty, decreased appetite, and increased aggression, anger, and irritability. In addition, participants reported an increase in “strange dreams” during the second abstinence period. Observers reported increased irritability and restlessness among the participants during abstinence.

“Marijuana withdrawal doesn’t include dramatic physical symptoms such as the pain, nausea, heavy sweating, and cramps associated with opiate withdrawal. Nevertheless, the symptoms of marijuana withdrawal appear clinically significant. It seems clear now that withdrawal from marijuana produces identifiable behavioral and emotional distress that may be as important as, if not more important than, physical symptoms in the development of dependence and undermining attempts to quit using the drug,” Dr. Budney says.

“Confirming withdrawal as part of marijuana dependence will increase the likelihood that treatment providers will alert patients to its symptoms and will help them cope with it through behavioral or pharmacological treatments,” says Dr. Khalsa.

Source

- Budney, A.J.; Hughes, J.R.; Moore, B.A.; Novy, P.L. Marijuana abstinence effects in marijuana smokers maintained in their home environment. *Archives of General Psychiatry* 58(10):917-924, 2001. **NN**

Cannabinoid Antagonist Reduces Marijuana's Effects in Humans

By Patrick Zickler, NIDA NOTES Staff Writer

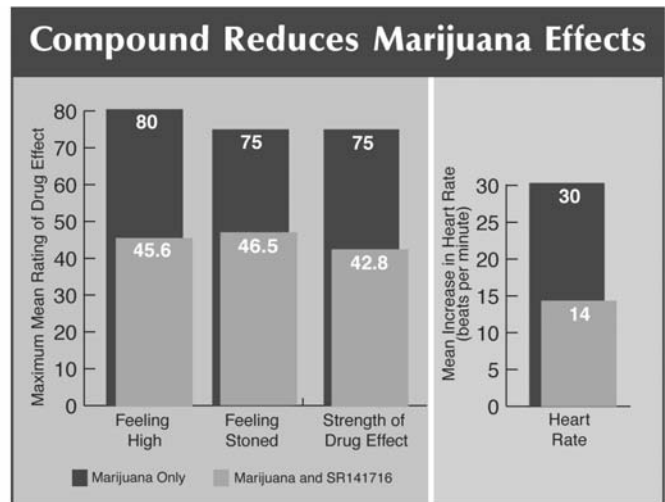
Marijuana smokers treated with an experimental compound reported reduced highs and had smaller heart rate increases than untreated smokers in a recent study at NIDA's Intramural Research Program (IRP) in Baltimore. The finding confirms the pivotal role played in marijuana intoxication by certain structures—called cannabinoid receptors—on brain cells. In addition, the study suggests that the compound, called SR141716, may be useful as a medication to help marijuana smokers quit. (See also, "Study Opens Promising New Approach to Developing Medications To Prevent Relapse to Cocaine Use," in this issue).

Marijuana, like other psychoactive drugs, achieves its effects by attaching to nerve cells in the brain and altering their function. The main psychoactive component of marijuana, tetrahydrocannabinol (THC), attaches to cannabinoid receptors. Animal studies have led scientists to believe that a particular type of cannabinoid receptor is the site at which THC initiates the effects that produce marijuana intoxication.

"Studies have shown in laboratory animals that the CB-1 cannabinoid receptors, which are found in high densities in regions of the brain associated with attention, motor control, and reasoning, play a major role in the effects of marijuana. However, until our study, this had not been confirmed in humans," says Dr. Marilyn Huestis, an IRP researcher.

To evaluate the role of human CB-1 receptors, Dr. Huestis and her colleagues studied the effects of SR141716 in 63 adult men with a history of smoking marijuana. The compound was developed by Sanofi-Synthelabo, Inc., of Malvern, Pennsylvania, and clinical testing of the compound in marijuana users was conducted through a Cooperative Research and Development Agreement with NIDA. SR141716 has effectively blocked the effects of marijuana at CB-1 receptors in studies involving rats, pigeons, and monkeys. Participants in the NIDA research received doses of 1, 3, 10, 30, or 90 mg SR141716 or placebo. Two hours later, they smoked a marijuana cigarette containing THC or a marijuana cigarette without THC. Immediately after smoking and up to 65 minutes later, participants rated the strength of marijuana's effects on a scale ranging from 0 (no effect at all) to 100 (extremely strong effect).

"Participants who received the 90-mg dose of SR141716 reported 40 to 75 percent less drug effect than those who



Participants received either placebo or active SR141716 before smoking marijuana and were then asked to describe, on a scale from 0 (not at all) to 100 (extremely), "How high do you feel now?" "How stoned on marijuana are you now?" and "How strong is the drug effect you feel now?" SR141716 (90 mg) reduced the maximum mean rating of the drug effects. Participants who received SR141716 also experienced smaller increases in heart rate after smoking marijuana.

didn't receive the compound. Those who received lower doses of the compound also reported less drug effect," Dr. Huestis says. "This demonstrates, first, that CB-1 receptors play a major role in THC's effects in humans and, second, that SR141716 can be used to at least partially block the drug's effects."

In addition to its psychological effects on humans, marijuana increases the heart rate. Heart rates of men who smoked marijuana with THC but received no SR141716 increased by roughly 30 percent above baseline within 10 minutes of smoking marijuana and were 15 percent higher at 1 hour after smoking. Increases in heart rate after marijuana with THC was smoked were diminished in a dose-related manner by SR141716.

Blood tests showed that men who smoked marijuana with THC and who received 90 mg SR141716 had blood concentrations of THC similar to those of participants who did not receive SR141716. This demonstrates that reduction of marijuana's effects is attributable not to any effect of SR141716 on THC concentration, but to blockade of CB-1 receptors, Dr. Huestis says.

Because SR141716 partially blocks THC's intoxicating effects, the compound may prove valuable in treating

marijuana addiction, the researchers say. If marijuana does not provide its usual high, patients in treatment would be less tempted to smoke it and less vulnerable to relapse. To evaluate the compound's role as a medication, NIDA researchers currently are studying SR141716's ability to reduce the effects of THC when given in repeated doses over 2 weeks. Other NIDA-supported research suggests that a different formulation of the compound may be effective in treatment of cocaine addiction (see this issue's "Study Opens Promising New Approach to Developing Medications To Prevent Relapse to Cocaine Use").

In addition, Sanofi-Synthelabo is investigating the compound's possible effects on other disorders related to cannabinoid receptors, such as increased appetite and food intake, and in smoking cessation treatment.

Source

- Huestis, M.A., et al. Blockade of effects of smoked marijuana by the CB1-selective cannabinoid receptor antagonist SR141716. *Archives of General Psychiatry* 58(4):322-328, 2001. **NN**

Shortened Family Prevention Programs Yield Long-Lasting Reductions in Adolescent Drug Abuse

By Robert Mathias, NIDA NOTES Staff Writer

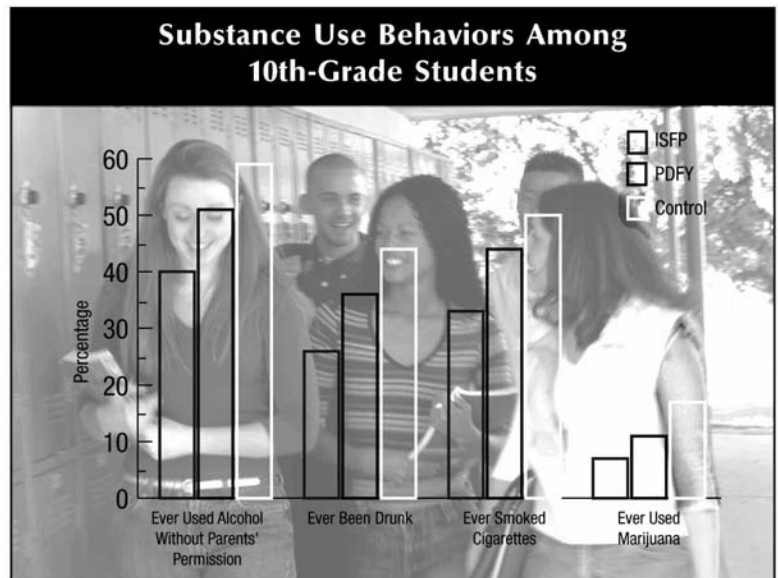
Two brief family-focused drug abuse prevention programs have produced long-term reductions in substance abuse among adolescents in rural Iowa public schools who were assigned to the programs in the sixth grade, a study funded by NIDA and the National Institute of Mental Health has shown. The programs may offer communities a practical approach to effective family-based drug abuse prevention.

The longer of the two programs reduced the proportion of students who used any marijuana, tobacco, or alcohol in grades 6 through 10 as well as students' current use of alcohol and tobacco. The shorter program decreased alcohol use among 10th-graders significantly, along with reducing lifetime substance use behaviors.

"The study demonstrates that brief family interventions can reduce drug use among young people during the high-risk years when they are making the transition from childhood to adolescence," says Dr. Richard Spoth of Iowa State University in Ames, who led the study. Reducing the number of children who begin substance use during these years may have important public health benefits because early initial use is associated with higher rates of substance dependence in later adolescence and young adulthood, he says.

A total of 667 families of sixth-graders from 33 public schools in Iowa were recruited for the study. The children's schools were randomly assigned to either a five-session program called Preparing for the Drug Free Years (PDFY), a seven-session Iowa Strengthening Families Program (ISFP), or a control group. The two programs were designed for families with young adolescents. The ISFP was adapted from a more extensive program that had previously been evaluated in a variety of settings and with several racial and ethnic groups.

"The purpose of modifying longer programs and trying to replicate their results in new settings is to make them more practical for communities to implement and for families to participate in them," notes Dr. Elizabeth Robertson of NIDA's Division of Epidemiology, Services and Prevention Research. "The fact that the adapted programs achieved very positive results indicates they can be whittled down and still maintain their effectiveness," she says.

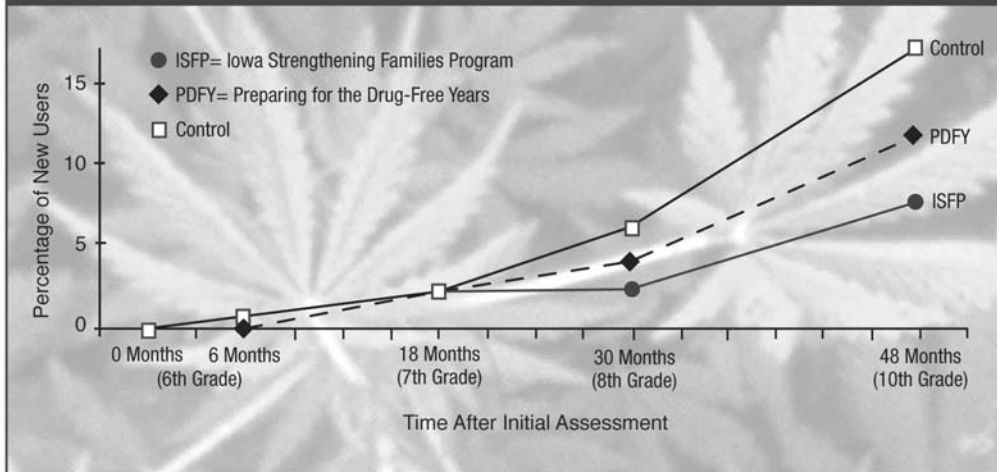


Lower percentages of ISFP and PDFY 10th-graders than control students had initiated a number of substance abuse behaviors involving use of alcohol, cigarettes, and marijuana 4 years after they had received the programs in the 6th grade.

Staff members from the Iowa Cooperative State Research, Education, and Extension Service of the U.S. Department of Agriculture worked with community facilitators to implement either PDFY or ISFP in a total of 22 schools with 459 families whose family, school, and community characteristics had previously been assessed. Eleven schools with 208 comparable families were assigned to a control group that was mailed leaflets on adolescent development and parent-child relationships. The programs were delivered in weekly evening sessions to participating families at the schools. Parents in PDFY attended four sessions and were joined by their children for a final joint session. In the relatively more intensive ISFP, parents and children attended both separate and joint sessions for 6 weeks and a final joint session. The weekly PDFY and ISFP sessions sought to improve how parents and children functioned individually and as a family in a variety of situations. Both programs taught skills such as effective parenting, appropriate management of family conflicts, and how to resist peer pressure. The development of such skills has been linked to delayed onset or reduction of substance abuse.

Four years after 6th-grade students had received the programs, the researchers interviewed them and found that

Brief Family Programs Reduce Rates of Marijuana Initiation Over 4-Year Study



Initiation of marijuana use occurred at a slower rate among students who participated in the ISFP and PDFY programs than among those in the control group.

significantly lower percentages of ISFP than control 10th-graders had ever initiated any of five substance abuse behaviors. Specifically, lower percentages of ISFP students than controls had begun to use alcohol, cigarettes, or marijuana; had ever used alcohol without parental permission; or had become drunk. The proportion of new marijuana users in the control group was 2.4 times greater than it was among ISFP youths. Similarly, the proportion of controls who had been drunk or smoked cigarettes were 1.7 and 1.5 times greater than they were among ISFP youths. Participants in the PDFY program also showed lower rates of initiation of all five substance use behaviors than controls, but only the differences in lifetime drunkenness and marijuana use approached statistical significance. Nevertheless, the rates of new marijuana use and ever getting drunk were 1.5 and 1.2 times greater for controls than they were for PDFY youths. Actual rates of substance use behaviors among 10th-graders in all three groups are shown in the illustration on the preceding page.

Among those 10th-graders in the three groups who had begun to use alcohol, tobacco, or marijuana, the study found lower proportions of PDFY and ISFP students than controls had used alcohol and tobacco in the preceding month and marijuana during the preceding year. For example, frequency of past-month alcohol use among

PDFY and ISFP students was about two-thirds that of controls. Among ISFP students, past-month cigarette use was approximately half that of control group students.

“Developmental timing is an important factor in the long-term effects of these interventions,” Dr. Spoth says. “Intervening at this time, in the sixth grade when kids are experimenting with substances, probably contributes greatly to the positive effects,” he says. The careful design of the interventions with their theory-based focus on parenting and family interactions also is important, he adds.

The critical element affected by both programs is the parent component, says NIDA’s Dr. Robertson. “When you provide parents with information about what to expect of children at that age, what is typical and what is not, and how to deal with some of the problems, you are shaping how parents relate to their children. Changing the family context can have a long-lasting effect because you are positively influencing the day-to-day environment of the child over a long period of time,” she says.

Whether the findings of this study would apply to more diverse populations in other settings remains an open question, Dr. Robertson says. However, the original programs from which the critical elements in these programs were derived have been successfully tested in a variety of settings, she notes. In addition, the ISFP has been adapted for and is now being tested with urban and rural African-Americans and Native American families.

Source

- Spoth, R.L.; Redmond, C.; and Shin, C. Randomized trial of brief family interventions for general populations: Adolescent substance use outcomes 4 years following baseline. *Journal of Consulting and Clinical Psychology* 69(4):627-642, 2001. **NN**

Chronic Marijuana Abuse May Increase Risk of Stroke

Dr. Ronald I. Hering and Dr. Jean Lud Cadet, with colleagues at NIDA's Intramural Research Program in Baltimore, report preliminary evidence suggesting that chronic abuse of marijuana can restrict blood flow to the brain and increase the risk of stroke for young men aged 18 to 30.

The investigators used transcranial Doppler sonography, a noninvasive technology that uses sound waves to take measurements and create images, to calculate the pulsatility index—a measure of resistance to blood flow—in cerebral arteries of 35 male participants, 16 long-term marijuana users and 19 nonusers of marijuana. Marijuana users had higher resistance to blood flow to their brains than did

nonusers upon initial measurement, and the deficits persisted after the marijuana abusers remained abstinent for a month, well past the time when acute withdrawal symptoms were reported. As a result, the deficits do not appear to be related to a temporary withdrawal syndrome.

The findings suggest that, at least within the first 4 weeks of marijuana abstinence, blood flow in the brain in young marijuana abusers is comparable to that of 60-year-olds, which may be of clinical importance because advancing age increases the risk of stroke.

The study was published in the June 2001 *Annals of the New York Academy of Science*. **NN**

Cognitive Deficits Associated With Heavy Marijuana Use Appear To Be Reversible

By Margi Grady, NIDA NOTES Contributing Writer

Memory and learning problems caused by heavy marijuana smoking persist for at least a week after cessation of use of the drug, but they appear to resolve completely within a month, a NIDA-supported study shows. "Cognitive impairment from heavy marijuana use may linger for a week or longer, but it does not appear to be permanent," says Dr. Harrison Pope, Jr., who led the study at Harvard University's McLean Hospital in Belmont, Massachusetts. "Even if users smoke a lot, these tests suggest they can eventually recover," he says. As a followup to this research, Dr. Pope and his colleagues are using functional magnetic resonance imaging to determine whether the more sensitive assessment tool reveals cognitive effects that his pencil-and-paper tests could not detect.

"Even though our study suggests that heavy users recover from cognitive deficits after 4 weeks of abstinence, it doesn't follow that marijuana is a benign substance," says Dr. Pope. He notes that the study revealed some startling demographic differences between long-term heavy users and a control group. Data collected on participants when they joined the study showed that those who had used marijuana heavily for many years had markedly lower income and education levels than the control group, regardless of whether they were still using the drug.

Dr. Pope and his colleagues examined cognitive function in 180 participants, including 63 current heavy marijuana users, 45 former heavy users, and 72 control subjects. Current heavy users had smoked marijuana a minimum of 5,000 times during their lives (the equivalent of at least once a day for 13 years) and were smoking at least 7 times a week at the beginning of the study. Former heavy users had also smoked at least 5,000 times in their lives but no more than 12 times during the previous 3 months. The control subjects had smoked at least once but no more than 50 times during their lives and no more than once in the previous year. Participants ranged in age from 30 to 55. All three groups were carefully screened for unrelated characteristics that might affect the study results.

All participants were required to remain abstinent from marijuana and other drugs for the course of the 28-day

Heavy Marijuana Users Report Lower Income And Less Education Than Control Subjects

	Current Heavy Users (N=63)	Former Heavy Users (N=45)	Control Subjects (N=72)
Education			
	Percentage		
Education, High School or Less	29%	13%	0%
Mother's Education, High School or Less	61	40	58
Father's Education, High School or Less	46	50	38
Household Income			
Household Income Less Than \$30,000	51	51	26
Parents' Household Income Less Than \$30,000	25	44	18

Information gathered on the Harvard study's participants revealed that both current and former long-term heavy users of marijuana had markedly lower income and less education than control subjects, even though the education and income of the two groups' parents were similar, says Dr. Harrison Pope, Jr., the study's lead investigator.

study and submit urine specimens that were used to confirm their abstinence. Their cognitive function was evaluated through standardized neuropsychological tests at study entry and on the 1st, 7th, and 28th days of the study. On study entry (day 0) and days 1 and 7, current heavy marijuana users scored significantly lower than control subjects on tests of verbal learning and memory. This finding confirms and extends the findings of previous studies by Dr. Pope's group and others that have shown impaired cognitive skills in heavy marijuana users for up to 3 days after use is stopped. By day 28, the difference between the scores of the control group and those of current heavy marijuana users disappeared.

Income and education data suggest consequences of heavy marijuana use.

Two findings allowed the researchers to conclude that the cognitive deficits were associated with recent heavy use rather than total lifetime use. First, former heavy users showed no significant difference from the control subjects on any of the tests on any of the testing days. Also, the researchers found a clear relationship between lower test

scores and higher levels of marijuana residues in urine at the beginning of the study, but no relationship between test scores and total lifetime marijuana use.

“This study is particularly significant for treatment,” says Dr. Steven Grant of NIDA’s Division of Treatment Research and Development. “By stopping drug use, heavy marijuana users are able to regain their memory and learning functions. Still, we cannot say there are no consequences to heavy marijuana use: The income and education data suggest the opposite.”

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Adolescent Treatment Programs Reduce Drug Abuse, Produce Other Improvements

By Kimberly R. Martin, *NIDA NOTES* Contributing Writer

In the first large-scale study designed to evaluate drug abuse treatment outcomes among adolescents in age-specific treatment programs, NIDA-supported researchers have found that longer stays in these treatment programs can effectively decrease drug and alcohol use and criminal activity as well as improve school performance and psychological adjustment.

The study, part of NIDA's ongoing Drug Abuse Treatment Outcome Studies for Adolescents (DATOS-A), analyzed data from 23 community-based adolescent treatment programs that addressed peer relationships, educational concerns, and family issues such as parent-child relationships and parental substance abuse. Successful elements of adult treatment programs, such as participation in group therapy and participation in a 12-step program, were also included in treatment plans.

"The results of this study are particularly impressive in light of the fact that the adolescents had multiple problems," says Dr. Christine Grella of the University of California, Los Angeles (UCLA), Drug Abuse Research Center, one of the study's investigators. "Although this is also typical of many adults in treatment, timely resolution of these problems is even more critical for adolescents. These young people are in the process of developing values, making lifestyle decisions, and preparing to assume adult roles and responsibilities, such as family and work; whereas when many adults enter treatment, they have completed this process."

Treatment Programs Varied

Dr. Yih-Ing Hser, also of UCLA, led the research team that evaluated the treatment outcomes for 1,167 adolescents, age 11 to 18, who were admitted to one of the treatment programs between 1993 and 1995. The treatment centers, located in Pittsburgh, Pennsylvania; Minneapolis, Minnesota; Chicago, Illinois; and Portland, Oregon, included eight residential programs, nine outpatient drug-free programs, and six short-term inpatient programs.

The 418 adolescents in the residential treatment programs received education, individual and group counseling, and interventions to develop social responsibility. The 292

Behaviors of Adolescents Before and One Year After Treatment

DRUG USE	Before	After
	Percentage	
Weekly Marijuana Use	80.4%	43.8%
Heavy Drinking	33.8	20.3
Hallucinogen Use	31.0	26.8
Stimulant Use	19.1	15.3
SCHOOL PERFORMANCE		
Regular Attendance	62.6	74.0
Grades Average or Better	53.4	79.6
CRIMINAL ACTIVITIES		
Any Illegal Act	75.6	52.8
Any Arrest	50.3	33.9

An evaluation of more than 1,100 adolescents who received substance abuse treatment in residential, short-term inpatient, or drug-free outpatient programs found improvement in rates of drug use and social behavior. Some 53 percent of those treated met or exceeded the minimum recommended stay in treatment.

adolescents in the outpatient drug-free programs received education, skills training, and individual and group counseling. The 467 adolescents in short-term inpatient programs received counseling and a 12-step program. Family therapy was strongly emphasized, and adolescents in these programs were referred to continued outpatient treatment. The average length of treatment for adolescents in the residential, outpatient drug-free, and short-term inpatient programs was 5 months, 1.6 months, and 18 days, respectively.

The adolescents were interviewed when they began treatment and again 1 year after discharge by professional interviewers who were not employed by the treatment centers. Problem severity was determined at the initial interview according to a number of criteria. Dependence on drugs or alcohol was determined from standardized diagnostic measures. To validate self-reports of drug use, one-quarter of the participants were selected randomly to submit urine samples during the posttreatment interview.

Before treatment, 25 percent of the participants used three or more drugs, 36 percent were dependent on alcohol,

In the year following treatment, more adolescents attended school and reported average or better-than-average grades.

64 percent were dependent on marijuana, and 10 percent were dependent on cocaine. In addition to substance abuse problems, 63 percent were diagnosed with a mental disorder and 67 percent were criminally active.

Outcomes Overall

Research has indicated that in general the rate of drug and alcohol use tends to increase during adolescence. In the present study, however, improvements were observed in many of the areas evaluated, although some of the participants did not complete their treatment program. Comparing the year before treatment to the year after treatment, the adolescents showed significant declines in the use of marijuana and alcohol, which are considered to be the major drugs of abuse for this age group. Weekly or more frequent marijuana use dropped from 80 percent to 44 percent, and abstinence from any use of other illicit drugs increased from 52 percent to 58 percent. Heavy drinking decreased from 34 percent to 20 percent, and criminal activity decreased from 76 percent to 53 percent. Adolescents also reported fewer thoughts of suicide, lower hostility, and higher self-esteem. In the year following treatment, more adolescents attended school and reported average or better-than-average grades. Some exceptions to the general pattern of improvement were that overall, cocaine and hallucinogen use did not improve during the year after treatment.

Treatment Length and Outcomes

Previous research indicates that a minimum of 90 days of treatment for residential and outpatient drug-free programs and 21 days for short-term inpatient programs is predictive of positive outcomes for adults in treatment. Better treatment outcomes were reported among adolescents who met or exceeded these minimum lengths of treatment than for those who did not. Among the treatment participants, 58 percent of those in residential programs, 27 percent in outpatient drug-free programs, and 64 percent in short-term inpatient programs met or exceeded the minimum stay. In the year following treatment, those who met or exceeded the minimum treatment were 1.52 times more likely to abstain from drug and alcohol use and 1.2 times more likely to not be involved in criminal activity. In addition, these adolescents were 1.34 times more likely to have average or better-than-average grades.

This study confirms that community-based drug treatment programs designed for adolescents can reduce substance abuse and have a positive impact on many other aspects of their life, says Dr. Tom Hilton of NIDA's Division of Epidemiology, Services and Prevention Research. These results justify new research to identify the key elements common to effective treatment programs for adolescents, he noted.

Source

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Television Public Service Announcements Decrease Marijuana Use in Targeted Teens

By Kimberly R. Martin, *NIDA NOTES* Contributing Writer

NIDA-supported researchers have helped clarify the necessary elements in effective anti-drug public service announcements (PSAs) directed at high-sensation-seeking adolescents.

NIDA researchers have previously shown that high-sensation-seekers—individuals characterized by their need for new, emotionally intense experiences and the willingness to take risks to obtain these experiences—are at greater risk for using marijuana and other drugs and for using them at an earlier age than other individuals.

Using a prevention approach developed from previous NIDA-supported studies, the researchers produced five anti-marijuana PSAs. The dramatic and attention-getting PSAs were aired during programs that appealed to high-sensation-seekers such as action-oriented television shows. The media placement was supported by paid as well as donated advertising to ensure the most effective outreach to the target audience.

“To appeal to high-sensation-seekers, a PSA must be dramatic, intense, and highly original,” says Dr. Philip Palmgreen, the research team leader at the University of Kentucky in Lexington. “An effective PSA needs to show the negative consequences that can occur as a direct result of drug use. For example, high-sensation-seekers need to see that they can end up in a wheelchair, lose their job, or lose their girlfriend or boyfriend as a result of drug use. We found that the threat of death is not a deterrent because high-sensation-seekers do not believe that death is a real possibility,” he says.

The PSAs were aired from January through April 1997 in Fayette County, Kentucky, and from January through April 1998 in Fayette County and Knox County, Tennessee. One hundred students in 7th through 10th grade were selected each month by random phone calls



Drs. Philip Palmgreen (left) and Lewis Donohew review a public service announcement at the University of Kentucky.

and asked to participate in the study. The students were interviewed to determine whether they saw the PSAs and their attitudes toward and whether they used marijuana and other drugs. Questions also were asked to determine their degree of sensation-seeking. More than 70 percent of the targeted age groups watched at least three PSAs per week, the researchers say.

Marijuana use declined substantially among teens during the campaigns in both counties and residual effects of the campaigns were evident for several months. According to Dr. Palmgreen, the second campaign in Fayette County had a “booster effect,” resulting in further declines. Overall, marijuana use decreased by 38 percent in Fayette County. In Knox County, marijuana use declined among high-sensation-seeking teens by 26.7 percent.

“We have shown that, for PSAs to be effective, they must be designed for a specific audience and must air frequently during programs watched by that audience,” says Dr. Palmgreen. “PSAs typically are shown during donated air-time. However, the trend toward paid placements of PSAs, as in various campaigns across the country, is a very positive approach.”

Source

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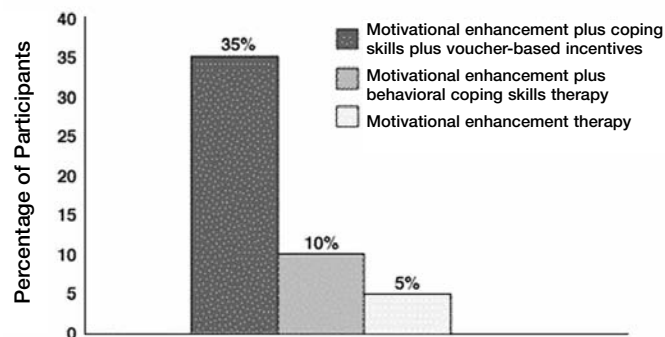
Adding Vouchers to Behavioral Therapies Improves Marijuana Treatment Results

Enhancing behavioral treatments by adding the opportunity to earn vouchers for remaining drug-free has been shown to improve abstinence rates among cocaine- and opiate-addicted patients. Now, a NIDA-funded study has shown that the combination of behavioral interventions and voucher-based incentives also can improve treatment results for heavy marijuana abusers.

Researchers at the University of Vermont in Burlington, led by Dr. Alan J. Budney, recruited 60 heavy marijuana users who wanted to quit. Most of the study participants had long histories of marijuana abuse, smoked marijuana almost daily, and smoked more than once a day. They were randomly assigned to one of three treatments: motivational enhancement therapy, motivational enhancement plus behavioral coping skills therapy, or motivational enhancement plus coping skills plus voucher-based incentives. Throughout the study, each participant gave urine samples twice weekly to be tested for marijuana use. If patients in the incentives group tested negative, they earned vouchers that they could exchange for retail goods or services, such as movie passes, sporting equipment, or vocational classes. Patients in the other two treatment groups did not receive such tangible rewards for abstinence.

Over the 14-week study, 40 percent of patients in the incentives group achieved at least 7 weeks of continuous abstinence from marijuana, compared with 5 percent of

Marijuana Abstinence at End of Treatment



Adding voucher-based incentives to behavioral and motivational treatments more than tripled the percentage of patients who stopped using marijuana by the end of treatment.

patients in each of the other groups. At the end of the treatment period, 35 percent of the incentives group had stopped using marijuana, compared to 10 percent of the motivational enhancement plus coping skills group and 5 percent of the motivational enhancement group.

The study was published in the December 2000 issue of the *Journal of Consulting and Clinical Psychology*. **NN**

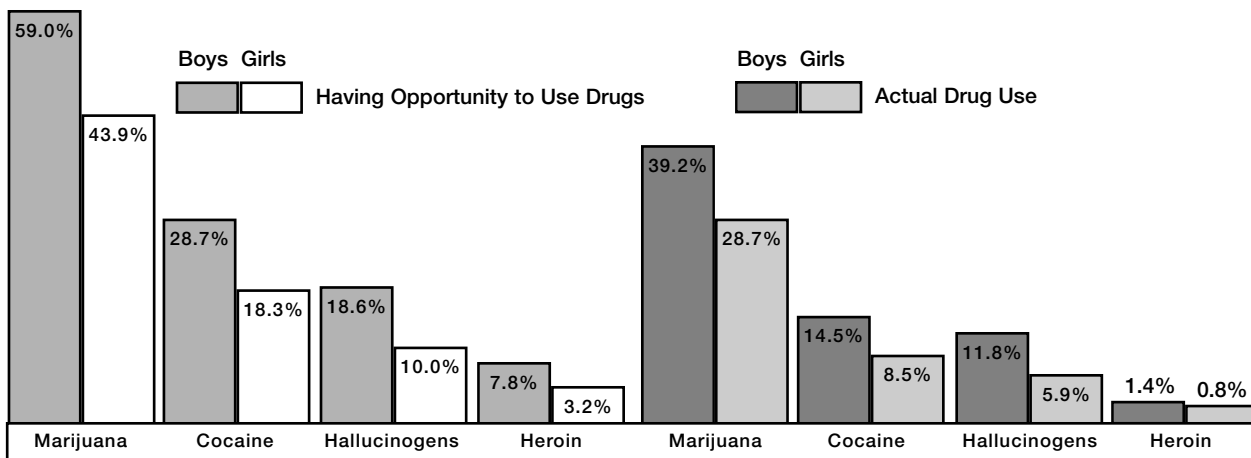
Gender Differences in Prevalence of Drug Abuse Traced to Opportunities to Use

By Patrick Zickler, NIDA NOTES Staff Writer

Males are more likely than females to abuse drugs. According to the 1999 National Household Survey on Drug Abuse (NHSDA)—an annual Substance Abuse and Mental Health Services Administration survey of more than 25,000 respondents—8.1 percent of males and 4.5 percent of females older than age 12 had used illicit drugs within the past month, and this ratio has remained fairly constant throughout the 29-year history of the survey.

compared with 43.9 percent of females; to use cocaine, 28.7 percent of males and 18.3 percent of females; to use hallucinogens, 18.6 percent of males and 10 percent of females; and to use heroin, 7.8 percent of males and 3.2 percent of females.

Once presented with an opportunity to use drugs, 44.2 percent of males and 42 percent of females began using marijuana within 1 year; 37.7 percent of males and 33.2



According to the 1993 National Household Survey on Drug Abuse, boys are more likely to abuse drugs than girls. The graph above shows the estimated percentage of boys and girls using each drug and the percentage having the opportunity to use each drug.

Research by Dr. James Anthony, a NIDA-supported scientist at the Johns Hopkins University School of Hygiene and Public Health in Baltimore, shows that these gender differences in drug abuse are not related to gender differences in susceptibility. Instead, they have their foundation in the very first stage of drug involvement—the opportunity to use drugs. Once given the opportunity to use, males and females are equally likely to use drugs.

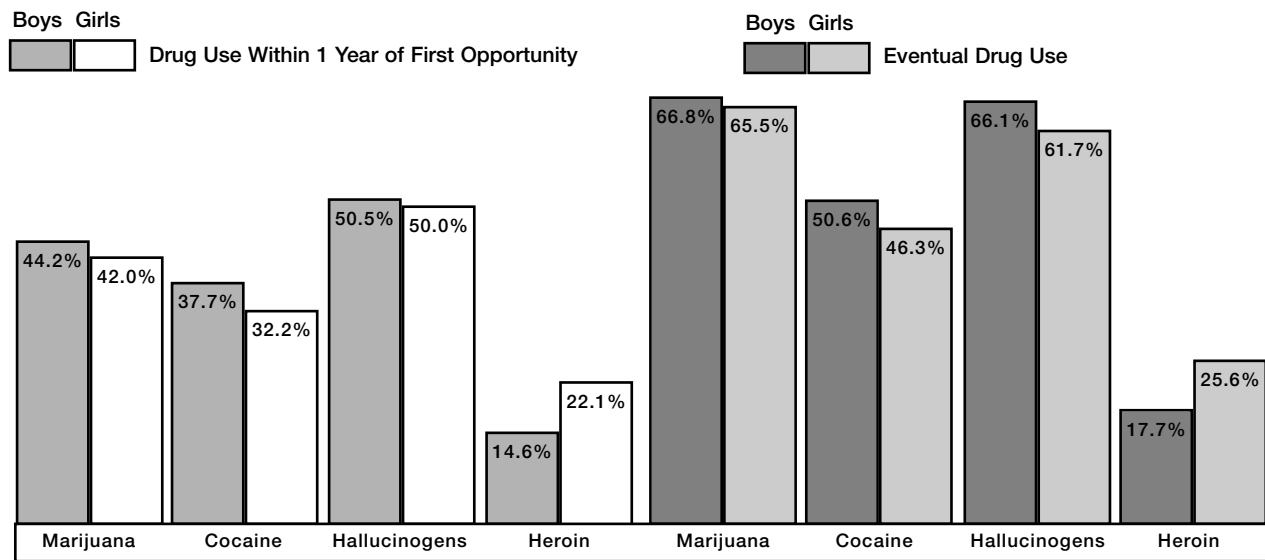
Dr. Anthony and his colleagues analyzed NHSDA data for 1993 to look for information that might explain the gender difference in rates of drug abuse. “Males are more likely than females to have an opportunity to use drugs. There is no male-female difference with respect to trying a drug once an opportunity to do so has been experienced,” Dr. Anthony says.

The findings are consistent for marijuana, cocaine, hallucinogens, and heroin, Dr. Anthony says. The proportion of opportunities to use marijuana was 59 percent of males

percent of females began using cocaine; 50.5 percent of males and 50 percent of females began using hallucinogens; and 14.6 percent of males and 22.1 percent of females began using heroin.

Dr. Anthony found that females were likely to get their first opportunity to use cocaine at an earlier age than were males (age 19 for females, age 20 for males) but that there were no differences among males and females in age of first opportunity to use marijuana, heroin, or hallucinogens.

One benefit of improved understanding of the link between opportunity and eventual use is that counselors or physicians may be able to learn about young patients’ drug use by asking about their opportunities to use drugs. “Young people may feel freer to answer a question about the opportunity to use drugs rather than a question about actual drug use, because the opportunity is less likely to be illegal or particularly sensitive,” Dr. Anthony says.



This graph shows the percentage of drug use within 1 year of the first opportunity to use drugs and the percentage of boys and girls to eventually use drugs, given the opportunity.

Understanding the differences in opportunities to use drugs may also help shape prevention efforts, according to Dr. Cora Lee Wetherington, NIDA's Women and Gender Research Coordinator. "The prevalence of drug abuse is greater for males than for females even though, given the initial opportunity to use drugs, males and females are equally likely to move on to drug use. It appears that the opportunities themselves play a very important role in drug abuse and need more investigation. Understanding the sex differences in opportunities could make it possible to develop prevention programs that reduce the opportunities and, therefore, the higher rate of drug abuse among males. In fact, NIDA-supported research into sex differences in opportunities (see this issue's "Boys and Girls Encounter Different Drug Offers, Use Different Refusal

Strategies") raises the possibility that gender-specific prevention interventions that focus on drug opportunities could serve to reduce drug use by both males and females," Dr. Wetherington says.

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Evidence Accumulates That Long-Term Marijuana Users Experience Withdrawal

By Patrick Zickler, NIDA NOTES Staff Writer

Laboratory studies have shown that animals exhibit symptoms of drug withdrawal after cessation of prolonged marijuana administration. Some human studies have also demonstrated withdrawal symptoms such as irritability, stomach pain, aggression, and anxiety after cessation of oral administration of tetrahydrocannabinol (THC), marijuana's principal psychoactive component. Now, NIDA-supported researchers at McLean Hospital in Belmont, Massachusetts, and Columbia University in New York City have shown that individuals who regularly smoke marijuana experience withdrawal symptoms after they stop smoking the drug.

"These studies suggest that in real-world situations abstinence from daily marijuana smoking creates withdrawal symptoms similar to those of other drugs of abuse," says Dr. Jag Khalsa of NIDA's Center on AIDS and Other Medical Consequences of Drug Abuse. "Marijuana smokers may continue to use the drug to prevent the irritability and discomfort they experience when they stop."

Aggression

Dr. Elena Kouri and her colleagues at the Biological Psychiatry Laboratory at McLean Hospital found that long-term heavy marijuana users became more aggressive during abstinence from marijuana than did former or infrequent users. Previous studies of withdrawal symptoms have relied largely on patients' subjective reports of a range of symptoms, Dr. Kouri notes. "We studied measurable changes in one specific symptom—aggression," she says.

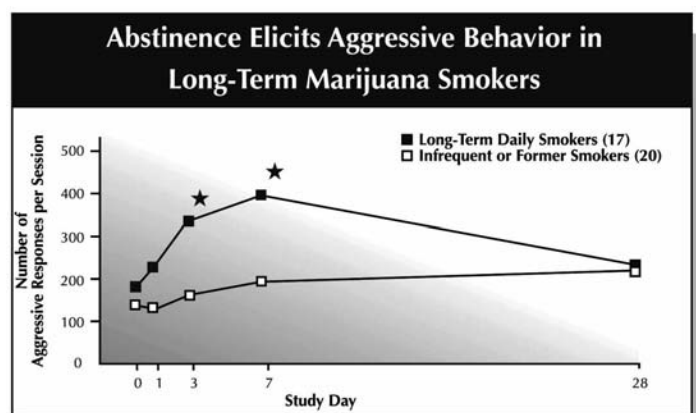
The researchers recruited two groups of male and female volunteers: 17 current long-term users of marijuana and a control group of 20 infrequent or former users. Current long-term users were smoking marijuana daily at the time of recruitment and had smoked marijuana at least 5,000 times—the equivalent of smoking once each day for more than 13 years. The infrequent or former users had not smoked more than 50 times in their life and had smoked less than once per month in the past year, or had formerly smoked at least daily but had not smoked more than once per week for the past 3 months.

At the beginning of the study, all participants were instructed to refrain from any marijuana use for 28 days.

Abstinence was monitored by analysis of daily observed urine sampling. Cigarette smokers were allowed to continue their usual tobacco use.

"The results demonstrate that abstinence is associated with unpleasant behavioral symptoms that may contribute to continued drug use."

Aggression was measured on the first day of the study and after 1, 3, 7, and 28 days of abstinence. To measure aggression, the researchers used a 20-minute computerized test that participants were told would measure motor skills and other physiological characteristics. Participants were told that pressing one button in a certain pattern would add points to their score and that pressing another button would subtract points from the score of their opponent, who could similarly add or subtract points.



During the first weeks of abstinence, long-term current marijuana smokers made more aggressive responses on a computerized game than did infrequent or former smokers. The graph shows the average number of aggressive responses in 17 long-term daily (Solid Square) and 20 infrequent or former (Open Square) marijuana smokers. (Star = significantly different from former smokers.)

In fact, Dr. Kouri says, there was no human opponent; the computer was programmed to subtract points randomly in order to give the illusion of a human opponent. At the end of each session, aggressive responses—those that subtracted from the supposed opponent’s points—were compared with nonaggressive responses—those that added to the participant’s points. Dr. Kouri notes that studies involving parolees with a history of violent behavior have shown a close correlation between performance on this game and actual aggression.

After 1, 3, and 7 days of abstinence, current marijuana users registered significantly more aggressive responses—more than twice as many on days 3 and 7—than the control group. By the 28th day, there was no significant difference between groups. Aggressive behavior was limited to responses in the test situation, Dr. Kouri notes; participants did not display overt hostility. “At this point we do not know exactly how these findings reflect changes in aggressive behavior outside the laboratory,” Dr. Kouri says. “But the results demonstrate that abstinence is associated with unpleasant behavioral symptoms that may contribute to continued drug use.”

Other Withdrawal Symptoms

Studies at Columbia University in New York City have demonstrated that, in addition to aggression, marijuana smokers experience other withdrawal symptoms such as anxiety, stomach pain, and increased irritability during abstinence from the drug. “These results suggest that dependence may be an important consequence of repeated daily exposure to marijuana,” says NIDA-supported researcher Dr. Margaret Haney.

Dr. Haney and her colleagues investigated the effects of abstinence on 12 adult males with an average age of 28 years who, in the laboratory, smoked marijuana with THC concentrations of 3.1 percent or 1.8 percent, or marijuana cigarettes containing no active THC. All participants smoked inactive marijuana during the first 4 days of the study followed by either the high concentration, low concentration, or inactive marijuana on alternating 4-day periods. Three times each day, the participants

completed a 50-item checklist that rated physical conditions such as hunger, dizziness, and headache and aspects

“The withdrawal symptoms are not as dramatic as those associated with withdrawal from opiates or alcohol, but are still significant.”

of their mood, for example, anxiety, talkativeness, friendliness, or depression.

Abstinence from either high- or low-concentration marijuana resulted in reduced hunger, decreased ratings of “friendly” and “content,” and increased ratings of “irritability,” “stomach pain,” and “anxiety.” Moreover, Dr. Haney notes, participants receiving high-concentration marijuana rated the drug’s effects higher (“good drug effect,” “stimulated,” “high”) on the first day of exposure than on the fourth day, indicating the development of tolerance to THC.

“It appears likely that the onset of the withdrawal symptoms we observed in this study may contribute to maintaining chronic marijuana use,” Dr. Haney says. “The withdrawal symptoms are not as dramatic as those associated with withdrawal from opiates or alcohol, but are still significant to the individual marijuana user. These symptoms must be taken into account in order to develop effective treatment programs for marijuana abuse.”

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Marijuana-Like Compound in Womb May Influence Early Pregnancy

By Steven Stocker, *NIDA NOTES* Contributing Writer

Ever since scientists began discovering in the early 1990s that marijuana-like compounds are normally produced in various parts of the body, they have been investigating the function of these compounds. Research has suggested that in the brain, the compounds, called endocannabinoids, inhibit pain perception and help to regulate movement. In the spleen and blood, endocannabinoids seem to be partly involved in suppressing inflammation and other responses of the immune system. Now NIDA-funded researchers have discovered that in the female mouse reproductive tract, one of these endocannabinoids, called anandamide, appears to help regulate the early stages of pregnancy.

Dr. Sudhansu K. Dey and his colleagues at the University of Kansas Medical Center in Kansas City, Kansas, have found that the mouse uterus contains the highest anandamide levels yet discovered in any mammalian tissue. At times, parts of the uterus contain anandamide levels that are more than 100 times higher than those in the brain. The researchers have also found that mouse embryos contain cannabinoid receptors—proteins on the cell surfaces that latch on to endocannabinoids in the vicinity—again, at levels that exceed those of the brain.

To find out why the uterus contains anandamide and the embryo contains cannabinoid receptors, the scientists first examined the effects of anandamide on embryo development. When they placed embryos from mice in cell culture, about 90 percent proceeded to the next stage of embryonic development, the blastocyst, which normally implants into the wall of the uterus and eventually becomes a fetus. With the addition of anandamide, only 36 percent proceeded to the blastocyst stage. However, if these embryos were then placed in cell culture without anandamide, most started developing again.

In addition to inhibiting the growth of embryos prior to implantation, anandamide probably also inhibits implantation itself, the researchers found. They determined that administering compounds similar to anandamide prevented blastocysts from implanting in the uterine wall.

Functions of Anandamide

Anandamide may be serving at least three functions before and during implantation, suggests Dr. Dey. First, the compound may be involved in synchronizing the development of the embryo with the preparation of the uterus for receiving it. For example, anandamide secreted into the fluid of the uterine tubes might retard embryo development until the uterus is ready to receive the implanting blastocyst and to sustain it once it has implanted.


Second, anandamide may be involved in embryo selection. “In the mouse, about 15 percent of embryos never implant, and in humans, as many as 60 percent either don’t implant or don’t survive after implantation,” says Dr. Dey. “Perhaps these rejected embryos are inferior in some way, and high anandamide levels in the uterine wall may prevent them from implanting or surviving after implantation.”

Finally, Dr. Dey suggests, anandamide may prevent a second blastocyst from implanting nearby one that has already implanted. After the first one implants, the anandamide level in the surrounding area increases again, which prevents other blastocysts from implanting at the same site.

Understanding how anandamide acts in the female reproductive tract may lead to an explanation for some cases of infertility in women, if anandamide is found to exist in the human uterus, suggests Dr. Dey. In these infertile women, excessive uterine levels of anandamide may be disrupting embryo development and implantation, says Dr. Dey.

This research may also lead to the development of new contraceptives that can inhibit embryo development and implantation in the same manner as anandamide. Conversely, it could also lead to the development of fertility agents that act in ways opposite to those of anandamide.

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Twin Studies Help Define the Role of Genes in Vulnerability to Drug Abuse

By Patrick Zickler, NIDA NOTES Staff Writer

Some individuals who use drugs become drug abusers—they continue taking drugs even though doing so causes serious problems in their lives. Others avoid abuse or addiction. By studying patterns of drug use in pairs of twins, NIDA-supported researchers are beginning to clarify the role that genes play in predisposing individuals to drug abuse.

“Twin studies explore the roles and interrelationship of genetic and environmental risk factors in the development of drug use, abuse, and dependence,” says Dr. Naimah Weinberg of NIDA’s Division of Epidemiology, Services, and Prevention Research.

In twin studies, researchers interview both members of identical (monozygotic) and fraternal (dizygotic) twin pairs, who typically are exposed to common environmental influences. If genes influence their risk for drug abuse, identical twin pairs, who share the same genes, will tend to be concordant—that is, both will abuse drugs or not abuse drugs. Fraternal twin pairs, on the other hand, are no more similar genetically than non-twin siblings, and so will be less concordant—there will be more pairs in which one twin abuses drugs and the other does not. By comparing the degree of concordance in identical and fraternal twins, researchers can estimate the extent to which genes influence vulnerability to drug abuse.

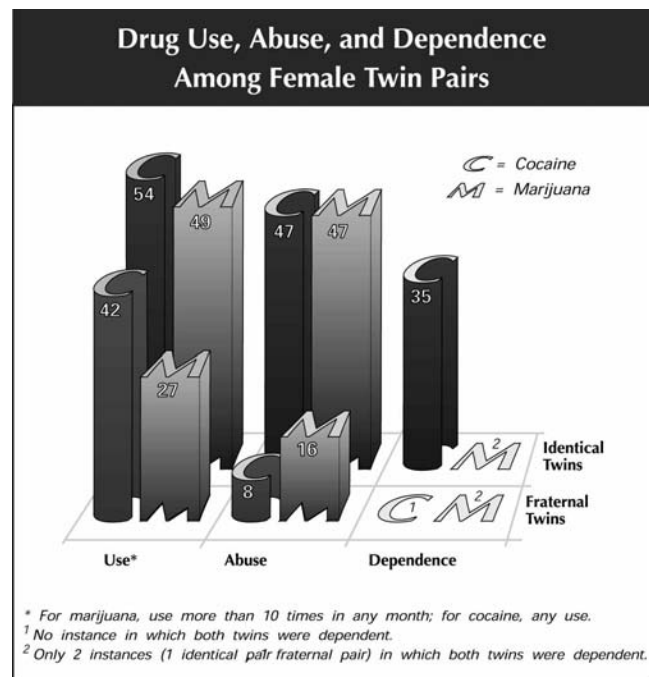


If genes influence the risk for drug abuse, identical twin pairs, who share the same genes, will tend to be concordant—that is, both will abuse drugs or both will not abuse drugs.

Marijuana and Cocaine Abuse Among Female Twins

NIDA-supported researchers Dr. Kenneth Kendler and Dr. Carol Prescott at the Medical College of Virginia in

Richmond have examined the patterns of marijuana and cocaine use by female twins and found that genetic factors play a major role in the progression from drug use to abuse and dependence. The researchers interviewed 1,934 twins, ranging in age from 22 to 62, recruited from the Virginia Twin Registry, a database compiled from Commonwealth birth records.



Percentages of pairs in which both twins used, abused, or were dependent on marijuana or cocaine were higher in identical twins than in fraternal twins.

In the study, drug “use” involved at least one nonprescribed use of a drug; “abuse” was based on the definition provided in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*, which includes symptoms such as recurrent use in situations where it presents a physical danger, failure to meet obligations at work or school, or recurrent social or interpersonal problems caused by effects of the drug; and “dependence” was based on the *DSM-IV* definition and included characteristics such as physical symptoms of tolerance or withdrawal, taking larger amounts of the drug or using it over a longer period than intended, or spending large

amounts of time seeking, obtaining, and recovering from the effects of the drug.

“Our research supports other studies that indicate family and social environmental factors are influential in determining whether an individual begins using these drugs,” Dr. Kendler says. “But our findings suggest that the progression from the use of cocaine or marijuana to abuse or dependence was due largely to genetic factors.”

In addition, Dr. Kendler says, the study found that concordance rates—both twins using, abusing, or being dependent on drugs—were higher for identical than fraternal twins (see chart). For cocaine use, concordance was 54 percent in identical twins and 42 percent in fraternal twins; for abuse, 47 percent in identical twins and 8 percent in fraternal twins; and for dependence, 35 percent in identical twins and zero for fraternal twins.

“Abuse and dependence are highly heritable,” Dr. Kendler says. “For both cocaine and marijuana, genetic factors are responsible for roughly 60 to 80 percent of the differences in abuse and dependence between fraternal and identical twin pairs.”

Genetic Risk Factors Differ Among Drugs and Between Males and Females

Dr. Ming Tsuang, a NIDA-supported researcher at Harvard University in Cambridge, Massachusetts, has found that, in males, genetic influences are stronger for abuse of some drugs than for others. Dr. Tsuang and his colleagues studied drug use in 1,874 identical male twin pairs and 1,498 fraternal male twin pairs recruited from the Vietnam Era Twin Registry, a database compiled from Department of Defense records. The average age of participants was 45.

The researchers found evidence to suggest that genetic influences contribute to a common vulnerability for abusing marijuana, sedatives, stimulants, heroin or opiates, and psychedelics. “There is some characteristic of the individual that imparts vulnerability to the abuse of all categories of drugs. Abusing any category of drugs was associated with a marked increase in the probability of abusing every other category of drugs,” Dr. Tsuang says. In addition to this shared vulnerability, the researchers found different vulnerabilities for different drugs. “Each category of drugs we looked at, except psychedelics, had unique genetic influences,” Dr. Tsuang says. “The genetic influence for abuse was greater for heroin than for any other drug.”

NIDA-supported studies involving male and female twins suggest that genetic factors for drug abuse are stronger in males than in females. Dr. Marianne van den Bree and Dr. Roy Pickens of NIDA’s Intramural Research Program and their colleagues studied 188 twin pairs in which at least

1 twin was recruited through a drug treatment program. The sample included 56 identical male pairs, 66 fraternal male pairs, 38 identical female pairs, and 28 fraternal female pairs. Participants were interviewed to determine drug use (five times or more) and clinical diagnosis (according to *DSM-IV* criteria) of drug abuse, dependence, or both for sedatives, stimulants, opiates, marijuana, or cocaine. For most drugs, clinical diagnosis of abuse, dependence, or both was more strongly influenced by genetic factors than was drug use. In addition, for most drugs, genetic influences for abuse or dependence were greater for males than for females.

“The progression from the use of cocaine or marijuana to abuse or dependence was due largely to genetic factors.”

“For females, genetic influences accounted for 47 percent of the differences between identical and fraternal twins in abuse, dependence, or both for any drug, compared with 79 percent for males,” Dr. van den Bree says. The impact of genetic factors also seems to differ for specific drugs, she notes. The researchers found no evidence for genetic influence for opiate or sedative abuse, dependence, or both in females, but in males genetic influences were generally larger than environmental influences.

“The results we see from these twin studies are making important advances in our understanding of the role of genetic influences in drug abuse,” observes NIDA’s Dr. Weinberg. “Although the studies can’t tell us anything about the risk for a particular individual, they are of enormous value in helping define the variations in drug abuse vulnerability in the population.”

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MERIT Award Research Helps Reveal Long-term and Developmental Impact of Drug Abuse

By Patrick Zickler, *NIDA NOTES* Staff Writer

Identifying the long-term impact of drugs is crucial to understanding drug abuse and addiction. Chronic use of drugs by adults may have effects that last long after drug use has stopped. In children, exposure to drugs may impair development or contribute to behavioral disorders. But understanding these long-term effects requires well-designed research projects that may last decades. Three recent MERIT Award recipients are carrying out investigations that will provide answers to important questions about the long-term impact of drug use.

Studying the Long-term Consequences of Prenatal Exposure to Marijuana and Cigarettes



For more than 15 years, Dr. Peter A. Fried, professor of psychology at Carleton University in Ottawa, Canada, has studied mother-child pairs to determine whether prenatal exposure to marijuana, cigarettes, or both affects the development and behavior of children and adolescents. Dr. Fried's MERIT Award will allow him to continue to follow the mother-child pairs as the children

Dr. Peter A. Fried

develop through their teenage years.

"Dr. Fried's research represents an immense opportunity to obtain previously unattainable information on the long-term consequences of prenatal exposure to marijuana and cigarettes," says Dr. Vincent Smeriglio of NIDA's Center for AIDS and Other Medical Consequences of Drug Abuse. "His research already has made a significant contribution not only to documenting infancy and childhood consequences, but also to exploring possible mechanisms for those consequences."

Dr. Fried's research involves more than 150 children born in the Ottawa area who were exposed before birth to cigarettes, marijuana, or both. Dr. Fried and his colleagues evaluated the children several hours after birth and at 4 days, 7 days, 9 days, 30 days, 6 months, and 1 year. The researchers have evaluated the children annually since their first year to look for developmental and behavioral problems that might be related to prenatal exposure to marijuana or cigarettes. The researchers' findings suggest that marijuana exposure is associated with impaired executive functioning—the ability to make decisions and plan

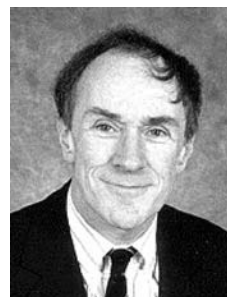
for the future—in the children at 9 to 12 years of age. "The major finding in this study about regular marijuana use during pregnancy is that marijuana can have an impact that may prevent a child from achieving his or her full potential," Dr. Fried says.

Children born to women who smoked cigarettes during pregnancy showed, from infancy through early adolescence, a reduction in auditory-based abilities. From ages 9 to 12, children who were exposed prenatally to tobacco smoke showed a reduction in language scores and poorer performance in tests involving the auditory aspects of reading compared with children born to nonsmokers, with the most heavily exposed children performing worse than those exposed to smaller amounts. "The continuity, over approximately 12 years, of the relationship between auditory and language variables and prenatal exposure to cigarette smoke suggests that these important aspects of behavior are directly affected by maternal smoking," Dr. Fried says.

The MERIT Award will simplify the continuation of this research through a crucial period of the children's development, Dr. Fried notes. "Testing the children at midadolescence is particularly critical. Subtle learning difficulties are most likely to manifest themselves at this stage of development, which involves complex behaviors requiring focused attention and cognitive skills," he says.

Investigating the Effects of Chronic Heavy Marijuana Use

Research has shown that heavy and long-term marijuana users suffer impaired cognitive function during and immediately following periods of marijuana use. But does this impairment last, and for how long, if marijuana use is discontinued?



Dr. Harrison Pope, Jr.

Answers to these questions may come from NIDA-supported research under way at the McLean Hospital Biological Psychiatry Laboratory in Belmont, Massachusetts.

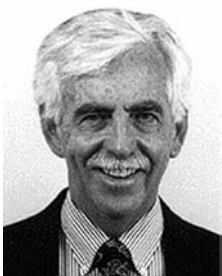
The research is part of the work being done by Dr. Harrison Pope, Jr., who recently received a NIDA MERIT Award to continue his investigations.

Dr. Pope's research focuses on 30- to 54-year-old individuals—including both men and women and representing a range of ethnic and socioeconomic groups—who have smoked marijuana at least 5,000 times. This rate of use is equivalent to having smoked marijuana at least once daily for more than 13 years. The study participants will be given a series of neuropsychological tests during a 28-day period of abstinence—monitored by analysis of observed daily urine collections—from marijuana and other drugs.

Using similar neuropsychological tests, Dr. Pope demonstrated that college-age heavy marijuana users performed more poorly than light users on memory, learning, and attention tests following a 24-hour period of supervised abstinence. "Testing after a longer abstinence period in our new study will allow us to distinguish between prolonged impairment that results from marijuana neurotoxicity and temporary impairment that might simply be the result of marijuana residues or withdrawal effects," Dr. Pope says.

"This unique research will allow us to get a much clearer understanding of the residual effects of chronic heavy marijuana use on brain function," says Dr. Jag Khalsa of NIDA's Clinical Medicine Branch. "Equally important is the MERIT Award's potential for expanding the current research using this rich database."

Looking for Links Between Substance Dependence and Adolescent Conduct Disorder



Dr. Thomas Crowley

Many adolescents who suffer from conduct disorder are also substance dependent, and the two disorders together represent a major health problem for adolescents. Research being conducted by MERIT Award recipient Dr. Thomas Crowley will help clarify the critical relationship between conduct disorders and substance dependence.

Dr. Crowley, at the University of Colorado School of Medicine's Addiction Research and Treatment Service in Denver, has spent more than 20 years treating adolescents referred by criminal justice agencies. "Among the patients diagnosed with conduct disorder, 80 percent are also dependent on marijuana, and more than half are dependent on nicotine," Dr. Crowley says. He found that conduct disorders preceded substance dependence in the majority of the adolescents referred to

his program with both conditions. Although many of the patients began their substance use—usually with marijuana or alcohol—as early as age 12, in 75 percent of the patients conduct disorders began even earlier.

"Conduct disorder is a major contributor to substance dependence in these patients, and our work suggests that conduct disorders will coexist with most substance dependence that begins early in adolescence," Dr. Crowley says.

Dr. Crowley says his MERIT-supported research will allow him to investigate more fully the relationship between conduct disorder, attention deficit/hyperactivity disorder, and substance dependence. In addition, Dr. Crowley and his colleagues will examine the possible role of genetic and familial factors in patients suffering from both conditions.

"Antisocial drug dependence—that is, substance dependence combined with conduct disorder or antisocial personality disorder—may be due in part to genetic influences and may need special treatment," Dr. Crowley says. He and other researchers will use behavioral studies and brain imaging to investigate the action of tetrahydrocannabinol, the principal psychoactive component in marijuana, in the brains of adolescents with coexisting conduct disorder and marijuana dependence. "We will identify and quantify the characteristic of comorbidity in these patients and use that information to investigate the underlying behavioral genetics," Dr. Crowley says.

"Dr. Crowley and his research team are one of the very few groups in the country who are addressing this clinical population. Their MERIT-supported studies will be of crucial importance in understanding the psychopathology of conduct disorder, attention deficit/hyperactivity disorder, and antisocial behavior in young adolescents with substance dependence disorder," says NIDA's Dr. Khalsa.

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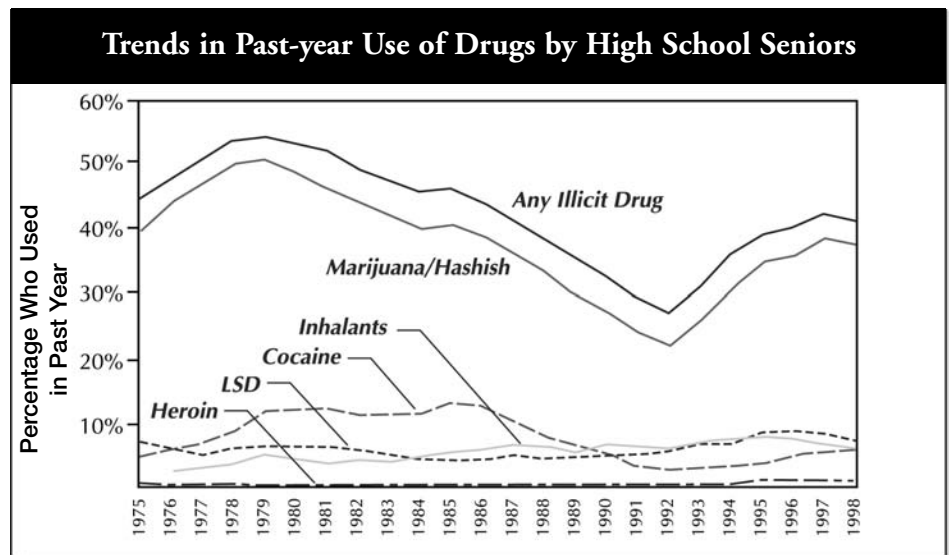
Tracking Trends in Teen Drug Abuse Over the Years

In 1975, shortly after NIDA was established, NIDA's first Monitoring the Future study (MTF) began to collect data on drug use among the Nation's high school seniors. In 1991, 8th- and 10th-grade students were added to the annual study to examine drug use among younger adolescents.

Over the course of its 24-year history, MTF has charted some significant changes in illicit drug use among America's school-aged children. For example, some trends in annual use—use in the past year—include:

- Annual use of any illicit drug by high school seniors peaked at 54.2 percent in 1979, declined to a low of 27.1 percent in 1992, then climbed steadily to 42.4 percent in 1997. Seniors' use of any illicit drug has been stable since then.
- Annual marijuana use among high school seniors crested in 1979 at 50.8 percent, then declined to 21.9 percent in 1992, before rising steadily to 38.5 in 1997. Marijuana use by seniors has remained steady since then.
- Annual cocaine use more than doubled among high school seniors from 5.6 percent in 1975 to 13.1 percent in 1985 then declined sharply to 4.9 percent in 1996. Seniors' cocaine use has been stable since then.

- Heroin use always has been relatively low among school children. However, in recent years, the availability of cheap, high-purity heroin that enables users to get high by snorting the drug rather than injecting it has contributed to heroin use approximately doubling among high school seniors from 0.4 percent in 1991 to 1.0 percent in 1998.



The Monitoring the Future study is funded by NIDA and conducted by the University of Michigan's Institute for Social Research.

- Marijuana, cocaine, and heroin use bottomed out in the early 1990s but has since risen among children at all grade levels. MTF figures for 1997 and 1998 suggest this trend toward increased illicit drug use is leveling off and may be in the process of reversing.

Institute Launches Science Education Campaign for Middle Schoolers

By Barbara Cire, *NIDA NOTES* Associate Editor

NIDA has launched a new science education campaign to provide middle school students with information about how drugs work in the brain. "NIDA Goes to School," a compilation of resource materials, is being mailed to science teachers at 18,084 public and private middle schools across the country and 256 Department of Defense schools overseas. The campaign, undertaken in partnership with the National Association of Biology Teachers, was announced in November at the National Leadership Forum of the Community Anti-Drug Coalitions of America in Washington, D.C. In December, at a national press conference about teen drug use, Health and Human Services Secretary Dr. Donna E. Shalala cited the campaign as an effective tool for teaching young people how drugs damage their minds and bodies and helping them to resist drugs.

"Science-based education about drug abuse should be a prominent part of the curriculum for all students," says NIDA Director Dr. Alan I. Leshner. "This new initiative provides teachers easily usable, student-oriented materials to help achieve this goal."

The "NIDA Goes to School" kit contains a variety of research-based materials for teachers and students about drugs and how they affect the brain. (See "A Toolbox for Teachers.") In addition, a "NIDA Goes to School" Web site has been established at NIDA's home page on the World Wide Web. Students and teachers can use this interactive Web site to get additional information about drugs of abuse. The site also will serve as a major source of feedback from students, teachers, and parents. As new science education materials are developed, they will be added to the site.

"We are very excited about this project," says Dr. Cathrine Sasek, science education coordinator in NIDA's Office of Science Policy and Communications. "Science teachers want information and resources that they can use in their

classes. "NIDA Goes to School" provides teachers with tools they can use to explain the neurobiology of substance abuse. We also hope that teachers will use NIDA as a source for additional fact-based information about drugs."



HHS Secretary Dr. Donna E. Shalala praised the "NIDA Goes to School" campaign at a recent national press conference on teen drug use.

Many of the materials are written specifically for students in grades 5 through 9. Seven *Mind Over Matter* magazines feature the adventures of Sara Bellum, a girl who explores the brain's response to particular drugs and introduces key concepts in neuroscience. The series includes magazines on marijuana, opiates, stimulants, hallucinogens, inhalants, steroids, and nicotine. Each magazine unfolds into a poster with a quote from a noted scientist superimposed on a vivid color image of a brain area or neuron. For example, on the reverse side of the magazine on inhalants is a quote from Nobel

Prize winner Albert von Szent-Györgyi (1893-1986): "Discovery consists of seeing what everybody has seen and thinking what nobody thought."

Also included in the materials is an interactive CD-ROM that features information on drugs of abuse in a variety of television show formats. Called ATOD-TV—ATOD stands for alcohol, tobacco, and other drugs—the CD-ROM was developed by Dr. Danny Wedding of the Missouri Institute of Mental Health with a NIDA Science Education Drug Abuse Partnership Award. In each ATOD-TV show, human and animated characters play out scenarios that illustrate different aspects of drug abuse and addiction. For example, "Neuronet" is a news program that provides information about the brain and how it is affected by drugs. "The Torn and the Troubled" is a soap opera that challenges myths about drugs and addiction. "Wheels of Misfortune" uses a game-show format to supply statistical information about drug use by different populations. An accompanying teacher's guide suggests student activities and provides a comprehensive list of resources for further information.


A Toolbox For Teachers

The “NIDA Goes to School” kit contains the following publications and materials:

- Seven *Mind Over Matter* magazines and 40-page teacher’s guide;
- “ATOD-TV” CD-ROM and 96-page teacher’s guide;
- *Marijuana: Facts for Teens*, a 16-page brochure;
- *Marijuana: Facts Parents Need to Know*, a 28-page brochure;
- *Preventing Drug Abuse in Children and Adolescents: A Research-Based Guide*, a 38-page brochure; and
- Twenty NIDA Infobox information sheets on topics of interest to teachers, such as youth drug abuse trends, descriptions of more than 14 commonly abused drugs, and prevention and treatment methods.

“Our goal for this campaign is to enhance science education, increase science literacy, and encourage young people to pursue careers in the sciences,” says Dr. Sasek. “By introducing students to the science of drug abuse, we hope to stimulate their interest in neuroscience and substance abuse research.”

To Receive This Resource

All materials in the “NIDA Goes to School” kit, with the exception of the ATOD-TV CD-ROM and teacher’s guide, are available free from the National Clearinghouse for Alcohol and Drug Information. The materials also can be downloaded from NIDA’s home page on the World Wide Web at <http://www.nida.nih.gov/>. The “NIDA Goes to School” Web site can be accessed from NIDA’s home page. 

New NIDA Drug Abuse Education Materials for Middle School Students

NIDA has released a new series of drug abuse education materials called *Mind Over Matter*. Designed for students in grades five through nine, the series consists of six full-color glossy magazines that unfold into posters. The package also includes a comprehensive teacher's guide. In each magazine, a girl named Sara Bellum—a play on "cerebellum," a section of the brain that helps control coordination—explores the brain's response to a particular drug and introduces key concepts in neuroscience.

The magazines teach students about the adverse effects of marijuana, opiates, stimulants, hallucinogens, inhalants, and steroids. A seventh in the series, which will discuss nicotine, will be available early in 1998. The magazines are designed to excite students about science in general and neuroscience in particular.

The series uses illustrations and cartoons to provide useful information. Some illustrations show Sara Bellum scuba diving in the depths of the brain, watching drug molecules alter nerve cell activity. The cartoons often depict a nerve cell or body organ performing abnormally under the influence of drugs. For example, a heart playing drums in a rock band loses its rhythm due to cocaine.

The posters on the reverse side of each magazine can be seen after the magazine is unfolded. Each 18- by 38-inch

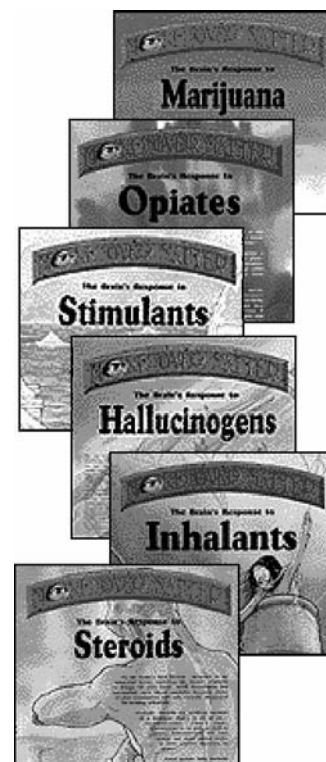
poster has a quote from a well-known scientist superimposed over a vivid color photograph of a brain image or neuron. For example, on the back side of the opiates magazine and superimposed over a photograph of neurons in the brain is a quote from Jacob Bronowski, the late British mathematician, which reads, "The essence of science: Ask an impertinent question, and you are on the way to a pertinent answer."

The teacher's guide provides detailed information on the brain and how drugs of abuse affect it. It also lists resources and suggests activities to help students remember the principles discussed in the magazines.

Mind Over Matter is a product of NIDA's Science Education Program, which funds programs to interest children in pursuing careers in science and to increase knowledge about drug abuse and addiction among the general public. The six magazine-posters and the teacher's guide are available free. To order copies, contact the National Clearinghouse for Alcohol and Drug Information, P.O. Box 2345, Rockville, MD 20847-2345, (800) 729-6686 or (240) 221-4019; TDD number: (800) 487-4889; fax: (240) 221-4292; e-mail: info@health.org. **NN**

Following are the six magazines and their subjects:

- *The Brain's Response to Marijuana* shows how marijuana affects emotions, memory, judgment, balance, and coordination.
- *The Brain's Response to Opiates* discusses how opiates such as heroin act on many places in the brain and spinal cord and how addiction and withdrawal affect neurons.
- *The Brain's Response to Stimulants* demonstrates how cocaine and amphetamines change the way neurons in the brain communicate and disrupt the functioning of the heart and blood vessels.
- *The Brain's Response to Hallucinogens* explains how hallucinogens such as LSD and PCP affect the senses by disrupting the actions of chemical messengers in the brain.
- *The Brain's Response to Inhalants* illustrates how inhalants break down the electrical insulation surrounding many of the body's neurons, making it difficult for them to transmit messages.
- *The Brain's Response to Steroids* describes how anabolic steroids can make people look stronger on the outside and yet cause extensive damage on the inside.



Smoking Any Substance Raises Risk of Lung Infections

By Michael D. Mueller, NIDA NOTES Staff Writer

Smoking any substance—tobacco, marijuana, or “crack,” a smokable form of cocaine—increases a smoker’s risk of developing bacterial pneumonia and other infections of the lungs, according to the findings of drug abuse, smoking and health, and AIDS researchers.

Although some drugs seem to have specific damaging effects when smoked, smoking anything appears to damage or paralyze the cilia, the hair-like projections in the lungs that sweep out microbes and other matter that can cause disease, according to NIDA-funded studies. Damaging the lung’s cilia, the respiratory system’s first line of defense, can have severe consequences for people with weak immune systems, the studies note.

A NIDA workshop held in August 1995 examined current research at that time on the cardio-pulmonary complications of crack cocaine use. In a report summarizing the major findings presented at the workshop, Dr. Pushpa V. Thadani, a pharmacologist in NIDA’s Division of Basic Research, notes that smoking cocaine appears to weaken the crack smoker’s natural resistance to infection in the lungs.

“Pulmonary alveolar macrophages—cells that protect the lungs from infectious agents—are exposed to the highest concentrations of cocaine,” says Dr. Thadani. NIDA-funded studies show that alveolar macrophages from crack cocaine smokers are less active than are alveolar macrophages from nonsmokers in destroying *Staphylococcus aureus*, a common cause of bacterial lung infection. Preliminary findings also indicate that alveolar macrophages of cocaine smokers are more susceptible to HIV-related infections than are alveolar macrophages of people who do not smoke cocaine.

“Much remains unknown about the effects of crack smoking on the alveolar macrophages and other cells of defense in the lungs,” says Dr. Thadani. “However, it appears that there are profound effects, and this needs to be further explored,” she says.

Dr. Donald P. Tashkin, a professor of medicine at the University of California at Los Angeles School of Medicine, and his colleagues recently examined the effects

that habitual smoking of tobacco, marijuana, and/or cocaine has on the lining of the lung’s air passages. The NIDA-funded study included 53 nonsmokers, 14 smokers of crack cocaine only, 40 smokers of marijuana only, and 31 regular tobacco smokers. In addition, there were 16 smokers of both cocaine and marijuana, 12 smokers of cocaine and tobacco, and 44 smokers of both marijuana and tobacco. Thirty-one patients smoked all three substances.

The researchers found that smoking either marijuana or tobacco produces significant damage to the cilia in the lining of the airways. Among smokers of both marijuana and tobacco, it appears that the effects of marijuana add to the effects of tobacco, and vice versa. “The damage to

the ciliated cells in the lining of the airways caused by smoking tobacco, and/or marijuana weakens the ability of the lungs to remove inhaled particles, making the lungs more vulnerable to infection,” says Dr. Tashkin.

Cocaine smokers had fewer significant abnormalities

than marijuana or tobacco smokers did—but more abnormalities than were detected among nonsmokers, Dr. Tashkin says. Among people who smoke both tobacco and cocaine, cocaine smoking appears to produce injury to the mucosal lining of the airways beyond that caused by smoking tobacco alone.

A NIDA-supported study by Dr. Waleska T. Caiaffa and her colleagues at Johns Hopkins University in Baltimore compared the medical records of 40 HIV-positive injecting drug users (IDUs) who had suffered from one bout of bacterial pneumonia with those of 197 HIV-positive IDUs with no history of bacterial pneumonia. The study found that HIV-positive IDUs who smoked illicit drugs were almost twice as likely to develop bacterial pneumonia as were their counterparts who did not smoke illicit drugs. This association was independent of age, degree to which the natural immune system had been suppressed, and cigarette smoking. Among the 77 HIV-positive IDUs who reported smoking drugs, 87.9 percent indicated that they had smoked marijuana, 25.9 percent said that they had used cocaine, and 9.1 percent admitted smoking crack.

Smoking anything appears to damage or paralyze the cilia, the hair-like projections in the lungs that sweep out microbes and other matter that can cause disease.


Smoking is a serious issue among AIDS patients, according to several NIDA-supported studies. The health effects of smoking illicit drugs are above and beyond those caused by smoking cigarettes, the studies note. People with AIDS often die of pneumonia and other lung problems, and smoking tobacco and/or illicit drugs increases the risks for these diseases.

“The effect that smoking has on the lungs is more serious than most people realize. Smoking anything is bad for your health, especially if your immune system has been weakened,” says Dr. Tashkin.

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Studies Show Cognitive Impairments Linger in Heavy Marijuana Users

By Robert Mathias, NIDA NOTES Staff Writer

Students who smoke marijuana heavily may be limiting their ability to learn, according to a NIDA-funded study. The study found that college students who used marijuana regularly had impaired skills related to attention, memory, and learning 24 hours after they had last used the drug. The finding supports the results of previous NIDA-funded research that reported that adults who were chronic heavy marijuana users showed residual impairment in cognitive abilities a day after they had last used marijuana.

"Now we know that for students who smoke marijuana heavily, the ability to learn is affected not just while they are high, but for at least a day after," says NIDA Director Dr. Alan I. Leshner. Together with other NIDA-funded research that has shown a marked increase in daily marijuana use among young people in recent years, this finding underlines the importance of the Marijuana Use Prevention Initiative launched by Health and Human Services Secretary Dr. Donna Shalala last year, Dr. Leshner says. NIDA is playing a leading role in the initiative by providing science-based information to educate the public about the consequences of marijuana use. (For more information, "Marijuana Conference Advances HHS Secretary's Marijuana Initiative," V10-6 November/December 1995, and "Facts About Marijuana and Marijuana Use," V11-1, March/April 1996.)

Regular heavy marijuana use compromises the ability to learn and remember information primarily by impairing the ability to focus, sustain, and shift attention, says Dr. Harrison Pope, Jr., of McLean Hospital in Belmont, Massachusetts, who directed the recent study. Noting that the actual ability to recall information remains relatively unaffected, Dr. Pope says, "If you could get heavy users to learn an item, then they could remember it; the problem was getting them to learn it in the first place."

In the study conducted among college students, Dr. Pope and Dr. Deborah Yurgelun-Todd, also of McLean Hospital, tested the cognitive functioning of 65 heavy cannabis users, most of whom had smoked marijuana at least 27 out of the previous 30 days. The researchers compared the heavy users' cognitive functioning to that of a comparison group of 64 light users, most of whom had smoked marijuana on no more than 3 of the previous 30 days. Heavy users ranged in age from 18 to 24 years and light users from 18 to 28 years. The two groups were similar demographically and had comparable numbers of men and women. Subjects in both groups had smoked marijuana for at least 2 years, and none had smoked regularly for more than a decade.



Using the Wisconsin Card Sorting Test, shown here, Dr. Harrison Pope, Jr. (left) found that 24 hours after they stopped using the drug, heavy marijuana smokers made a greater number of errors than light users made in sorting cards into different categories.

To ensure that the subjects did not smoke marijuana or use other illicit drugs or alcohol during the study, researchers monitored them for 19 to 24 hours. Then the subjects performed a battery of standard tests designed to assess their ability to pay attention, learn, and recall new information. The tests indicated that heavy marijuana users had more difficulty than light users in sustaining and shifting attention and hence in registering, organizing, and using information. Heavy users exhibited these cognitive deficits by being less able than light users were to learn word lists; by making a greater number of errors in sorting cards by different characteristics, such as by color or shape; and by making more errors when the rules for sorting the cards were changed without warning. Men in the heavy users group showed somewhat greater impairment than women in the same group.

While the residual cognitive impairments detected in the study were not severe, they could be significant in the day-to-day life of chronic users, Dr. Pope says. The diminished ability to pay attention and decreased mental flexibility exhibited in these tests may cause chronic marijuana users

important difficulties in adapting to intellectual and interpersonal tasks, he says.

“This is a fairly definitive study because it was methodologically sound and controlled for a wide number of factors, including the possible confounding effects of alcohol and other drug use,” says Dr. Jagjitsing Khalsa of NIDA’s Division of Clinical and Services Research.

Previous studies have produced mixed findings about the residual effects of heavy marijuana use on neuropsychological performance, notes Dr. Khalsa. Methodological problems such as ambiguous terminology, failing to take into account cognitive differences in study participants prior to initiation of marijuana use, and failing to note the possible effect of alcohol and other drugs have raised questions about the results of many of these studies. (For more information about methodological issues, see the Pope, Gruber, and Yurgelun-Todd article listed below.)

The study joins a growing body of research that indicates protracted cognitive impairment among heavy marijuana users.

The study by Dr. Pope and Dr. Yurgelun-Todd joins a growing body of well-controlled and well-designed studies that indicate protracted cognitive impairment among heavy marijuana users, says Dr. Khalsa. For example, in 1993, Dr. Robert Block of the University of Iowa College of Medicine compared adult heavy marijuana users and nonusers ranging in age from 18 to 42 years who had been matched on the basis of their intellectual functioning before the onset of drug use. Subjects who used marijuana frequently—7 or more times weekly for at least 2 years—showed deficits in mathematical skills and verbal expression and selective impairments in memory retrieval processes, the study reported. Although the two studies used different neuropsychological tests, “in general, both

studies showed some impairments in cognitive abilities among heavy marijuana users,” Dr. Block says.

It remains unclear whether marijuana’s short-term residual cognitive impairments are due either to a residue of the drug that remains in the brain after marijuana’s acute effects have dissipated, to a withdrawal effect from abrupt discontinuation of the drug, or to a neurotoxic effect of the drug on brain structure or function. Research has yet to demonstrate conclusively that chronic heavy marijuana use results in cognitive deficits that persist after a prolonged period of abstinence. However, NIDA-supported animal studies do show structural damage to the hippocampus, a structure critical in learning and memory, from the principal psychoactive ingredient in marijuana.

To help answer these and other questions about the long-term effects of marijuana, both Dr. Pope and Dr. Block plan followup studies to examine the effects of chronic heavy marijuana use on cognition and brain function after longer periods of abstinence. Dr. Block proposes to use neuroimaging techniques to look at heavy users’ brains while they perform cognitive tasks to determine whether brain function or structure is altered after abstinence from marijuana for a minimum of 30 hours. Dr. Pope is planning a study to determine if cognitive impairments persist in long-time heavy marijuana users for up to 28 days after they have stopped using marijuana.

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Marijuana Impairs Driving-Related Skills and Workplace Performance

By Robert Mathias, NIDA NOTES Staff Writer

Marijuana use impairs driving-related functions and is linked to a pattern of behaviors that leads to poor job performance, according to two NIDA-supported studies on the effects of marijuana on human performance. Findings from the studies were presented at NIDA's first National Conference on Marijuana Use.

"Driving and marijuana do not mix; that's the bottom line," said Dr. Stephen J. Heishman, a research psychologist in the Clinical Pharmacology Branch of NIDA's Division of Intramural Research. Figures from previous studies of automobile accident victims show that from 6 to 12 percent of nonfatally injured drivers and 4 to 16 percent of fatally injured drivers had tetrahydrocannabinol (THC), the psychoactive ingredient in marijuana, in their bloodstream, Dr. Heishman said. One study showed that 32 percent of drivers in a shock trauma unit in Baltimore had marijuana in their bloodstream, he noted. However, in most of these studies, the majority of subjects who tested positive for THC also tested positive for alcohol, making it difficult to single out THC's effect on driving.

In a laboratory study at NIDA's Addiction Research Center in Baltimore that controlled for alcohol's confounding effect, Dr. Heishman tested marijuana's effects on the functional components of driving. Study subjects smoked a marijuana cigarette, waited 10 minutes, then smoked another cigarette. Both cigarettes contained either 0, 1.8, or 3.6 percent THC. Twenty minutes after smoking the cigarettes, the subjects were given a standard sobriety test similar to a roadside sobriety test. The test showed that marijuana significantly impaired their ability to stand on one leg for 30 seconds or touch their finger to their nose. As the dose of THC increased, the subjects swayed more, raised their arms, and had to put their feet down in an attempt to maintain their balance. Subjects also committed 2.5 times more errors when they attempted to touch their nose with their finger.

The data from these laboratory studies show that marijuana impairs balance and coordination—functional components important to driving—in a dose-related way, said Dr. Heishman. These effects may be related to reported marijuana-induced impairment of automobile driving, he stated.

Highway and urban driving studies conducted in the Netherlands show less impact on actual driving. However,



At NIDA's National Conference on Marijuana Use, Dr. Stephen Heishman presented data from laboratory studies showing that marijuana impairs functions important to driving.

these driving studies used very low doses of marijuana for safety reasons, Dr. Heishman said. Future research using appropriate safety measures should test the effect of higher doses of marijuana on driving as well as the combined effect of marijuana and alcohol on driving, he concluded.

In another study, Dr. Wayne Lehman of Texas Christian University looked at how marijuana affects job performance. A series of surveys he conducted among 4,600 municipal employees in four cities in the Southwest indicated that 8 percent of employees had smoked marijuana in the past year, and a large percentage of these users had smoked marijuana in the past month, Dr. Lehman said.

"Employees who report marijuana use are different from nonusers," said Dr. Lehman. They are much more likely than nonusers to have arrest histories, low self-esteem, high rates of depression, and friends who are deviant. Many marijuana smokers also have alcohol-related problems. One-third of marijuana users in the surveys reported they drank frequently, one-half said they got drunk, and 60 percent reported a problem with alcohol use, according to Dr. Lehman.

This behavioral pattern in the personal backgrounds of marijuana-smoking employees was associated with negative attitudes toward work and job performance, Dr. Lehman said. The surveys found that marijuana users were less likely than nonusers to commit to the organization, had less faith in management, and experienced low job satisfaction. These workers reported more absenteeism, tardiness, accidents, workers' compensation claims, and job turnover than workers who had not used marijuana. They were also more likely to report to work with a hangover, miss work because of a hangover, and be drunk or use drugs at work.

These data indicate that marijuana use is strongly associated with problematic alcohol use and a pattern of general deviance that leads to impaired behaviors and poor workplace performance, Dr. Lehman concluded. **NN**

Marijuana Antagonist Reveals Evidence of THC Dependence in Rats

By Neil Swan, NIDA NOTES Contributing Writer

For the first time, researchers have demonstrated that marijuana may cause drug dependency in animals. This finding was made possible by the recent development of a potent marijuana antagonist—an agent that blocks many effects of the drug. The marijuana antagonist appears to act like an on-off switch, allowing researchers to control the effects of withdrawal from delta-9-tetrahydrocannabinol (THC), the principal psychoactive ingredient of marijuana.

Dr. Billy Martin, a NIDA-funded marijuana researcher at Virginia Commonwealth University's Medical College of Virginia, who conducted one of two initial studies, presented his findings at NIDA's National Conference on Marijuana Use: Prevention, Treatment, and Research last summer. During his research, rats were exposed to THC for 4 days, then given a dose of the THC antagonist SR 141716A, which was developed by French scientists last year. The rats immediately and "dramatically" exhibited classic rodent behavioral withdrawal symptoms, indicating that they were dependent on THC, Dr. Martin said.

Within 10 minutes after administration of the marijuana antagonist, the rats exhibited behavior that included "wet-dog shakes" and facial rubbing, which constitute "definite evidence of withdrawal" from the effects of THC, said Dr. Martin. This behavior mimics long-observed opiate withdrawal symptoms in rodents.

The shakes and rubbing were so striking and frequent that they could be quantified by trained observers. Other, less frequent withdrawal-like behaviors included head shakes, biting, drooping eyelids, retropulsion (backing away), ear twitching, chewing, licking, and arching the back, Dr. Martin said.

The wet-dog shakes were dose-dependent, meaning they became more pronounced as dose levels of the antagonist were increased in the THC-exposed animals.

Dr. Martin acknowledged that such behavior is not like any marijuana withdrawal syndrome in humans.

"The fact that people do seek treatment for marijuana dependence is evidence of marijuana withdrawal in humans, but, even among those seeking treatment, we do not see dramatic withdrawal symptoms," said Dr. Martin.



Dr. Billy Martin found that when rats that are administered the main psychoactive ingredient in marijuana are then given doses of a compound that blocks the action of this ingredient, the rats "dramatically" exhibit classic rodent withdrawal symptoms.

"That's because the withdrawal process in humans is so long and drawn out, evidenced chiefly by mild distress or anxiety. But with the rats, using SR 141716A as an effective antagonist, we compress and accentuate that withdrawal process. The challenge for us now is to use these animal data to design human studies—to determine how small a dose of THC is needed to become dependent on marijuana," said Dr. Martin.

Dr. Martin, senior investigator Dr. Mario D. Aceto, and colleagues at the Department of Pharmacology and Toxicology of Virginia Commonwealth University have published the results of their research.

"We have been searching for a marijuana antagonist for many years," said Dr. Martin, who has been a marijuana researcher for 22 years.

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