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Cognitive Functioning of Long-term Heavy Cannabis Users Seeking Treatment

Nadia Solowij, PhD
Robert S. Stephens, PhD
Roger A. Roffman, DSW
Thomas Babor, PhD, MPH
Ronald Kadden, PhD
Michael Miller, PhD
Kenneth Christiansen, PsyD
Bonnie McRee, MPH
Janice Vendetti, MPH
for the Marijuana Treatment Project Research Group

Context Cognitive impairments are associated with long-term cannabis use, but the parameters of use that contribute to impairments and the nature and endurance of cognitive dysfunction remain uncertain.

Objective To examine the effects of duration of cannabis use on specific areas of cognitive functioning among users seeking treatment for cannabis dependence.

Design, Setting, and Participants Multisite retrospective cross-sectional neuropsychological study conducted in the United States (Seattle, Wash; Farmington, Conn, and Miami, Fla) between 1997 and 2000 among 102 near-daily cannabis users (51 long-term users: mean, 23.9 years of use; 51 shorter-term users: mean, 10.2 years of use) compared with 33 nonuser controls.

Main Outcome Measures Measures from 9 standard neuropsychological tests that assessed attention, memory, and executive functioning, and were administered prior to entry to a treatment program and following a median 17-hour abstinence.

Results Long-term cannabis users performed significantly less well than shorter-term users and controls on tests of memory and attention. On the Rey Auditory Verbal Learning Test, long-term users recalled significantly fewer words than either shorter-term users ($P = .001$) or controls ($P = .005$), there was no difference between shorter-term users and controls. Long-term users showed impaired learning ($P = .007$), retention ($P = .003$), and retrieval ($P = .002$) compared with controls. Both user groups performed poorly on a time estimation task ($P < .001$ vs controls). Performance measures often correlated significantly with the duration of cannabis use, being worse with increasing years of use, but were unrelated to withdrawal symptoms and persisted after controlling for recent cannabis use and other drug use.

Conclusions These results confirm that long-term heavy cannabis users show impairments in memory and attention that endure beyond the period of intoxication and worsen with increasing years of regular cannabis use.

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IN THE CURRENT CLIMATE OF DEBATE about marijuana laws and interest in marijuana as medicine,[1] one issue remains unresolved. Does heavy, frequent, or prolonged use of cannabis lead to a deterioration in cognitive function that persists well beyond any period of acute intoxication? Is the functioning of the brain altered in the long term? With over 7 million people using cannabis weekly or more often in the United States alone[2] and the potential for increased physician recommendations for select patients to use cannabis therapeutically,[1] answers to these questions are of significant public health concern.[3,4] Scientific evidence from past research clearly showed that gross impairment related to chronic cannabis use did not occur but was inconclusive with regard to the presence of more specific deficits.[5,6] Recent studies with improved methods have demonstrated changes in cognition and brain function associated with long-term or frequent use of cannabis. Specific impairments of attention, memory, and executive function have been found in cannabis users in the unintoxicated state (and in children exposed to cannabis in utero[7]) in controlled studies using brain event-related potential techniques[6,8-10] and neuropsychological assessments[11-15] including complex tasks.

Brain imaging studies of cannabis users have demonstrated altered function, blood flow, and metabolism in prefrontal and cerebellar regions.[16-19] Studies failing to detect cognitive decline associated with cannabis use[20] may reflect insufficient heavy or chronic use of cannabis in the sample or the use of insensitive assessment instruments. Impairments appear to increase with duration and frequency of cannabis use; however, the parameters of use that are associated with short- or long-lasting cognitive and brain dysfunction have not

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Author Affiliations: National Drug and Alcohol Research Centre, University of New South Wales, Sydney, and Department of Psychology, University of Wollongong, Wollongong (Dr Solowij), New South Wales, Australia; Department of Psychology, Virginia Polytechnic Institute and State University, Blacksburg, Va (Dr Stephens); Innovative Programs Research Group, School of Social Work, University of Washington, Seattle (Dr Roffman); Department of Community Medicine (Dr Babor and Mss McRee and Vendetti) and Department of Psychiatry (Dr Kadden), University of Connecticut Health Center, Farmington, and The Village South Inc, Miami, Fla (Drs Miller and Christiansen).
Other Members of the Marijuana Treatment Project Research Group are listed at the end of this article.
Corresponding Author and Reprints: Nadia Solowij, PhD, National Drug and Alcohol Research Centre, University of New South Wales, Sydney, NSW 2052, Australia (e-mail: n.solowij@unsw.edu.au).

been fully elucidated. The attribution of deficits to lingering acute effects, drug residues, abstinence effects, or lasting changes caused by chronic use continues to be debated.[5,6] Animal research suggests an important role for the cannabinoid receptor in regulating the neural activity critical for memory processing.[21-24] Long-term use of cannabis may result in altered functioning of the cannabinoid receptor and its associated neuromodulator systems.

This study investigated the nature of cognitive impairments associated with long-term cannabis use employing data collected from a large clinical trial of chronic users seeking treatment for cannabis dependence. The study compared 102 cannabis users assessed prior to treatment on carefully selected neuropsychological tests with 33 nonuser controls. The parameters of cannabis use that contribute to impairment were examined. It was hypothesized that performance would deteriorate as the number of years of regular use increased.

METHODS

Design

A multisite, retrospective, cross-sectional comparison-group design was used to compare (1) long-term users with a mean of 23.9 years of regular cannabis use, (2) shorter-term users with a mean of 10.2 years of regular use, and (3) nonusers of cannabis. Key confounding variables (age, IQ, other drug use) were controlled through matching or statistical methods. The sample size required for this study was determined by estimating a 94% chance of detecting a moderate effect size of 0.5 SD units at a 2-tailed α of .05.

Recruitment Procedure and Assessment of Drug Use

Sixty-five of the 102 cannabis users were delayed-treatment participants from the Marijuana Treatment Project, a multisite US study (Seattle, Wash; Farmington, Conn; and Miami, Fla) conducted between 1997 and 2000 of the effectiveness of brief treatments for cannabis dependence.[25] The remainder were recruited through the Marijuana Treatment Project specifically for this study. Participants provided written informed consent as approved by the ethics committees of the participating institutions and were paid $75 for completing the cognitive assessments. Controls (n = 33) were recruited from the general population through media advertisements at only 1 site. The controls were told that the researchers were studying the effects of exposure to drugs and alcohol on cognitive functioning, and that at present only individuals at the lighter end of the spectrum of drug experience were required. The aim was to minimize cannabis use among controls while approximating the other characteristics of the cannabis-using sample. Assessors were not blinded with regard to group assignment. Self-reported drug and alcohol use were assessed by the Addiction Severity Index,[26] a separate structured interview, and the Time Line Follow Back procedure.[27,28] The Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV)* Axis I Disorders (SCID)[29] assessed cannabis dependence. Duration of regular (at least twice per month) cannabis use was an averaged composite measure derived from the Addiction Severity Index, SCID, and the structured interview. Current frequency of cannabis use was calculated from the Time Line Follow Back procedure.

Inclusion/Exclusion Criteria

Cannabis users were included if they had used cannabis regularly for at least 3 years, were currently using at least once a week, were seeking treatment to assist them to cease or reduce their use of cannabis, and were willing to participate in the treatment program offered. Participants were excluded if they had ever had a serious illness or injury that may have affected the brain, any psychotic disorder, met a current *DSM-IV* diagnosis of dependence on any other drug or alcohol, or had a poor command of the English language.

Sample Characteristics

TABLE 1 provides demographic information and cannabis use parameters.

Table 1. Demographic and Cannabis Use Details of the Sample*

	Cannabis Users			
	All	Shorter-term Users	Long-term Users	Controls
No.	102	51	51	33
Sex, male (%)	75 (74)	36 (71)	39 (76)	22 (67)
Age, mean (SD) [range], y	35.4 (8.6) [19-55]	28.7 (5.5) [19-45]†	42.1 (5.2) [34-55]†	34.8 (11.1) [19-65]
Education, mean (SD) [range], y‡	14.3 (2.3) [10-22]	14.1 (2.5) [10-22]	14.5 (2.0) [11-20]	14.8 (1.8) [12-18]
Full-scale IQ, mean (SD) [range]§	105.4 (6.7) [87.4-118.5]‖	105.1 (7.4) [87.4-118.5]	105.7 (5.9) [92.7-118.3]	107.9 (4.7) [94.5-117.2]
Duration of use, mean (SD) [range], y¶	17.1 (7.9) [2.7-31.7]	10.2 (3.8) [2.7-17.0]	23.9 (4.1) [17.3-31.7]	
Frequency of use, median (range), d/mo#	27.9 (3.5-30)	28.3 (5.2-30)	27.4 (3.5-30)	

*Ellipses indicate not applicable.
†Significantly different from controls at $P < .001$.
‡The self-reported number of years of formal education completed.
§Estimated from a combination of North American Adult Reading Test, Wide Range Achievement Test–Revised reading subtest scores, and the Barona index.
‖Significantly different from controls at $P < .05$.
¶The number of years that cannabis had been used since regular use commenced (at least twice per month), composite from self-report, Addiction Severity Index, and Structured Clinical Interview Axis 1 Disorders assessments.
#The median number of days per month that cannabis was used at entry to the study, based on average use per 30 days from self-reported use during the past 14 weeks.

The user group was split at the median for duration of cannabis use to enable comparisons of long-term users, shorter-term users, and controls. No meaningful division of groups could be achieved on the basis of frequency of cannabis use, which was almost daily for the majority of the sample. Sex distribution and years of education did not differ between groups. The majority of users (68.6%) and controls (63.6%) were white. Overall, users and controls did not differ in age, but long-term users were significantly older and shorter-term users were significantly younger than controls ($P<.001$). Premorbid intelligence was estimated by several methods and averaged: the Wide Range Achievement Test—Revised reading subtest (WRAT-R READ)[30,31]; the North American Adult Reading Test (NAART)[32]; and the Barona Index.[33] The mean estimated full-scale IQ (FSIQ) did not differ between the 3 groups based on duration of cannabis use. The majority of the sample (82.4% long-term, 88.2% shorter-term users) reported experiencing problems with memory, attention, or concentration, which they attributed to their use of cannabis.

Cannabis Use, Required Abstinence, and Urinalysis

Users first tried cannabis at a mean age of 15.3 (SD, 2.6) years with regular use (at least twice a month) commencing at age 17.5 (SD, 3.2) years. Cannabis had been used on a median 29 of the past 30 days (range, 1-30). Almost the entire sample (98%) met the *DSM-IV* criteria for cannabis dependence. The median amount of cannabis smoked per week was 1 quarter of an ounce (range, 0.01-2.00 oz) with 2 average-sized joints typically smoked per day (range, 0.12-20.00). None of these cannabis-use parameters differed between the long- and shorter-term user groups. Twenty-two controls had either never tried cannabis or used it 10 or fewer times in their lives and 11 had used cannabis weekly to monthly while at school or college between 4 and 30 years ago. Controls with a history of cannabis use were excluded from "pure sample" analyses.

Participants were required to abstain from cannabis for at least 12 hours prior to testing and to provide 2 urine samples (1 the night before testing, another during the test session). The median self-reported time since last use of cannabis was 17 hours (range, 7-240 hours); this did not differ between long- and shorter-term users. At the time of testing, 70% of the sample reported that they were not experiencing any discomfort after abstaining from cannabis. Twice as many shorter-term users than long-term users ($P=.03$) reported mild withdrawal symptoms such as cravings, irritability, depression, anxiety, sleep, or appetite disturbances. In 78.3% of cases, creatinine-normalized urinary cannabinoid metabolite (THC-COOH) levels on the day of testing were less than or equivalent to those from the night before.[34,35] Abstinence from cannabis was supported by significant correlations between the level of normalized urinary cannabinoid metabolite on the day of testing and the self-reported time since last use (bivariate correlation coefficient [r], −0.46, $P<.001$), and the quantity used on the last occasion divided by the time since last use (r, 0.39; $P<.001$). The effects of these measures of recent use were examined in relation to test performance. "Pure sample" analyses excluded users with higher metabolites in the second urine sample. No cannabinoid metabolites were detected in the urine of the control participants.

Other Drug Use

No other drug metabolites were detected in any urine sample. Tobacco and alcohol use was minimal. Alcohol was consumed on a median of 3.4 and 1.7 days per month among users and controls, respectively. Almost one third of users and 46.8% of controls drank less than once a month or not at all. Forty-eight percent of the cannabis users had only tried drugs other than cannabis a few times or never; 52% had used other drugs socially/recreationally primarily during high school and college. Past histories of regular drug use included cocaine (n=24), amphetamines (n=11), hallucinogens (n=17), and sedatives/hypnotics or minor tranquilizers (n=7). Current use of other drugs was less than once a month or not at all for 93.1% of the sample. More than half of the controls (51.5%) had never tried any other drug and the remainder had only tried other drugs experimentally. "Pure sample" analyses excluded all participants with histories of regular or heavy use of alcohol or other drugs.

Neuropsychological Tests and Procedures

Nine neuropsychological tests were administered in the order listed in TABLE 2,[36-46] along with the 2 tests used to assess premorbid IQ.[30-32] A 10-minute rest break was given after the Rey Auditory Verbal Learning Test (RAVLT) Recognition test. Tests were administered by trained assistants and took approximately 2 hours to complete. Quality assurance procedures were adopted to ensure that procedures were standardized at each site with ongoing supervision and review of audiotaped assessments by centralized staff throughout the course of the study.

Data Analysis

Each cognitive test was analysed using SPSS version 10.0 (SPSS Institute, Chicago, Ill) with analysis of covariance (ANCOVA) for normally distributed variables or nonparametric tests of group differences for skewed data. The FSIQ and age were included as covariates in analyses where they correlated with test performance. All participants were initially included in analysis, with the overall cannabis user sample first compared with the control group (evaluated at $P<.05$), followed by comparisons on the basis of duration of cannabis use (long- vs shorter-term users vs controls, evaluated at $P<.01$). For 2-way interactions, the Greenhouse-Geisser method was used to adjust the df where appropriate and for multiple comparisons, a Bonferroni adjustment controlled for type I error. Analysis of covariance was repeated on a purer sample that strictly

Table 2. Neuropsychological Tests Administered and Cognitive Functions Assessed*

Neuropsychological Test	Cognitive Functions Assessed
Wide Range Achievement Test–Revised reading subtest (WRAT-R READ)[36,37]	Premorbid IQ
Speed of Comprehension (SOC) test (Speed and Capacity of Language Processing [SCOLP])[38]	Rate of verbal information processing
Rey Auditory Verbal Learning Test (RAVLT)[39-41]	Memory span, verbal learning and retrieval efficiency, susceptibility to interference
Stroop Test[42] with additional interference condition[43]	Attention, cognitive flexibility, inhibition of distractor stimuli, suppression of habitual response
Wisconsin Card Sorting Test: (WCST) computerized[44]	Problem solving, conceptual ability
Alphabet Task†	Cognitive flexibility, executive function
Omitted Numbers‡	Working memory
Time Estimation and Production§	Temporal judgment
RAVLT 20-minute delay trial (VII) Recognition test	Long-term retention, recognition memory
North American Adult Reading Test (NAART)[37]	Premorbid IQ
Auditory Consonant Trigrams (Brown-Peterson)[45]	Short-term retention under distractor conditions
Paced Auditory Serial Addition Test (PASAT)[46]	Information processing, working memory, divided and sustained attention

*Tests were administered in the order listed.
†Composed of timed loud, silent, and alternating recite trials.
‡Recognition of omitted item from a jumbled aural list of numbers from 1 to 10 (10 trials).
§Composed of 3 trials: unwarned estimation of time to complete the preceding task (mean, 1 minutes 18 seconds) (Time Estimation A), time production (1 minute 40 seconds), and warned passive estimation (2 minutes) (Time Estimation B).

excluded those participants with either a history of other drug use or possible recent use of cannabis prior to testing. Semipartial correlations examined the unique contributions of FSIQ, age, duration of cannabis use, and recency of cannabis use to the variance in cognitive test performance.

RESULTS

Results from the 9 neuropsychological tests are shown in TABLE 3 for cannabis users overall, for groups based on duration of cannabis use, and for controls. Effect sizes are calculated between long-term users and controls using the SD of the controls.

Speed of Comprehension

Cannabis user groups did not differ from controls in the number of items completed (range, 23-100) but users overall made more errors ($P = .03$) (range, 0-5). These results suggest that cannabis users are more likely to sacrifice accuracy for speed.

Rey Auditory Verbal Learning Test

Mean words recalled on each trial are depicted in the FIGURE. The learning curves of shorter-term users and controls were similar but long-term users showed a learning curve with a less steep gradient and long-term users recalled fewer words on every trial. The sum of words recalled across all trials I through VII inclusive of trial B (referred to here as RAVLT sum, range, 37-114) correlated significantly and inversely with the duration of cannabis use after controlling for age and FSIQ (partial $r_s = 0.23$; $P = .01$). When analysed by ANCOVA, there was a significant effect of group ($F_{2,127} = 8.36$, $P < .001$) whereby long-term users recalled significantly fewer words than either shorter-term users (95% confidence interval [CI] for difference, 3.84-19.18; $P = .001$) or controls (95% CI for difference, 2.83-19.93; $P = .005$) with no difference between shorter-term users and controls. When all trials were included in a repeated measures ANCOVA, a significant interaction between group and trial ($F_{14.889} = 2.84$, $P = .007$) suggested that long-term users recalled fewer words than shorter-term users or controls on every trial ($P < .05$ for each comparison) except the first, with a trend on trial B (the interference list presented only once; $P = .08$).

The proportion of subjects with a very poor learning ability (acquisition <3 words over 5 trials) was greater among long-term users (13.7%) than controls (0%) ($P = .007$) but not shorter-term users (5.9%). The proportion of long-term users recalling fewer than 10 words on trial V (27.5%) was more than among shorter-term users (8.5%) or controls (3.0%) ($P = .002$). Significantly more long-term users (23.5%) lost 3 or more words over the 20-minute delay between trials VI and VII than shorter-term users (4.3%) or controls (3.0%) ($P = .003$). Long-term users showed a smaller primacy effect in the serial position curve than either other group ($P = .02$). Groups did not differ in the recency effect or in words recalled from the middle of the list.

Users overall and long-term users recognized fewer words than controls from list A (overall, $P = .03$; long-term, $P = .01$) and list B (overall, $P = .01$; long-term, $P = .04$) but long-term users did not differ from shorter-term users. More than half of the long-term users (55%) had a recognition score for list A of 12 or less compared with 28% of shorter-term users and 21% of controls ($P = .002$). Long-term users misassigned more words (median, 2) than shorter-term users and controls (each median, 0) ($P < .001$). A greater proportion of long-term users (13.7%) compared with shorter-term users (6.4%) and controls (0%) actually identified fewer words on recognition than they had just prior during recall on trial VII ($P = .02$). Long-term users' performance was significantly poorer than published norms[47] for the general population on most measures from the RAVLT.

Stroop Test

Cannabis users did not differ significantly from controls after inclusion of covariates in any condition or on interference scores. While there were no performance differences between Color-Word (CW) and Color-Read (CR) in the control group, performance on CR was, however, poorer than on CW in both long- ($P < .001$) and shorter-term

users ($P = .03$). Color-Read was the additional interference condition designed to increase demands on executive function.[43] There was an inverse relationship between duration of cannabis use and number of items completed on CR (partial $r = -0.27$; $P = .003$) and CW (partial $r = -0.27$, $P = .004$) after controlling for age and FSIQ. These results suggest that cannabis users are vulnerable to task complexity with increasing demands creating more sources of interference that adversely affect performance.

Wisconsin Card Sorting Test

There were no significant group differences on any Wisconsin Card Sorting Test (WCST) measure but a trend on one. Long-term users failed to maintain the set more often than shorter-term users ($P = .05$) or controls ($P = .07$). Research suggests that this measure best represents attentional dysfunction.[30] There was no evidence of impaired performance with increasing years of cannabis use after controlling for covariates.

Table 3. Neuropsychological Test Results

Test*	Cannabis Users*			Controls (n = 33)	Effect Size	*P* Value for Comparisons			
	All (n = 102)	Shorter-term Users (n = 51)	Long-term Users (n = 51)			All vs Controls	Shorter-term Users vs Controls	Long-term Users vs Controls	Shorter- vs Long-term Users
SCOLP-SOC median (range)†									
Correct	10 (3-18)	11 (6-18)	10 (3-17)	10 (6-15)		.06	.07	.10	.65
Errors	1 (0-8)	1 (0-8)	1 (0-6)	0 (0-3)		.03	.05	.05	.99
RAVLT, mean (SD)‡									
Trial I	6.3 (1.9)	6.5 (1.9)	6.1 (1.9)	7.0 (1.9)	0.47	.12	> .99	.15	.59
Trial II	9.3 (2.7)	9.9 (2.6)	8.5 (2.5)*	9.9 (2.3)	0.61	.27	> .99	.05	.004
Trial III	10.8 (2.5)	11.5 (2.3)	10.1 (2.6)*	11.4 (2.2)	0.59	.37	> .99	.07	.003
Trial IV	11.5 (2.3)	12.1 (2.2)	10.9 (2.4)*	12.4 (2.2)	0.68	.10	> .99	.02	.01
Trial V	12.2 (2.3)	12.7 (2.1)	11.5 (2.4)*	12.9 (1.6)	0.88	.19	> .99	.03	.005
Trial B	6.0 (2.3)	6.5 (2.4)	5.5 (2.2)	6.9 (2.5)	0.56	.18	> .99	.05	.07
Trial VI	10.0 (3.0)	10.9 (2.8)	9.2 (3.1)*	11.4 (2.2)	1.00	.07	> .99	.005	.002
Trial VII	9.6 (3.5)*	11.1 (3.1)	8.5 (3.5)*	11.0 (2.7)	0.93	.13	> .99	.004	< .001
RAVLT, sum	75.6 (17.2)*	81.4 (15.8)	70.3 (16.8)*	82.9 (14.8)	0.85	.14	> .99	.005	< .001
Recognition	12.1 (3.1)*	13.1 (2.3)	11.1 (3.4)*	13.3 (1.7)	1.29	.03	> .99	.01	.14
Recognition	6.1 (3.7)*	7.2 (3.7)	5.0 (3.5)*	8.2 (3.2)	1.00	.01	> .99	.04	.26
Stroop, mean (SD)§									
Word	101.3 (15.1)	100.2 (16.4)	102.2 (14.0)	107.0 (15.9)	0.30	.13	.99	.34	> .99
Color	75.6 (12.2)	75.8 (13.4)	75.4 (11.1)	74.5 (13.3)	0.07	.50	> .99	> .99	> .99
Color-Word	45.4 (9.2)*	46.8 (9.4)	44.0 (8.8)	44.4 (10.2)	0.04	.25	.55	> .99	> .99
Color-Read	40.1 (7.9)*	42.2 (9.0)	37.7 (6.2)	41.4 (7.9)	0.47	.92	> .99	> .99	.42
WCST, median (range)									
Errors	28 (16-81)	27 (16-77)	29 (17-81)	30 (15-78)		.67	.29	.77	.08
Perseverative responses	16 (7-49)	16 (7-45)	15 (6-49)	14 (8-63)		.95	.55	.49	.17
% Concept	72.7 (12.5-86.7)	73.1 (14.8-85.9)	71.9 (12.5-86.7)	71.9 (16.4-88.3)		.82	.38	.64	.12
Trials	13 (10-75)	13 (11-64)	12 (10-75)	13 (10-101)		.75	.90	.67	.74
Failures	1 (0-7)	1 (0-5)	2 (0-7)	1 (0-4)		.42	.74	.07	.05
Alphabet Task, median (range)¶									
Alternating	18.6 (10.4-52.4)*	16.8 (10.4-37.2)	19.8 (13.0-52.4)	17.5 (11.5-33.2)		.31	.91	.08	.07
Difference	11.3 (4.8-39.9)*	10.3 (5.0-29.6)	12.3 (4.8-39.9)	8.8 (3.2-24.7)		.14	.54	.04	.09
Omitted Numbers, mean (SD)#	6.7 (1.8)	7.0 (1.8)	6.4 (1.9)	6.3 (2.1)	0.05	.13	.64	.53	> .99
Time Estimation, s**									
Unwarned Task A, mean (SD)	-64.4 (53.5)*	-61.3 (54.1)*	-67.7 (53.2)*	-7.6 (88.6)	0.68	<.001	<.001	.01	> .99
Warned Task B, median (range)	-1.0 (-55 to 85)	-1.5 (-55 to 85)	-0.5 (-40 to 75)	5 (-70 to 102)		.65	.67	.70	.96
Time Production, mean (SD)	-15.6 (24.6)	-14.9 (25.7)	-16.4 (23.6)	-19.0 (26.2)	0.10	.24	> .99	.34	.79
Auditory Consonant Trigrams, mean (SD), seconds of delay††									
9	11.4 (2.7)*	12.1 (2.3)	10.7 (2.9)*	12.9 (1.9)	1.16	.03	> .99	.002	.007
18	11.3 (2.5)	11.7 (2.0)	10.9 (3.0)	11.5 (2.8)	0.21	.79	.92	> .99	.23
36	10.9 (2.9)	11.2 (2.9)	10.7 (2.9)	11.0 (2.7)	0.11	.84	> .99	> .99	.94

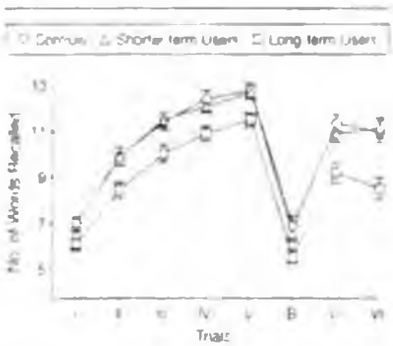
(continued)

Table 3. Neuropsychological Test Results (cont)

Test	Cannabis Users					*P* Value for Comparisons			
	All (n = 102)	Shorter-term Users (n = 51)	Long-term Users (n = 51)	Controls (n = 33)	Effect Size	All vs Controls	Shorter-term Users vs Controls	Long-term Users vs Controls	Shorter- vs Long-term Users
PASAT, median (range)‡‡									
PR Trial 1	2.56 (2.40-4.56)	2.51 (2.40-3.60	2.58 (2.40-4.56)*	2.56 (2.40-3.56)		.92	.16	.23	.007
PR Trial 2	2.23 (2.00-3.53)	2.18 (2.00-2.83)	2.28 (2.00-3.53)	2.24 (2.00-3.05)		.43	.84	.10	.03
PR Trial 3	1.79 (1.60-3.56)	1.78 (1.60-3.56)	1.81 (1.60-2.52)	1.76 (1.60-2.63)		.20	.49	**	.35
PR Trial 4	1.36 (1.20-2.31)	1.35 (1.20-1.80)	1.38 (1.20-2.31)	1.33 (1.20-2.00)			.54	.15	.22
Total PR	8.07 (7.32-10.81)	7.90 (7.36-9.95)	8.21 (7.32-10.81)	7.85 (7.37-10.53)			.87	.06	.02
Total attempted	142.5 (74-191)	146.0 (96-191)	139.0 (74-188)	145.5 (110-190)		.75	.99	.56	.45
Total correct	127.0 (26.5)	132.0 (26.8)	121.9 (25.4)	131.6 (28.9)	0.34	.74	> .99	.84	.22
% Correct	64.8 (13.5)	67.3 (13.7)	62.2 (13.0)	67.1 (14.7)	0.33	.74	> .99	.84	.22
Seconds	2.76 (1.86-5.88)	2.64 (1.88-4.67)	2.94 (2.09-5.88)	2.71 (1.89-4.54)		.52	.97	.23	.14

*Significant correlation with the number of years of cannabis use after controlling for covariates ($P < .05$).
†SCOLP-SOC indicates Speed and Capacity of Language Processing Speed of Comprehension test. Median scaled scores for the number of SOC test items completed in 2 minutes and errors (n = 98 users, n = 32 controls). Ellipses indicate not applicable.
‡RAVLT indicates Rey Auditory Verbal Learning Test. Mean words recalled on each trial of the RAVLT, total recalled across all trials (RAVLT sum), and median words recognized from lists A and B (NR, 100 users varied on each trial).
§Mean items completed in 45 seconds for the Word, Color, and Color-Word conditions of the Stroop (age corrected, n = 100 users) and the modified Color Reed condition (n = 101 users).
‖WCST indicates Wisconsin Card Sorting Test. Median errors, perseverative responses, percentage of conceptual-level responses, trials to complete the first category, and failures to maintain the set (n = 101 users, n = 32 controls).
¶Median time to recite the alphabet alternating from loud to silent and median difference between the loud and alternating trials in seconds (n = 94 users, n = 29 controls).
#Mean number of correctly identified items from the Omitted Numbers task.
**Mean difference between actual time elapsed and estimated time in unwarned Time Estimation task A (negative scores indicate underestimation; n = 94 users, n = 31 controls); median difference in warned Time Estimation task B (n = 98 users, n = 32 controls); and mean difference between time produced and time required in the Time Production task (n = 102 users, n = 30 controls).
††Mean letters recalled with 9-, 18-, and 36-second delays (n = 31 controls).
‡‡Paced Auditory Serial Addition Test (PASAT). Median processing rates (PRs) for PASAT trials 1-4, total PR, total attempted, total correct (mean [SD]), percentage correct (mean [SD]), and seconds per correct response across the 4 trials (n = 98-100 users, n = 33 controls).

Figure. Mean Number of Words Recalled on Each Trial of the Rey Auditory Verbal Learning Test by Long- and Shorter-term Cannabis Users and Controls



Error bars represent SDs

Alphabet Task and Omitted Numbers

Groups did not differ in the time taken to complete any trial of the Alphabet Task or in the number of items correct in the Omitted Numbers task. The log time to complete the alternating trial of the Alphabet Task increased as a function of duration of cannabis use (partial r, 0.26, $P = .006$), as did the square root difference between times taken to complete the alternating and loud trials, an index of interference and lack of flexibility (partial r, 0.26, $P = .006$).

Time Estimation Tasks

Cannabis users differed from controls ($P < .001$) in Time Estimation Task A where they estimated the time taken to complete the preceding (Omitted Numbers) task. Both long- and shorter-term users underestimated the time by about one third of the actual time taken (64.4 seconds) and differed significantly from controls ($P = .01$ and $P < .001$, respectively). Groups did not differ in the simple and brief warned passive Time Estimation Task B or Time Production, where they could use strategies such as counting. Time estimation measures did not correlate with duration of cannabis use.

Auditory Consonant Trigrams

Long-term users recalled significantly fewer items than shorter-term users ($P = .007$), controls ($P = .002$), and published norms[46] on only the 9-second delay condition. The number of items recalled did not correlate with duration of cannabis use. In the general population, the greater the delay interval the worse the performance. In cannabis users, this general pattern was apparent, though there was greater interference at the shorter delay interval than would be expected.

Paced Auditory Serial Addition Test

Long-term users had slower processing rates than shorter-term users on trial 1 ($P = .007$), with trends on trial 2 ($P = .03$) and the total processing rate across all trials ($P = .02$). Group differences on all other measures failed to reach significance but the performance of the long-term users was poorer in comparison with one set of norms[46] but not another.[30]

Pure Effects Attributable to Cannabis Use and Effects of Recent vs Chronic Use

Excluding all participants with histories of regular other drug or alcohol use, dependence or treatment, and controls with any history of regular cannabis use within the past 20 years reduced the sample to 27 long-term users, 33 shorter-term users, and 26 controls. Despite the

reduction in power to detect differences between groups, there remained a significant difference with $\alpha = .05$ between long-term users and controls on RAVLTsum ($P = .03$), recognition of lists A ($P = .004$) and B ($P = .01$), and between users overall and controls on the unwarned Time Estimation task ($P = .02$). These results support the hypothesis that impaired memory function and time estimation are specific to chronic use of cannabis.

In a separate analysis, exclusion of users whose urinary cannabinoid metabolite levels exceeded those from the night before testing by 50 ng/mg or more ($n = 18$) still resulted in significant differences between long- and shorter-term users, and long-term users and controls on RAVLT sum ($P = .002$ and $P = .002$, respectively), on recognition of lists A ($P = .005$ and $P = .006$) and B ($P = .01$ and $P < .001$), on the 9-second delay of the Auditory Consonant Trigrams test ($P = .02$ and $P = .03$), and users still differed from controls on time estimation ($P = .005$). When the sample was split at the median for time since last use or level of urinary cannabinoid metabolite on the day of testing and analyzed by ANCOVA, there were no differences on any measure between those who had used cannabis within the past 17 hours and those who had used cannabis 17 or more hours ago, or those with high vs low levels of urinary metabolites and no interactions with duration of cannabis use. Including measures of recent use as covariates in ANCOVA did not change the significance of differences between long- and shorter-term users. These results support the hypothesis that impaired performance is not a consequence of recent use prior to testing or the extent of cannabinoid residues present.

To explore further the influences of duration of cannabis use and recency of use, semipartial correlations were calculated using the following predictors: FSIQ, age, duration of cannabis use, and hours since last use of cannabis. As shown in TABLE 4, the unique contribution of duration of cannabis use to the variance of each test variable was superior or at least equivalent to that of recency of use in all 6 test variables that had significant contributions from at least 1 cannabis use parameter. Recent use contributed only to performance on the memory tests. The fact that a minority of the sample, primarily shorter-term users, reported experiencing mild withdrawal symptoms, yet shorter-term users' performance was not impaired, supports the interpretation of the cognitive impairments observed as a long-term consequence of cannabis use and not a manifestation of overtly experienced withdrawal.

COMMENT

The results of this study have confirmed and extended previous findings of cognitive impairments among chronic heavy cannabis users. Long-term users with a mean 24 years of regular cannabis use performed significantly less well on tests of memory and attention than nonuser controls and shorter-term users with a mean of 10 years' use. The greatest impairment on almost every measure was from the RAVLT, indicating a generalized memory deficit with impaired learning, retention, and retrieval. Long-term users recalled 2.5 fewer words than controls on the delayed recall trial where 49% of the long-term users' scores were more than 1 SD, and 21.6% were more than 2 SDs, below the control mean and normative data.[47] A large proportion of long-term users' recognition scores were more than 1 SD (51%) or 2 SDs (31.4%) below the control mean and norms.[47] Effect sizes for measures that differed significantly between long-term users and controls ranged from 0.56 to 1.29 across all tests, indicating moderate to large effects.

These results do not indicate a severe memory problem but could nevertheless translate into clinically significant cognitive impairment and could impact functioning in daily life. There were significant differences between long-term users and controls on 6 of the 9 tests administered and performance on 4 tests worsened as a function of increasing years of cannabis use. Despite this and a range of up to 17 years of cannabis use in the shorter-term user group, they differed significantly from controls only on time estimation.

Table 4. Predictor Correlations Between Hypothesized Predictors and Select Test Variables*

	Full-Scale IQ			Age			Duration of Cannabis Use			Recency of Cannabis Use†		
Test Variables	Zero-Order	Semipartial	*P* Value	Zero-Order	Semipartial	*P* Value	Zero-Order	Semipartial	*P* Value	Zero-Order	Semipartial	*P* Value
SCOLP-SOC, No. correct	0.55	**0.52**	<.001	0.12	**0.24**	.005	0.01	**−0.24**	.005	0.11	**0.05**	.53
Stroop												
Color-Word	0.27	**0.29**	.002	−0.26	**0.09**	.33	−0.34	**−0.24**	.01	0.09	**0.05**	.58
Color-Reac	0.36	**0.36**	<.001	−0.19	**0.12**	.17	−0.27	**−0.24**	.008	0.18	**0.13**	.15
RAVLT												
RAVLTsum	0.21	**0.22**	.02	−0.31	**0.06**	.54	−0.37	**−0.21**	.02	0.25	**0.21**	.02
RAVLT recency	0.11	**0.10**	.32	−0.19	**0.12**	.20	−0.27	**−0.22**	.02	0.24	**0.23**	.02
Alphabet Task Alternating, log	−0.21	**−0.21**	.03	0.12	**−0.17**	.09	0.21	**0.25**	.01	−0.04	**−0.02**	.81

*SCOLP-SOC indicates Speed and Capacity of Language Processing Speed of Comprehension; RAVLT, Rey Auditory Verbal Learning Test. *P* values are for semipartial correlations. Test variables were significantly predicted by at least 1 cannabis use parameter.
†Defined as hours since last use of cannabis.

Altered brain metabolism in shorter-term users may be detected with sensitive techniques, such as functional magnetic resonance imaging and positron emission tomography, but the clinical significance of such changes remains obscure. The strength of this study is in its assessment of overtly relevant cognitive processes; our results suggest that shorter-term cannabis users are not impaired to an extent that would interfere with cognitive functioning in their daily lives. The fact that the frequency of use was near daily among long- and shorter-term users suggests that the duration of cannabis use is a more salient contributor to the development of cognitive impairment than quantity or frequency of use.

While most cannabis users cease using in their mid-20s to late 20s, approximately 20% continue to use through their 30s and beyond.[2] This is the first study to our knowledge of a relatively large sample of long-term entrenched cannabis users seeking treatment. Concern about perceived cognitive impairment was one of many problems associated with cannabis use that led the users in this study to seek treatment. This concern is unlikely to have biased the results of this study since a slightly higher proportion of shorter-term vs long-term users reported experiencing cognitive problems, yet shorter-term users mostly did not differ from controls on the cognitive tests. Nevertheless, it is possible that long-term cannabis users in the community who are not seeking treatment may not experience impairments to the same degree as those assessed in this study.

While acknowledging the limitations of retrospective designs, if carefully controlled and analyzed, this approach is the most efficient way to evaluate the long-term cognitive effects of cannabis, given the costs and logistical difficulties in using prospective research designs. The matching of groups on measures of premorbid intellectual functioning that are resilient to brain damage, together with the observed relationships between duration of cannabis use and test performance, support the assumption that the cognitive impairments observed in the long-term users were not preexisting but developed as a result of their prolonged use of cannabis. Impairment appeared unrelated to withdrawal phenomena. The cognitive functions assessed in this study are dependent on the intact functioning of the hippocampus, prefrontal cortex, and cerebellum,[39,51-55] which are dense with cannabinoid receptors.[56] The effects that exogenous cannabinoids exert on the cannabinoid receptor system and the role of endogenous cannabinoids as suggested by animal research[6,21,24] provide a credible neurophysiological explanation for the development of cognitive impairments as the result of hypothesized long-term changes occurring over many years of exposure to the drug.

In conclusion, our results confirm that cognitive impairments develop as a result of prolonged cannabis use, they endure beyond the period of acute intoxication, and they worsen with increasing years of use. Impairments develop gradually but may only become clinically significant and detectable by standard neuropsychological tests after 1 to 2 decades of cannabis use. Nevertheless, altered brain function with subtle impairment has been shown to manifest earlier.[9,10,11,17,18] It is also likely that impairments would be greater among comorbid substance-dependent persons. The risk to most medical cannabis users is likely to be small, as long as they are not maintained at high doses for many years. For habitual users, the kinds of impairments observed in this study have the potential to impact academic achievements, occupational proficiency, interpersonal relationships, and daily functioning. The extent to which these cognitive impairments may recover following cessation or reduction of cannabis use will be addressed in a follow-up of this sample subsequent to treatment for cannabis dependence.

Author Contributions: *Study concept and design*: Solowij, Stephens, Roffman.
Acquisition of data: Stephens, Roffman, Kadden, Miller, Christiansen, McRee, Vendetti.
Analysis and interpretation of data: Solowij, Stephens.
Drafting of the manuscript: Solowij.
Critical revision of the manuscript for important intellectual content: Solowij, Stephens, Roffman, Babor, Kadden, Miller, Christiansen, McRee, Vendetti.
Statistical expertise: Solowij, Stephens.
Obtained funding: Solowij, Stephens, Roffman, Babor, Kadden, Miller.
Administrative, technical, or material support: Solowij, Roffman, McRee, Vendetti.
Study supervision: Solowij, Stephens, Roffman, Babor, Kadden, Miller, Christiansen, McRee, Vendetti.
Other Members of the Marijuana Treatment Project Research Group include Kathleen Carroll, PhD, Karen Steinberg, PhD (Coordinating Center, University of Connecticut Health Center, Department of Community Medicine); Mark Litt, PhD (Farmington Clinical Research Unit, University of Connecticut Health Center, Department of Psychiatry); Jean Donaldson, MA, and James Herrell, PhD (Center for Substance Abuse Treatment).
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REFERENCES

1. Watson SJ, Benson JA, Joy JE. Marijuana and medicine: assessing the science base: a summary of the 1999 Institute of Medicine report. *Arch Gen Psychiatry*. 2000;57:547-552.
2. Substance Abuse and Mental Health Services Administration (SAMHSA). *National Household Survey on Drug Abuse Series: H-6: Preliminary Results from the 1997 National Household Survey on Drug Abuse*. Rockville, Md: Office on Applied Studies; 1998. DHHS publication SMA 98-3251.
3. Hall W, Babor TF. Cannabis use and public health: assessing the burden. *Addiction*. 2000;95:485-490.
4. Voelker R. "Decent research and closure" needed on medical marijuana, says head of NIH panel. *JAMA*. 1997;278:802.
5. Pope HG, Gruber AJ, Yurgelun-Todd D. The residual neuropsychological effects of cannabis: the current status of research. *Drug Alcohol Depend*. 1995;38:25-34.
6. Solowij N. *Cannabis and Cognitive Functioning*. Cambridge, England: Cambridge University Press; 1998.
7. Fried PA, Watkinson B, Gray R. Differential effects on cognitive functioning in 9- to 12-year olds prenatally exposed to cigarettes and marihuana. *Neurotoxicol Teratol*. 1998;20:293-306.

8. Solowij N, Michie PT, Fox AM. Effects of long-term cannabis use on selective attention: an event-related potential study. *Pharmacol Biochem Behav*. 1991;40:683-688.
9. Solowij N, Michie PT, Fox AM. Differential impairments of selective attention due to frequency and duration of cannabis use. *Biol Psychiatry*. 1995;37:731-739.
10. Solowij N. Do cognitive impairments recover following cessation of cannabis use? *Life Sci*. 1995;56:2119-2126.
11. Pope HG, Yurgelun-Todd D. The residual cognitive effects of heavy marijuana use in college students. *JAMA*. 1996;275:521-527.
12. Pope HG, Jacobs A, Mialet JP, Yurgelun-Todd D, Gruber S. Evidence for a sex-specific residual effect of cannabis on visuospatial memory. *Psychother Psychosom*. 1997;66:179-184.
13. Fletcher JM, Page JB, Francis DJ, et al. Cognitive correlates of long-term cannabis use in Costa Rican men. *Arch Gen Psychiatry*. 1996;53:1051-1057.
14. Elwan O, Hassan AAH, Naseer MA, et al. Brain aging in a sample of normal Egyptians: cognition, education, addiction and smoking. *J Neurol Sci*. 1997;148:79-86.
15. Solowij N, Grenyer BFS, Peters R, Chesher G. Long-term cannabis use impairs memory processes and frontal lobe function. In: *1997 Symposium on the Cannabinoids*. Burlington, Vt: International Cannabinoid Research Society; 1997:84.
16. Loeber RT, Yurgelun-Todd DA. Human neuroimaging of acute and chronic marijuana use: implications for frontocerebellar dysfunction. *Hum Psychopharmacol Clin Exp*. 1999;14:291-301.
17. Block RI, O'Leary DS, Hichwa RD, et al. Cerebellar hypoactivity in frequent marijuana users. *Neuroreport*. 2000;11:749-753.
18. Block RI, O'Leary DS, Hichwa RD, et al. Effects of frequent marijuana use on memory-related regional cerebral blood flow. *Pharmacol Biochem Behav*. In press.
19. Block RI, O'Leary DS, Augustinack JC, et al. Effects of frequent marijuana use on attention-related regional cerebral blood flow. *Abstr Soc Neurosci*. 2000;26:2080.
20. Lyketsos CG, Garrett E, Liang K-Y, Anthony JC. Cannabis use and cognitive decline in persons under 65 years of age. *Am J Epidemiol*. 1999;149:794-800.
21. Hampson RE, Deadwyler SA. Cannabinoids, hippocampal function and memory. *Life Sci*. 1999;65:715-723.
22. Hampson RE, Deadwyler SA. Cannabinoids reveal the necessity of hippocampal neural encoding for short-term memory in rats. *J Neurosci*. 2000;20:8932-8942.
23. Reibaud M, Obinu MC, Ledent C, et al. Enhancement of memory in cannabinoid CB1 receptor knockout mice. *Eur J Pharmacol*. 1999;379:R1-R2.
24. Bohme GA, Laville M, Ledent C, Parmentier M, Imperato A. Enhanced long-term potentiation in mice lacking cannabinoid CB1 receptors. *Neuroscience*. 2000;95:5-7.
25. Marijuana Treatment Project Research Group. Treating marijuana dependence: findings from a multisite study. *Arch Gen Psychiatry*. In press.
26. McLellan AT, Kushner H, Metzger D, et al. The Fifth Edition of the Addiction Severity Index. *J Subst Abuse Treat*. 1992;9:199-213.
27. Sobell LC, Sobell MB. Timeline follow-back: a technique for assessing self-reported alcohol consumption. In: Litten RZ, Allen JP, eds. *Measuring Alcohol Consumption: Psychological and Biochemical Methods*. Totowa, NJ: Humana Press; 1992.
28. Miller WR. *Form 90: A Structured Assessment Interview for Drinking and Related Behaviors: Test Manual: Project MATCH Monograph Series; Vol 5*. Bethesda, Md: National Institute on Alcohol Abuse and Alcoholism; 1996. NIH Publication 96-4004.
29. First MB, Gibbon M, Spitzer RL, Williams JB. *User's Guide for the Structured Clinical Interview for DSM-IV Axis I Disorders—Research Version*. New York, NY: Biometrics Research Department, New York State Psychiatric Institute; 1996.
30. Jastak S, Wilkinson G. *The Wide Range Achievement Test: Manual of Instructions*. Wilmington, Del: Jastak Associates; 1984.
31. Kareken DA, Gur RC, Saykin AJ. Reading on the Wide Range Achievement Test-Revised and parental education as predictors of IQ: comparison with the Barona formula. *Arch Clin Neuropsychol*. 1995;10:147-157.
32. Blair JR, Spreen O. Predicting premorbid IQ: a revision of the National Adult Reading Test. *Clin Neuropsychol*. 1989;3:129-136.
33. Barona A, Reynolds CR, Chastain R. A demographically based index of pre-morbid intelligence for the WAIS-R. *J Consult Clin Psychol*. 1984;52:885-887.
34. Bell R, Taylor EH, Ackerman B, Pappas AA. Interpretation of urine quantitative 11-nor-delta-9-tetrahydrocannabinol-9-carboxylic acid to determine abstinence from marijuana smoking. *Clin Toxicol*. 1989;27:109-115.
35. Dackis CA, Pottash ALC, Annitto W, Gold MS. Persistence of urinary marijuana levels after supervised abstinence. *Am J Psychiatry*. 1982;139:1196-1198.
36. Ellis GM, Mann MA, Judson BA, Schramm NT, Tashchian A. Excretion patterns of cannabinoid metabolites after last use in a group of chronic users. *Clin Pharmacol Ther*. 1985;38:572-578.
37. Fraser AD, Worth D. Urinary excretion profiles of 11-nor-9-carboxy-delta-9-tetrahydrocannabinol and delta-9-THCCOOH to creatinine ratio study. *J Anal Toxicol*. 1999;23:531-534.
38. Baddeley A, Emslie H, Nimmo-Smith I. *The Speed and Capacity of Language Processing Test Manual*. Bury St Edmonds, England: Thames Valley Test Co; 1992.
39. Lezak MD. *Neuropsychological Assessment*. 3rd ed. New York, NY: Oxford University Press; 1995.
40. Rey A. *L'examen clinique en psychologie*. Paris, France: Presse Universitaire de France; 1964.
41. Spreen O, Strauss E. *A Compendium of Neuropsychological Tests: Administration, Norms and Commentary*. 2nd ed. New York, NY: Oxford University Press; 1998.
42. Golden CJ. *Stroop Color and Word Test: A Manual for Clinical and Experimental Uses*. Wood Dale, Ill: Stoelting; 1978.
43. Bohnen N, Jolles J, Twijnstra A. Modification of the Stroop Color Word Test improves differentiation between patients with mild head injury and matched controls. *Clin Neuropsychol*. 1992;6:178-184.
44. *The Wisconsin Card Sorting Test: Computer Version*. Alpharetta, Ga: Psychological Assessment Resources Inc, CyberMetrics Testing Software Services; 1989.
45. Stuss DT, Stethem LL, Poirier CA. Comparison of three tests of attention and rapid information processing across six age groups. *Clin Neuropsychol*. 1987;1:139-152.
46. Levin HS, Mattis S, Ruff RM, et al. Neurobehavioral outcome following minor head injury: a three-center study. *J Neurosurg*. 1987;66:234-243.
47. Geffen G, Moar KJ, O'Hanlon AP, Clark CR, Geffen LB. Performance measures of 16- to 86-year-old males and females on the Auditory Verbal Learning Test. *Clin Neuropsychol*. 1990;4:45-63.
48. Stuss DT, Stethem L, Pelchat G. Three tests of attention and rapid information processing: an extension. *Clin Neuropsychol*. 1988;2:246-250.
49. Roman DD, Edwall GE, Buchanan RJ, Patton JH. Extended norms for the Paced Auditory Serial Addition Task. *Clin Neuropsychol*. 1991;5:33-40.
50. Brittain JL, La Marche JA, Reeder KP, Roth DL, Boll TJ. Effects of age and IQ on Paced Auditory Serial Addition Task (PASAT) performance. *Clin Neuropsychol*. 1991;5:163-175.
51. Levy R, Goldman-Rakic PS. Segregation of working memory functions within the dorsolateral prefrontal cortex. *Exp Brain Res*. 2000;133:23-32.
52. Herman BP, Seidenberg M, Wyler A, et al. The effects of human hippocampal resection on the serial position curve. *Cortex*. 1996;32:323-334.
53. Middleton FA, Strick PL. Anatomical evidence for cerebellar and basal ganglia involvement in higher cognitive function. *Science*. 1994;266:458-461.
54. Schacter DL. Memory and awareness. *Science*. 1998;280:59-60.
55. Schmahmann JD, ed. *The Cerebellum and Cognition*. San Diego, Calif: Academic Press; 1997.
56. Herkenham M, Lynn AB, Little MD, et al. Cannabinoid receptor localization in brain. *Proc Natl Acad Sci U S A*. 1990;87:1932-1936.

Table. Relative Risk of Parkinson Disease Among Patients With Polio Compared With a Nonexposed Cohort Matched by Age and Sex

Patient Group	Persons, No.		Observed Parkinson Cases, No.		
	Patients With Polio	Age-/Sex-Matched Cohort	Patients With Polio	Age-/Sex-Matched Cohort	RR (95% CI)*
Total	5421	21626	29	60	2.3 (1.4-3.6)
Paralytic	2003	7979	13	23	2.2 (1.1-4.3)
Nonparalytic	2335	9317	7	14	1.9 (0.7-4.7)
Primary lymphocytic meningitis	592	2367	7	7	4.1 (1.4-11.9)
Suspected polio	491	1953	2	6	1.3 (0.2-5.7)

*Relative risk (RR) calculated according to person-years at risk. CI indicates confidence interval.

CI, 0.7-4.7) and in patients only suspected of having poliomyelitis (RR, 1.3; 95% CI, 0.2-5.7).

Comment Although it has long been hypothesized that poliomyelitis is associated with an increased risk of PD,[1,2] to our knowledge this has never been empirically demonstrated. The observed increased PD risk does not necessarily imply that poliovirus is directly implicated in PD pathogenesis. Rather, we speculate that by reducing the number of neurons essential to normal neuronal functions, the virally induced damage may enhance the effect of normal age-related neuronal degeneration and thus precipitate PD.[1,3]

We acknowledge possible limitations of our data. Because patients with poliomyelitis may be admitted to hospitals or may attend outpatient clinics more often than other persons, detection bias could arise. However, in Denmark, the diagnosis, evaluation, and treatment of PD normally take place at neurological departments or neurological outpatient clinics. Moreover, although patients with PD initially may consult private neurologists or general practitioners, the vast majority of patients with PD will at some point undergo clinical evaluation or hospitalization at specialized hospital departments because of the complexity of the disease. Therefore, we think that most Danish patients with PD would be registered in the NHDR, and we consider detection bias to be an unlikely explanation for our findings.

Patients with polio may present a wide range of neurological symptoms, which could cause diagnostic ambiguity. If diagnostic misclassification would explain our observations we would have expected the risk of PD to be particularly increased in patients with paralytic polio. However, an increased risk of PD was also observed in patients with nonparalytic polio. Moreover, the likely inclusion of patients with nonpolio virus-related meningitis in the group of patients with primary lymphocytic meningitis may indicate that the observed PD risk is not particular to the poliovirus but also applies to other viruses infecting the central nervous system.

Nete Munk Nielsen, MD, PhD
Klaus Rostgaard, MSc
Henrik Hjalgrim, MD, PhD
Peter Aaby, MSc, DMSc
Department of Epidemiology Research
Danish Epidemiology Science Centre
Statens Serum Institut
Copenhagen, Denmark

Dorthe Askgaard, MD
Department of Infectious Diseases M
National University Hospital
Copenhagen

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1. Calne DB, Eisen A, McGeer E, Spencer P. Alzheimer's disease, Parkinson's disease, and motoneurone disease: abiotrophic interaction between ageing and environment? *Lancet*. 1986;2:1067-1070.
2. Scott WK, Nance MA, Watts RL, et al. Complete genomic screen in Parkinson disease: evidence for multiple genes. *JAMA*. 2001;286:2239-2244.
3. Bodian D. Histopathologic basis of clinical findings in poliomyelitis. *Am J Med*. 1949;6:563-577.
4. Vincent FM, Myers WG. Poliomyelitis and parkinsonism. *N Engl J Med*. 1978;298:686-689.
5. Munk NM, Wohlfahrt J, Aaby P, et al. Cancer risk in a cohort of polio patients. *Int J Cancer*. 2001;92:605-608.
6. Lassen HCA. Sammenlignende undersøgelser over primær seros meningitis og paralytisk poliomyelitis [Comparative studies of primary lymphocytic meningitis and paralytic polio]. *Ugeskr Læg*. 1939;3:73-80.

CORRECTION

Incorrect Measure. In the Original Contribution entitled "Cognitive Functioning of Long-term Heavy Cannabis Users Seeking Treatment" published in the March 6, 2002, issue of THE JOURNAL (2002;287:1123-1131), the legend for the Figure should indicate that error bars represent SEM, not SD.

Cognitive Functioning of Long-term Heavy Cannabis Users Seeking Treatment

Nadia Solowij, PhD
Robert S. Stephens, PhD
Roger A. Roffman, DSW
Thomas Babor, PhD, MPH
Ronald Kadden, PhD
Michael Miller, PhD
Kenneth Christiansen, PsyD
Bonnie McRee, MPH
Janice Vendetti, MPH
for the Marijuana Treatment Project Research Group

Context Cognitive impairments are associated with long-term cannabis use, but the parameters of use that contribute to impairments and the nature and endurance of cognitive dysfunction remain uncertain.

Objective To examine the effects of duration of cannabis use on specific areas of cognitive functioning among users seeking treatment for cannabis dependence.

Design, Setting, and Participants Multisite retrospective cross-sectional neuropsychological study conducted in the United States (Seattle, Wash; Farmington, Conn; and Miami, Fla) between 1997 and 2000 among 102 near-daily cannabis users (51 long-term users: mean, 23.9 years of use; 51 shorter-term users: mean, 10.2 years of use) compared with 33 nonuser controls.

Main Outcome Measures Measures from 9 standard neuropsychological tests that assessed attention, memory, and executive functioning, and were administered prior to entry to a treatment program and following a median 17-hour abstinence.

Results Long-term cannabis users performed significantly less well than shorter-term users and controls on tests of memory and attention. On the Rey Auditory Verbal Learning Test, long-term users recalled significantly fewer words than either shorter-term users ($P=.001$) or controls ($P=.005$); there was no difference between shorter-term users and controls. Long-term users showed impaired learning ($P=.007$), retention ($P=.003$), and retrieval ($P=.002$) compared with controls. Both user groups performed poorly on a time estimation task ($P<.001$ vs controls). Performance measures often correlated significantly with the duration of cannabis use, being worse with increasing years of use, but were unrelated to withdrawal symptoms and persisted after controlling for recent cannabis use and other drug use.

Conclusions These results confirm that long-term heavy cannabis users show impairments in memory and attention that endure beyond the period of intoxication and worsen with increasing years of regular cannabis use.

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IN THE CURRENT CLIMATE OF DEBATE about marijuana laws and interest in marijuana as medicine,[1] one issue remains unresolved. Does heavy, frequent, or prolonged use of cannabis lead to a deterioration in cognitive function that persists well beyond any period of acute intoxication? Is the functioning of the brain altered in the long term? With over 7 million people using cannabis weekly or more often in the United States alone[2] and the potential for increased physician recommendations for select patients to use cannabis therapeutically,[3] answers to these questions are of significant public health concern.[3,4] Scientific evidence from past research clearly showed that gross impairment related to chronic cannabis use did not occur but was inconclusive with regard to the presence of more specific deficits.[5,6] Recent studies with improved methods have demonstrated changes in cognition and brain function associated with long-term or frequent use of cannabis. Specific impairments of attention, memory, and executive function have been found in cannabis users in the unintoxicated state (and in children exposed to cannabis in utero[7]) in controlled studies using brain event-related potential techniques[8-10] and neuropsychological assessments[11-15] including complex tasks.

Brain imaging studies of cannabis users have demonstrated altered function, blood flow, and metabolism in prefrontal and cerebellar regions.[16-19] Studies failing to detect cognitive decline associated with cannabis use[20] may reflect insufficient heavy or chronic use of cannabis in the sample or the use of insensitive assessment instruments. Impairments appear to increase with duration and frequency of cannabis use; however, the parameters of use that are associated with short- or long-lasting cognitive and brain dysfunction have not

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Author Affiliations: National Drug and Alcohol Research Centre, University of New South Wales, Sydney, and Department of Psychology, University of Wollongong, Wollongong (Dr Solowij), New South Wales, Australia; Department of Psychology, Virginia Polytechnic Institute and State University, Blacksburg, Va (Dr Stephens); Innovative Programs Research Group, School of Social Work, University of Washington, Seattle (Dr Roffman); Department of Community Medicine (Dr Babor and Miss McRee and Ms Vendetti) and Department of Psychiatry (Dr Kadden), University of Connecticut Health Center, Farmington, and The Village South Inc, Miami, Fla (Drs Miller and Christiansen). **Other Members of the Marijuana Treatment Project Research Group** are listed at the end of this article. **Corresponding Author and Reprints:** Nadia Solowij, PhD, National Drug and Alcohol Research Centre, University of New South Wales, Sydney, NSW 2052, Australia (e-mail: n.solowij@unsw.edu.au).

been fully elucidated. The attribution of deficits to lingering acute effects, drug residues, abstinence effects, or lasting changes caused by chronic use continues to be debated.[3,6] Animal research suggests an important role for the cannabinoid receptor in regulating the neural activity critical for memory processing.[31-34] Long-term use of cannabis may result in altered functioning of the cannabinoid receptor and its associated neuromodulator systems.

This study investigated the nature of cognitive impairments associated with long-term cannabis use employing data collected from a large clinical trial of chronic users seeking treatment for cannabis dependence. The study compared 102 cannabis users assessed prior to treatment on carefully selected neuropsychological tests with 33 nonuser controls. The parameters of cannabis use that contribute to impairment were examined. It was hypothesized that performance would deteriorate as the number of years of regular use increased.

METHODS

Design

A multisite, retrospective, cross-sectional comparison-group design was used to compare (1) long-term users with a mean of 23.9 years of regular cannabis use; (2) shorter-term users with a mean of 10.2 years of regular use, and (3) nonusers of cannabis. Key confounding variables (age, IQ, other drug use) were controlled through matching or statistical methods. The sample size required for this study was determined by estimating a 94% chance of detecting a moderate effect size of 0.5 SD units at a 2-tailed α of .05.

Recruitment Procedure and Assessment of Drug Use

Sixty-five of the 102 cannabis users were delayed-treatment participants from the Marijuana Treatment Project, a multisite US study (Seattle, Wash; Farmington, Conn; and Miami, Fla) conducted between 1997 and 2000 of the effectiveness of brief treatments for cannabis dependence.[35] The remainder were recruited through the Marijuana Treatment Project specifically for this study. Participants provided written informed consent as approved by the ethics committees of the participating institutions and were paid $75 for completing the cognitive assessments. Controls (n=33) were recruited from the general population through media advertisements at only 1 site. The controls were told that the researchers were studying the effects of exposure to drugs and alcohol on cognitive functioning, and that at present only individuals at the lighter end of the spectrum of drug experience were required. The aim was to minimize cannabis use among controls while approximating the other characteristics of the cannabis-using sample. Assessors were not blinded with regard to group assignment. Self-reported drug and alcohol use were assessed by the Addiction Severity Index,[36] a separate structured interview, and the Time Line Follow Back procedure.[37,38] The Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV)* Axis I Disorders (SCID)[39] assessed cannabis dependence. Duration of regular (at least twice per month) cannabis use was an averaged composite measure derived from the Addiction Severity Index, SCID, and the structured interview. Current frequency of cannabis use was calculated from the Time Line Follow Back procedure.

Inclusion/Exclusion Criteria

Cannabis users were included if they had used cannabis regularly for at least 3 years, were currently using at least once a week, were seeking treatment to assist them to cease or reduce their use of cannabis, and were willing to participate in the treatment program offered. Participants were excluded if they had ever had a serious illness or injury that may have affected the brain, any psychotic disorder, met a current *DSM-IV* diagnosis of dependence on any other drug or alcohol, or had a poor command of the English language.

Sample Characteristics

TABLE 1 provides demographic information and cannabis use parameters.

Table 1. Demographic and Cannabis Use Details of the Sample*

	Cannabis Users			
	All	Shorter-term Users	Long-term Users	Controls
No.	102	51	51	33
Sex, male (%)	75 (74)	36 (71)	39 (76)	22 (67)
Age, mean (SD) [range], y	35.4 (8.6) [19-55]	28.7 (5.5) [19-45]†	42.1 (5.2) [34-55]†	34.8 (11.1) [19-65]
Education, mean (SD) [range], y‡	14.3 (2.3) [10-22]	14.1 (2.5) [10-22]	14.5 (2.0) [11-20]	14.6 (1.8) [12-18]
Full-scale IQ, mean (SD) [range]§	105.4 (6.7) [87.4-118.5]‖	105.1 (7.4) [87.4-118.5]	105.7 (5.9) [92.7-118.3]	107.9 (4.7) [94.5-117.2]
Duration of use, mean (SD) [range], y¶	17.1 (7.9) [2.7-31.7]	10.2 (3.8) [2.7-17.0]	23.9 (4.1) [17.3-31.7]	
Frequency of use, median (range), d/mo#	27.9 (3.5-30)	28.3 (5.2-30)	27.4 (3.5-30)	

*Ellipses indicate not applicable.
†Significantly different from controls at $P<.001$.
‡The self-reported number of years of formal education completed.
§Estimated from a combination of North American Adult Reading Test, Wide Range Achievement Test–Revised reading subtest scores, and the Barona index.
‖Significantly different from controls at $P<.05$.
¶The number of years that cannabis had been used since regular use commenced (at least twice per month), composite from self-report, Addiction Severity Index, and Structured Clinical Interview Axis 1 Disorders assessments.
#The median number of days per month that cannabis was used at entry to the study, based on average use per 30 days from self-reported use during the past 14 weeks.

The user group was split at the median for duration of cannabis use to enable comparisons of long-term users, shorter-term users, and controls. No meaningful division of groups could be achieved on the basis of frequency of cannabis use, which was almost daily for the majority of the sample. Sex distribution and years of education did not differ between groups. The majority of users (66.6%) and controls (63.6%) were white. Overall, users and controls did not differ in age, but long-term users were significantly older and shorter-term users were significantly younger than controls ($P<.001$). Premorbid intelligence was estimated by several methods and averaged: the Wide Range Achievement Test—Revised reading subtest (WRAT-R READ)[30,31], the North American Adult Reading Test (NAART)[32], and the Barona Index.[33] The mean estimated full-scale IQ (FSIQ) did not differ between the 3 groups based on duration of cannabis use. The majority of the sample (82.4% long-term, 88.2% shorter-term users) reported experiencing problems with memory, attention, or concentration, which they attributed to their use of cannabis.

Cannabis Use, Required Abstinence, and Urinalysis

Users first tried cannabis at a mean age of 15.3 (SD, 2.6) years with regular use (at least twice a month) commencing at age 17.5 (SD, 3.2) years. Cannabis had been used on a median 29 of the past 30 days (range, 1-30). Almost the entire sample (98%) met the *DSM-IV* criteria for cannabis dependence. The median amount of cannabis smoked per week was 1 quarter of an ounce (range, 0.01-2.00 oz) with 2 average-sized joints typically smoked per day (range, 0.12-20.00). None of these cannabis-use parameters differed between the long- and shorter-term user groups. Twenty-two controls had either never tried cannabis or used it 10 or fewer times in their lives and 11 had used cannabis weekly to monthly while at school or college between 4 and 30 years ago. Controls with a history of cannabis use were excluded from "pure sample" analyses.

Participants were required to abstain from cannabis for at least 12 hours prior to testing and to provide 2 urine samples (1 the night before testing, another during the test session). The median self-reported time since last use of cannabis was 17 hours (range, 7-240 hours); this did not differ between long- and shorter-term users. At the time of testing, 70% of the sample reported that they were not experiencing any discomfort after abstaining from cannabis. Twice as many shorter-term users than long-term users ($P=.03$) reported mild withdrawal symptoms such as cravings, irritability, depression, anxiety, sleep, or appetite disturbances. In 78.3% of cases, creatinine-normalized urinary cannabinoid metabolite (THC-COOH) levels on the day of testing were less than or equivalent to those from the night before.[34-37] Abstinence from cannabis was supported by significant correlations between the level of normalized urinary cannabinoid metabolite on the day of testing and the self-reported time since last use (bivariate correlation coefficient [r], −0.46; $P<.001$), and the quantity used on the last occasion divided by the time since last use (r, 0.39; $P<.001$). The effects of these measures of recent use were examined in relation to test performance. "Pure sample" analyses excluded users with higher metabolites in the second urine sample. No cannabinoid metabolites were detected in the urine of the control participants.

Other Drug Use

No other drug metabolites were detected in any urine sample. Tobacco and alcohol use was minimal. Alcohol was consumed on a median of 3.4 and 1.7 days per month among users and controls, respectively. Almost one third of users and 46.8% of controls drank less than once a month or not at all. Forty-eight percent of the cannabis users had only tried drugs other than cannabis a few times or never; 52% had used other drugs socially/recreationally primarily during high school and college. Past histories of regular drug use included cocaine (n=24), amphetamines (n=11), hallucinogens (n=17), and sedatives/hypnotics or minor tranquilizers (n=7). Current use of other drugs was less than once a month or not at all for 93.1% of the sample. More than half of the controls (51.5%) had never tried any other drug and the remainder had only tried other drugs experimentally. "Pure sample" analyses excluded all participants with histories of regular or heavy use of alcohol or other drugs.

Neuropsychological Tests and Procedures

Nine neuropsychological tests were administered in the order listed in TABLE 2,[38-45] along with the 2 tests used to assess premorbid IQ.[30-33] A 10-minute rest break was given after the Rey Auditory Verbal Learning Test (RAVLT) Recognition test. Tests were administered by trained assistants and took approximately 2 hours to complete. Quality assurance procedures were adopted to ensure that procedures were standardized at each site with ongoing supervision and review of audiotaped assessments by centralized staff throughout the course of the study.

Data Analysis

Each cognitive test was analysed using SPSS version 10.0 (SPSS Institute, Chicago, Ill) with analysis of covariance (ANCOVA) for normally distributed variables or nonparametric tests of group differences for skewed data. The FSIQ and age were included as covariates in analyses where they correlated with test performance. All participants were initially included in analysis, with the overall cannabis user sample first compared with the control group (evaluated at $P<.05$), followed by comparisons on the basis of duration of cannabis use (long- vs shorter-term users vs controls, evaluated at $P<.01$). For 2-way interactions, the Greenhouse-Geisser method was used to adjust the df where appropriate and for multiple comparisons, a Bonferroni adjustment controlled for type I error. Analysis of covariance was repeated on a purer sample that strictly

Table 2. Neuropsychological Tests Administered and Cognitive Functions Assessed*

Neuropsychological Test	Cognitive Functions Assessed
Wide Range Achievement Test–Revised reading subtest (WRAT-R READ)[36,37]	Premorbid IQ
Speed of Comprehension (SOC) test (Speed and Capacity of Language Processing [SCOLP])[38]	Rate of verbal information processing
Rey Auditory Verbal Learning Test (RAVLT)[39-41]	Memory span, verbal learning and retrieval efficiency, susceptibility to interference
Stroop Test[42] with additional interference condition[43]	Attention, cognitive flexibility, inhibition of distractor stimuli, suppression of habitual response
Wisconsin Card Sorting Test (WCST), computerized[44]	Problem solving, conceptual ability
Alphabet Task†	Cognitive flexibility, executive function
Omitted Numbers‡	Working memory
Time Estimation and Production§	Temporal judgment
RAVLT 20-minute delay trial (VII) Recognition test	Long-term retention, recognition memory
North American Adult Reading Test (NAART)[36]	Premorbid IQ
Auditory Consonant Trigrams (Brown-Peterson)[45]	Short-term retention under distractor conditions
Paced Auditory Serial Addition Test (PASAT)[46]	Information processing, working memory, divided and sustained attention

*Tests were administered in the order listed.
†Composed of timed loud, silent, and alternating recital trials.
‡Recognition of omitted item from a jumbled aural list of numbers from 1 to 10 (10 trials).
§Composed of 3 trials: unwarned estimation of time to complete the preceding task (mean, 3 minutes, 18 seconds) (Time Estimation A); time production (1 minute 40 seconds); and warned passive estimation (2 minutes) (Time Estimation B).

excluded those participants with either a history of other drug use or possible recent use of cannabis prior to testing. Semipartial correlations examined the unique contributions of FSIQ, age, duration of cannabis use, and recency of cannabis use to the variance in cognitive test performance.

RESULTS

Results from the 9 neuropsychological tests are shown in TABLE 3 for cannabis users overall, for groups based on duration of cannabis use, and for controls. Effect sizes are calculated between long-term users and controls using the SD of the controls.

Speed of Comprehension

Cannabis user groups did not differ from controls in the number of items completed (range, 23-100) but users overall made more errors ($P = .03$) (range, 0-5). These results suggest that cannabis users are more likely to sacrifice accuracy for speed.

Rey Auditory Verbal Learning Test

Mean words recalled on each trial are depicted in the FIGURE. The learning curves of shorter-term users and controls were similar but long-term users showed a learning curve with a less steep gradient and long-term users recalled fewer words on every trial. The sum of words recalled across all trials I through VII inclusive of trial B (referred to here as RAVLT sum; range, 37-114) correlated significantly and inversely with the duration of cannabis use after controlling for age and FSIQ (partial $r_s = -0.23$; $P = .01$). When analysed by ANCOVA, there was a significant effect of group ($F_{2,132} = 8.35$; $P < .001$) whereby long-term users recalled significantly fewer words than either shorter-term users (95% confidence interval [CI] for difference, 3.84-19.18; $P = .001$) or controls (95% CI for difference, 2.83-19.93; $P = .005$) with no difference between shorter-term users and controls. When all trials were included in a repeated measures ANCOVA, a significant interaction between group and trial ($F_{14,880} = 2.84$; $P = .007$) suggested that long-term users recalled fewer words than shorter-term users or controls on every trial ($P < .05$ for each comparison) except the first, with a trend on trial B (the interference list presented only once; $P = .08$).

The proportion of subjects with a very poor learning ability (acquisition <3 words over 5 trials) was greater among long-term users (13.7%) than controls (0%) ($P = .007$) but not shorter-term users (5.9%). The proportion of long-term users recalling fewer than 10 words on trial V (27.5%) was more than among shorter-term users (8.5%) or controls (3.0%) ($P = .002$). Significantly more long-term users (23.5%) lost 3 or more words over the 20-minute delay between trials VI and VII than shorter-term users (4.3%) or controls (3.0%) ($P = .003$). Long-term users showed a smaller primacy effect in the serial position curve than either other group ($P = .02$). Groups did not differ in the recency effect or in words recalled from the middle of the list.

Users overall and long-term users recognized fewer words than controls from list A (overall, $P = .03$; long-term, $P = .01$) and list B (overall, $P = .01$; long-term, $P = .04$) but long-term users did not differ from shorter-term users. More than half of the long-term users (55%) had a recognition score for list A of 12 or less compared with 28% of shorter-term users and 21% of controls ($P = .002$). Long-term users misassigned more words (median, 2) than shorter-term users and controls (each median, 0) ($P < .001$). A greater proportion of long-term users (13.7%) compared with shorter-term users (6.4%) and controls (0%) actually identified fewer words on recognition than they had just prior during recall on trial VII ($P = .02$). Long-term users performance was significantly poorer than published norms[47] for the general population on most measures from the RAVLT.

Stroop Test

Cannabis users did not differ significantly from controls after inclusion of covariates in any condition or on interference scores. While there were no performance differences between Color-Word (CW) and Color-Read (CR) in the control group, performance on CR was, however, poorer than on CW in both long- ($P < .001$) and shorter-term

users ($P = .03$). Color-Read was the additional interference condition designed to increase demands on executive function.[43] There was an inverse relationship between duration of cannabis use and number of items completed on CR (partial $r, -0.27$; $P = .003$) and CW (partial $r, -0.27$; $P = .004$) after controlling for age and FSIQ. These results suggest that cannabis users are vulnerable to task complexity with increasing demands creating more sources of interference that adversely affect performance.

Wisconsin Card Sorting Test

There were no significant group differences on any Wisconsin Card Sorting Test (WCST) measure but a trend on one: long-term users failed to maintain the set more often than shorter-term users ($P = .05$) or controls ($P = .07$). Research suggests that this measure best represents attentional dysfunction.[39] There was no evidence of impaired performance with increasing years of cannabis use after controlling for covariates.

Table 3. Neuropsychological Test Results

Test	Cannabis Users*			Controls	Effect Size	P Value for Comparisons			
	All (n = 102)	Shorter-term Users (n = 51)	Long-term Users (n = 51)	(n = 33)		All vs Controls	Shorter-term Users vs Controls	Long-term Users vs Controls	Shorter- vs Long-term Users
SCOLP-SOC, median (range)†									
Correct	10 (3-18)	11 (6-18)	10 (3-17)	10 (6-15)		.06	.07	.10	.65
Errors	1 (0-8)	1 (0-8)	1 (0-6)	0 (0-3)		.03	.05	.05	.99
RAVLT, mean (SD)‡									
Trial I	6.3 (1.9)	6.5 (1.9)	6.1 (1.9)	7.0 (1.9)	0.47	.12	>.99	.15	.59
Trial II	9.3 (2.7)	9.9 (2.6)	8.5 (2.5)*	9.9 (2.3)	0.61	.27	>.99	.02	.004
Trial III	10.8 (2.5)	11.5 (2.3)	10.1 (2.6)*	11.4 (2.2)	0.59	.37	>.99	.07	.003
Trial IV	11.6 (2.3)	12.1 (2.2)	10.9 (2.4)*	12.4 (2.2)	0.68	.10	>.99	.02	.01
Trial V	12.2 (2.3)	12.7 (2.1)	11.5 (2.4)*	12.9 (1.8)	0.88	.19	>.99	.03	.005
Trial B	6.0 (2.3)	6.5 (2.4)	5.5 (2.2)	6.9 (2.5)	0.50	.16	>.99	.06	.07
Trial VI	10.0 (3.0)	10.9 (2.8)	9.2 (3.1)*	11.4 (2.2)	1.00	.07	>.99	.005	.002
Trial VII	9.6 (3.5)*	11.1 (3.1)	8.5 (3.5)*	11.0 (2.7)	0.93	.13	>.99	.004	<.001
RAVLTsum	75.6 (17.2)*	81.4 (15.8)	70.3 (16.8)*	82.9 (14.8)	0.85	.14	>.99	.005	<.001
Recog_A	12.1 (3.1)*	13.1 (2.3)	11.1 (3.4)*	13.3 (1.7)	1.29	.03	>.99	.01	.14
Recog_B	6.1 (3.7)*	7.2 (3.7)	5.0 (3.5)*	8.2 (3.2)	1.00	.01	>.99	.04	.26
Stroop, mean (SD)§									
Word	101.3 (15.1)	100.2 (16.4)	102.2 (14.0)	107.0 (15.9)	0.30	.13	.99	.34	>.99
Color	75.6 (12.2)	75.8 (13.4)	75.4 (11.1)	74.5 (13.3)	0.07	.50	>.99	>.99	>.99
Color-Word	45.4 (9.2)*	46.8 (9.4)	44.0 (8.8)	44.4 (10.2)	0.04	.25	.55	>.99	>.99
Color-Reac	40.1 (7.9)*	42.2 (9.0)	37.7 (6.2)	41.4 (7.9)	0.47	.92	>.99	>.99	.42
WCST, median (range)									
Errors	28 (15-81)	27 (16-77)	29 (17-81)	30 (15-78)		.67	.29	.77	.06
Perseverative responses	16 (7-49)	16 (7-45)	15 (5-49)	14 (8-63)		.95	.55	.49	.17
% Concept	72.7 (12.5-86.7)	73.1 (14.8-85.9)	71.9 (12.5-86.7)	71.9 (16.4-86.3)		.82	.38	.64	.12
Trials	13 (10-75)	13 (11-64)	12 (10-75)	13 (10-101)		.75	.90	.67	.74
Failures	1 (0-7)	1 (0-5)	2 (0-7)	1 (0-4)		.42	.74	.07	.05
Alphabet Task, median (range)¶									
Alternating	18.6 (10.4-52.4)*	16.8 (10.4-37.2)	19.8 (13.0-52.4)	17.5 (11.5-33.2)		.31	.91	.06	.07
Difference	11.3 (4.8-39.9)*	10.3 (5.0-29.6)	12.3 (4.8-39.9)	8.8 (3.2-24.7)		.14	.54	.04	.09
Omitted Numbers, mean (SD)#	6.7 (1.8)	7.0 (1.8)	6.4 (1.9)	6.3 (2.1)	0.05	.13	.64	.53	>.99
Time Estimation, s**									
Unwarned Task A, mean (SD)	−64.4 (53.5)*	−61.3 (54.1)*	−67.7 (53.2)*	−7.6 (88.6)	0.68	<.001	<.001	.01	>.99
Warned Task B, median (range)	−1.0 (−55 to 85)	−1.5 (−55 to 85)	−0.5 (−40 to 75)	5 (−70 to 102)		.65	.67	.70	.96
Time Production, mean (SD)	−15.6 (24.6)	−14.9 (25.7)	−16.4 (23.6)	−19.0 (26.2)	0.10	.24	>.99	.34	.79
Auditory Consonant Trigrams, mean (SD), seconds of delay††									
9	11.4 (2.7)*	12.1 (2.3)	10.7 (2.9)*	12.9 (1.9)	1.16	.03	>.99	.002	.007
18	11.3 (2.5)	11.7 (2.0)	10.9 (3.0)	11.5 (2.8)	0.21	.79	.92	>.99	.23
36	10.9 (2.9)	11.2 (2.9)	10.7 (2.9)	11.0 (2.7)	0.11	.84	>.99	>.99	.94

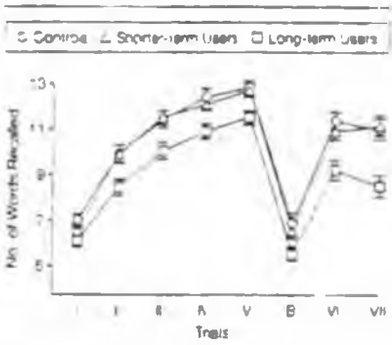
(continued)

Table 3. Neuropsychological Test Results (cont)

Test	Cannabis Users			Controls	Effect Size	*P* Value for Comparisons			
	All (n = 102)	Shorter-term Users (n = 51)	Long-term Users (n = 51)	(n = 33)		All vs Controls	Shorter-term Users vs Controls	Long-term Users vs Controls	Shorter- vs Long-term Users
PASAT, median (range)‡‡									
PR Trial 1	2.56 (2.40-4.56)	2.51 (2.40-3.60)	2.58 (2.40-4.56)*	2.56 (2.40-3.55)		.92	.16	.23	.007
PR Trial 2	2.23 (2.00-3.53)	2.18 (2.00-2.83)	2.28 (2.00-3.53)*	2.24 (2.00-3.06)		.42	.84	.10	.03
PR Trial 3	1.79 (1.60-3.56)*	1.78 (1.60-3.56)	1.81 (1.60-2.52)	1.76 (1.60-2.63)		.20	.49	.11	.36
PR Trial 4	1.36 (1.20-2.31)*	1.35 (1.20-1.80)	1.38 (1.20-2.31)	1.33 (1.20-2.00)		.25	.54	.15	.22
Total PR	8.07 (7.32-10.81)*	7.90 (7.36-9.95)	8.21 (7.32-10.81)*	7.85 (7.37-10.53)		.32	.87	.05	.02
Total attempted	142.5 (74-191)	146.0 (96-191)	139.0 (74-188)	145.5 (110-190)		.71	.99	.56	.43
Total correct	127.0 (28.5)	132.0 (26.8)	121.9 (25.4)	131.6 (26.9)	0.34	.74	>.99	.84	.22
% Correct	64.8 (13.5)	67.9 (13.7)	62.2 (13.0)	67.1 (14.7)	0.33	.74	>.99	.84	.22
Seconds	2.76 (1.86-5.88)	2.64 (1.86-4.57)	2.94 (2.06-5.88)	2.71 (1.89-4.54)		.52	.97	.23	.14

*Significant correlation with the number of years of cannabis use after controlling for covariates ($P < .05$).
†SCOLP-SOC indicates Speed and Capacity of Language Processing-Speed of Comprehension test. Median scaled scores for the number of SOC test items completed in 2 minutes and errors (n = 96 users, n = 32 controls). Ellipses indicate not applicable.
‡RAVLT indicates Rey Auditory Verbal Learning Test. Mean words recalled on each trial of the RAVLT, total recalled across all trials (RAVLTsum), and median words recognized from lists A and B (96-102 users varied on each trial).
§Mean items completed in 45 seconds for the Word, Color, and Color-Word conditions of the Stroop (age-corrected, n = 100 users) and the modified Color-Read condition (n = 101 users).
‖WCST indicates Wisconsin Card Sorting Test. Median errors, perseverative responses, percentage of conceptual level responses, trials to complete the first category, and failures to maintain the set (n = 101 users, n = 32 controls).
¶Median time to recite the alphabet alternating from loud to silent and median difference between the loud and alternating trials in seconds (n = 94 users, n = 29 controls).
#Mean number of correctly identified items from the Omitted Numbers task.
**Mean difference between actual time elapsed and estimated time in unwarned Time Estimation task A; negative scores indicate underestimation (n = 94 users, n = 31 controls), median difference in warned Time Estimation task B (n = 98 users, n = 32 controls), and mean difference between time produced and time required in the Time Production task (n = 102 users, n = 30 controls).
††Mean letters recalled with 9-, 18-, and 36-second delays (n = 31 controls).
‡‡Paced Auditory Serial Addition Test (PASAT). Median processing rates (PR) for PASAT trials 1-4, total PR, total attempted, total correct (mean [SD]), percentage correct (mean [SD]), and seconds per correct response across the 4 trials (n = 96-100 users, n = 32 controls).

Figure. Mean Number of Words Recalled on Each Trial of the Rey Auditory Verbal Learning Test by Long- and Shorter-term Cannabis Users and Controls



Error bars represent SDs

Alphabet Task and Omitted Numbers

Groups did not differ in the time taken to complete any trial of the Alphabet Task or in the number of items correct in the Omitted Numbers task. The log time to complete the alternating trial of the Alphabet Task increased as a function of duration of cannabis use (partial r, 0.26; $P = .006$), as did the square root difference between times taken to complete the alternating and loud trials, an index of interference and lack of flexibility (partial r, 0.26; $P = .006$).

Time Estimation Tasks

Cannabis users differed from controls ($P < .001$) in Time Estimation Task A where they estimated the time taken to complete the preceding (Omitted Numbers) task. Both long- and shorter-term users underestimated the time by about one third of the actual time taken (64.4 seconds) and differed significantly from controls ($P = .01$ and $P < .001$, respectively). Groups did not differ in the simple and brief warned passive Time Estimation Task B or Time Production, where they could use strategies such as counting. Time estimation measures did not correlate with duration of cannabis use.

Auditory Consonant Trigrams

Long-term users recalled significantly fewer items than shorter-term users ($P = .007$), controls ($P = .002$), and published norms[46] on only the 9-second delay condition. The number of items recalled did not correlate with duration of cannabis use. In the general population, the greater the delay interval the worse the performance. In cannabis users, this general pattern was apparent, though there was greater interference at the shorter-delay interval than would be expected.

Paced Auditory Serial Addition Test

Long-term users had slower processing rates than shorter-term users on trial 1 ($P = .007$), with trends on trial 2 ($P = .03$) and the total processing rate across all trials ($P = .02$). Group differences on all other measures failed to reach significance but the performance of the long-term users was poorer in comparison with one set of norms[49] but not another.[50]

Pure Effects Attributable to Cannabis Use and Effects of Recent vs Chronic Use

Excluding all participants with histories of regular other drug or alcohol use, dependence or treatment, and controls with any history of regular cannabis use within the past 20 years reduced the sample to 27 long-term users, 33 shorter-term users, and 26 controls. Despite the

reduction in power to detect differences between groups, there remained a significant difference with $\alpha = .05$ between long-term users and controls on RAVLTsum ($P = .03$), recognition of lists A ($P = .004$) and B ($P = .01$), and between users overall and controls on the unwarned Time Estimation task ($P = .02$). These results support the hypothesis that impaired memory function and time estimation are specific to chronic use of cannabis.

In a separate analysis, exclusion of users whose urinary cannabinoid metabolite levels exceeded those from the night before testing by 50 ng/mg or more ($n = 18$) still resulted in significant differences between long- and shorter-term users, and long-term users and controls on RAVLT sum ($P = .002$ and $P = .002$, respectively), on recognition of lists A ($P = .005$ and $P = .006$) and B ($P = .01$ and $P < .001$), on the 9-second delay of the Auditory Consonant Trigrams test ($P = .02$ and $P = .03$), and users still differed from controls on time estimation ($P = .005$). When the sample was split at the median for time since last use or level of urinary cannabinoid metabolite on the day of testing and analyzed by ANCOVA, there were no differences on any measure between those who had used cannabis within the past 17 hours and those who had used cannabis 17 or more hours ago, or those with high vs low levels of urinary metabolites and no interactions with duration of cannabis use. Including measures of recent use as covariates in ANCOVA did not change the significance of differences between long- and shorter-term users. These results support the hypothesis that impaired performance is not a consequence of recent use prior to testing or the extent of cannabinoid residues present.

To explore further the influences of duration of cannabis use and recency of use, semipartial correlations were calculated using the following predictors: FSIQ, age, duration of cannabis use, and hours since last use of cannabis. As shown in TABLE 4, the unique contribution of duration of cannabis use to the variance of each test variable was superior or at least equivalent to that of recency of use in all 6 test variables that had significant contributions from at least 1 cannabis use parameter. Recent use contributed only to performance on the memory tests. The fact that a minority of the sample, primarily shorter-term users, reported experiencing mild withdrawal symptoms, yet shorter-term users' performance was not impaired, supports the interpretation of the cognitive impairments observed as a long-term consequence of cannabis use and not a manifestation of overtly experienced withdrawal.

COMMENT

The results of this study have confirmed and extended previous findings of cognitive impairments among chronic heavy cannabis users. Long-term users with a mean 24 years of regular cannabis use performed significantly less well on tests of memory and attention than nonuser controls and shorter-term users with a mean of 10 years' use. The greatest impairment on almost every measure was from the RAVLT, indicating a generalized memory deficit with impaired learning, retention, and retrieval. Long-term users recalled 2.5 fewer words than controls on the delayed recall trial where 49% of the long-term users' scores were more than 1 SD, and 21.6% were more than 2 SDs, below the control mean and normative data.[47] A large proportion of long-term users' recognition scores were more than 1 SD (51%) or 2 SDs (31.4%) below the control mean and norms.[47] Effect sizes for measures that differed significantly between long-term users and controls ranged from 0.56 to 1.29 across all tests, indicating moderate to large effects.

These results do not indicate a severe memory problem but could nevertheless translate into clinically significant cognitive impairment and could impact functioning in daily life. There were significant differences between long-term users and controls on 6 of the 9 tests administered and performance on 4 tests worsened as a function of increasing years of cannabis use. Despite this and a range of up to 17 years of cannabis use in the shorter-term user group, they differed significantly from controls only on time estimation.

Table 4. Predictor Correlations Between Hypothesized Predictors and Select Test Variables*

	Full-Scale IQ			Age			Duration of Cannabis Use			Recency of Cannabis Use†		
Test Variables	Zero-Order	Semipartial	*P* Value	Zero-Order	Semipartial	*P* Value	Zero-Order	Semipartial	*P* Value	Zero-Order	Semipartial	*P* Value
SCOLP-SOC, No. correct (r)	0.55	**0.52**	<.001	0.12	**0.24**	.005	0.01	**−0.24**	.005	0.11	**0.05**	.53
Stroop												
Color-Word	0.27	**0.29**	.002	−0.26	**0.09**	.33	−0.34	**−0.24**	.01	0.09	**0.05**	.56
Color-Read	0.36	**0.36**	<.001	−0.19	**0.12**	.17	−0.27	**−0.24**	.008	0.18	**0.13**	.15
RAVLT												
RAVLTsum	0.2*	**0.22**	.02	−0.31	**0.06**	.54	−0.37	**−0.21**	.02	0.25	**0.21**	.02
RAVLT recency	0.11	**0.10**	.32	−0.19	**0.12**	.20	−0.27	**−0.22**	.02	0.24	**0.23**	.02
Alphabet Task Alternating, log	−0.21	**−0.21**	.03	0.12	**−0.17**	.09	0.21	**0.25**	.01	−0.04	**−0.02**	.81

*SCOLP-SOC indicates Speed and Capacity of Language Processing-Speed of Comprehension; RAVLT, Rey Auditory Verbal Learning Test. *P* values are for semipartial correlations. Test variables were significantly predicted by at least 1 cannabis use parameter.
†Defined as hours since last use of cannabis.

Altered brain metabolism in shorter-term users may be detected with sensitive techniques, such as functional magnetic resonance imaging and positron emission tomography, but the clinical significance of such changes remains obscure. The strength of this study is in its assessment of overtly relevant cognitive processes, our results suggest that shorter-term cannabis users are not impaired to an extent that would interfere with cognitive functioning in their daily lives. The fact that the frequency of use was near daily among long- and shorter-term users suggests that the duration of cannabis use is a more salient contributor to the development of cognitive impairment than quantity or frequency of use.

While most cannabis users cease using in their mid-20s to late 20s, approximately 20% continue to use through their 30s and beyond.[2] This is the first study to our knowledge of a relatively large sample of long-term entrenched cannabis users seeking treatment. Concern about perceived cognitive impairment was one of many problems associated with cannabis use that led the users in this study to seek treatment. This concern is unlikely to have biased the results of this study since a slightly higher proportion of shorter-term vs long-term users reported experiencing cognitive problems, yet shorter-term users mostly did not differ from controls on the cognitive tests. Nevertheless, it is possible that long-term cannabis users in the community who are not seeking treatment may not experience impairments to the same degree as those assessed in this study.

While acknowledging the limitations of retrospective designs, if carefully controlled and analyzed, this approach is the most efficient way to evaluate the long-term cognitive effects of cannabis, given the costs and logistical difficulties in using prospective research designs. The matching of groups on measures of premorbid intellectual functioning that are resilient to brain damage, together with the observed relationships between duration of cannabis use and test performance, support the assumption that the cognitive impairments observed in the long-term users were not preexisting but developed as a result of their prolonged use of cannabis. Impairment appeared unrelated to withdrawal phenomena. The cognitive functions assessed in this study are dependent on the intact functioning of the hippocampus, prefrontal cortex, and cerebellum,[30,51-55] which are dense with cannabinoid receptors.[56] The effects that exogenous cannabinoids exert on the cannabinoid receptor system and the role of endogenous cannabinoids as suggested by animal research[6,21-24] provide a credible neurophysiological explanation for the development of cognitive impairments as the result of hypothesized long-term changes occurring over many years of exposure to the drug.

In conclusion, our results confirm that cognitive impairments develop as a result of prolonged cannabis use, they endure beyond the period of acute intoxication, and they worsen with increasing years of use. Impairments develop gradually but may only become clinically significant and detectable by standard neuropsychological tests after 1 to 2 decades of cannabis use. Nevertheless, altered brain function with subtle impairment has been shown to manifest earlier.[6,8,9,11,17,18] It is also likely that impairments would be greater among comorbid substance-dependent persons. The risk to most medical cannabis users is likely to be small, as long as they are not maintained at high doses for many years. For habitual users, the kinds of impairments observed in this study have the potential to impact academic achievements, occupational proficiency, interpersonal relationships, and daily functioning. The extent to which these cognitive impairments may recover following cessation or reduction of cannabis use will be addressed in a follow-up of this sample subsequent to treatment for cannabis dependence.

Author Contributions: *Study concept and design:* Solowij, Stephens, Roffman.
Acquisition of data: Stephens, Roffman, Kadden, Miller, Christiansen, McRee, Vendetti.
Analysis and interpretation of data: Solowij, Stephens.
Drafting of the manuscript: Solowij.
Critical revision of the manuscript for important intellectual content: Solowij, Stephens, Roffman, Babor, Kadden, Miller, Christiansen, McRee, Vendetti.
Statistical expertise: Solowij, Stephens.
Obtained funding: Solowij, Stephens, Roffman, Babor, Kadden, Miller.
Administrative, technical, or material support: Solowij, Roffman, McRee, Vendetti.
Study supervision: Solowij, Stephens, Roffman, Babor, Kadden, Miller, Christiansen, McRee, Vendetti.
Other Members of the Marijuana Treatment Project Research Group include Kathleen Carroll, PhD, Karen Steinberg, PhD, (Coordinating Center, University of Connecticut Health Center, Department of Community Medicine); Mark Litt, PhD (Farmington Clinical Research Unit, University of Connecticut Health Center, Department of Psychiatry); Jean Donaldson, MA, and James Herrell, PhD (Center for Substance Abuse Treatment).
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REFERENCES

1. Watson SJ, Benson JA, Joy JE. Marijuana and medicine: assessing the science base: a summary of the 1999 Institute of Medicine report. *Arch Gen Psychiatry*. 2000; 57:547-552.
2. Substance Abuse and Mental Health Services Administration (SAMHSA). *National Household Survey on Drug Abuse Series H-6: Preliminary Results from the 1997 National Household Survey on Drug Abuse*. Rockville, Md: Office on Applied Studies; 1998. DHHS publication SMA 98-3251.
3. Hall W, Babor TF. Cannabis use and public health: assessing the burden. *Addiction*. 2000;95:485-490.
4. Voelker R. "Decent research and closure" needed on medical marijuana, says head of NIH panel. *JAMA*. 1997;278:802.
5. Pope HG, Gruber AJ, Yurgelun-Todd D. The residual neuropsychological effects of cannabis: the current status of research. *Drug Alcohol Depend*. 1995; 38:25-34.
6. Solowij N. *Cannabis and Cognitive Functioning*. Cambridge, England: Cambridge University Press; 1998.
7. Fried PA, Watkinson B, Gray R. Differential effects on cognitive functioning in 9- to 12-year olds prenatally exposed to cigarettes and marihuana. *Neurotoxicol Teratol*. 1998;20:293-306.

8. Solowij N, Michie PT, Fox AM. Effects of long-term cannabis use on selective attention: an event-related potential study. *Pharmacol Biochem Behav*. 1991;40:683-688.
9. Solowij N, Michie PT, Fox AM. Differential impairments of selective attention due to frequency and duration of cannabis use. *Biol Psychiatry*. 1995;37:731-739.
10. Solowij N. Do cognitive impairments recover following cessation of cannabis use? *Life Sci*. 1995;56:2119-2126.
11. Pope HG, Yurgelun-Todd D. The residual cognitive effects of heavy marijuana use in college students. *JAMA*. 1996;275:521-527.
12. Pope HG, Jacobs A, Mialet JP, Yurgelun-Todd D, Gruber S. Evidence for a sex-specific residual effect of cannabis on visuospatial memory. *Psychother Psychosom*. 1997;66:179-184.
13. Fletcher JM, Page JB, Francis DJ, et al. Cognitive correlates of long-term cannabis use in Costa Rican men. *Arch Gen Psychiatry*. 1996;53:1051-1057.
14. Elwan O, Hassan AAH, Naseer MA, et al. Brain aging in a sample of normal Egyptians: cognition, education, addiction and smoking. *J Neurol Sci*. 1997;148:79-86.
15. Solowij N, Grenyer BFS, Peters R, Chesher G. Long term cannabis use impairs memory processes and frontal lobe function. In: *1997 Symposium on the Cannabinoids*. Burlington, Vt: International Cannabinoid Research Society; 1997:84.
16. Loeber RT, Yurgelun-Todd DA. Human neuroimaging of acute and chronic marijuana use: implications for frontocerebellar dysfunction. *Hum Psychopharmacol Clin Exp*. 1999;14:291-301.
17. Block RI, O'Leary DS, Hichwa RD, et al. Cerebellar hypoactivity in frequent marijuana users. *Neuroreport*. 2000;11:749-753.
18. Block RI, O'Leary DS, Hichwa RD, et al. Effects of frequent marijuana use on memory-related regional cerebral blood flow. *Pharmacol Biochem Behav*. In press.
19. Block RI, O'Leary DS, Augustinack JC, et al. Effects of frequent marijuana use on attention-related regional cerebral blood flow. *Abstr Soc Neurosci*. 2000;26:2080.
20. Lyketsos CG, Garrett E, Liang K-Y, Anthony JC. Cannabis use and cognitive decline in persons under 65 years of age. *Am J Epidemiol*. 1999;149:794-800.
21. Hampson RE, Deadwyler SA. Cannabinoids, hippocampal function and memory. *Life Sci*. 1999;65:715-723.
22. Hampson RE, Deadwyler SA. Cannabinoids reveal the necessity of hippocampal neural encoding for short-term memory in rats. *J Neurosci*. 2000;20:8932-8942.
23. Reibaud M, Obinu MC, Ledent C, et al. Enhancement of memory in cannabinoid CB1 receptor knockout mice. *Eur J Pharmacol*. 1999;379:R1-R2.
24. Bohme GA, Laville M, Ledent C, Parmentier M, Imperato A. Enhanced long-term potentiation in mice lacking cannabinoid CB1 receptors. *Neuroscience*. 2000;95:5-7.
25. Marijuana Treatment Project Research Group. Treating marijuana dependence: findings from a multisite study. *Arch Gen Psychiatry*. In press.
26. McLellan AT, Kushner H, Metzger D, et al. The Fifth Edition of the Addiction Severity Index. *J Subst Abuse Treat*. 1992;9:199-213.
27. Sobell LC, Sobell MB. Timeline follow-back: a technique for assessing self-reported alcohol consumption. In: Litten RZ, Allen JP, eds. *Measuring Alcohol Consumption: Psychological and Biochemical Methods*. Totowa, NJ: Humana Press; 1992.
28. Miller WR. *Form 90: A Structured Assessment Interview for Drinking and Related Behaviors: Test Manual: Project MATCH Monograph Series*. Vol 5. Bethesda, Md: National Institute on Alcohol Abuse and Alcoholism; 1996. NIH Publication 96-4004.
29. First MB, Gibbon M, Spitzer RL, Williams JB. *User's Guide for the Structured Clinical Interview for DSM-IV Axis I Disorders—Research Version*. New York, NY: Biometrics Research Department, New York State Psychiatric Institute; 1996.
30. Jastak S, Wilkinson G. *The Wide Range Achievement Test: Manual of Instructions*. Wilmington, Del: Jastak Associates; 1984.
31. Kareken DA, Gur RC, Saykin AJ. Reading on the Wide Range Achievement Test-Revised and parental education as predictors of IQ: comparison with the Barona formula. *Arch Clin Neuropsychol*. 1995;10:147-157.
32. Blair JR, Spreen O. Predicting premorbid IQ: a revision of the National Adult Reading Test. *Clin Neuropsychol*. 1989;3:129-136.
33. Barona A, Reynolds CR, Chastain R. A demographically based index of pre-morbid intelligence for the WAIS-R. *J Consult Clin Psychol*. 1984;52:885-887.
34. Bell R, Taylor EH, Ackerman B, Pappas AA. Interpretation of urine quantitative 11-nor-delta-9-tetrahydrocannabinol-9-carboxylic acid to determine abstinence from marijuana smoking. *Clin Toxicol*. 1989;27:109-115.
35. Dackis CA, Pottash ALC, Annitto W, Gold MS. Persistence of urinary marijuana levels after supervised abstinence. *Am J Psychiatry*. 1982;139:1196-1198.
36. Ellis GM, Mann MA, Judson BA, Schramm NT, Tashchian A. Excretion patterns of cannabinoid metabolites after last use in a group of chronic users. *Clin Pharmacol Ther*. 1985;38:572-578.
37. Fraser AD, Worth D. Urinary excretion profiles of 11-nor-9-carboxy-delta-9-tetrahydrocannabinol: a delta-9-THCCOOH to creatinine ratio study. *J Anal Toxicol*. 1999;23:531-534.
38. Baddeley A, Emslie H, Nimmo-Smith I. *The Speed and Capacity of Language-Processing Test Manual*. Bury St Edmonds, England: Thames Valley Test Co; 1992.
39. Lezak MD. *Neuropsychological Assessment*. 3rd ed. New York, NY: Oxford University Press; 1995.
40. Rey A. *L'examen clinique en psychologie*. Paris, France: Presse Universitaire de France; 1964.
41. Spreen O, Strauss E. *A Compendium of Neuropsychological Tests: Administration, Norms and Commentary*. 2nd ed. New York, NY: Oxford University Press; 1998.
42. Golden CJ. *Stroop Color and Word Test: A Manual for Clinical and Experimental Uses*. Wood Dale, Ill: Stoelting; 1978.
43. Bohnen N, Jolles J, Twijnstra A. Modification of the Stroop Color Word Test improves differentiation between patients with mild head injury and matched controls. *Clin Neuropsychol*. 1992;6:178-184.
44. *The Wisconsin Card Sorting Test: Computer Version*. Alpharetta, Ga: Psychological Assessment Resources Inc, CyberMetrics Testing Software Services; 1989.
45. Stuss DT, Stethem LL, Poirier CA. Comparison of three tests of attention and rapid information processing across six age groups. *Clin Neuropsychol*. 1987;1:139-152.
46. Levin HS, Mattis S, Ruff RM, et al. Neurobehavioral outcome following minor head injury: a three-center study. *J Neurosurg*. 1987;66:234-243.
47. Geffen G, Moar KJ, O'Hanlon AP, Clark CR, Geffen LB. Performance measures of 16- to 86-year old males and females on the Auditory Verbal Learning Test. *Clin Neuropsychol*. 1990;4:45-63.
48. Stuss DT, Stethem L, Pelchat G. Three tests of attention and rapid information processing: an extension. *Clin Neuropsychol*. 1988;2:246-250.
49. Roman DD, Edwall GE, Buchanan RJ, Patton JH. Extended norms for the Paced Auditory Serial Addition Task. *Clin Neuropsychol*. 1991;5:33-40.
50. Brittain JL, La Marche JA, Reeder KP, Roth DL, Bolt TJ. Effects of age and IQ on Paced Auditory Serial Addition Task (PASAT) performance. *Clin Neuropsychol*. 1991;5:163-175.
51. Levy R, Goldman-Rakic PS. Segregation of working memory functions within the dorsolateral prefrontal cortex. *Exp Brain Res*. 2000;133:23-32.
52. Herman BP, Seidenberg M, Wyler A, et al. The effects of human hippocampal resection on the serial position curve. *Cortex*. 1996;32:323-334.
53. Middleton FA, Strick PL. Anatomical evidence for cerebellar and basal ganglia involvement in higher cognitive function. *Science*. 1994;266:458-461.
54. Schacter DL. Memory and awareness. *Science*. 1998;280:59-60.
55. Schmahmann JD, ed. *The Cerebellum and Cognition*. San Diego, Calif: Academic Press; 1997.
56. Herkenham M, Lynn AB, Little MD, et al. Cannabinoid receptor localization in brain. *Proc Natl Acad Sci U S A*. 1990;87:1932-1936.

Table. Relative Risk of Parkinson Disease Among Patients With Polio Compared With a Nonexposed Cohort Matched by Age and Sex

Patient Group	Persons, No.		Observed Parkinson Cases, No.		
	Patients With Polio	Age-/Sex-Matched Cohort	Patients With Polio	Age-/Sex-Matched Cohort	RR (95% CI)*
Total	5421	21626	29	50	2.3 (1.4-3.6)
Paralytic	2003	7979	13	23	2.2 (1.1-4.3)
Nonparalytic	2335	8317	7	14	1.9 (0.7-4.7)
Primary lymphocytic meningitis	592	2367	7	7	4.1 (1.4-11.9)
Suspected polio	491	1963	2	6	1.3 (0.2-5.7)

*Relative risk (RR) calculated according to person-years at risk. CI indicates confidence interval.

CI, 0.7-4.7) and in patients only suspected of having poliomyelitis (RR, 1.3; 95% CI, 0.2-5.7).

Comment. Although it has long been hypothesized that poliomyelitis is associated with an increased risk of PD,[4] to our knowledge this has never been empirically demonstrated. The observed increased PD risk does not necessarily imply that poliovirus is directly implicated in PD pathogenesis. Rather, we speculate that by reducing the number of neurons essential to normal neuronal functions, the virally induced damage may enhance the effect of normal age-related neuronal degeneration and thus precipitate PD.[1,4]

We acknowledge possible limitations of our data. Because patients with poliomyelitis may be admitted to hospitals or may attend outpatient clinics more often than other persons, detection bias could arise. However, in Denmark, the diagnosis, evaluation, and treatment of PD normally take place at neurological departments or neurological outpatient clinics. Moreover, although patients with PD initially may consult private neurologists or general practitioners, the vast majority of patients with PD will at some point undergo clinical evaluation or hospitalization at specialized hospital departments because of the complexity of the disease. Therefore, we think that most Danish patients with PD would be registered in the NHDR, and we consider detection bias to be an unlikely explanation for our findings.

Patients with polio may present a wide range of neurological symptoms, which could cause diagnostic ambiguity. If diagnostic misclassification would explain our observations we would have expected the risk of PD to be particularly increased in patients with paralytic polio. However, an increased risk of PD was also observed in patients with nonparalytic polio. Moreover, the likely inclusion of patients with nonpolio virus-related meningitis in the group of patients with primary lymphocytic meningitis may indicate that the observed PD risk is not particular to the poliovirus but also applies to other viruses infecting the central nervous system.

Nete Munk Nielsen, MD, PhD
Klaus Rostgaard, MSc
Henrik Hjalgrim, MD, PhD
Peter Aaby, MSc, DMSc
Department of Epidemiology Research
Danish Epidemiology Science Centre
Statens Serum Institut
Copenhagen, Denmark

Dorthe Askgaard, MD
Department of Infectious Diseases M
National University Hospital
Copenhagen

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1. Calne DB, Eisen A, McGeer E, Spencer P. Alzheimer's disease, Parkinson's disease, and motoneurone disease: abiotrophic interaction between ageing and environment? *Lancet*. 1986;2:1067-1070.
2. Scott WK, Nance MA, Watts RL, et al. Complete genomic screen in Parkinson disease: evidence for multiple genes. *JAMA*. 2001;286:2239-2244.
3. Bodian D. Histopathologic basis of clinical findings in poliomyelitis. *Am J Med*. 1949;6:563-577.
4. Vincent FM, Myers WC. Poliomyelitis and parkinsonism. *N Engl J Med*. 1978;298:686-689.
5. Munk NM, Wohlfahrt J, Aaby P, et al. Cancer risk in a cohort of polio patients. *Int J Cancer*. 2001;92:605-608.
6. Lassen HCA. Sammenlignende undersøgelser over primær seros meningitis og paralytisk poliomyelitis [Comparative studies of primary lymphocytic menigitis and paralytic polio]. *Ugeskr Læg*. 1939;3:73-80.

CORRECTION

Incorrect Measure: In the Original Contribution entitled "Cognitive Functioning of Long-term Heavy Cannabis Users Seeking Treatment" published in the March 6, 2002, issue of THE JOURNAL (2002;287:1123-1131), the legend for the Figure should indicate that error bars represent SEM, not SD.

ORIGINAL CONTRIBUTION

Escalation of Drug Use in Early-Onset Cannabis Users vs Co-twin Controls

Michael T. Lynskey, PhD
Andrew C. Heath, DPhil
Kathleen K. Bucholz, PhD
Wendy S. Slutske, PhD
Pamela A. F. Madden, PhD
Elliot C. Nelson, MD
Dixie J. Statham, MA
Nicholas G. Martin, PhD

Context Previous studies have reported that early initiation of cannabis (marijuana) use is a significant risk factor for other drug use and drug-related problems.

Objective To examine whether the association between early cannabis use and subsequent progression to use of other drugs and drug abuse/dependence persists after controlling for genetic and shared environmental influences.

Design Cross-sectional survey conducted in 1996-2000 among an Australian national volunteer sample of 311 young adult (median age, 30 years) monozygotic and dizygotic same-sex twin pairs discordant for early cannabis use (before age 17 years).

Main Outcome Measures Self-reported subsequent nonmedical use of prescription sedatives, hallucinogens, cocaine/other stimulants, and opioids, abuse or dependence on these drugs (including cannabis abuse/dependence); and alcohol dependence.

Results Individuals who used cannabis by age 17 years had odds of other drug use, alcohol dependence, and drug abuse/dependence that were 2.1 to 5.2 times higher than those of their co-twin who did not use cannabis before age 17 years. Controlling for known risk factors (early-onset alcohol or tobacco use, parental conflict/separation, childhood sexual abuse, conduct disorder, major depression, and social anxiety) had only negligible effects on these results. These associations did not differ significantly between monozygotic and dizygotic twins.

Conclusions Associations between early cannabis use and later drug use and abuse/dependence cannot solely be explained by common predisposing genetic or shared environmental factors. The association may arise from the effects of the peer and social context within which cannabis is used and obtained. In particular, early access to and use of cannabis may reduce perceived barriers against the use of other illegal drugs and provide access to these drugs.

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OVER THE PAST DECADE there has been a steady increase both in the prevalence of cannabis (marijuana) use among young people[1-3] and in the number of people entering treatment for cannabis-related problems.[4] In 1999 there were 220 000 cannabis-related admissions to publicly funded substance abuse treatment programs in the United States.[5] This represented 14% of all such treatment admissions, with admissions occurring primarily among youth; approximately a third of all cannabis-related admissions were among people 12 to 17 years of age and a further third were among those 18 to 25 years of age. These increases in treatment seeking have been paralleled by heightened concerns about the long-term consequences of chronic cannabis use[6] and a recognition of the need for treatment and other interventions to ameliorate the effects of drug dependence, which is best characterized as a chronic, recurring condition.[7]

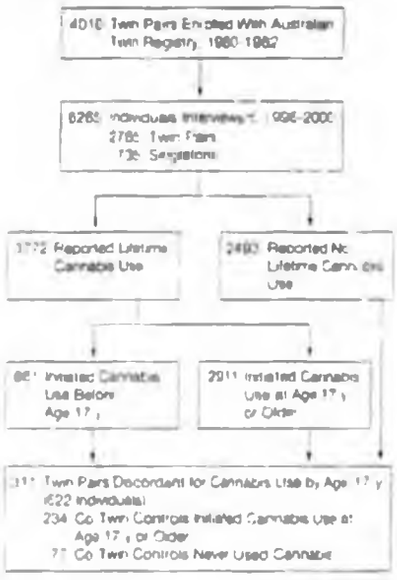
The majority of cannabis-related admissions among youth result from referrals either from the justice or educational systems,[5] and it is probable that at least some of these referrals were motivated more by concern over the future consequences of early initiation to cannabis use than by apparent negative effects of current cannabis use. A major focus of concern is the extent to which early cannabis use may increase the risks for escalation to other drug use and drug dependence. Stage theory posits that there is an invariant sequence in initiation and use of drugs, with use of cannabis preceding the use of "hard" drugs such as cocaine and heroin.[8-10] This theory has been highly influential in drug policy debates and has provided a major rationale for sustaining prohibition against cannabis,[11] as it is assumed that delaying or preventing early cannabis use may reduce risks of other illicit drug use.

While this broad theory has found some empirical support,[8-10,12-14] such data on temporal sequencing do not establish that the use of one drug *causes* the

For editorial comment see p 482.

Author Affiliations: Queensland Institute of Medical Research, Brisbane, Queensland, Australia (Drs Lynskey and Martin and Ms Statham); Missouri Alcoholism Research Center and Department of Psychiatry, Washington University School of Medicine, St Louis (Drs Lynskey, Heath, Bucholz, Madden, and Nelson); and Missouri Alcoholism Research Center and Department of Psychology, University of Missouri, Columbia (Dr Slutske).
Corresponding Author and Reprints: Michael T. Lynskey, PhD, Missouri Alcoholism Research Center, Department of Psychiatry, Washington University School of Medicine, 40 N Kingshighway, Suite One, St Louis, MO 63108 (e-mail: mlynskey@matlock.wustl.edu).

Figure. Sample Size and Sample Selection Criteria



use of drugs higher up the sequence.[1,2,4] Rather, the observed pattern of initiation and use may reflect other factors such as availability and access.[1] Nonetheless, several studies using event history analysis[11] and regression analyses[4,12,13] have reported that early initiation to cannabis use remains a significant risk factor for both the use of other drugs and experiencing drug-related problems.

We are unaware of any studies that have controlled for genetic influences on the association between earlier initiation of cannabis use and other drug use and drug-related problems. Nonetheless, one viable hypothesis to explain this apparent association is that it arises from the joint influence of genetic and/or shared environmental factors on both risks of early initiation to cannabis use and, independently of this, on increased risks of subsequent drug use and dependence. This hypothesis is supported by evidence that cannabis and other drug use and drug abuse/dependence are moderately to highly heritable.[20-22]

The examination of other drug use and drug abuse/dependence in twin pairs discordant for early cannabis use provides a powerful test of the hypothesis that the association between early cannabis use and later outcomes can be explained by common predisposing genetic and/or shared environmental risk factors. Since these predisposing factors are shared by twin pairs raised together, if the association between early cannabis use and later drug use can be explained by shared environmental factors, then in twin pairs discordant for early cannabis use, individuals who do not initiate early cannabis use should be at equal risk of developing drug-related problems as their co-twin who initiates cannabis use early. If correlated genetic effects explain these associations, then monozygotic pairs discordant for early use should still have equal risks. In contrast, if the association is causal or explained by environmental factors for which twin pairs are discordant, we would expect to find higher rates of other drug use and abuse/dependence in the early cannabis user than in his or her co-twin. In this article, this issue is explored using data from a large community sample of young adult Australian monozygotic and dizygotic twins.

METHODS

Interviewees were members of the young adult cohort of the Australian Twin Register, a volunteer twin panel born between 1964-1971.[20,23,24] The data presented in this report are derived from responses to a single telephone interview during the period 1996-2000 when the median age of the sample was 30 years (range, 24-36 years). Informed consent was obtained from participants prior to administering the interviews, as approved by the institutional review boards of Washington University School of Medicine and the Queensland Institute of Medical Research.

An overview of the study design is shown in the FIGURE. Of 4010 pairs that could be traced, interviews were completed with both members of 2765 pairs (69% pair-wise response rate) and 1 member of another 735 pairs (78% individual response rate). A total of 861 members of the sample (13.7%) reported initiating cannabis use before age 17 years, 311 of these (36.1%) were from same-sex twin pairs in which their co-twin had not used cannabis by age 17 years. The analyses in this article are based on this subset of 622 same-sex twins from pairs discordant for early cannabis use. There were 74 female and 62 male monozygotic twin pairs and 84 female and 91 male same-sex dizygotic twin pairs. Zygosity was determined on the basis of responses to standard questions about physical similarity and confusion of the twins by parents, teachers, and strangers, methods that have been found to give better than 95% agreement with results of genotyping.[25,26]

Assessments

A structured diagnostic interview designed for genetic studies on alcoholism, the Semi-Structured Assessment for the Genetics of Alcoholism,[26] was adapted for telephone use with an Australian sample and updated for *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)* diagnostic criteria.[27] The interview also included assessments of sociodemographic factors, childhood family environment, and experiencing childhood sexual abuse.[23] These measures are described below.

Measures of Subsequent Drug Involvement

Lifetime Drug Use. Respondents were asked whether they had ever engaged in nonmedical use of other drugs. In the analysis sample of 622 individuals from same-sex pairs discordant for early cannabis use, the following results were found: (1) sedative use (ie, benzodiazepines, barbiturates) was reported by 12.7% of women and 14.8% of men; (2) hallucinogen use was reported by 18.7% of women and 35.2% of men; (3) cocaine or other stimulant use was reported by 32.4% of women and 42.4% of men; and (4) opioid use was reported by 6.7% of women and 13.5% of men.

Lifetime Drug Abuse/Dependence. Individuals reporting using cannabis, sedatives, cocaine/other stimulants, or opioids on at least a monthly basis were asked additional questions concern-

Table 1. Men, Women, and the Total Sample of Discordant Twins Who Met Criteria for Drug Abuse and Dependence*

	Men (n = 306)			Women (n = 316)			Total (N = 622)		
Drug	Abuse	Dependence	Abuse/ Dependence	Abu	Dependence	Abuse/ Dependence	Abuse	Dependence	Abuse/ Dependence
Cannabis	57 (18.6)	96 (31.4)	153 (50.0)	23 (7.3)	65 (20.6)	88 (27.9)	80 (12.9)	161 (25.9)	241 (38.7)
Sedatives	2 (0.7)	4 (1.3)	6 (2.0)		5 (1.6)	5 (1.6)	2 (0.3)	9 (1.5)	11 (1.8)
Cocaine/stimulants	13 (4.2)	23 (7.5)	36 (11.8)	4 (1.3)	13 (4.1)	17 (5.4)	17 (2.7)	36 (5.8)	53 (8.5)
Opioids	2 (0.7)	6 (2.0)	8 (2.6)		6 (1.9)	6 (1.9)	2 (0.3)	12 (1.9)	14 (2.3)
Any illicit drug	56 (18.3)	101 (33.0)	157 (51.3)	22 (7.0)	71 (22.5)	93 (29.4)	78 (12.5)	172 (27.7)	250 (40.2)
Alcohol		†37 (44.8)			†86 (27.9)			225 (36.2)	

*Data are presented as No. (%). Ellipses indicate not applicable.

ing the extent to which they may have experienced symptoms of drug abuse (use in physically hazardous situations; use interfering with major role obligations) or dependence (using more frequently or for longer periods than intended, needing larger amounts to achieve an effect [tolerance], continued use despite use causing emotional problems, recurrent desire to cut down on use). Abuse was operationalized by endorsement of either abuse symptom; dependence was operationalized by endorsement of 2 or more dependence symptoms. While the dependence measure did not provide formal *DSM-IV* criteria, previous analyses exploring the validity of these modified criteria for cannabis dependence indicated that they had both excellent sensitivity (96.7%) and specificity (94.6%) when compared with *DSM-IV* criteria.[20]

Given the relatively low prevalence of drug abuse and dependence, measures of abuse and dependence for each drug class were combined. We assessed abuse/dependence for the following drug classes: (1) cannabis; (2) sedatives (ie, benzodiazepines, barbiturates); (3) cocaine/other stimulants; and (4) opioids. Additionally, these drug classes were combined to form a measure of any drug abuse or dependence. The prevalence of these outcomes is summarized separately by sex in TABLE 1.

Lifetime Alcohol Dependence. Lifetime alcohol dependence was assessed using full *DSM-IV*[19] criteria. 27.9% of women and 44.8% of men met criteria for alcohol dependence.

Family, Social, and Individual Factors

A number of family, social, and individual factors were included in the analysis as control variables. These were selected on the basis of a previous analysis with this sample that identified risk factors associated with cannabis dependence.[20]

Psychiatric Disorders. Criteria for conduct disorder and major depression from the *DSM-IV*[19] were assessed using the modified Semi-Structured Assessment for the Genetics of Alcoholism, and diagnoses were assigned by computer algorithm.[21] A nondiagnostic measure of social anxiety was also defined.[21]

Early Tobacco Use. A measure of early tobacco use was constructed by classifying subjects who reported smoking at least 1 day a week for a period of 3 weeks or more before age 17 years as early tobacco users (36.6% of twins from pairs discordant for early cannabis use reported such use).

Early Regular Alcohol Use. A measure of early alcohol use was constructed by classifying subjects who reported that they started drinking alcohol at least once a month for a period of 6 months or more before age 17 years as early regular alcohol drinkers (11.6% of twins from pairs discordant for early cannabis use reported such use).

Statistical Analyses

All statistical analyses were conducted using SAS[22] and STATA.[23] As an initial test of heritability of onset of cannabis use, rates of concordance for early (before age 17 years) cannabis use were compared between monozygotic and dizygotic twin pairs. Differences in concordance rates were tested using the Breslow-Day test of heterogeneity of odds ratios (ORs),[24] and separate tests were conducted for males and females. Conditional logistic regression models were then fitted to test for excess risk to early-onset cannabis users from same-sex discordant pairs, compared with their co-twin controls. The significance of the interactions between early cannabis use and both twin pair zygosity and sex were tested and, as these were nonsignificant ($P > .10$ in all cases), data were pooled across zygosity and sex. Analyses were repeated including the family and individual control variables described above. Stepwise regression with backward selection was conducted with the measure of early cannabis use forced into the model. These analyses were used to estimate conditional ORs for drug use and drug abuse/dependence in twins discordant for early cannabis use with control for other significant predictors.

Power was estimated using computer simulation. For example, for cocaine/stimulant abuse or dependence, we first obtained estimates of the prevalence ($p_E = 12.5\%$, exposed twin; $p_U = 4.5\%$, unexposed co-twin) and of the twin-pair tetrachoric correlation ($r = 0.47$). We then estimated the minimum $OR = p_E(1 - p_E)/p_U(1 - p_U)$, such that a difference between the prevalence in the exposed twin and the unexposed co-twin would be detected with 80% power given a sample of 311 twin pairs at the .01 significance level, with

Table 2. Drug Use Outcomes in Twin Pairs Discordant for Cannabis Use Before Age 17 Years (N = 31[illegible] Pairs)

	Lifetime Prevalence			Conditional OR Adjusted for Covariates	
	Early Cannabis Users, No. (%)	Co-twins, No. (%)	Unadjusted Conditional OR (95% CI)	OR (95% CI)	Significant Covariates*
Use					
Sedatives	59 (19.0)	26 (8.4)	2.83 (1.66-4.65)	2.28 (1.20-4.31)	1, 3, 4
Hallucinogens	110 (35.4)	56 (18[illegible]	5.15 (2.85-9.33)	5.15 (2.85-9.33)	
Cocaine/stimulants	149 (47.9)	82 (26.4)	4.19 (2.60-6.75)	4.06 (2.30-7.17)	1, 2, 4
Opioids	42 (13.5)	20 (6.4)	2.57 (1.39-4.77)	2.34 (1.13-4.85)	4
New drug abuse/dependence					
Cannabis	142 (45.7)	99 (31.8)	2.13 (1.45-3.13)	1.96 (1.25-3.09)	1, 2, 5
Sedatives	6 (2.6)	3 (1.0)	2.67 (0.71-10.05)	2.67 (0.71-10.05)	
Cocaine/stimulants	39 (12.5)	14 (4.5)	4.13 (1.91-8.93)	3.98 (1.73-9.17)	3
Opioids	11 (3.5)	3 (1.0)	3.67 (1.02-13.14)	3.67 (1.02-13.14)	
Any illicit drug abuse/dependence	148 (47.6)	102 (32.8)	2.24 (1.52-3.30)	1.98 (1.26-3.10)	1, 2, 5
Alcohol dependence	133 (42.8)	92 (29.6)	2.17 (1.46-3.24)	1.85 (1.21-2.83)	3, 4

Abbreviations: CI, confidence interval; OR, odds ratio.
*For significant covariates, 1 indicates early (before age 17 years) regular use of tobacco; 2, early (before age 17 years) regular use of alcohol; 3, conduct disorder; 4, major depression; and 5, social anxiety. Entries indicate that there were no significant covariates for the outcome.

p_1 and r fixed at their observed values. Our results indicate that power would be 80% or better for an OR greater than 1.7 for 5 measures (hallucinogen use, cocaine/stimulant use, cannabis abuse/dependence, any abuse or dependence, and alcohol dependence). Power was over 80% for an OR greater than 2.5 for the measures (sedative use, opioid use, and cocaine/stimulant abuse or dependence). Power was low under the reasonable range of OR for the measures sedative abuse/dependence and opioid abuse/dependence.

RESULTS

Rates of concordance for early cannabis use (before age 17 years) among the full interview sample (2765 pairs; see Figure) were significantly higher in monozygotic than dizygotic twin pairs for both men (65 concordant and 86 discordant monozygotic pairs vs 59 concordant and 110 discordant dizygotic pairs; $\chi^2_1 = 7.92$, $P = .005$) and women (61 concordant and 98 discordant monozygotic pairs vs 44 concordant and 111 discordant dizygotic pairs; $\chi^2_1 = 7.80$, $P = .005$), indicating heritable influences on age of initiation of cannabis use. The first 2 columns of TABLE 2 show estimates of the lifetime prevalence of drug use and drug abuse/dependence for those initiating cannabis use before age 17 years and for their co-twins who either reported no lifetime cannabis use or who reported initiating cannabis use at age 17 years or older. The majority of subjects reporting both cannabis and other illicit drug use reported initiating cannabis use before initiating the use of other drugs. Three individuals reported initiating sedative use before cannabis use, 6 individuals initiated hallucinogen use, 5 initiated stimulant use, and 3 initiated opioid use before the use of cannabis. These individuals were excluded from the analyses. Table 2 also shows the conditional ORs, both unadjusted and adjusted for major risk factors, for the drug use outcomes. The results in Table 2 can be summarized as follows.

1. Relative to their co-twins who had not used cannabis by age 17 years, those who had used cannabis by this age had elevated lifetime rates of other drug use, illicit drug abuse/dependence, and alcohol dependence.

2. The unadjusted conditional ORs indicated that in individuals who initiated cannabis use before age 17 years, the odds of other drug use, alcohol dependence, and other drug abuse/dependence were 2.1 to 5.2 times higher than in their co-twins who did not report early cannabis use. In all but 1 comparison (sedative abuse/dependence), these associations were statistically significant.

3. Controlling for known risk factors for later drug use and drug abuse/dependence had only negligible effects. Specifically, after such adjustment, relative to their discordant co-twins, those who had used cannabis before age 17 years had significantly elevated rates of 9 of the 10 outcomes. The nonsignificant association between early cannabis use and sedative abuse/dependence is likely to be a reflection of reduced statistical power due to the low base rate of this outcome.

The final column of Table 2 shows the significant or marginally significant ($P < .10$) predictors of each outcome. While covariates differed between equations, early regular use of tobacco and alcohol emerged as the 2 factors most consistently associated with later illicit drug use and abuse/dependence. While early regular alcohol use did not emerge as a significant independent predictor of alcohol dependence, this finding should be treated with considerable caution, as our study did not provide an optimal strategy for assessing the effects of early alcohol use.

Analyses Restricted to Those Reporting Lifetime Cannabis Use

Our analysis found that 24.8% of twins in pairs discordant for early cannabis use in fact reported no lifetime cannabis use. To examine the extent to which the asso-

Table 3. Drug Use Outcomes in Twin Pairs Discordant for Cannabis Use Before Age 17 Years With Sample Restricted to Those Reporting Lifetime Cannabis Use (N = 234 Pairs)

	Lifetime Prevalence			Conditional OR Adjusted for Covariates	
	Early Cannabis Users, No. (%)	Co-twins, No. (%)	Unadjusted Conditional OR (95% CI)	OR (95% CI)	Significant Covariates*
Use					
Sedatives	46 (19.7)	20 (8.5)	3.00 (1.60-5.62)	3.33 (1.53-7.23)	1, 4
Hallucinogens	94 (40.2)	56 (23.9)	3.92 (2.13-7.21)	3.92 (2.13-7.21)	
Cocaine/stimulants	123 (52.6)	81 (34.6)	3.00 (1.83-4.92)	3.05 (1.75-5.33)	1, 2
Opioids	33 (14.1)	17 (7.3)	2.33 (1.19-4.59)	2.40 (1.05-5.49)	4
Illicit drug abuse/dependence					
Cannabis	121 (51.7)	99 (42.3)	1.58 (1.05-2.37)	1.57 (0.96-2.52)	1, 2, 5
Sedatives	6 (2.6)	1 (0.4)	6.00 (0.72-49.83)	6.00 (0.72-49.83)	
Cocaine/stimulants	36 (15.4)	13 (5.6)	3.29 (1.88-9.76)	3.79 (1.60-9.01)	3
Opioids	10 (4.3)	2 (0.9)	5.00 (1.10-22.82)	5.00 (1.10-22.82)	
Any illicit drug abuse/dependence	127 (54.3)	100 (42.7)	1.75 (1.16-2.64)	1.76 (1.06-2.84)	1, 2, 5
Alcohol dependence	109 (46.6)	79 (33.8)	2.03 (1.30-3.17)	1.85 (1.21-2.83)	3, 4

Abbreviations: CI, confidence interval; OR, odds ratio.
*For significant covariates, 1 indicates early (before age 17 years) regular use of tobacco; 2, early (before age 17 years) regular use of alcohol; 3, conduct disorder; 4, major depression; and 5, social anxiety. Ellipses indicate that there were no significant covariates for the outcome.

ciations in Table 2 may have been related to risks associated with *any* cannabis use rather than *early* cannabis use, these analyses were replicated with the sample restricted to those who reported lifetime cannabis use (54 monozygotic female pairs, 53 monozygotic male pairs, 56 dizygotic female pairs, 71 dizygotic male pairs). The results of these analyses, shown in TABLE 3, were broadly consistent with the previous results. In particular, before adjustment for covariates, early use remained a significant predictor of all but 1 of the outcomes (sedative abuse/dependence) among twin pairs concordant for lifetime cannabis use but where 1 twin reported initiation of cannabis use before age 17 years and the other did not. After statistical control for measured risk factors, early use was not a significant predictor of sedative abuse/dependence and there was only a marginally significant association ($P = .06$) between early initiation of cannabis use and subsequent abuse/dependence on cannabis.

Subsidiary Analyses

Separate analyses of monozygotic- and dizygotic-discordant pairs were conducted in which early cannabis use was defined as use before age 15 years, before age 16 years, and before age 18 years. The results of these analyses confirmed the previous conclusions. For all definitions of early cannabis use, individuals who initiated cannabis use at an early age had elevated odds of later drug use and abuse/dependence relative to their discordant co-twin.

COMMENT

The results of our co-twin control analyses indicated that early initiation of cannabis use was associated with significantly increased risks for other drug use and abuse/dependence and were consistent with early cannabis use having a causal role as a risk factor for other drug use and for any drug abuse or dependence. Individuals who used cannabis before age 17 years had a 2.3- to 3.9-fold increase in odds of other drug use and a 1.6- to 6.0-fold increase in odds of alcohol dependence and other drug abuse/dependence, relative to their co-twin who had not used cannabis by age 17 years, regardless of whether or not the pair were monozygotic. Alternatively, there may be unmeasured environmental influences not shared by members of a twin pair that increase risks both of early cannabis use and of other drug use or abuse/dependence. We consider this less plausible, since twin pairs, having been reared in the same household, would be expected to be highly concordant for environmental experiences. Unmeasured family background risk factors or heritable risk factors cannot explain the observed association, since twin pairs will share the same family background, and monozygotic pairs the same genetic risk factors.

Potential limitations of this study include the reliance on self-report and retrospective data, and the lack of data about ages at progression to more frequent use or onset of problems. Age of first use was obtained earlier in our interview than the assessment of drug use problems to minimize recall biases, and the associations with early cannabis use that we observed in this twin pair sample have previously been reported in prospective studies.[14,15] An association due to underreporting of drug use by 1 twin seems implausible, since cannabis use, even by self-report, was highly prevalent and some use at least would be considered normative for this birth cohort in Australia, and since significant associations remained when analyses were limited to pairs concordant for lifetime cannabis use. It is also unlikely that we are observing only delayed onset of other drug use or drug abuse/dependence, rather than lower lifetime rates in the co-twins, since the median age of the sample (30 years) is considerably higher than typical ages of onset of drug use and drug abuse/

dependence.[11] For example, more than 95% of cannabis users in our total sample reported onset of marijuana use by age 24 years, the youngest age represented in the sample. Our estimates of the lifetime use of cannabis and other drugs are high but are consistent with those reported by other large-scale epidemiological surveys of drug use in Australia.[14] Further, a recent study of cannabis use in a US national twin sample concluded that twin studies of substance use are unlikely to be biased and that findings from such studies can be generalized to other (non-twin) family relationships.[15] The relative crudeness of our measure of exposure (any use before age 17 years as opposed to frequent, heavy, or problem use) makes the findings of an association even more remarkable.

If the association with early cannabis use is indeed causal, the mechanisms by which this association arises remain unclear. Pharmacological mechanisms might be hypothesized in which it is assumed that exposure to cannabis induces subtle biochemical changes that encourage drug-taking behavior.[16] This hypothesis is supported to some extent by recent findings that Δ^9-tetrahydrocannabinol and heroin have similar effects on dopamine transmission through a common μ_1 opioid receptor mechanism[17] and that chronic treatment with Δ^9-tetrahydrocannabinol induces cross-tolerance to amphetamine[18] and opioids[18,19] in rats. However, an argument against such biological hypotheses is that the levels of cannabis use at the beginning of drug-using careers are substantially lower than the equivalents used in laboratory-based research and perhaps too low to induce long-term biochemical changes.

Other mechanisms that might mediate a causal association between early cannabis use and subsequent drug use and drug abuse/dependence include the following.

1. Initial experiences with cannabis, which are frequently rated as pleasurable,[20] may encourage continued use of cannabis and also broader experimentation.

2. Seemingly safe early experiences with cannabis may reduce the perceived risk of, and therefore barriers to, the use of other drugs. For example, as the vast majority of those who use cannabis do not experience any legal consequences of their use, such use may act to diminish the strength of legal sanctions against the use of all drugs.

3. Alternatively, experience with and subsequent access to cannabis use may provide individuals with access to other drugs as they come into contact with drug dealers.[21] This argument provided a strong impetus for the Netherlands to effectively decriminalize cannabis use in an attempt to separate cannabis from the hard drug market.[22] This strategy may have been partially successful as rates of cocaine use among those who have used cannabis are lower in the Netherlands than in the United States.[23]

While the findings of this study indicate that early cannabis use is associated with increased risks of progression to other illicit drug use and drug abuse/dependence, it is not possible to draw strong causal conclusions solely on the basis of the associations shown in this study. Further research in other cultures and using a range of innovative research designs (including evaluation of prevention efforts aimed at delaying the onset of cannabis use) is needed to explore whether there is a causal link between early cannabis use and progression to other drug use and, if so, to elucidate the mechanisms that may underlie any such causal association.

Regardless of the mechanisms underlying these associations, it is apparent that young people who initiate cannabis use at an early age are at heightened risk for progressing to other drug use and drug abuse/dependence. In addition to cannabis dependence, the health risks associated with chronic cannabis use may include chronic bronchitis, impaired lung function, and increased risks of cancers of the aerodigestive tract.[4] Given historical increases in the use of cannabis and other drugs,[1,2] it is probable that more individuals will experience these adverse consequences and there will be an increasing need to develop strategies both to prevent and to ameliorate the adverse consequences of chronic drug use. Given that early initiation of use may be associated with increased risks both for progressing to the use of other drugs and for developing drug abuse/dependence, there is a need for greater physician awareness of those risks associated with early use. There is also a need to develop focused interventions to prevent escalation to use of other drugs among young people identified as being at risk due to their early initiation of cannabis use.

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Acquisition of data: Heath, Bucholz, Slutske, Madden, Statham, Martin.
Analysis and interpretation of data: Lynskey, Heath, Nelson, Slutske.
Drafting of the manuscript: Lynskey, Heath.
Critical revision of the manuscript for important intellectual content: Bucholz, Slutske, Madden, Nelson, Statham, Martin.
Statistical expertise: Lynskey, Heath, Martin.
Obtained funding: Heath, Martin.
Administrative, technical, or material support: Heath, Slutske, Statham, Martin.
Study supervision: Heath, Madden.
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REFERENCES

1. Bachman JG, Johnston LD, O'Malley PM. Explaining recent increases in students' marijuana use: impacts of perceived risks and disapproval, 1976 through 1996. *Am J Public Health*. 1998;88:887-892.
2. Reid A, Lynskey MT, Copeland J. Cannabis use among Australian youth. *Aust N Z J Public Health*. 2000;24:596-602.
3. Substance Abuse and Mental Health Services Administration. The DASIS Report: Marijuana treatment admissions increase: 1993-1999. Available at: http://www.samhsa.gov/oas/2k2/MJt.pdf. Accessed May 17, 2002.
4. Hall W, Solowij N. Adverse effects of cannabis. *Lancet*. 1998;352:1611-1616.
5. Solowij N, Stephens RS, Roffman RA, et al. Cognitive functioning of long-term heavy cannabis users seeking treatment. *JAMA*. 2002;287:1123-1131.
6. McLellan AT, Lewis DC, O'Brien CP, Kleber HD. Drug dependence, a chronic medical illness: implications for treatment, insurance, and outcomes evaluation. *JAMA*. 2000;284:1689-1695.
7. Substance Abuse and Mental Health Services Administration. The DASIS Report: Treatment referral sources for adolescent marijuana users. Available at: http://www.samhsa.gov/oas/2k2/YouthMJt/YouthMJt.pdf. Accessed May 17, 2002.
8. Kandel DB. Stages in adolescent involvement in drug use. *Science*. 1975;190:912-914.

9. Kandel DB, Faust R. Sequences and stages in patterns of adolescent drug use. *Arch Gen Psychiatry*. 1975;32:923-932.
10. Kandel DB, Yamaguchi K, Chen K. Stages of progression in drug involvement from adolescence to adulthood: further evidence for the gateway theory. *J Stud Alcohol*. 1992;53:447-457.
11. MacCoun R. In what sense (if any) is marijuana a gateway drug? FAS Drug Policy Analysis Bulletin. 1998; Issue 4. Available at: http://www.fas.org/drugs/issue4.htm#gateway. Accessed May 17, 2002.
12. Ellickson PL, Hawes RD, Bell RM. Stepping through the drug use sequence: longitudinal scalogram analysis of initiation and regular use. *J Abnorm Psychol*. 1992;101:441-451.
13. Graham JW, Collins LM, Wugalter SE, Chung NK, Hansen WB. Modeling transitions in latent stage-sequential processes: a substance use prevention example. *J Consult Clin Psychol*. 1991;59:48-57.
14. Baumrind D. Specious causal attribution in the social sciences: the reformulated stepping stone hypothesis as exemplar. *J Pers Soc Psychol*. 1983;45:1289-1298.
15. Yamaguchi K, Kandel DB. Patterns of drug use from adolescence to young adulthood: III. predictors of progression. *Am J Public Health*. 1984;74:673-681.
16. Fergusson DM, Horwood LJ. Early onset cannabis use and psychosocial adjustment in young adults. *Addiction*. 1997;92:279-296.
17. Fergusson DM, Horwood LJ. Does cannabis use encourage other forms of illicit drug use? *Addiction*. 2000;95:505-520.
18. Grant BF, Dawson DA. Age of onset of drug use and its association with DSM-IV drug abuse and dependence: results from the National Longitudinal Alcohol Epidemiologic Survey. *J Subst Abuse*. 1998;10:163-173.
19. Kosterman R, Hawkins JD, Guo J, Catalano RF, Abbott RD. The dynamics of alcohol and marijuana initiation: patterns and predictors of first use in adolescence. *Am J Public Health*. 2000;90:360-366.
20. Lynskey MT, Heath AC, Nelson EC, et al. Genetic and environmental contributions to cannabis dependence in a national young adult twin sample. *Psychol Med*. 2002;32:195-207.
21. Kendler KS, Karkowski LM, Neale MC, Prescott CA. Illicit psychoactive substance use, heavy use, abuse, and dependence in a US population-based sample of male twins. *Arch Gen Psychiatry*. 2000;57:261-269.
22. Tsuang MT, Lyons MJ, Meyer JM, et al. Co-occurrence of abuse of different drugs in men: the role of drug-specific and shared vulnerabilities. *Arch Gen Psychiatry*. 1998;55:967-972.
23. Nelson EC, Heath AC, Madden PAF, et al. The consequences and correlates of childhood sexual abuse—a retrospective examination using the twin study design. *Arch Gen Psychiatry*. 2002;59:139-145.
24. Heath AC, Howells W, Kirk KM, et al. Predictors of non-response to a questionnaire survey of a volunteer twin panel: findings from the Australian 1989 twin cohort. *Twin Res*. 2001;4:73-80.
25. Cederlof R, Friberg L, Jonsson E, Kaij L. Studies on similarity diagnosis in twins with the aid of a mailed questionnaire. *Acta Genetica et Statistica Medica*. 1961;11:338-362.
26. Kasriel J, Eaves LJ. The zygosity of twins: further evidence on the agreement between diagnosis by blood groups and written questionnaires. *J Biosoc Sci*. 1976;8:263-266.
27. Nichols RC, Bilbro WC Jr. The diagnosis of twin zygosity. *Acta Genet Stat Med*. 1966;16:265-275.
28. Saina S, Pardo J, Sistonen P, Koskenvuo M. Diagnosis of twin zygosity by mailed questionnaire. *Hum Hered*. 1978;28:241-254.
29. Bucholz KK, Cloninger CR, Dinwiddie SH, et al. A new, semi-structured psychiatric interview for use in genetic linkage studies: a report of the reliability of the SSAGA. *J Stud Alcohol*. 1994;55:149-158.
30. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*. Washington, DC: American Psychiatric Association; 1994.
31. SAS Institute Inc. *SAS/STAT Software: Changes and Enhancements for Release 6.12*. Cary, NC: SAS Institute Inc; 1996.
32. StataCorp. *Stata Statistical Software: Release 6.0*. College Station, Tex: Stata Corp; 1999.
33. Chen K, Kandel DB. The natural history of drug use from adolescence to the mid-thirties in a general population sample. *Am J Public Health*. 1995;85:41-47.
34. Australian Institute of Health and Welfare. *1998 National Drug Strategy Household Survey: First Results*. Canberra: Australian Institute of Health and Welfare; 1999.
35. Kendler KS, Neale MC, Thornton LM, Aggen SH, Gilman SE, Kessler RC. Cannabis use in the last year in a US national sample of twin and sibling pairs. *Psychol Med*. 2002;32:551-554.
36. Nahas G. *Keep Off the Grass*. Middlebury, Vt: Paul Eriksson; 1990.
37. Tanda G, Pontieri F, Di Chiara G. Cannabinoid and heroin activation of mesolimbic dopamine transmission by a common mu 1 opioid receptor mechanism. *Science*. 1997;276:2048-2050.
38. Lamarque S, Taghzouti K, Simon H. Chronic treatment with Δ9-tetrahydrocannabinol enhances the locomotor response to amphetamine and heroin: implications for vulnerability to drug addiction. *Neuropharmacology*. 2001;41:118-129.
39. Cadoni C, Pisanu A, Solinas M, Acquas E, Di Chiara G. Behavioural sensitization after repeated exposure to Δ9-tetrahydrocannabinol and cross-sensitization with morphine. *Psychopharmacology (Berl)*. 2001;158:259-266.
40. Fergusson DM, Lynskey MT, Horwood LJ. Patterns of cannabis use among 13-14 year old New Zealanders. *N Z Med J*. 1993;106:247-250.
41. Cohen H. Multiple drug use considered in the light of the stepping-stone hypothesis. *Int J Addict*. 1972;7:27-55.
42. MacCoun R, Reuter P. Evaluating alternative cannabis regimes. *Br J Psychiatry*. 2001;178:123-128.

A new self-report survey documents the deviant and delinquent behaviors of U.S. youth ages 12–16

A new survey will follow a cohort of youth as they make the transition from school to work

The first wave of the 1997 National Longitudinal Survey of Youth (NLSY97) interviewed a nationally representative sample of 9,000 youth who were between the ages of 12 and 16 at year-end 1996. The survey asked youth to report whether they had engaged in a variety of deviant and delinquent behaviors. Plans are to interview members of this cohort every 2 years to track changes in delinquent and criminal activity over the life course.

Youth who had ever used or sold drugs were more likely to engage in other problem behavior

One of the strengths of the survey is its ability to assess which delinquent behaviors cluster together. Members of the NLSY97 cohort were asked a variety of questions regarding drugs, guns, and gangs, including whether and how recently they had engaged in these activities. Analysis of these items demonstrates the connection between drug use or sale and other problem behaviors, such as carrying handguns, belonging to a gang, and consuming alcohol.

The proportion of youth engaging in deviant and delinquent behaviors varied significantly by age, sex, and race/ethnicity

Behavior	Total	Ages 12–13	Ages 14–15	Age 16	Male	Female	White	Nonwhite	Rural	Urban
Had sex										
Ever	29%	—	23%	43%	30%	28%	26%	37%	29%	30%
Last 12 months	21	—	16	32	22	21	19	27	21	22
Became pregnant										
Ever	6	—	4	10	—	6	5	9	5	7
Smoked cigarettes										
Ever	42	27	48	58	42	42	45	34	43	41
Last 30 days	20	10	23	33	20	20	22	14	21	19
Drank alcohol										
Ever	39	26	52	68	46	44	48	26	45	45
Last 30 days	21	8	25	37	21	21	23	16	20	21
Before or during school or work in the last 30 days	5	2	6	9	6	4	5	5	5	5
Used marijuana										
Ever	21	8	25	38	22	20	22	19	19	22
Last 30 days	9	4	11	17	10	9	10	8	8	10
Before or during school or work in the last 30 days	4	1	5	7	4	3	4	3	4	4
Ran away from home										
Ever	11	6	12	17	10	11	10	11	10	12
Carried a handgun										
Ever	10	8	11	12	16	3	10	9	11	9
Last 12 months	6	4	6	7	9	2	6	5	6	5
Last 30 days	3	2	3	3	5	1	3	3	3	3
To school in last 30 days	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1
Belonged to a gang										
Ever	5	3	6	6	6	3	4	7	5	5
Last 12 months	2	2	2	3	3	1	2	3	2	2
Purposely destroyed property										
Ever	28	25	31	30	37	20	30	25	29	28
Last 12 months	16	14	17	15	20	11	16	14	15	16
Stole something worth over $50*										
Ever	8	4	10	11	10	5	7	9	7	9
Last 12 months	5	3	6	7	7	3	5	6	4	6

- Youth who had ever used marijuana were more likely to have sold marijuana (24% vs. <1%), carried a handgun (21% vs. 7%), or been in a gang (14% vs. 2%) at some point than youth who never used marijuana.
- Youth who had ever sold marijuana were more likely to have sold hard drugs (i.e., cocaine, LSD, or heroin) (40% vs. 1%), carried a handgun (35% vs. 8%), or been in a gang (24% vs. 4%) than youth who never sold marijuana.
- Active marijuana users (i.e., youth who used marijuana during the month prior to the survey) were more likely to have consumed alcohol (78% vs. 14%) or carried a handgun (12% vs. 2%) during that period than youth who did not use marijuana.
- Youth who had carried a handgun in the last 12 months were also more likely to have been in a gang than youth who did not carry a handgun during this period (15% vs. 1%).

Behavior	Total	Ages 12–13	Ages 14–15	Age 16	Male	Female	White	Nonwhite	Rural	Urban
Stole a vehicle for use or sale										
Ever	1%	< 0.5%	2%	2%	2%	1%	1%	1%	1%	1%
Sold any drugs										
Ever	7	2	9	12	9	5	8	5	7	7
Last 12 months	5	2	7	9	7	4	6	4	5	6
Sold hard drugs (e.g., cocaine, LSD, or heroin)										
Ever	3	1	3	6	3	2	3	3	3	3
Sold marijuana										
Ever	5	2	7	10	7	4	6	4	5	6
Committed assault										
Ever	18	15	19	22	23	12	16	21	17	18
Last 12 months	12	10	13	13	16	8	11	14	12	12
Was arrested										
Ever	8	4	10	12	10	5	7	9	6	9
Number of times										
Once	5	2	6	7	6	3	4	5	4	5
2 or more	3	1	4	5	4	2	3	4	2	4

- Of all youth, 3% had carried a handgun in the month prior to the interview, and fewer than 1 in 200 had carried a handgun to school during that time.
- With a few exceptions, urban and rural youth reported participation in problem behaviors in equal proportions; however, urban youth were significantly more likely than rural youth to have run away from home (12% vs. 10%), ever used marijuana (22% vs. 19%), or ever been arrested (9% vs. 6%).
- Of all youth, 9% used marijuana in the last 30 days, and less than 4% used marijuana before or during school or work hours during this time. Similarly, 21% of all youth drank alcohol in the last 30 days, and 5% drank alcohol before or during school or work hours during this time.
- The proportion of youth who had ever used marijuana increased dramatically with age, from 8% of youth ages 12 and 13 to 25% of youth ages 14 and 15. The proportion of youth ages 14 and 15 who had ever used alcohol (52%) was double that of youth ages 12 and 13 (26%).

Note: Only youth 14 and older were asked about their sexual activity and pregnancy. Only females were asked about pregnancy.

* Includes stealing a vehicle for use or sale.

Source: Authors' analysis of the Bureau of Labor Statistics' *The National Longitudinal Survey of Youth 1997* [machine-readable data file]

National Household Survey on Drug Abuse

The NHSDA Report

July 19, 2002

Marijuana Use among Youths

The National Household Survey on Drug Abuse (NHSDA) asks respondents to report on past year use and age at first use of marijuana. Respondents aged 12 to 17 were also asked to report whether they had been enrolled in any type of school at any time during the year before the survey. Youths enrolled in school were asked to report their average letter grade for the last semester or grading period they completed.

In Brief

- In 2000, over 3 million youths aged 12 to 17 used marijuana at least once during the past year
- White youths were more likely to use marijuana than Hispanic, black, or Asian youths
- Youths with an average grade of D or below were more than 4 times as likely to have used marijuana in the past year as youths who reported an average grade of A

Prevalence of Marijuana Use among Youths

In 2000, the NHSDA estimated that over 3 million, or 13 percent, of the 23 million youths aged 12 to 17 used marijuana during the year prior to the survey. The rate of past year marijuana use was lower for youths compared with the rate for young adults aged 18 to 25 (24 percent), but it was higher than the rate for adults aged 26 or older (5 percent).

Trends in Initiation of Marijuana Use among Youths

Between 1996 and 1999, the number of youths aged 12 to 17 trying marijuana for the first time each year was greater than during the prior 20 years (Figure 1). Approximately 1,690,000 youths first used marijuana during 1996, more than during any other year since 1978. However, the number of youths trying marijuana for the first time decreased to 1,392,000 by 1999.

The NHSDA Report is published periodically by the Office of Applied Studies, Substance Abuse and Mental Health Services Administration (SAMHSA). Other reports from the Office of Applied Studies are also available on-line: http://www.DrugAbuseStatistics.samhsa.gov/.

Figure 1. Estimated Numbers of Youths Aged 12 to 17 Who First Used Marijuana During the Years 1965 to 1999

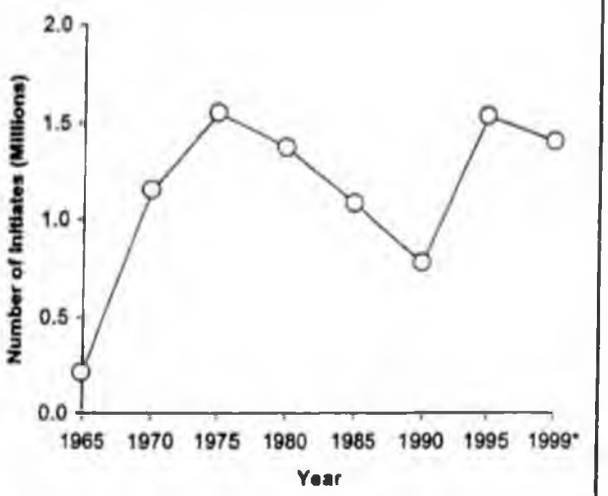
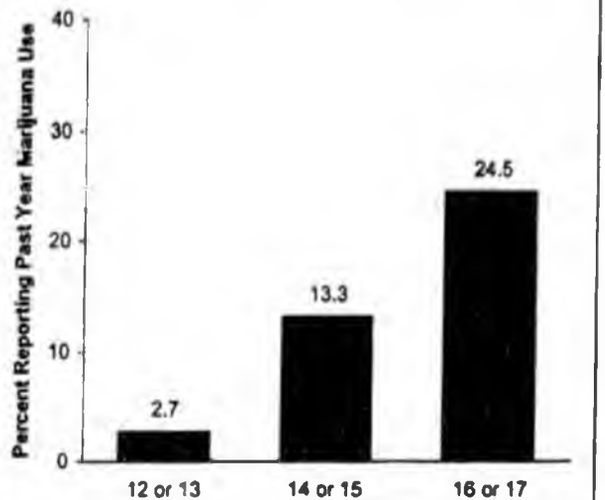


Figure 2. Percentages of Youths Aged 12 to 17 Reporting Past Year Marijuana Use, by Age Group: 2000



Demographic Differences in Prevalence

Older youths were more likely to have used marijuana during the past year than younger youths (Figure 2). Almost 25 percent of youths aged 16 or 17 reported past year marijuana use compared with 3 percent of 12 or 13 year olds. White youths were more likely to have used marijuana during the past year (15 percent) than Hispanic (13 percent), black (9 percent), or Asian youths (6 percent) (Figure 3).

Although males were more likely than females to have used marijuana during the past year among adults aged 18 or older, there were no gender differences in past year marijuana use among youths. For example, among 18 to 25 year olds, males were more likely to have used marijuana during the past year than females (28 percent of males vs. 20 percent of females), but among youths, rates of past year marijuana use were similar (14 percent of males, 13 percent of females).

Youths living in the South (12 percent) were less likely than youths living in the Northeast (14 percent) and West (15 percent) to report past year marijuana use (Figure 4).[1] Youths living in small metropolitan areas were more likely to have used marijuana during the past year (14 percent) than youths living in large metropolitan (13 percent) or non-metropolitan areas (13 percent).[2]

Academic Performance and Marijuana Use among Youths

In 2000, almost 30 percent of youths aged 12 to 17 enrolled in school earned an A average during the last semester or grading period they completed, 41 percent earned a B average, 23 percent earned a C average, and 7 percent earned an average of D or below.[3] Prior research has associated poor grades with substance use among youths.[4,5] Rates of past year marijuana use were higher among youths with lower grades than among those with higher grades (Figure 5). For example, youths with an average grade of D or below were more than 4 times as likely to have used marijuana in the past year (33 percent) as youths who reported an average grade of A (7 percent).

End Notes

1. Regions include the following groups of States: **Northeast Region:** Maine, New Hampshire, Vermont, Massachusetts, Rhode Island, Connecticut, New York, New Jersey, Pennsylvania. **Midwest Region:** Wisconsin, Illinois, Michigan, Indiana, Ohio, North Dakota, South Dakota, Nebraska, Kansas, Minnesota, Iowa, Missouri. **South Region:** West Virginia, Virginia, Maryland, Delaware, District of Columbia, North Carolina, South Carolina, Georgia, Florida, Mississippi, Tennessee, Kentucky, Alabama, Texas, Oklahoma, Arkansas, Louisiana. **West Region:** Idaho, Nevada, Anzona, New Mexico, Utah, Colorado, Wyoming, Montana, California, Oregon, Washington, Hawaii, Alaska.
2. Large metropolitan areas have a population of 1 million or more. Small metropolitan areas have a population of less than 1 million. Non-metropolitan areas are outside of metropolitan statistical areas (MSAs), as defined by the Office of Management and Budget.
3. Approximately 69 percent of surveyed youths aged 12 to 17 were included in these analyses. The remaining 31 percent of youths either attended schools that did not give letter grades, left the question blank, did not attend school, or were not asked about letter grades. Unpub-

Figure 3. Percentages of Youths Aged 12 to 17 Reporting Past Year Marijuana Use, by Race/ Ethnicity: 2000**

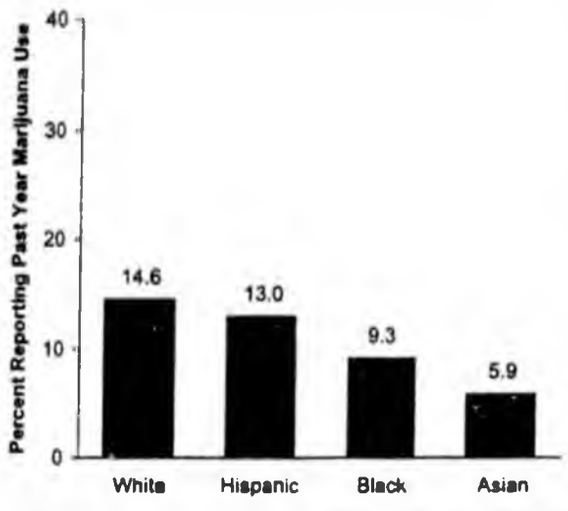
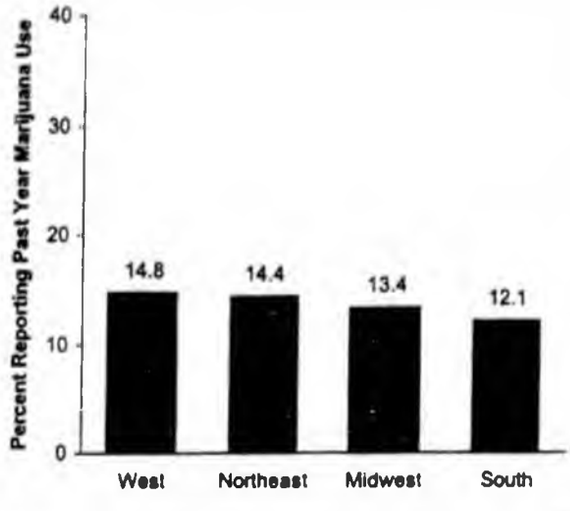


Figure 4. Percentages of Youths Aged 12 to 17 Reporting Past Year Marijuana Use, by Geographic Region: 2000



The National Household Survey on Drug Abuse (NHSDA) is an annual survey sponsored by the Substance Abuse and Mental Health Services Administration (SAMHSA). The 2000 data are based on information obtained from nearly 72,000 persons aged 12 or older, including more than 25,000 youths aged 12 to 17. The survey collects data by administering questionnaires to a representative sample of the population through face-to-face interviews at their place of residence.

The NHSDA Report is prepared by the Office of Applied Studies (OAS), SAMHSA, and by RTI in Research Triangle Park, North Carolina. Information and data for this issue are based on the following publication and statistics.

Substance Abuse and Mental Health Services Administration. (2001) *Summary of findings from the 2000 National Household Survey on Drug Abuse* (NHSDA Series: H-13, DHHS Publication No. SMA 01-3549). Rockville, MD: Author.

Also available on-line: www.DrugAbuseStatistics.samhsa.gov.

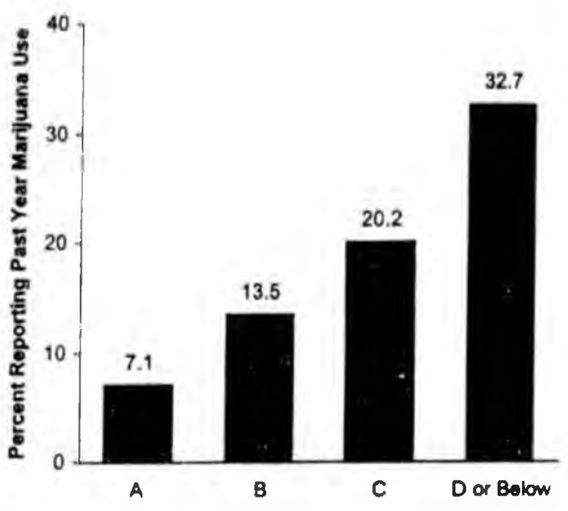
Additional Tables 1.2A, 1.2B, 1.3B, 1.4B, 1.5B, 1.6B, 1.7B, 1.32B, 1.77B, 1.78B, and 1.79B from http://www.samhsa.gov/oas/nhsda/2kdetailedtabs/Vol_1_Part_1/V1P1.htm and

Table 4.1A from http://www.samhsa.gov/oas/nhsda/2kdetailedtabs/Vol_1_Part_3/V1P3a.htm.

Additional tables available upon request.

U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES
Substance Abuse & Mental Health Services Administration
Office of Applied Studies
www.samhsa.gov

Figure 5. Percentages of Youths Aged 12 to 17 Enrolled in School Reporting Past Year Marijuana Use, by Average Grades for the Last Semester or Grading Period Completed: 2000



lished analyses of 1999 NHSDA data using revised sample weights specific to youths who were asked about letter grades indicated that any differences in demographics between those who were asked about grades and the full sample did not have a marked effect on the distribution of letter grades or on the association between letter grades and past year marijuana use.

4. Hawkins, J.D., Catalano, R.F., & Miller, J.Y. (1992). Risk and protective factors for alcohol and other drug problems in adolescence and early adulthood: Implications for substance abuse prevention. *Psychological Bulletin, 112,* 64-105.

5. Lane, J., Gerstein, D., Huang, L., & Wright, D. (2001). *Risk and protective factors for adolescent drug use: Findings from the 1997 National Household Survey on Drug Abuse* (Analytic Series: A-12, DHHS Publication No. SMA 01-3499). Rockville, MD: Substance Abuse and Mental Health Services Administration.

Figure Notes

*Estimated using 2000 data only.

**American Indian/Alaska Native, Native Hawaiian/Other Pacific Islander, and multiracial youths are not included in these analyses.

Source (Figure 1): SAMHSA 1999 and 2000 NHSDAs.

Source (Figures 2-5): SAMHSA 2000 NHSDA.

CME

Dose-related neurocognitive effects of marijuana use

K.I. Bolla, PhD; K. Brown, MPH; D. Eldreth, BA; K. Tate, BA; and J.L. Cadet, MD

Abstract—*Background:* Although about 7 million people in the US population use marijuana at least weekly, there is a paucity of scientific data on persistent neurocognitive effects of marijuana use. *Objective:* To determine if neurocognitive deficits persist in 28-day abstinent heavy marijuana users and if these deficits are dose-related to the number of marijuana joints smoked per week. *Methods:* A battery of neurocognitive tests was given to 28-day abstinent heavy marijuana abusers. *Results:* As joints smoked per week increased, performance decreased on tests measuring memory, executive functioning, psychomotor speed, and manual dexterity. When dividing the group into light, middle, and heavy user groups, the heavy group performed significantly below the light group on 5 of 35 measures and the size of the effect ranged from 3.00 to 4.20 SD units. Duration of use had little effect on neurocognitive performance. *Conclusions:* Very heavy use of marijuana is associated with persistent decrements in neurocognitive performance even after 28 days of abstinence. It is unclear if these decrements will resolve with continued abstinence or become progressively worse with continued heavy marijuana use.

NEUROLOGY 2002;59:1337–1343

Marijuana is the most widely used illicit drug in the United States and the western hemisphere. In 2000, an estimated 76% of America's 14.8 million illicit drug users used marijuana alone (59%) or in conjunction with other illicit drugs (17%).[1] About 7 million people in the US population use marijuana at least weekly.[1] Because of debate about medicinal uses and legalization of marijuana, knowing whether marijuana has persistent effects on the brain is of interest.

Studies of residual cognitive effects of marijuana following a brief period of abstinence show that heavy marijuana use is associated with deficits in executive cognitive functioning, sustained attention, and memory.[2-5] These studies have some methodologic limitations. First, marijuana users were only monitored for abstinence for 17 to 72 hours before testing. Because marijuana has an apparent half-life of 4.1 ± 1.1 days,[6] it is difficult to determine if the these observations[2-5] were due to drug residues in the body or to withdrawal symptoms such as anxiety or irritability.[7] Second, the quantification of heavy versus light users may be problematic. Marijuana users have been grouped by frequency of use[2] and duration of use.[3,4] When marijuana users are separated by duration of use, it is troublesome to separate the effects of marijuana from differences in age and education (a cohort effect). Third, no structured psychiatric interview was used to exclude disorders like depression,[3] which is associated with poor cognitive performance.[8]

Until 2001, there were no published reports of the residual effects of marijuana use on cognitive functioning after a period of abstinence longer than 12 to 72 hours. In a carefully designed study, marijuana users were grouped by frequency of use and neurocognitive testing was repeated over 28 days of abstinence (0, 1, 7, and 28 days).[9] Decrements in memory for word lists were found at 7 days of abstinence but not after 28 days of abstinence. The authors thus concluded that cognitive deficits are reversible after 7 days of abstinence and are related to recent, not cumulative, cannabis use. Knowledge about the cognitive effects of marijuana could also provide a basis for determining the relative contribution of marijuana when used in combination with other drugs such as methylenedioxymethamphetamine (MDMA).[10,11]

The current study was conducted to determine whether neurocognitive deficits persist in 28-day abstinent heavy marijuana users and if these deficits are dose-related (joints smoked/week). Based on our previous work in cocaine and MDMA users,[12,13] we hypothesized that deficits in cognitive performance would be observed only in the heaviest users of marijuana.

Methods. *Participants.* This protocol was approved by the National Institute on Drug Abuse–Intramural Re-

Additional material related to this article can be found on the *Neurology* Web site. Go to www.neurology.org and scroll down the Table of Contents for the November 12 issue to find the title link for this article.

From the Department of Neurology (Dr. Bolla and D. Eldreth), Johns Hopkins University School of Medicine, Hopkins Bayview Research Campus; and Molecular Neuropsychiatry Section (K. Brown, K. Tate, and Dr. Cadet), NIH/NIDA-IRP, Baltimore, MD.

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Address correspondence and reprint requests to Dr. Karen I. Bolla, Johns Hopkins Bayview Medical Center, Department of Neurology, 4940 Eastern Ave., Baltimore, MD 21224; e-mail: kbolla@jhmi.edu

search Program (NIDA-IRP), the Joint Committee on Clinical Investigation, and the Johns Hopkins Bayview Medical Institutional Review Boards. All participants gave written informed consent and were compensated for their time. Marijuana abusers were recruited using newspaper advertisements. Participant selection was based on drug use history obtained using structured interviews including the Drug Use Survey Questionnaire (DUSQ),[14] the Addiction Severity Index (ASI,)[15] and the Diagnostic Interview Schedule (DIS).[16]

Marijuana group. The marijuana group consisted of nontreatment-seeking individuals claiming marijuana as their drug of choice who used marijuana for at least 2 years, smoked marijuana at least three times per week, reported alcohol consumption of less than 14 alcoholic drinks per week, and had a urine toxicology screen that was positive for cannabis metabolites at the time of admission to the study. This ensured that all participants were abstinent for a uniform period of time. Participants were still eligible for inclusion if dependent on caffeine or tobacco. Participants were excluded if they met the Diagnostic and Statistical Manual of Mental Disorders–IV (DSM-IV) criteria gleaned from the DIS for current or past dependence on any other psychoactive substance other than marijuana, including alcohol, or if their urine toxicology screen was positive for substances other than marijuana and its metabolites. The ASI and DUSQ were used to estimate the number of joints smoked per week and the duration of marijuana use.

Exclusion criteria for all participants. Volunteers were excluded for past or current psychiatric disorder by DSM-IV criteria using the DIS (i.e., anxiety disorder, posttraumatic stress disorder, and major depressive disorder). Volunteers were also excluded for a past or current history of neurologic illness (e.g., head trauma resulting in loss of consciousness, seizure disorder, stroke), an abnormal neurologic examination, or pregnancy.

Data collection. At the initial visit to the Clinical Inpatient Research Unit (CIRU) at NIDA-IRP, all participants had a medical evaluation, a neurologic examination, urine toxicology screen, and pregnancy test for women. Participants were then admitted to the CIRU for approximately 30 days. This allowed us to examine persistent effects of marijuana on the brain, rather than acute effects. Random drug screens were performed during the inpatient stay to ensure abstinence. No treatment or medications were given over the 30-day stay.

Neuropsychological measures. The neurocognitive test battery was administered by a trained psychometrician under the supervision of a neuropsychologist (K.I.B.). The neurocognitive battery consisted of tests that assess a variety of cognitive domains. General intelligence was estimated using the Shipley Institute of Living Scale.[17] The Shipley estimated IQ correlates with the Wechsler Adult Intelligence Scale–Revised (WAIS-R) full-scale IQ (r = 0.79). Measures of IQ are believed to be good estimates of native intellectual abilities (premorbid intelligence) and are resistant to the effects of brain injury. Language skills were assessed using Controlled Oral Verbal Fluency.[18] Verbal memory was assessed by the Logical Memory from the Wechsler Memory Scales–Revised (WMS-R)[19] and the Rey Auditory Verbal Learning Test (RAVLT),[20] whereas visual memory was assessed using the Rey Osterreith Complex Figure[21] and the Symbol Digit Paired Associate Learning Test.[22] Attention and concentration were assessed using the Verbal and Non-Verbal Cancellation Test[23] for both randomly placed letters and symbols. Executive functioning was measured with the Digit Symbol Substitution from the WAIS-R,[24] Trails A, Trails B,[25] Stroop,[26] and the Wisconsin Card Sorting Test (WCST).[27] The Rey Complex Figure (copy), Block Design (WAIS-R),[24] and Judgment of Line Orientation[28] assessed visuoperception/visuoconstruction. The California Computerized Assessment Package (CALCAP)[29] was used to assess both simple and

Table 1 Demographic characteristics of marijuana users by amount used

Characteristic	All, n = 22	Light group, n = 7	Middle group, n = 8	Heavy group, n = 7
Age, y	22.4 ± 4.9 (18–37)	24.6 ± 6.1 (18–37)	21.9 ± 5.3 (18–34)	20.7 ± 2.4 (18–25)
Education, y	11.4 ± 1.5 (8–14)	12.7 ± 0.7* (12–14)	10.9 ± 1.5 (8–12)	10.7 ± 1.5 (8–12)
Shipley IQ	95.9 ± 10.9 (78–115)	101.9 ± 9.9 (86–115)	95.0 ± 11.2 (80–114)	91 ± 10 (78–101)
Sex, M/F	19/3	5/2	7/1	7/0
Ethnicity, W/AA/other	1/18/3	1/5/1	0/6/2	0/7/0
Handedness, R/L	19/3	7/0	6/2	6/1
Marijuana use				
Joints/wk	48.5 ± 36.9 (2–117)	10.5 ± 4 (2–14)	42.1 ± 18.2 (18–70)	93.9 ± 15.4 (78–117)
Days/wk	5.8 ± 1.7	4.4 ± 1.0	6.9 ± 1.9	7.0 ± 0.2
Duration, y	4.8 ± 3.1 (2–15)	3.4 ± 1.6 (2–6)	5.4 ± 4.2 (2–15)	5.3 ± 2.4 (3–10)
Alcohol use				
Days/wk	1.1 ± 1.3 (0–5)	1.0 ± 1.4 (0–3)	0.6 ± 0.7 (0–2)	1.5 ± 1.7 (0–5)
Drinks/wk	3.2 ± 4.2 (0–13)	2.4 ± 4.1 (0–11)	3.1 ± 4.6 (0–13)	4.1 ± 4.3 (0–13)
Duration, y	3.8 ± 6.1 (0–26)	2.3 ± 3.9 (0–10)	2.0 ± 2.1 (0–5)	3.0 ± 2.7 (0–7)

Values are mean ± SD (range).

* $p < 0.05$; Mean difference is between the light and middle and light and heavy groups.

Light group = 2–14 joints/wk; middle group = 18–70 joints/wk; heavy group = 78–117 joints/wk. W = white; AA = African American.

choice reaction times (psychomotor speed). Manual dexterity was assessed using Finger Tapping[28] and Grooved Pegboard.[30] Participants were tested on the 27th or 28th day after admission to the inpatient research unit. This eliminated any acute drug effects and possible confounding effects on neurocognitive performance from the physical or psychological symptoms associated with drug or alcohol withdrawal. All testing was performed in the morning to reduce diurnal fluctuations in performance. The examiner was blind to the intensity and duration of drug use.

Data analyses. Multiple linear regression models were used for data analyses. Neurocognitive variables were log transformed if not normally distributed. Exploratory analyses examined the possible effects of age, education, Shipley IQ, depression score (Center for Epidemiologic Studies–Depression), and sex on the neurocognitive performance measures. An independent variable was retained in the model if associated ($p < 0.05$) with the neurocognitive outcome variable. A separate multiple regression analysis was performed for each of the neurocognitive tests. As with our previous studies that found dose-related effects of cocaine[13] and MDMA[12] on neurocognitive performance predominately at higher doses, it was desirable to establish a dose-related relationship between quantity and duration of marijuana use and possible neurocognitive decrements. Therefore, models included either joints per week, duration of use, or a cross-product of joints per week × duration. A joints per week squared term was also included in the models to test for nonlinear effects that would indicate a threshold effect. We did not examine the association between frequency of use and neurocognitive performance because 82% of our sample smoked marijuana 20 or more days a month. Interaction terms (i.e., Shipley IQ × joints/week) were also examined. All analyses were performed with SPSS statistical software program (Chicago, IL).

Results. Table 1 shows the demographic and drug use characteristics of the marijuana users. When taken as a whole, the entire group consisted of predominantly heavy marijuana users (median joints per week = 35; range 2 to 117). The group was also divided into light, middle, and heavy users by dividing the group using terciles of joints per week smoked (see table 1). Except for years of education, there were no significant differences for any of the subject characteristics listed in table 1 (see also below).

Table 2 summarizes significant dose-related effects on key outcome variables for the regression analyses. The R^2 total reflects the overall proportion of the variance accounted for by the model after the last significant variable was entered in the equation. The results show both linear and nonlinear dose-response effects (i.e., as joints per week increase, neurocognitive performance declines; $p < 0.05$). This was found for tests of verbal memory (RAVLT, delayed recall, $F[1,21] = 7.30$), visual learning and memory (Symbol-Digit Paired Associate Learning, $F[1,21] = 6.57$), executive functioning (WCST categories completed, $F[1,20] = 7.09$), psychomotor speed (simple reaction time [CALCAP], $F[1,21] = 8.32$; complex reaction time–number correct, $F[1,21] = 11.96$), and manual dexterity (Grooved pegboard–nondominant hand, $F[1,21] = 6.55$). A significant dose-related effect in the opposite direction (i.e., as joints per week increased, performance increased) was found for the CALCAP–numbers in sequence, false positive responses ($F[1,21] = 4.87$). Moreover, the models accounted for a moderate to a large amount of variance (19 to 57%) in neurocognitive performance. Duration of use was associated only with a decrease in perfor-

Table 2 Linear regression analyses of outcome variables, demonstrating a significant dose-related effect with marijuana use

Dependent variable	Independent variable*	Exposure variable	*p* Value	Total R^2
RAVLT—delayed recall		Joints/wk	0.01	0.27
Symbol–digit paired associate learning	Joints/wk^2 × Shipley IQ ($p = 0.01$)	Joints/wk^2	0.02	0.45
Stroop	Joints/wk × Shipley IQ ($p = 0.01$)	Joints/wk	0.01	0.45
WCST—categories completed		Joints/wk	0.02	0.28
Rey complex figure—copy		Duration	0.05	0.19
RT—simple		Joints/wk^2	0.01	0.52
RT—repetition of numbers, number correct	Joints/wk^2 × Shipley IQ ($p = 0.03$)	Joints/wk	0.01	0.57
RT—numbers in sequence, false positives†	Shipley IQ ($p = 0.01$)	Joints/wk	0.04	0.32
Grooved Pegboard—nondominant hand	Joints/wk^2 × Shipley IQ ($p = 0.01$)	Joints/wk^2	0.02	0.44

* To control for possible confounding effects, these variables were retained in the model if a significant association ($p < 0.05$) was found with performance.

† For this variable, as marijuana use increases, performance improves; for all the other variables, as marijuana use increases, performance declines.

RAVLT = Rey Auditory Verbal Learning Test; WCST = Wisconsin Card Sorting Test; RT = reaction time from the California Computerized Assessment Package.

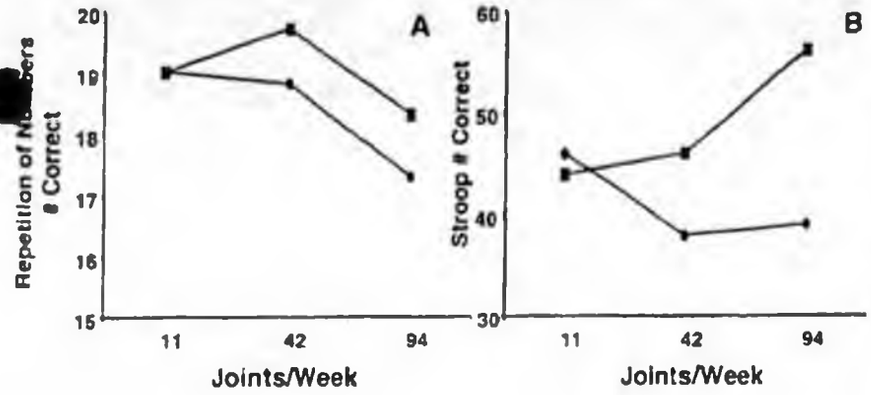

Figure. (A) Relation between amount of marijuana smoked[2] and Repetition of Numbers Task, number correct for the high Shipley IQ group (squares) and the low Shipley IQ group (circles). (B) Relation between amount of marijuana smoked[2] and performance on the Stroop task for the high Shipley IQ group (squares) and the low Shipley IQ group (circles). The lower the IQ score the worse the performance. Both A and B reveal a significant joints per week × Shipley IQ interaction.

mance on one test, a test of visuoperception/visuoconstruction (Rey Osterreith Complex Figure–copy, $F[1,21] = 4.38$). Finally, the combination of amount and duration was not related to performance on any of the tests.

To illustrate differences in neurocognitive performance between the lightest and heaviest marijuana users, the group was divided into three groups based on the amount of marijuana smoked as noted above (see table 1). The light group smoked a mean of 11 ± 4 joints/week (range 2 to 14), the middle group reported smoking a mean of 42 ± 18 joints/week (range 18 to 70), and the heavy marijuana group reported smoking a mean of 94 ± 15 joints/week (range 78 to 117) (see table 1). The groups did not differ significantly on age, Shipley IQ score, number of women and men, duration of marijuana use, and alcohol use (see table 1). However, because the mean Shipley IQ score was different for the light (102), middle (95), and heavy (91) users, we elected to take a conservative approach and analyze the group differences using an analysis of covariance (ANCOVA) with Shipley IQ score as a covariate. The mean performance scores, adjusted for differences in Shipley IQ, are presented in the online supplementary table (available at www.neurology.org). Differences among the three groups were examined with post-hoc *t*-tests. Comparison of group means shows the heavy users performing worse than the light users on 24/35 (69%) of the neurocognitive performance measurements; this difference was significant on five of the neurocognitive measures. Significant group differences were also found between the light and middle users on four of the tests, and between the middle and heavy users on two of the tests. When the scores of the heavy users were compared to published age-appropriate normative values for each of the tests, scores considered to be clinically relevant (below the ninth percentile for the general population) were found for the WCST–categories completed, Rey Complex Figure (copy and delayed recall), and Finger Tapping (dominant hand).

Interaction effects. There were four significant interactions involving joints/week and Shipley IQ. A Shipley IQ × joints per week interaction was found for the Stroop ($F[1,21] = 10.31$). A Shipley IQ × joints per week^2 interaction was found for Symbol-Digit Paired Associate Learning ($F[1,21] = 8.67$), reaction time repetition of numbers-correct ($F[1,21] = 5.89$), and Grooved Pegboard–nondominant hand ($F[1,21] = 8.25$) (see table 2). In general, individuals with lower Shipley IQ scores (less than 96) showed decreasing cognitive performance with increasing number of joints smoked/week whereas individuals with higher Shipley IQ scores had fewer decrements and better performance with increasing marijuana use. To visualize the joints smoked × Shipley IQ interaction, joints smoked/week was divided into terciles and the mean for each tercile was used for the joints/week × Shipley IQ adjusted plots (figure, A and B). Shipley IQ groups were formed by splitting the group by the median Shipley IQ score of 96.

Discussion. In very heavy marijuana users, persistent, negative dose-related effects are found on tests measuring verbal and visual memory, executive functioning, visuoperception, psychomotor speed, and manual dexterity. This effect was nonlinear for some tests, suggesting a threshold effect. Although we find a dose-related association between joints per week smoked of marijuana and cognitive decline, duration of use is only associated with performance on one test and a combination of joints/week × duration is not associated with performance on any test. In contrast to previous findings,[4] duration is not strongly related to performance. This is probably because our marijuana group has shorter duration of use (4.8 ± 3.1 years, range 2 to 15 years) compared to other samples of marijuana users (7.1 ± 7.9 years, range 2.7 to 31.7 years).[4] Additionally, our findings do not confirm previous reports showing resolution of cognitive effects after 24 days of marijuana abstinence.[9] This discrepancy may be due to our approach to estimating marijuana use (i.e., joints per week) in contrast to those of other investigators (i.e., duration and frequency).[2-5,9] Indeed, joints smoked per week may be a better estimate of total marijuana intake than frequency or duration of use because a marijuana user smoking 10 joints/day for 10 years would probably show greater neurocognitive effects than a marijuana user smoking one joint/day for 10 years.

Heavy marijuana use was associated with lower performance on tests of memory, executive functioning, and manual dexterity. These findings are similar to the findings of others.[2,4] The RAVLT delayed memory test shows a significant association with the amount of marijuana smoked and there is a trend showing that heavy users performed below the light users on all measures of verbal learning and memory. In fact, the magnitude of the difference in mean performance between the heavy and light users is substantial (1.0 to 3.3 SD units). However, because the heavy marijuana group can recognize previously

learned material (RAVLT–Recognition), this pattern suggests difficulty with information recall, not problems with acquisition or retention of information. This pattern of memory performance is characteristic of subcortical, prefrontal lobe involvement, and normal aging. Visual learning and memory (Symbol-Digit Paired Associate Learning) are also affected by heavy marijuana use.

There was also an association between increasing marijuana use and decreasing executive cognitive functioning. This is apparent on the WCST and the effect sizes are large (4.1 to 4.2 SD units). Poor performance on the WCST indicates difficulty incorporating feedback to guide and change incorrect response selection. The Stroop test requires suppression of a more habitual response in favor of an atypical one (response inhibition) and involves performance monitoring. Performance on the Stroop is affected by marijuana use but only in individuals with lower cognitive reserves, as illustrated by the significant joints per week × Shipley IQ interaction (see the figure, B). This is consistent with the suggestion that individuals with higher intellectual functions, or cognitive reserve, demonstrate a higher threshold for developing neurocognitive deficits after insults to the brain.[31] This argument is supported by observations that individuals exposed to solvents,[32] aluminum,[33] and MDMA (Ecstasy)[12] show similar interactions. Difficulties with executive functions indicate a prefrontal lobe dysfunction. The prefrontal lobe is suspected to play an important role in substance abuse/addiction and dysfunction of this region may be associated with perpetuation of self-destructive drug using behavior and resistance to treatment.[34]

The heavy marijuana users also showed slower reaction times on a simple reaction time test (CALCAP). However, when presented with more complex reaction time tests, the difference between the heavy and light marijuana users became less pronounced. The reason for this is unclear. In addition, heavier use of marijuana is not associated with less accurate performance except for the Repetition of Numbers task but only for those with lower Shipley IQ (see the figure, A). No dose-related association is found for false positive responses, a measure of impulsivity. Thus, heavy marijuana use appears to be unrelated to decrements in response time, accuracy, or impulsive performance on complex psychomotor speed/reaction time tests. Heavy marijuana use is also associated with lower performance on both manual dexterity measures (Finger Tapping and Grooved Pegboard).

This study has a number of limitations. Despite making multiple comparisons, we used a p value of 0.05 in order to detect small adverse effects of marijuana on neurocognitive functioning. More adverse associations were found than could be accounted for by chance alone. In addition, although our ability to detect more effects might have been limited by the relatively small sample size, significant effects were found on several measures. Moreover, in the regression analyses, the sizes of the effects were moderate to large (R^2 = 0.22 to 0.57). Likewise, the heavy users performed two standard deviations or more below the light users on 8/35 (23%) of the measures; this is not a trivial effect. Furthermore, heavy users showed clinically abnormal scores on four of our test measures. Although we use a different estimate of marijuana use (i.e., joints per week) in general, our findings show decrements on similar tests of neuropsychological functioning.[4] Those decrements are not secondary to concomitant use of other drugs because participants were excluded for a current or past history of significant use of other substances including alcohol. Although the presence of a dose-related response strengthens the ability to make causal inferences, no definitive statements about causality can be made. This can only be determined with a prospective study of controlled marijuana administration, an approach that would be ethically untenable. Finally, because our primary interest is the determination of a dose-related effect of marijuana on neurocognitive function, we did not include a group of nonusers. We agree with others that a comparison between light users and heavy users is less influenced by confounding variables (i.e., background differences) than a comparison between marijuana users and nonusers.[2]

It may be difficult to generalize these findings to all users of marijuana because of our strict selection criteria. For example, comorbid psychiatric disorders (i.e., anxiety disorders, major depression) and heavy alcohol use are common in substance abusers. However, we excluded individuals with these disorders to avoid any possible confounding effects on neurocognitive functioning. Finally, it could be argued that the self-reports of marijuana use are inaccurate. The finding of a biologically plausible dose-response suggests that the estimates of drug use were accurate, although this cannot be proven definitively.

The neurocognitive functions most negatively affected were memory, executive function, and manual dexterity. The hippocampus, prefrontal cortex, and cerebellum play a major role in these functions. All of these regions are dense with cannibinoid receptors,[35] and these results are biologically plausible because tetrahydrocannabinol (THC) has been shown to cause deleterious effects on these brain regions. Our observations in humans are consistent with studies in laboratory animals that find learning and memory impairments after administration of Δ^9-THC.[36] In rats, morphologic changes are found in the CA1 region of the hippocampus with acute administration of a synthetic THC analogue.[37] Damage to the CA1 is also seen after ischemia,[38] toxin exposure,[39] or traumatic brain injury.[40] Therefore, cannabinoids may exert changes in the hippocampus that are similar to those found with other types of brain injury. Changes in CB1 receptors in the hippocampus are also observed in rats after THC administration and are associated with selective deficits in working memory.[41] These animal studies provide strong evi-

dence that hippocampal changes might indeed underlie the memory deficits in the current report.

Following marijuana administration, brain images show lower rCBF in the human motor cortex and superior temporal gyrus and higher rCBF in paralimbic brain regions during a dichotic listening task.[42] The authors suggest that the increases in rCBF may modulate the intoxicating and mood-related effects of marijuana whereas reductions in task-related rCBF in the temporal lobe regions may account for impaired cognition associated with marijuana intoxication. In 26-hour abstinent marijuana abusers, lower rCBF was found during a resting condition in the ventral prefrontal cortex, bilaterally.[43] Thus, when taken together with the evidence of THC-induced hippocampal damage in animals and with the THC-associated neurophysiologic alterations in humans, our current data suggest that THC may exert a significant negative impact on the human brain.

Finally, whereas heavy use of marijuana is associated with decrements in neurocognitive performance, except for a few tests, performance was not clinically abnormal. However, the average age of our group was only 22 years. Given the large extent of the effects, very heavy continuous use of marijuana could produce progressive declines in performance that might reach clinical significance. In fact, because the pattern of performance on the learning and memory tests is consistent with normal age-related declines in the elderly, continued heavy marijuana abuse might result in premature cognitive decline.

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References

1. US Department of Health and Human Services Substance Abuse and Mental Health Services Administration Office of Applied Studies. National household survey on drug abuse. Washington, DC: US Government Printing Office, 1999.
2. Pope HG, Yurgelun-Todd D. The residual cognitive effects of heavy marijuana use in college students. JAMA 1996;275:521–527.
3. Fletcher JM, Page JB, Francis DJ, et al. Cognitive correlates of long-term cannabis use in Costa Rican men. Arch Gen Psychiatry 1996;53:1051–1057.
4. Solowij N, Stephens RS, Roffman RA, et al. Cognitive functioning of long-term heavy cannabis users seeking treatment. JAMA 2002;287:1123–1131.
5. Solowij N. Cannabis and cognitive functioning. Cambridge: Cambridge University Press, 1998.
6. Johansson E, Agurell S, Hollister LE, et al. Prolonged apparent half-life of delta1-tetrahydrocannabinol plasma of chronic marijuana users. J Pharm Pharmacol 1988;40:374–375.
7. Haney M, Ward AS, Comer SD, et al. Abstinence symptoms following smoked marijuana in humans. Psychopharmacology 1999;141:395–404.
8. Austin M-P, Mitchell P, Goodwin GM. Cognitive deficits in depression: possible implications for functional neuropathology. Br J Psychiatry 2001;178:200–206.
9. Pope HG, Gruber AJ, Hudson JI, et al. Neuropsychological performance in long-term cannabis users. Arch Gen Psychiatry 2001;58:909–915.
10. Gouzoulis-Mayfrank E, Daumann J, Tuchtenhagen F, et al. Impaired cognitive performance in drug-free recreational ecstasy (MDMA) users. J Neurol Neurosurg Psychiatry 2000;68:719–725.
11. Croft RJ, Mackay AJ, Milles ATD, et al. The relative contributions of ecstasy and cannabis to cognitive impairment. Psychopharmacology 2001;153:373–379.
12. Bolla KI, McCann RG. Memory impairment in abstinent MDMA ("ecstasy") users. Neurology 1998;51:1532–1537.
13. Bolla KI, Rothman RB, Cadet J-L. Dose-related neurobehavioral effects of chronic cocaine use. J Neuropsychiatry Clin Neurosci 1999;11:361–369.
14. Smith SS. Addictive drug survey manual. Baltimore, MD: NIDA Addiction Research Center, 1991.
15. McLellan AT, Luborsky L, Woody GE, et al. An improved evaluation instrument for substance abuse patients: the Addiction Severity Index. J Nerv Ment Disord 1980;168:26–33.
16. Robins LN, Helzer JE, Croughan J, et al. National Institute of Mental Health Diagnostic Interview Schedule: its history, characteristics, and validity. Arch Gen Psychiatry 1981;38:381–389.
17. Shipley WC. Institute of Living Scale. Los Angeles: Western Psychological Services, 1946.
18. Benton AL, Hamsher K. Multilingual Aphasia Examination manual. Iowa City: University of Iowa, 1978.
19. Wechsler D. Wechsler Memory Scale–Revised. San Antonio, TX: Psychological Corporation, 1987.
20. Rey A. L'examen clinique en psychologie. Paris: Presses Universitaires de France, 1964.
21. Taylor LB. Localization of cerebral lesions by psychological testing. Clin Neurosurg 1969;16:269–287.
22. Kapur N, Butters N. An analysis of the visuoperceptual deficits in alcoholics. J Stud Alcohol 1977;38:2025–2055.
23. Mesulam MM. Principles of behavioral neurology. Philadelphia: FA Davis, 1985.
24. Wechsler D. Wechsler Adult Intelligence Scale–Revised (WAIS-R). New York, NY: The Psychological Corporation, 1981.
25. Reitan RM. Manual for administration of neuropsychological test batteries for adults and children. Tucson, AZ: NM Neuropsychology Laboratory, 1977.
26. Stroop JR. Studies of interference in serial verbal reactions. J Exp Psychol 1935;18:643–662.
27. Heaton RK. Wisconsin Card Sorting Test Manual. Odessa, FL: Psychological Assessment Resources, 1981.
28. Benton AL, Hamsher K, Varney N, et al. Contributions to neuropsychological assessment. New York: Oxford University Press, 1983.
29. Miller EN, Satz P, Visscher BV. Computerized and conventional neuropsychological assessment of HIV-1 infected homosexual men. Neurology 1991;41:1608–1616.
30. Klove H. Clinical neuropsychology. In: Forster FM, ed. The medical clinics of North America. New York: WB Saunders, 1963;1647–1658.
31. Stern Y. What is cognitive reserve? Theory and research application of the reserve concept. J Int Neuropsychol Soc 2002;8:448–460.
32. Bolla KI, Schwartz BS, Stewart W, et al. A comparison of neurobehavioral function in workers exposed to a mixture of organic and inorganic lead and in workers exposed to solvents. Am J Ind Med 1995;27:231–246.
33. Bolla KI, Briefel G, Spector D, et al. Neurocognitive effects of aluminum. Arch Neurol 1992;49:61–64.
34. Bolla KI, Cadet J-L, London ED. The neuropsychiatry of chronic cocaine use. J Neuropsychol Clin Neurosci 1998;10:280–289.
35. Herkenham M, Lynn AB, Little MD, et al. Cannabinoid receptor localization in brain. Proc Natl Acad Sci USA 1990;87:1932–1936.
36. Presburger G, Robinson JK. Spatial signal detection in rats is differentially disrupted by delta-9-tetrahydrocannabinol, scopolamine, and MK-801. Behav Brain Res 1999;99:27–34.
37. Lawston J, Borella A, Robinson JK, et al. Changes in hippocampal morphology following chronic treatment with the synthetic cannabinoid WIN 55,212-2. Brain Res 2000;877:407–410.
38. Mazer C, Muneyyirci J, Taheny K, et al. Serotonin depletion during synaptogenesis leads to decreased synaptic density and learning deficits in the adult rat: a possible model of

neurodevelopmental disorders with cognitive deficits. Brain Res 1997;760:68–73.
39. Koczyk D. Differential response of microtubule-associated protein 2 (MAP-2) in rat hippocampus after exposure to trimethyltin (TMT): an immuncytochemical study. Acta Neurobiol Exp 1994;54:55–58.
40. Galea LA, McEwen BS, Tanapat P, et al. Sex differences in dendritic atrophy of CA3 pyramidal neurons in response to chronic restraint stress. Neuroscience 1997;81:689–697.
41. Varvel SA, Hamm RJ, Martin BR, et al. Differential effects of delta9-THC on spatial reference and working memory in mice. Psychopharmacology 2001;157:142–150.
42. O'Leary DS, Block RI, Flaum M, et al. Acute marijuana effects on rCBF and cognition: a PET study. NeuroReport 2000;11:3835–3841.
43. Block RI, O'Leary DS, Hichwa RD, et al. Cerebellar hypoactivity in frequent marijuana users. NeuroReport 2000;11:749–753.

Abnormal brain activation on functional MRI in cognitively asymptomatic HIV patients

T. Ernst, PhD; L. Chang, MD; J. Jovicich, PhD; N. Ames, BA; and S. Arnold, MS

Abstract—*Background/Objectives*: A previous fMRI study demonstrated increased brain activation during working memory tasks in patients with HIV with mild dementia. The current study aims to determine whether patients who are HIV-1 positive and have normal cognitive function also show increased brain activation on fMRI. *Methods*: Blood oxygenation level-dependent (BOLD) fMRI was performed in 10 patients with HIV (CD <500) and 10 age-, sex-, education-, and handedness-matched seronegative subjects. Each subject performed a battery of neuropsychological tests and fMRI with three tasks (0-back, 1-back, and 2-back) that required different levels of attention for working memory. *Results*: Compared with control subjects, patients with HIV showed greater magnitude of brain activation (BOLD signal intensity changes, $p \leq 0.001$) in the lateral prefrontal cortex, with normal performance during fMRI and on a battery of neuropsychological tests. The patients with HIV also showed increased activated brain volume in the lateral prefrontal cortex ($p = 0.007$) but not in other activated regions, including the posterior parietal cortex, supplementary motor area, thalamus, caudate, and occipital cortex. The increase in activated brain volume was independent of task difficulty. *Conclusion*: Increased brain activation in subjects who are positive for HIV precedes clinical signs or deficits on cognitive tests. Early injury to the neural substrate may necessitate increased usage of brain reserve to maintain normal cognitive function. BOLD fMRI appears to be more sensitive than clinical and neuropsychological evaluations for detecting early HIV-associated brain injury.

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Cognitive abnormalities commonly occur in patients with HIV-1 infection.[1] Among healthy individuals who are seropositive for HIV, cognitive deficits are thought to be infrequent[2]; however, some investigators suggest that more sensitive measures may be needed to detect the mild cognitive decline during the asymptomatic stage.[3] In later stages of HIV disease, with CD4 counts <100 cells/μL, approximately 20% of patients may develop a more disabling dementia syndrome directly related to HIV infection[4]; this syndrome has been termed HIV cognitive motor complex (CMC).[5] Early diagnosis and treatment of HIV dementia are especially important because patients with early stages of the dementia may show reversal of their cognitive deficits and neurochemical abnormalities after treatment.[6,7]

Typical neuropsychological deficits in patients with HIV include decreased sustained attention, mental flexibility, general motor speed, and memory[8,9]; in particular, working memory may be affected.[10-13] However, little is known about the neuroanatomic substrate underlying these neuropsychological deficits. A variety of functional neuroimaging techniques, including PET,[14] SPECT,[15,16] and MRS,[17-19] found alterations in cerebral blood flow and metabolism in the brains of individuals infected with HIV. Although the majority of these studies were performed in patients with HIV with cognitive impairment or de-

From the Medical Department (Drs. Ernst and Chang, and S. Arnold) and Chemistry Department (Dr. Ernst), Brookhaven National Laboratory, Upton, NY; Department of Brain and Cognitive Sciences (Dr. Jovicich), Massachusetts Institute of Technology, Cambridge; and Department of Neurology (N. Ames), Harbor–University of California, Los Angeles Medical Center, Torrance.

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Address correspondence and reprint requests to Dr. Thomas Ernst, Medical Department, Brookhaven National Laboratory, Bldg. 490, Upton, NY, 11973-5000; e-mail: TErnst@bnl.gov

Drug-Taking Behavior Among School-Aged Youth

The Alaska Experience and Comparisons with Lower-48 States

Bernard Segal, PhD

figures the name of each substance has been abbreviated. The following is a list of the abbreviations to help interpret the data when the findings are presented graphically: MJ = Marijuana, CK = Cocaine, CR = Crack, ST = Stimulants, HL = Hallucinogens, DP = Depressants, HR = Heroin, IN = Inhalants, TQ = Tranquilizers, AL = Alcohol, and TB = Cigarettes.

A. PREVALENCE AND PATTERNS OF DRUG-TAKING BEHAVIOR

1. Opportunity to Try Drugs

Drugs cannot be experienced unless there is an opportunity to try them. Data addressing the opportunity to try drugs convey an indication of the availability of drugs, what trends in use may be present and, by extrapolation, information about the extent which those who have a chance to try a drug do so. Figure 4-1 describes how many adolescents in the sample indicated having had an opportunity to try any of the different chemical substances, except for alcohol and tobacco. Both weighted and unweighted results are provided in the table. The sample was weighted to adjust for differences in community representation.

A comparison of the actual (unweighted) and projected (weighted) findings shows that the differences between them tend to be small, suggesting that the actual sample is representative of the population sampled, except for sampling error. The following discussion is therefore based on the unweighted or actual sample results, as is the interpretation of other findings unless noted otherwise.

What can be observed from the data in Figure 4-1 is that opportunity to try different chemical substances is pervasive, but with some variations. Marijuana is the drug most in evidence (70.1 percent), followed by inhalants (44.9 percent). Just less than two-fifths (39.3 percent) of the sample reported an opportunity to try cocaine. Stimulants are next, with 36.4 percent of the sample having indicated an opportunity to try them. Reports on the opportunity to try the remaining substances are less extensive, but over a quarter of the sample had an opportunity to try hallucinogens (23.1 percent), and

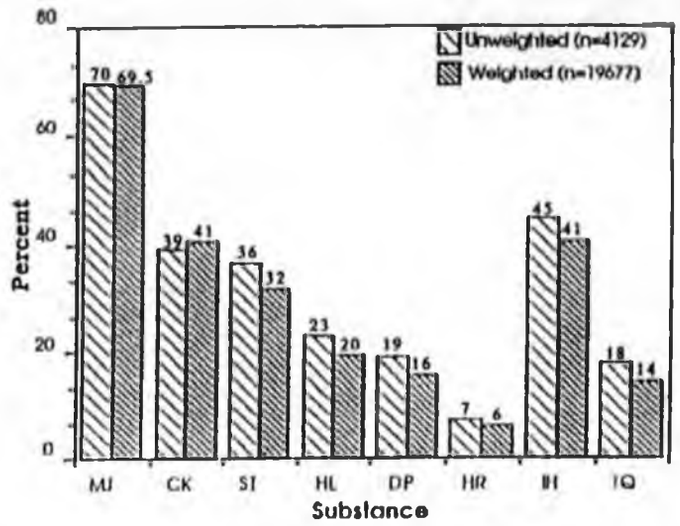

FIGURE 4-1. Opportunity to Try Chemical Substances Weighted and U weighted Comparison, Total Sample, 1988 (Figures are rounded to neare whole.)

less than a fifth indicated a chance to try depressants (18.6 percen or tranquilizers (17.6 percent). Last among the opportunity to t was heroin, with 7.4 percent of the sample noting an opportunity try it.

2. Opportunity to Try and Trying a Drug

An important piece of information related to the opportunity try a drug is the number of students who did try a substance wh the chance arose. Table 4-1 reports the percent of students wl indicated that they tried a substance when they had an opportunit As noted from the data, except for crack and heroin, over half t students tried one of the substances when an opportunity occurre Consistent with its level of apparent availability, three-quarte (75.9 percent) of those who had an opportunity to try marijuana d so. Stimulants are the next highest tried substance, with two-thir (66 percent) of the sample showing that they tried it when a chan arose. Over half of those who had a chance to try cocaine (52 pe

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Nation's Youth Turning Away from Marijuana, as Perceptions of Risk Rise; Most Adults with Substance Abuse Problems Are Employed

HHS Secretary Tommy G. Thompson announced today that there is a five percent decline in lifetime use of marijuana among American youth between the ages of 12 and 17. Current use of marijuana plummeted nearly 30 percent among 12 and 13 year olds. The findings were included in the 2003 National Survey on Drug Use and Health released today at the annual Recovery Month press conference.

The findings, released by HHS' Substance Abuse and Mental Health Services Administration (SAMHSA), show that while overall, the change in the category "current use of any illicit drug" was not statistically significant, the use of some drugs decreased sharply. For youth, 12-17, past year use of Ecstasy and LSD dropped precipitously, by 41 percent for Ecstasy and 54 percent for LSD. Overall, 19.5 million Americans ages 12 and older, 8 percent of this population, currently use illicit drugs. The data indicate that of the 16.7 million adult users (18 and older) of illicit drugs in 2003, about 74 percent were employed either full time or part time.

"It is encouraging news that more American youths are getting the message that drugs are dangerous," Secretary Thompson said. "But President Bush recognizes that we as a nation must do more to ensure that our children don't use drugs in the first place and to help Americans get the treatment for alcohol and drug addiction that they need."

President Bush's fiscal year 2005 budget request includes a 5 percent increase for substance abuse treatment, prevention and research, including a doubling of the funding for the Access to Recovery treatment program. President Bush is requesting $200 million for Access to Recovery, which provides vouchers to individuals to access drug- and alcohol-abuse treatment programs. With the doubling of the budget, Access to Recovery would help 100,000 people who want to obtain drug and alcohol treatment services but can't afford them.

"The prevention efforts of millions of parents, educators, and community leaders are working. Young people are getting the message that marijuana, which is substantially more potent today than it was 20 years ago, is a dangerous drug, and they are increasingly staying away from it," said John Walters, Director of National Drug Control Policy. "These new data reaffirm the critical roles parents and anti-drug advertising play in keeping our children safer, healthier, and drug-free."

SAMHSA Administrator Charles Curie said: "Employers who think alcohol and drug abuse will never be a problem in their workplace need to consider that more than three quarters of adults who have serious drug and or alcohol problems are employed. Encouraging employees to find help when they need

it can result in fewer accidents and fewer workers absent on Monday morning. It may even save an employee's life, family, or job. Creating a drug-free workplace program or enhancing an existing

program can lead to a healthier, more productive work force and be an important part of solving one of our nation's most persistent problems."

The survey found that of the 19.4 million adults (age 18 and over) characterized with abuse of or dependence on alcohol or drugs (19.4 million) in 2003, 14.9 million (77 percent) were employed either full or part time. This amounts to over ten percent of full-time workers as well as over ten percent of part-time workers.

Marijuana

Marijuana continues to be the most commonly used illicit drug, with 14.6 million current users (6.2 percent of the population). The study shows that there were an estimated 2.6 million new marijuana users in 2002. About two thirds of these new users were under age 18, and about half were female.

An important positive change detected by the survey was an increase in the perception of risk in using marijuana once a month or more frequently. Both youth and young adults reported a significant increase in their awareness of the risks of smoking marijuana. Particularly striking was the 20 percent decline between 2002 and 2003 in the number of youth that were "heavy users" of marijuana (those smoking either daily or 20 or more days per month). Perceived availability of the drug also declined significantly among youth.

The results of this year's survey demonstrate that anti-drug messages inside and outside of school, participation in religious and other activities, parental disapproval of substance use and positive attitudes about school are linked to lower rates of youth marijuana use. For example, those exposed to anti-drug messages outside of school had rates of current marijuana use that were 25 percent lower than those not reporting such exposure (7.5 percent vs. 10.0 percent). Youth who believe that their parents would "strongly disapprove" of marijuana had use rates fully 80 percent lower than those who reported that their parents would not "strongly disapprove" (5.4 percent vs. 28.7 percent).

Alcohol

The numbers of binge and heavy drinkers did not change between 2002 and 2003. About 54 million Americans ages 12 and older participated in binge drinking at least once in the 30 days prior to being surveyed. These people had five or more drinks on one or more occasion in the past month. There were 16.1 million heavy drinkers, who had five or more drinks on five or more occasions in the past month. The highest prevalence of binge and heavy drinking in 2003 was among young adults ages 18-25, with both binge and heavy drinking at their peak at age 21.

There were 10.9 million drinkers under legal age (ages 12-20) in the month prior to the survey interview in 2003. This is 29 percent of this age group. Of these, nearly 7.2 million (19.2 percent) were binge drinkers and 2.3 million (6.1 percent) were heavy drinkers.

Drunk driving declined from the 2002 survey, but drugged driving remained similar to that

reported in the 2002 survey. An estimated 13.6 percent of persons aged 12 or older drove under the

- influence of alcohol at least once in the 12 months prior to their interviews (32.3 million people) in 2003, a decrease from 14.2 percent (33.5 million) in 2002. An estimated 10.9 million persons reported driving under the influence of an illicit drug during the past year. This is 4.6 percent of the population ages 12 and older.

Prescription Drug Abuse

Against the backdrop of generally good news, the non-medical lifetime use of prescription pain relievers showed a five percent increase for the population 12 and older, with young adults (18-25) experiencing a 15 percent increase in lifetime, as well as current use. Over all, current use of prescription pain relievers non-medically remained stable from 2002-2003. There was a statistically significant increase in lifetime non-medical use of Vicodin, Lortab, or Lorcet from 13.1 million to 15.7 million. Percocet, Percodan, or Tylox misuse in a lifetime increased from 13.1 million to 15.7 million people. Hydrocodone lifetime non-medical use increased from 4.5 million people to 5.7 million; OxyContin lifetime misuse increased from 1.9 million people to 2.8 million; non-medical methadone use increased from 0.9 million to 1.2 million; and non-medical use of Tramadol increased from 52,000 to 186,000 from 2002 to 2003.

Estimates for persons who currently used psychotherapeutic drugs taken non-medically are similar in 2003 to estimates for 2002. There were 6.3 million persons currently using prescription medications non-medically in 2003, about 2.7 percent of the population ages 12 or older. Of these, an estimated 4.7 million used prescription pain relievers; 1.8 million used tranquilizers; 1.2 million used stimulants, including methamphetamine; and 0.3 million used sedatives.

Other Drugs of Abuse

There were an estimated 2.3 million persons who currently used cocaine in 2003, 604,000 of whom used crack. One million persons used hallucinogens, including LSD, PCP, Ecstasy and other substances, and 119,000 people were estimated to currently use heroin. These projections are all similar to estimates for these drugs in 2002. But, past month inhalant use among youth ages 16 or 17 increased from 0.6 percent in 2002 to 1.0 percent in 2003. Methamphetamine use did not change significantly between 2002 and 2003, with 600,000 past month users each year.

The survey reported 21.6 million Americans in 2003 classified with dependence on drugs, alcohol, or both (9.1 percent of the population ages 12 and older). Over 20 million persons needed but did not receive treatment for an alcohol or drug problem in 2002 and 2003, but the number receiving specialized substance abuse treatment declined from 2.3 million in 2002 to 1.9 million in 2003. Of the 20 million people in need of treatment in 2003 who did not receive it, about 1 million recognized that need. Only 273,000 tried to obtain treatment and were unable to access it. The other 764,000 made no effort to get treatment.

Serious Mental Illness and Substance Abuse

The report found a major correlation between serious mental illness and substance dependence and abuse. In 2003, an estimated 4.2 million adults suffered from serious mental illness and substance dependence or abuse in the past year. Adults who used illicit drugs were more than twice as likely to have serious mental illness, compared to adults who did not use an illicit drug. In 2003, 18.1 percent of

- adult past-year users of illicit drugs had serious mental illness that year, while the rate was 7.8 percent among adults who had not used an illicit drug. Among adults with substance dependence

or abuse, 21.6 percent had serious mental illness, compared to 8.0 percent among those who did not have dependence or abuse.

- Among adults with serious mental illness in 2003, 21.3 percent (4.2 million people) were dependent on or abused alcohol or illicit drugs. The rate among adults without serious mental illness was only 7.9 percent.

Tobacco

Tobacco use rates in the past month remained essentially the same from 2002 to 2003, with 70.8 million people reporting current use of a tobacco product. Of these, 60.4 million smoked cigarettes in the past mont.., 12.8 million smoked cigars, 7.7 million used smokeless tobacco and 1.6 million smoked tobacco in pipes. There were significant declines in past year and lifetime cigarette use among youths ages 12 to 17 between 2002 and 2003, and a decline in the rate of cigarette smoking among young females.

The 2003 survey is based on interviews with 67,784 respondents ages 12 and older who were interviewed in their homes. This includes persons residing in dormitories or homeless shelters. Not included in the survey are persons on active military duty, in prisons, or other institutionalized populations or people who are homeless but not in shelters.

Recovery Month is observed in September to recognize the accomplishments of people in recovery, the contributions of treatment providers, and advances in substance abuse treatment. This year is the 15th annual observance. The theme, "Join the Voices for Recovery...Now!" emphasizes that addiction to alcohol and drugs is a chronic, but treatable, public health problem that affects everyone in the community.

- HHS agencies -- including SAMHSA, the Centers for Disease Control and Prevention (CDC), the National Institute on Drug Abuse (NIDA) and the National Institute on Alcohol Abuse and Alcoholism (NIAAA) -- play a key role in the administration's substance abuse strategy, leading the federal government's programs in drug abuse research and funding programs and campaigns aimed at prevention and treatment, particularly programs designed for youth. An HHS fact sheet with more information is available at http://www.hhs.gov/news/press/. Other background and resources are available at the Web sites for SAMHSA (http://www.samhsa.gov), CDC (http://www.cdc.gov), NIDA (http://www.nida.nih.gov) and NIAAA (www.niaaa.nih.gov).

Findings from the 2003 National Survey on Drug Use and Health are available on the Web at *www.oas.samhsa.gov*

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Note: All HHS press releases, fact sheets and other press materials are available at *http://www.hhs.gov/news*.

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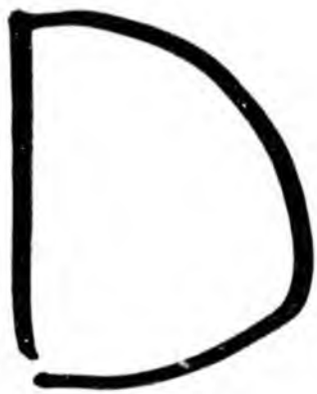

MARIJUANA AND PUBLIC HEALTH

I. Marijuana And Respiratory Health / Cancer.

- The chronic effects of smoking marijuana are associated with lung damage, increased symptoms of chronic bronchitis, and possibly increased risk of lung cancer. *Oxidative Stress Produced By Marijuana Smoke, Sarafian, et.al., American Journal Respiratory Cell and Molecular Biology, June, 1999; Respiratory Effects of Marijuana and Tobacco Use in a U.S. Sample, Moore, et.al., Journal of General Internal Medicine, 2004; British Lung Foundation, A Smoking Gun, 2002.*
- In persons who smoke both tobacco and marijuana, the marijuana use may interfere with attempts to quit smoking tobacco. *April 2003, Press Release, NIDA, citing a study by Dr. Daniel Ford, Johns Hopkins University.*
- Simple exposure to marijuana smoke in the air has pharmacological consequences. *The Pharmacological Activity of Inhalation Exposure to Marijuana Smoke in Mice, Lichtman, et.al., Drug and Alcohol Dependence, July, 2001.*
- Smoking marijuana may increase the risk of head and neck cancers. *Marijuana Use and Increased Risk of Squamous Cell Carcinoma of the Head and Neck, Zhang, et.al., Cancer Epidemiology Biomarkers and Prevention, December, 1999.*

- Smoking marijuana may increase the susceptibility to and/or incidence of breast cancer as well as other cancers that do not express cannabinoid receptors. *Delta 9-Tetrahydrocannabinol Enhances Breast Tumor Growth and Metastis by Suppression of the Antitumor Immune Response, McKillop, R, et.al., Journal of Immunology, March, 2005.*
- Certain segments of Alaska's population, such as Alaska Natives already have very high incidence rates for specific cancer sites and poor survival rates for most cancers.

II. **Marijuana Use Can Impact The Fetus.**

- Fetal growth, gestational age, and parts of the fetal brain that regulate emotional behavior may be impaired by smoking marijuana. *Prenatal Exposure to a Cannabinoid Agonist Produces Memory Deficits Linked to Dysfunction in Hippocampal Long Term Potentiation and Glutamate Release, Mereu, et.al., Journal of Pharmacology, April 15, 2003; Parental Tobacco and Marijuana Use Among Adolescents, Cornelius, M, et.al., Pediatrics, May 1995; Wang, X, et.al., In Utero Exposure Associated with Abnormal Amygdal-dopamine D2 Expression in the Human Fetus, Biological Psychiatry, December, 2004; Marijuana Impairs Growth in Mid Gestation Fetuses, Hurd, YL, et.al., Neurotoxicoloty, March-April, 2005.*

III. **Marijuana related Emergency Room Visits By Youth Have Greatly Increased.**

- The rate of marijuana related ED visits by youth aged 12-17 rose 126 % between 1994 and 2001, while their overall rate of drug related ED visits was stable. *Drug Abuse Warning Network, DAWN Report, August, 2003.*
- When marijuana alone was implicated in the ED visit, having an "unexpected reaction" was the most commonly cited reason for the ED visit (40% of the cases). *Id.*

IV. **Marijuana and Cardiovascular Death In Young Adults.**

- Marijuana use has been correlated with heart problems in some young adult users. *Acute Cardiovascular Fatalities Following Marijuana Use, Bachs, L., et.al., Forensic Science International, Feb., 2001.*

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Molecular Biology

Am. J. Respir. Cell Mol. Biol., Volume 20, Number 6, June 1999 1286-1293

Oxidative Stress Produced by Marijuana Smoke

An Adverse Effect Enhanced by Cannabinoids

Theodore A. Sarafian, Jose Antonio Marques Magallanes, Hungyi Shau, Donald Tashkin, and Michael D. Roth

Division of Pulmonary and Critical Care Medicine, Department of Medicine; and Division of Surgical Oncology, Department of Surgery, University of California at Los Angeles School of Medicine, Los Angeles, California

Abstract

Marijuana (MJ) smoking produces inflammation, edema, and cell injury in the tracheobronchial mucosa of smokers and may be a risk factor for lung cancer. Because oxidative stress may mediate some of these effects, this study was designed to test the hypothesis that cannabinoids in MJ smoke contribute to cellular oxidative stress. Oxidative stress was evaluated in an endothelial cell line (ECV 304) following exposure to smoke produced from MJ cigarettes containing either 0, 1.77, or 3.95% Δ^9-tetrahydrocannabinol (Δ^9-THC). Brief exposure to smoke from 3.95% MJ cigarettes stimulated the formation of reactive oxygen species (ROS) by 80% over control levels and lowered intracellular glutathione levels by 81%. Smoke-induced ROS generation increased in a dose- and time-dependent manner. In contrast, exposure to smoke from MJ containing 0% Δ^9-THC produced no increase in ROS despite a 70% decline in glutathione levels. Smoke from MJ containing 1.77% Δ^9-THC stimulated intermediate levels of ROS. A brief, 30-min exposure to MJ smoke, regardless of the Δ^9-THC content, also induced necrotic cell death that increased steadily up to 48 h of observation. MJ smoke passed through a Cambridge filter that removed particulate matter was 3.4-fold more active in ROS production compared with unfiltered smoke, suggesting that most of the oxidative effects are produced by the gaseous phase. Alveolar macrophages obtained from habitual MJ smokers displayed low levels of glutathione compared with macrophages from nonsmokers. We conclude that MJ smoke containing Δ^9-THC is a potent source of cellular oxidative stress that could contribute significantly to cell injury and dysfunction in the lungs of smokers.

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Marijuana (MJ) is one of the most commonly abused substances in the United States, where 3.3% of young adults 19 to 28 yr of age use MJ on a daily basis and 54% of people between 26 and 34 have used marijuana at least once (1). Medicinal uses of cannabis date back thousands of years and both crude smoke and the psychoactive component, Δ^9-tetrahydrocannabinol (Δ^9-THC), have been used for treating migraine headache, glaucoma, nausea, and anorexia (2). Despite this widespread use, little information is available regarding toxic effects of MJ smoke. Persistent efforts to legalize MJ and political movements advocating medicinal uses tend to promote the notion that little or no hazardous risk is associated with MJ smoking.

The vast majority of research on biologic effects of cannabinoids has addressed the neurologic and psychotropic activity of these compounds (3). Some publications, however, have documented detrimental effects on the tracheobronchial mucosa, including mucosal edema and inflammation (4), cellular atypia and dysplasia (5), and molecular dysregulation of genes associated with malignant transformation (6). MJ also appears to alter the function of alveolar macrophages (7), key cells in the lung's immune defenses against infection and malignancy. Moreover, several small case-series reports have suggested an association between regular MJ use and upper aerodigestive-tract cancers (8- 13). Approximately 60 different cannabinoids classified as C-21 terpenophenolic compounds can be found in the smoke derived from MJ, and the cannabinoid content of an MJ plant varies considerably depending on the type of plant and conditions of cultivation. Some reports suggest that, over the past 10 to 20 yr, the cannabinoid content in MJ cigarettes may have increased severalfold (14, 15). There is little information on toxicologic effects of individual constituents found in MJ smoke. In the present studies we examined the effects of whole MJ cigarette smoke with and without Δ^9-THC and of the gas phase of the smoke on the generation of reactive oxygen species (ROS) and on levels of antioxidants in the cultured human endothelial cell line, ECV 304. Cellular production of ROS and reduced antioxidant activity were considered to be toxicologic markers of oxidative stress that could lead to cell injury, DNA damage, and ultimately, malignant transformation. Human alveolar macrophages collected from the lungs of habitual MJ smokers were also evaluated for evidence of *in situ* exposure to oxidative stress, and were compared with findings in macrophages from control nonsmokers.

Materials and Methods

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MJ cigarettes containing either 0, 1.77, or 3.95% Δ^9-THC were obtained from the National Institute on Drug Abuse (NIDA, Rockville, MD) with characteristics as previously described (16). Cigarettes with 1.77 or 3.95% Δ^9-THC were prepared at NIDA by blending MJ leaves of differing potencies, and cigarettes containing 0% Δ^9-THC were prepared from MJ leaves that had been extracted with ethanol to remove cannabinoids. Cigarettes weighed 700 to 900 mg and were weight-matched to within 20 mg for each experiment. For comparison, tobacco cigarettes weighing 850 mg were purchased commercially (Marlboro Red hard-pack filtered cigarettes; Phillip Morris, Richmond, VA). 2,7-Dichlorofluorescein diacetate (DCF-DA)

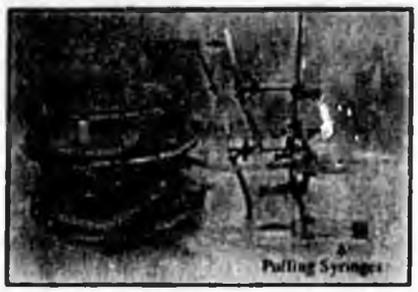
and monochlorobimane (MCB) were from Molecular Probes (Eugene, OR). Propidium iodide, ascorbic acid, and pyrrolidinedithiocarbamate (PDTC) were from Sigma (St. Louis, MO). The Promega (Madison, WI) Apoptosis Assay Kit was used for cytotoxicity evaluation.

The endothelial cell line, ECV 304, was obtained from American Type Culture Collection (Rockville, MD). Methods for transfection-mediated overexpression of the human peroxiredoxin (Prx) gene and characterization of antioxidant properties have been described elsewhere (17). The Prx protein confers cellular protection against oxidative stress by consuming hydrogen peroxide (H_2O_2). Cells were cultured in RPMI 1640 media containing 10% fetal calf serum (FCS) and 1% penicillin/streptomycin/fungizone mix (GIBCO BRL, Grand Island, NY) on poly-L-lysine dishes and multiwell plates. Cells were passaged every 7 d. Prx-transfected cells were cultured alongside control (vector-only)-transfected cells in 24-well plates.

Lung alveolar macrophages were obtained by bronchoalveolar lavage from human volunteers, including both nonsmokers and habitual smokers of MJ only as previously described (5, 7). Macrophages were suspended in Dulbecco's modified Eagle's medium (DMEM) containing 10% FCS and 1% penicillin/streptomycin/fungizone. Cells were plated at a density of 5×10^4/well in 96-well plates. Cells were analyzed for endogenous ROS generation and reduced glutathione (GSH) content at 1 and 24 h after plating.

ECV 304 cells transfected with either hygromycin-resistance vector DNA (vec) or a human Prx DNA construct were treated for 2 h with various agents (ascorbate, Δ^9-THC, H_2O_2, or control medium) in 24-well culture plates (2×10^4 cells/well) before loading with 40 μM DCF-DA for 20 min in Krebs-Ringer buffer. After washing twice with Krebs-Ringer buffer, agents were reapplied to cells in 200 μl Krebs-Ringer buffer and plates were placed in separate 5,000-ml chambers (Billups-Rothenberg, Del Mar, CA) connected to manually controlled smoking devices (Figure 1). A cigarette holder was attached to a 50-ml sintered glass syringe using 0.7 cm inner-diameter tygon tubing and a three-way stopcock connector. After aspiration of smoke into the syringe, the stopcock valve was turned and smoke expelled into the vented chamber with brief flushing to ensure thorough distribution of smoke. Each chamber received 10 50-ml boluses, equivalent to smoke from a full cigarette, and remained exposed to the smoke for 5 min. Separate chambers exposed to either tobacco or different potencies of MJ smoke were run in parallel and compared with chambers containing room air as a control. Cellular oxidative stress was measured fluorometrically by monitoring the oxidation of intracellular 2,7-dichlorofluorescein (DCF) using a Cytofluor 2300 plate reader (PerSeptive Biosystems, Framingham, MA) at excitation (Ex) = 485, emission (Em) = 530 as previously described (18). Cells were then returned to their respective chambers for a second exposure to the appropriate smoke for a period of 15 min. After a second fluorescence measurement, GSH content, cell viability, and total cell number were measured in a sequential manner as described previously (18). Smoke contains both gaseous and particulate phases. In some experiments, the independent effects of the gaseous phase were determined by passing smoke through a high-efficiency Cambridge filter before venting it into chambers containing the ECV 304 cells.

Figure 1. Apparatus used for exposing cultured cells to cigarette smoke. Culture plates (24-well) containing DCF-



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loaded cells were placed into vented 5,000-ml exposure chambers. MJ or tobacco cigarettes were inserted into holders and lit; 50-ml puffs of cigarette smoke were delivered into the chambers by means of a three-way valve system. The chambers were vented to allow for mixing and equilibration of pressure.

The capacity for MJ smoke to induce intracellular oxidative stress was compared with its ability to directly oxidize DCF in a cell-free environment. In these studies, 24-well plates were filled with 200 μl of Krebs-Ringer buffer containing either DCF-DA-loaded ECV 304 cells as previously described or 5 μM partially de-esterified DCF-DA in the absence of any cells. DCF-DA was partially de-esterified by diluting DCF-DA to 5 μM in Krebs-Ringer buffer for 1 h at room temperature before smoke exposure. Plates were exposed concurrently to the smoke from one MJ cigarette for 20 min and sealed with Mylar tape, and DCF fluorescence was measured at 30-min intervals. Selected wells were treated with various agents (ascorbate, THC, H_2O_2) immediately before smoke exposure to determine their roles as either pro- or antioxidants.

Long-term viability studies were performed by exposing ECV 304 cells in 96-well plates to MJ smoke with or without Δ^9-THC for 30 min. Control cells were exposed to room air for a similar time period. After smoke exposure, smoke was cleared and cells were confined to chambers containing 10% CO_2 at 37°C for subsequent fluorescent determination of glutathione levels and viability using MCB, propidium iodide, and the Cytofluor 2300. Cells were maintained in serum-containing culture media throughout these studies. Apoptotic and necrotic death was evaluated quantitatively using the Promega Apoptosis Assay Kit. Staining was analyzed by fluorescent microscopy and quantified using the Cytofluor 2300 plate reader.

Data were analyzed in most cases using Student's *t* test for paired data. Data from Figure 1 were analyzed by analysis of variance (ANOVA). Levels of ROS were compared between unexposed cells (control), cells exposed to MJ smoke, and cells exposed to 0% Δ^9-THC smoke by ANOVA, treating all culture plates as independent measurements. Analyses were performed separately for vec and Prx cells, and also with both types of cells combined. Multiple-comparison testing was performed between exposure groups using Tukey's method. Results were considered to be significant at $P < 0.05$. ANOVA was performed using SAS software (SAS Institute Inc., Cary, NC).

Results

Intracellular Effects of Smoke Exposure

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In vitro studies in which ECV 304 cells were exposed to whole unfiltered MJ or tobacco smoke revealed rapid oxidation of intracellular DCF. Although not statistically different, the effect of MJ smoke was generally of greater magnitude than that of tobacco on a per-cigarette basis. After 20 min total exposure of vector-transfected cells to two MJ cigarettes, values for DCF oxidation were 1.8-fold greater than control cells exposed to room air ($P < 0.05$) (Figure 2). In Prx-transfected cells, MJ smoke increased DCF oxidation 1.6-fold. At the same time, intracellular GSH levels were decreased to 19% of control values ($P < 0.001$) regardless of the presence of the Prx gene (Figure 3). MJ cigarette smoke devoid of Δ^9-THC produced no significant increase in DCF oxidation relative to controls (Figure 2), despite a drop in GSH levels comparable to that caused by the Δ^9-THC containing MJ smoke (Figure 3). Treatment of cells with ascorbic acid (1 mM) or PDTC (1 mM) suppressed the MJ-induced DCF oxidation by 100 and 99%, respectively (Figure 4), without appreciably affecting GSH levels (data not shown). Similar results were obtained using cultures of lung alveolar macrophages obtained from bronchoscopy from nonsmoking subjects (data not shown). Exposure of ECV 304 cells to synthetic purified Δ^9-THC (0.5 mg/ml) produced no significant DCF oxidation above that of vehicle control (ethanol) (data not shown).

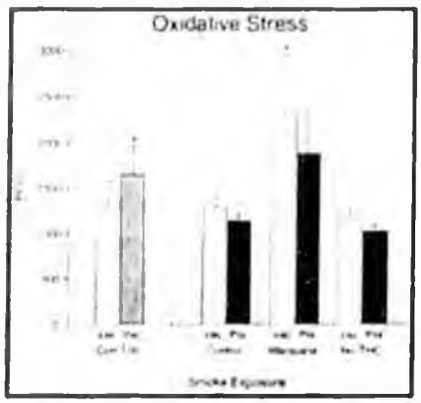

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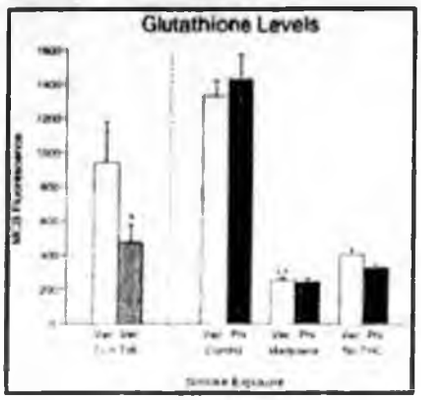
Figure 2. Accumulation of ROS in cultured endothelial ECV 304 cells exposed to smoke from tobacco (Tob) or MJ cigarettes. Cells transfected with either hygromicin-resistance vector DNA (Vec) or human peroxiredoxin-B (Prx) DNA were loaded with DCF before smoke exposure. After exposure to smoke from two cigarettes with porthole ventilation, culture chambers were sealed at room temperature for 20 min. DCF fluorescence was then measured at Ex = 485, Em = 530, subtracting a background value from a well containing no cells. These values were then divided by values reflecting total cell number per well, derived from propidium iodide fluorescence (Ex = 530, Em = 560) in the presence of 160 μM digitonin to permeabilize all cells. These normalized fluorescence values were multiplied by 1,000 to give relative measures of ROS. *Left:* Comparison of untreated control cells (Con) with cells exposed to tobacco cigarette (Marlboro) smoke (Tob) ($n = 6$; $^*P < 0.05$ using Student's t test). *Right:* Separate experiments comparing unexposed control cells with cells exposed to smoke from MJ cigarettes with or without Δ^9-THC ($n = 12$; $^*P < 0.05$ comparing MJ smoke to control or to MJ without Δ^9-THC using ANOVA). *Error bars* indicate standard error of the mean (SEM).

Figure 3. GSH levels in cultured endothelial cells exposed to smoke from tobacco (Tob) or MJ cigarettes as described in Figure 1. MCB fluorescence (Ex = 395, Em = 460) was measured as described in MATERIALS AND METHODS and normalized to cell number per well as in Figure 1. *Left:* $n = 6$; $^*P < 0.05$ comparing tobacco with control. *Right:* $n = 6$;



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**$P < 0.001$ comparing control with MJ or with MJ without Δ^9-THC using Student's *t* test. *Error bars* indicate SEM.

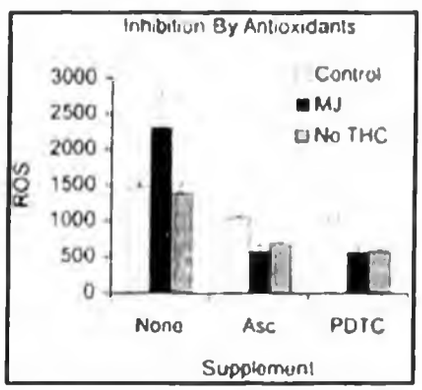

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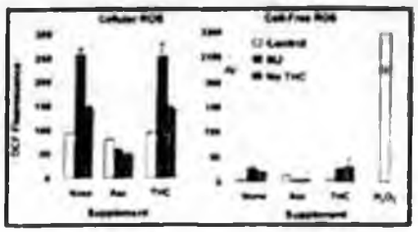
Figure 4. ROS accumulation (expressed as relative normalized DCF fluorescence) inhibited by 1 mM Asc or 1 mM PDTC. Values are means of five determinations ± SEM. *P* values were < 0.05 comparing ascorbate- and PDTC-treated samples with corresponding untreated samples by Student's *t* test.

Extracellular Oxidation by Smoke

The capacity for MJ smoke to produce oxidative stress in ECV 304 cells (cellular ROS) was compared with its oxidative effects on media alone (cell-free ROS; Figure 5). In the absence of any smoke exposure, DCF fluorescence was 30-fold higher in wells containing DCF-loaded cells as compared with wells containing DCF alone, suggesting basal generation of ROS by ECV 304 cells. After exposure to smoke from 3.9% MJ cigarettes, there was an increase in cell-free DCF fluorescence ($P < 0.02$), but it was only 10% of the value observed for cellular ROS. Both the cellular and cell-free oxidation produced by smoke exposure were inhibited by ascorbic acid (Asc), but the addition of Δ^9-THC directly to the wells had no effect on either basal or smoke-induced oxidation. In contrast to the pattern of ROS that resulted after smoke exposure, the addition of 30 mM H_2O_2 directly into the wells produced a rapid increase in DCF fluorescence that was 4-fold higher in cell-free wells than in wells containing ECV 304 cells. Similar results were observed following exposure to tobacco smoke (data not shown).

Figure 5. Smoke-induced ROS generation in DCF-loaded



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ECV 304 cells (Cellular ROS) and in Kreb-Ringer buffer containing 5 μM DCF (Cell-Free ROS). Paired cellular and cell-free plates were enclosed together in chambers infused with room air (control; *open columns*), with 3.95% Δ^9-THC MJ smoke (*filled columns*), or with 0% Δ^9-THC MJ smoke (No THC; *shaded columns*). After 20 min exposure, plates were sealed with Mylar tape; and DCF flourescence was measured after 2 h at room temperature in the dark. Specific wells were supplemented with 0.4 mM Asc, 0.2 mg/ml synthetic Δ^9-THC (THC), or 30 mM H_2O_2 in triplicate. Values represent means ± SEM from a single experiment that was representative of four experiments. Addition of 30 mM H_2O_2 to DCF-loaded cells produced a DCF fluorescence value of 530.

Smoke Dose-Response

Dose-response studies for MJ smoke were performed by varying the amount of smoke delivered to ECV 304 cells *in vitro* over a fixed interval of time. Either two, six, or 10 injections of 50 ml each were delivered into chambers with 5-s intervals between injections. The chambers were sealed for 10 min starting from exposure to the final bolus. Although the increases in DCF oxidation observed over the first 25 min of exposure were not statistically different between groups, dose- and time-dependent increases in DCF oxidation were significant by 45 min of exposure (Figure 6). After 60 min, the cells exposed to six and 10 50-ml injections displayed 25 and 38% higher levels, respectively, of ROS than did unexposed control cells. Exposure to only two 50-ml injections had no significant effect on ROS generation at any time after exposure.

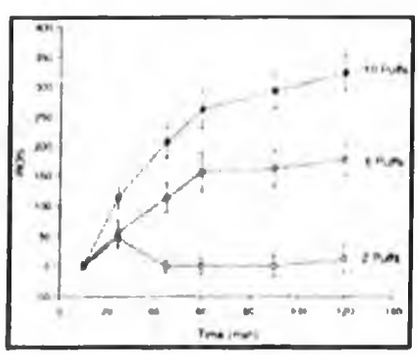

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Figure 6. Time course and dose-response for MJ smoke-induced ROS accumulation. ECV 304 cells were exposed to indicated number of 50-ml smoke puffs and chamber was then sealed. Total time for smoke exposure was 10 min for each sample. Normalized DCF fluorescence was measured and values from untreated control cells were subtracted. Values represent means of five or six determinations ± SEM. The experiment was repeated twice with similar results.

Comparison of smoke from 0, 1.77, and 3.95% Δ^9-THC MJ cigarettes revealed a dose-dependent relationship between cannabinoid content and ROS generation (Table 1). However, injection of pure synthetic Δ^9-THC in ethanol directly into 0% Δ^9-THC cigarettes 24 h before smoking failed to increase ROS generation significantly (data not shown).

TABLE 1

View this table: *THC content and ROS generation*
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Effects on Viability

The effect of MJ smoke on cell viability was examined by exposing cells to smoke for 30 min in chambers at room temperature. Cells were exposed in the presence of complete culture media and viability was monitored at periodic intervals. MJ smoke caused a time-dependent increase in cell death that reached 78% at 2 d (Figure 7). Control cells consistently displayed low (3 to 10%) death throughout this period. Cells exposed to 0% Δ^9-THC smoke also displayed high levels of death (70%) at 2 d. MJ smoke caused a rapid and sustained decrease in cellular GSH level of 83% after 10 min exposure and 77% after 6 h, with little further change up to 48 h (Figure 8). Smoke lacking Δ^9-THC lowered GSH levels by only a slightly lesser degree (71 and 69%, respectively) at these same times. (Differences were not significant.)

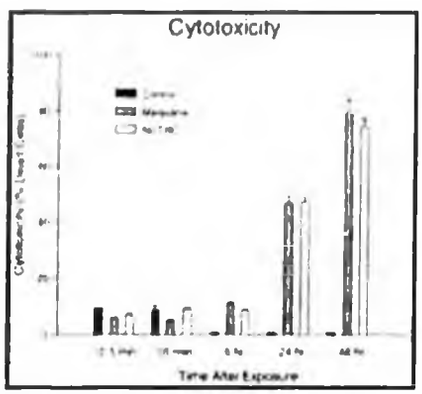

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Figure 7. Time course for ECV 304 cell death following 10 min exposure to smoke from a single MJ cigarette. Cytotoxicity was quantitated as described in MATERIALS AND METHODS. Values represent means of six determinations ± SEM. The experiment was repeated twice with similar results.

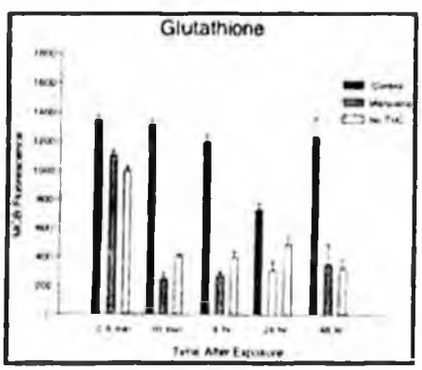

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Figure 8. Time course for GSH levels measured as MCB fluorescence following 10 min exposure to smoke from a single cigarette. Values represent means of six determinations ± SEM. Experiments were repeated twice with similar results.

The majority of dead cells after 2 d exposure to MJ smoke had died by necrosis. While the terminal uridine nucleotide end-terminal labeling apoptosis assay revealed sporadic cells with strongly positive staining, condensed nuclei, and fragmentation into apoptotic bodies, the majority of cells were unstained and slightly swollen. In addition, most cells showed positive staining with propidium iodide, indicating loss of membrane integrity. GSH levels displayed biphasic changes, initially declining after smoke exposure and subsequently tending to increase slightly, a pattern characteristic of many oxidation-mediated effects on the cellular antioxidant.

Filtered Smoke

To evaluate independently the gaseous and particulate phases of smoke for their ability to generate cellular ROS, smoke was first passed through high-efficiency Cambridge filters that remove > 98% of particulate components but allow passage of gas-phase components. Exposure of cells to gas-phase MJ smoke resulted in an approximately 2-fold increase in DCF oxidation relative to whole-smoke exposure (Figure 9). DCF oxidation caused by exposure to filtered smoke from ethanol-extracted MJ (0% Δ^9-THC) was also elevated 3-fold relative to that from exposure to unfiltered THC-free smoke. Filtered smoke from THC-containing cigarettes caused approximately 30% higher DCF oxidation than did filtered smoke from ethanol- extracted cigarettes. When particulate matter on filters was extracted with dimethyl sulfoxide (DMSO) and applied to cultured cells, DCF oxidation by whole smoke was attenuated by 50 to 70% (data not shown). DMSO alone had no effect on either basal or MJ smoke-induced DCF oxidation.

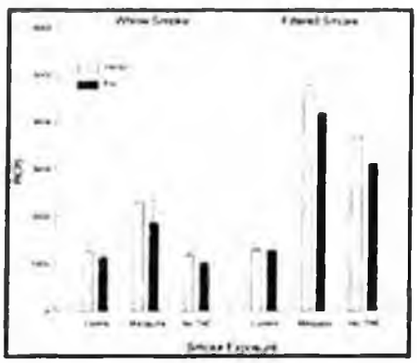

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Figure 9. ROS accumulation following exposure to gaseous-phase MJ cigarette smoke. Smoke from two cigarettes was filtered through Cambridge filters to remove particulates before exposure to ECV 304 cells. Values represent means of 34 determinations ± SEM. $P < 0.005$ comparing filtered smoke with whole smoke using Student's *t* test

Alveolar Macrophages

Cultured lung alveolar macrophages obtained by bronchoalveolar lavage from habitual MJ smokers revealed GSH levels 31% lower than levels in cells obtained from nonsmokers ($P < 0.025$) (Table 2). However, incubation of these cells with DCF revealed a lower rate of ROS production of borderline statistical significance ($P = 0.05$) compared with cells from nonsmokers. Cells from both MJ and

tobacco smokers contained high amounts of dense intracellular inclusions.

TABLE 2

View this table: *Lung alveolar macrophage oxidative stress*
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Discussion

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Very little research has been devoted to the cytotoxic effects of direct exposure to MJ smoke. Alterations that have been found in the tracheobronchial mucosa of habitual MJ smokers include mucosal edema and inflammation (4), cellular atypia and dysplasia (5), and molecular dysregulation of genes associated with malignant transformation (6). *In vitro* and whole-animal studies suggest that Δ^9-THC has a direct immunosuppressive effect on a variety of immune cells, including macrophages, natural killer cells, and T lymphocytes (11, 19). Habitual MJ smoking has also been shown to alter alveolar macrophage morphology (20, 21), phagocytic function (7), fungicidal and bactericidal activity (7, 22), and oxidative burst superoxide production (22).

In the present studies we examined the effects of short-term (5 to 30 min) exposure to MJ smoke on generation of ROS, levels of reduced GSH, and cell viability *in vitro*. Exposure to MJ smoke caused a dramatic increase in ROS over control levels, an increase that was as much as 3-fold higher than the increment resulting from exposure to a similar amount of tobacco smoke. The attenuation of DCF oxidation in cells overexpressing the antioxidant gene, Prx, supports the notion that pro-oxidants such as H_2O_2 were responsible for some of the MJ-induced effects. Prx is a novel antioxidant cytoplasmic enzyme that appears to eliminate peroxides, one of the several classes of ROS known to be generated intracellularly. In the present study, Prx-overexpressing cells displayed consistently lower DCF oxidation than did vector-only-transfected cells. However, the number of experimental determinations for each exposure group was not sufficiently high to achieve statistical significance.

The MJ-induced ROS appeared to be cannabinoid- dependent because smoke from cigarettes lacking Δ^9-THC produced no increase in ROS compared with control cells exposed to room air only. Although the alcohol extraction procedure used to deplete MJ leaves of cannabinoids could have removed other tar components essential for generating oxidative stress, methanol extraction of Marlboro cigarettes did not alter ROS generation produced by equivalent volumes of smoke (data not shown). Further, MJ cigarettes containing 1.77% Δ^9-THC stimulated intermediate levels of ROS, suggesting a direct dose-response relationship. The particulate phase of MJ smoke is qualitatively similar in composition to that of tobacco smoke, with the major exception being that MJ tar contains Δ^9-THC and approximately 60 other cannabinoid compounds not found in tobacco. Conversely, tobacco tar contains nicotine not found in MJ (7). Because purified Δ^9-THC added to cells failed to produce significant changes in ROS, GSH, or cell viability, it is likely that pyrrolysis products produced in the presence of cannabinoids, rather than Δ^9-

THC itself, were responsible for the observed oxidative injuries. The strong effects of MJ smoke on GSH levels and cell viability were not appreciably influenced by Δ^9-THC content. This disparity suggests that DCF oxidation and GSH depletion are affected to some extent by different components in MJ smoke.

After intracellular loading and de-esterification, dihydro-DCF can be oxidized to its fluorescent derivative, DCF, by a variety of agents including hydrogen peroxide, hydroxyl radical, and peroxynitrite (23, 24). Evidence indicates that the fluorescent compound is not permanently retained within cells as originally proposed (25), but is gradually released into the surrounding medium. This slow release of dihydro-DCF could diminish the signal caused by oxidants of intracellular origin and increase signal from extracellular oxidants adsorbed directly from smoke. However, our studies comparing cellular and noncellular oxidation of DCF by MJ smoke revealed that DCF in buffer solution is poorly oxidized by direct smoke exposure, in contrast to results obtained with cellular DCF measurements (Figure 5). These results suggest that most of the DCF fluorescence results from smoke exposure generated by cellular mechanisms. Smoke-induced disruption of mitochondrial or endoplasmic reticular electron transport is among the possible mechanisms for such ROS generation.

Our studies revealed that, compared with smoke generated from MJ cigarettes containing 0% Δ^9-THC, unmodified MJ smoke deposited 50% higher amounts of nitrates ($NO/NO_2^-/NO_3^-$) into culture wells (data not shown). Nitrates can generate peroxynitrite in the presence of superoxide anion. This effect may partially account for the difference in ROS produced from MJ with or without Δ^9-THC. However, smoke from a tobacco cigarette of equivalent weight contained nearly twice as much nitrate as smoke from 3.9% Δ^9-THC MJ cigarettes, yet produced somewhat lower ROS. Thus, smoke nitrate levels did not correlate directly with ROS generation.

Loss of cellular GSH can occur by two major pathways (26). Free radical-mediated oxidative activity results in generation and/or efflux of oxidized glutathione, which we did not measure in this study. Alternatively, nucleophiles, including aldehydes known to be prevalent in cigarette smoke (e.g., formaldehyde), form covalent conjugates with GSH. These reactions, catalyzed by glutathione-S-transferase (GST) enzymes, result in lower MCB-detectable GSH levels. These reactions do not necessarily reflect oxidative stress per se, but would partially impair cellular defenses and inhibit the removal of ROS. MCB has been used extensively to estimate intracellular levels of reduced GSH (27). Although fluorescence can also be generated by protein-MCB conjugate formation (31), the rate of this reaction at low (10 to 100 μM) concentrations of MCB is lower than that for the complex with GSH. Thus, limiting the reaction time to 20 min allows for a more accurate estimation of GSH. Recent studies suggest that reactivity of MCB with GSH is low in human peripheral blood monocytes compared with reactivity with other low molecular-weight compounds (32). This low reactivity is apparently due to the low affinity of some forms of GSTs for MCB. In the present study, the human alveolar macrophages displayed 20 to 60% lower levels of MCB fluorescence than did the ECV 304 cell line. However, in both cell types, MCB fluorescence was inhibited 80 to 90% by 10 min pretreatment with 2 mM diethylmaleate, which rapidly removes cytoplasmic GSH (33).

Cannabinoids, including THC, contribute substantially to the particulate mass of MJ smoke comprising

20 to 30% of the total tar weight for cigarettes containing 3.9% Δ^9-THC (13). To determine whether the increased particulate material in MJ smoke was responsible for the enhanced DCF oxidation, MJ cigarette smoke was passed through Cambridge filters before exposure to cells. Such filters trap > 98% of particulate material but permit passage of all gaseous elements. This procedure not only failed to attenuate DCF oxidation, but also greatly stimulated oxidation in both unmodified MJ and THC-deficient smoke. This stimulation was consistent with reports of strong oxidizing activity of the gaseous phase of tobacco cigarette smoke after removal of particulates by filtration. For example, in studies on the role of tobacco smoke in atherosclerosis, oxidation of low-density lipoprotein (LDL) has been observed with filtered smoke but not whole smoke (34). Filter-trapped particulates can inhibit LDL oxidation induced by cupric chloride or azo-bis (2-amidinopropane), and it has been suggested that antioxidants, such as polyphenolic compounds found in smoke particulate fractions, may be responsible for inhibition of LDL oxidation (35, 36). In the present studies, the concept that particulate components of MJ smoke had antioxidant properties was further supported by the finding that DMSO extracts of a Cambridge filter pad absorbed with MJ smoke particulates suppressed ROS generation. Thus, the level of smoke-induced cellular ROS appears to be a function of the relative amounts of gaseous-phase pro-oxidants and particle-phase antioxidants.

The cannabinoids present in the particle phase of MJ smoke, including Δ^9-THC and cannabinol, have been reported to have antioxidant properties as measured by cyclic voltametry and by their ability to prevent H_2O_2-mediated oxidation of a fluorescent probe (37). This is consistent with their known structure, which includes hydroxyl groups and aliphatic rings. However, the addition of Δ^9-THC to our assays before smoke exposure did not provide any measurable antioxidant protection, suggesting that this effect is relatively weak compared with the pro-oxidant activity induced by smoke.

Preliminary studies with cultured lung alveolar macrophages from human MJ smokers demonstrated lower levels of GSH in these cells than in alveolar macrophages from nonsmokers. These results suggest that habitual exposure to MJ smoke causes a sustained decrease in GSH-dependent oxidative defenses. Such a decrease could be due to inhibition of GSH synthetic or recycling enzymes concomitant with depletion of cytoplasmic GSH. Inhibition of GST could also contribute to diminished MCB fluorescence because this enzyme accelerates MCB-GSH conjugation. The observed decrease in rate of ROS production in cells from MJ smokers relative to nonsmokers is, seemingly, paradoxical. One explanation consistent with the cytotoxic effects of MJ smoke is that chronic *in vivo* exposure of cells to this smoke produced general metabolic impairments diminishing either mitochondrial electron transport or oxidative burst capacity.

The generation of ROS has several undesirable consequences, including the impairment of cellular energetic (38) and defense (39) systems and the promotion of malignant transformation (40). Cell death induced by MJ smoke is largely necrotic. These deleterious effects of MJ smoke could have serious implications for tissues in direct contact with cannabinoid-containing smoke, including lung macrophages and surface epithelial cells in the upper aerodigestive tract and the tracheobronchial mucosa. Such effects need to be taken into consideration when evaluating risk-benefit factors associated with MJ consumption.

Footnotes

Address correspondence to: T. A. Sarafian, Div. of Pulmonary and Critical Care Medicine, Dept. of Medicine, UCLA School of Medicine, Los Angeles, CA 90095.

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Abbreviations: analysis of variance, ANOVA; ascorbic acid, Asc; 2,7-dichlorofluorescein, DCF; DCF diacetate, DCF-DA; dimethyl sulfoxide, DMSO; emission, Em; excitation, Ex; fetal calf serum, FCS; reduced glutathione, GSH; glutathione-S-transferase, GST; hydrogen peroxide, H_2O_2; low-density lipoprotein, LDL; monochlorobimane, MCB; marijuana, MJ; pyrrolidinedithiocarbamate, PDTC; peroxiredoxin, Prx; reactive oxygen species, ROS; standard error of the mean, SEM; tetrahydrocannabinol, THC.

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1. Johnston, L. D., P. M. O'Malley, and J. G. Bachman. 1997. National survey results on drug use from the Monitoring the Future Study, 1975-1995, Vol II. College students and young adults. USDHHS, NIH Publication No. 98-4140, Washington, DC. 35-74.

2. Grinspoon, L., and J. B. Bakalar, 1997. Marijuana: The Forbidden Medicine, Revised and Expanded Edition, Yale University Press, New Haven, CT.

3. Adams, I. B., and B. R. Martin. 1996. Cannabis: pharmacology and toxicology in animals and humans. *Addiction* 91: 1585-1614 [Medline].

4. Roth, M. D., A. Arora, S. H. Barsky, E. C. Kleerup, M. Simmons, and D. P. Tashkin. 1998. Visual and pathologic evidence of injury to the airways of young marijuana smokers. *Am. J. Respir. Crit. Care Med.* 157: 928-937 [Abstract/Free Full Text].

5. Fligiel, S. E., M. D. Roth, E. C. Kleerup, S. H. Barsky, M. S. Simmons, and D. P. Tashkin. 1997. Tracheobronchial histopathology in habitual smokers of cocaine, marijuana, and/or tobacco. *Chest* 112: 319-326 [Abstract/Free Full Text].

6. Barsky, S. H., M. D Roth, E. C. Kleerup, M. Simmons, and D. P. Tashkin. 1998. Histopathologic and molecular alterations in bronchial epithelium in habitual smokers of marijuana, cocaine, and/or tobacco. *J. Natl. Cancer Inst.* 90: 1198-1205 [Abstract/Free Full Text].

7. Baldwin, G. C., D. P. Tashkin, D. M. Buckley, A. N. Park, S. M. Dubinett, and M. D. Roth. 1997. , Habitual smoking of marijuana and cocaine impairs alveolar macrohage function and cytokine

production. *Am. J. Respir. Crit. Care Med.* 156: 1606-1613 [Abstract/Free Full Text].

8. Taylor, F. M.. 1988. Marijuana as a potential respiratory tract carcinogen: a retrospective analysis of a community hospital population. *South Med. J* 81: 1213-1216 [Medline].

9. Caplan, G. A., and B. A. Brigham. 1990. Marijuana smoking and carcinoma of the tongue: is there an association? *Cancer* 66: 1005-1006 [Medline].

10. Donald, P. J.. 1991. Advanced malignancy in the young marijuana smoker. *Adv. Exp. Med. Biol.* 288: 33-46 [Medline].

11. Klein, T. S., Y. Kawakami, C. Newton, and H. Friedman. 1991. Marijuana components suppress induction and cytolytic function of murine cytotoxic T cells in vitro and in vivo. *J. Toxicol. Env. Health* 32: 465-477 [Medline].

12. Kusher, D. I., L. O. Dawson, A. C. Taylor, and J. Y. Djeu. 1994. Effect of the psychoactive metabolite of marijuana, Δ^9-tetrahydrocannabinol (THC), on the synthesis of tumor necrosis factor by human large granular lymphocytes. *Cell. Immunol.* 154: 99-108 [Medline].

13. Hoffman, D., D. K. Brunneman, G. B. Gori, and E. L. 'ynder. 1975. On the carcinogenicity of marijuana smoke. *Rec. Adv. Phytochem.* 9: 63-81 .

14. ElSohly, M. A., and S. A. Ross. 1994. Quarterly Report, NIDA Potency Monitoring Project, Report No. 50. National Institute on Drug Abuse, Rockville, MD.

15. Zimmer, L., and J. P. Morgan. 1997. Marijuana Myths, Marijuana Facts. Lindesmith Center, New York. 135-141.

16. Matthias, P., D. P. Tashkin, J. A. Marques, Magallanes, J. N. Wilkins, and M. S. Simmons. 1997. Effects of varying marijuana potency on deposition of tar and delta-9-THC in the lung during smoking. *Pharmacol. Biochem. Behav.* 58: 1145-1150 [Medline].

17. Sarafian, T. A., N. Rajper, B. Grigorian, A. Kim, and H. Shau. 1997. Cellular antioxidant properties of human natural killer enhancing factor B. *Free Rad. Res.* 26: 281-289 [Medline].

18. Sarafian, T. A., L. Vartavarian, D. J. Kane, D. E. Bredesen, and M. A. Verity. 1994. bcl-2 expression decreases methyl mercury-induced free-radical generation and cell killing in a neural cell line. *Toxicol. Lett.* 74: 149-155 [Medline].

19. Burnette-Curley, D., and G. A. Cabral. 1995. Differential inhibition of RAW264.7 macrophage tumoricidal activity by Δ^9-tetrahydrocannabinol. *Proc. Soc. Exp. Biol. Med.* 210: 64-76 [Abstract].

20. Davies, P., G. C. Somberger, and G. L. Huber. 1979. Effects of experimental marijuana and tobacco smoke inhalation on alveolar macrophages. *Lab. Invest.* 41: 220-223 [Medline].

21. Beals, T. F., S. E. G. Fligiel, S. Stuth, and D. P. Tashkin. 1989. Morphological alterations of alveolar macrophages from marijuana smokers. *Am. Rev. Respir. Dis.* 139: A336 . (Abstr.) .

22. Sherman, M. P., L. A. Campbell, H. Gong Jr., M. D. Roth, and D. P. Tashkin. 1991. Respiratory

burst and microbicidal characteristics of pulmonary alveolar macrophages recovered from smokers of marijuana alone, smokers of tobacco alone, smokers of marijuana and tobacco and nonsmokers. *Am. Rev. Respir. Dis.* 144: 1351-1356 [Medline].

23. Lebel, C. P., H. Ischiropoulos, and S. C. Bondy. 1992. Evaluation of the probe 2',7'-dichlorofluorescein as an indicator of reactive oxygen species formation and oxidative stress. *Chem. Res. Toxicol.* 5: 227-231 [Medline].

24. Possel, H., H. Noack, W. Augustin, G. Keilhoff, and G. Wolf. 1997. 2,7-Dihydrodichlorofluorescein diacetate as a fluorescent marker for peroxynitrite formation. *FEBS Lett.* 416: 175-178 [Medline].

25. Bass, D. A., J. W. Parce, L. R. Dechatelet, P. Szejda, M. C. Seeds, and M. Thomas. 1983. Flow cytometric studies of oxidative product formation by neutrophils: a graded response to membrane stimulation. *J. Immunol.* 130: 1910-1917 [Abstract/Free Full Text].

26. Bellomo, G., H. Thor, and S. Orrenius. 1990. Modulation of cellular glutathione and protein thiol status during quinone metabolism. *Methods Enzymol.* 186: 627-635 [Medline].

27. Rice, G. C., E. A. Bump, D. C. Shrieve, W. Lee, and M. Kovacs. 1986. Quantitative analysis of cellular glutathione by flow cytometry utilizing monochlorobimane: some applications to radiation and drug resistance *in vitro* and *in vivo*. *Cancer Res.* 46: 6105-6110 [Abstract].

28. Shrieve, D. C., E. A. Bump, and G. C. Rice. 1988. Heterogeneity of cellular glutathione among cells derived from a murine fibrosarcoma or a human renal cell carcinoma detected by flow cytometric analysis. *J. Biol. Chem.* 263: 14107-14114 [Abstract/Free Full Text].

29. Kavanagh, T. J., A. Grossman, J. C. Jinnerman, S. B. Kanner, C. C. White, D. L. Eaton, J. A. Ledbetter, and P. S. Rabinovitch. 1993. The effect of 1-chloro-2,4-dinitrobenzene exposure on antigen receptor (CD3)-stimulated transmembrane signal transduction in purified subsets of human peripheral blood lymphocytes. *Toxicol. Appl. Pharmacol.* 119: 91-99 [Medline].

30. Reichelt, W., J. Stabel-Burow, T. Pannicke, H. Weichert, and U. Heinemann. 1997. The glutathione level of retinal Muller glial cells is dependent on the high-affinity sodium-dependent uptake of glutamate. *Neuroscience* 77: 1213-1224 [Medline].

31. Cook, J. A., H. I. Pass, S. N. Iype, N. Friedman, W. DeGraff, A. Russo, and J. B. Mitchell. 1991. Cellular glutathione and thiol measurements from surgically resected human lung tumor and normal lung tissue. *Cancer Res.* 51: 4287-4294 [Abstract].

32. van der Ven, A. J. A. M., P. Mier, W. H. M. Peters, H. Dolstra, P. E. J. van Erp, P. P. Koopmans, and J. W. M. van der Meer. 1994. Monochlorobimane does not selectively label glutathione in peripheral blood mononuclear cells. *Anal. Biochem.* 217: 41-47 [Medline].

33. Ku, R. H., and R. E. Billings. 1986. The role of mitochondrial glutathione and cellular protein sulfhydryls in formaldehyde toxicity in glutathione- depleted rat hepatocytes. *Arch. Biochem.* 247: 183-189 .

34. Frei, B., T. M. Forte, B. N. Ames, and C. E. Cross. 1991. Gas phase oxidants of cigarette smoke induce lipid peroxidation and changes in lipoprotein properties in human blood plasma: protective effects of ascorbic acid. *Biochem. J.* 277: 133-138 [Medline].

35. Chen, C., and G. Loo. 1995. Cigarette smoke extract inhibits oxidative modification of low density lipoprotein. *Atherosclerosis* 112: 177-185 [Medline].

36. Church, D. F., and W. A. Prior. 1985. Free-radical chemistry of cigarette smoke and its toxicological implications. *Environ. Health Perspect.* 64: 111-126 [Medline].

37. Hampson, A. J., M. Grimaldi, J. Axelrod, and D. Wink. 1998. Cannabidiol and (-)Δ^9-tetrahydrocannabinol are neuroprotective antioxidants. *Proc. Natl. Acad. Sci. USA* 95: 8268-8273 [Abstract/Free Full Text].

38. Wallace, K. B., J. T. Eelss, V. M. C. Madeira, G. Cortopassi, and D. P. Jones. 1997. Mitochondria-mediated cell injury. *Fundam. Appl. Toxicol.* 38: 23-37 [Medline].

39. Repine, J. E., A. Bast, I. Lankhorst, and The Oxidative Stress Study Group. 1997. Oxidative stress in chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* 156: 341-357 [Free Full Text].

40. Bankson, D. D., M. Kestin, and N. Rifai. 1993. Role of free radicals in cancer and atherosclerosis. *Clin. Lab. Med.* 13: 463-480 [Medline].

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Respiratory Effects of Marijuana and Tobacco Use in a U.S. Sample

Brent A. Moore, PhD[1], Erik M. Augustson, PhD, MPH[2], Richard P. Moser, PhD[3], Alan J. Budney, PhD[4]

[1]Department of Psychiatry, Yale University School of Medicine, New Haven, CT, USA; [2]Tobacco Control Research Branch, Division of Cancer Control and Population Sciences, and [3]Behavioral Research Program, Division of Cancer Control and Population Sciences, National Cancer Institute, Rockville, MD, USA; [4]Departments of Psychology and Psychiatry, University of Vermont, Burlington, VT, USA

OBJECTIVE: Although a number of studies have examined the respiratory impact of marijuana smoking, such studies have generally used convenience samples of marijuana and tobacco users. The current study examined respiratory effects of marijuana and tobacco use in a nationally representative sample while controlling for age, gender, and current asthma.

DESIGN: Analysis of the nationally representative third National Health and Nutrition Examination Survey (NHANES III).

SETTING: U.S. households.

PARTICIPANTS: A total of 6,728 adults age 20 to 59 who completed the drug, tobacco, and health sections of the NHANES III questionnaire in 1988 and 1994. Current marijuana use was defined as self-reported 100+ lifetime use and at least 1 day of use in the past month.

MEASUREMENTS AND MAIN RESULTS: Self-reported respiratory symptoms included chronic bronchitis, frequent phlegm, shortness of breath, frequent wheezing, chest sounds without a cold, and pneumonia. A medical exam also provided an overall chest finding and a measure of reduced pulmonary functioning. Marijuana use was associated with respiratory symptoms of chronic bronchitis ($P = .02$), coughing on most days ($P = .001$), phlegm production ($P = .0005$), wheezing ($P < .0001$), and chest sounds without a cold ($P = .02$).

CONCLUSION: The impact of marijuana smoking on respiratory health has some significant similarities to that of tobacco smoking. Efforts to prevent and reduce marijuana use, such as advising patients to quit and providing referrals for support and assistance, may have substantial public health benefits associated with decreased respiratory health problems.

KEY WORDS: marijuana; tobacco; smoking; respiratory symptoms; epidemiology.
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Marijuana smoking remains the second most widely smoked substance in the United States, with conservative estimates indicating that more than 11 million people smoked marijuana during the last month, and approximately 20% of these smoke almost daily.[1–3] Marijuana smoke contains similar levels of tar as tobacco smoke and up to 50% more carcinogens.[4,5] Marijuana users smoke unfiltered material, inhale the smoke more deeply, and hold the smoke longer than tobacco smokers, resulting in substantially greater tar deposits in the lungs than tobacco smokers.[6–9] Reports from clinical samples suggest that marijuana smokers exhibit a range of chronic respiratory symptoms,[10–13] although it is unclear whether these symptoms are representative of marijuana smokers as a whole. In addition, marijuana users have greater utilization of outpatient medical services for respiratory and other illnesses.[14] Moreover, the histopathologic and molecular abnormalities observed in marijuana smokers are almost identical to that observed in tobacco smokers.[10,15–17] Cellular abnormalities include reductions in the number of ciliated epithelial cells lining the trachea and bronchi. These histopathologic alterations are associated with a range of potential lung disorders such as chronic bronchitis, chronic obstructive pulmonary disease, and cancer. Although the extent of the problem remains unclear, the current literature of case reports and clinical samples suggests that marijuana-related respiratory problems may constitute a significant public health burden that could be prevented or treated by general internists.

Only two studies have attempted to quantitatively define the odds of respiratory symptoms among marijuana users in the general population. One examined respiratory symptoms in marijuana-dependent 20 year olds in a longitudinal sample from New Zealand.[13] The other examined non-tobacco smoking individuals in a longitudinal study in Arizona.[11] Both studies found increased odds of respiratory symptoms such as cough, wheezing, and sputum production among users. However, the first focused only on young marijuana-dependent individuals in New Zealand. The second was limited to Tucson, AZ and did not specifically focus on marijuana use but rather on "non-tobacco" cigarette use, which was assumed to be predominately marijuana. The purpose of the present report is to provide estimates of respiratory symptoms for current marijuana use in a nationally representative sample in the United States with a broader range of ages and marijuana exposure. The third National Health and Nutrition Examination Survey (NHANES III) was used to examine the independent contributions of marijuana use and tobacco use while controlling for gender, age, and current asthma.

METHODS

Sample

The NHANES III, conducted between 1988 and 1994, used a multistage probability design with oversampling of African Americans and Mexican Americans to obtain a nationally representative sample of the U.S. population.[18] Household members were initially selected and requested to complete a general health survey. Eighty-six percent of selected individuals were interviewed in person and all were invited to participate in the medical exam. All respondents signed an informed

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Address correspondence and requests for reprints to Dr. Moore: Department of Psychiatry, Yale University School of Medicine, 219S CMHC SAC, 34 Park Street, New Haven, CT 06519 (e-mail: Brent.Moore@Yale.edu).

consent, which guaranteed that information was kept in strictest confidence. Seventy-eight percent of invited individuals completed the medical exam. The medical exam included an interview that asked a range of general health questions regarding marijuana and tobacco use, a physician's exam, and a spirometry component. Adults age 20 to 59 who completed the drug and tobacco sections of the NHANES III medical exam questionnaire were selected for this study. NHANES III restricted drug use questions to individuals younger than 60. Individuals were asked first whether they had ever used marijuana. Individuals who reported ever using marijuana were asked, "About how many times in your lifetime have you used marijuana," with the following response categories: "1 or 2 times," "3 to 10 times," "11 to 99 times," and "100 or more times."

Individuals who reported lifetime use were also asked, "During the past month, on how many days did you use marijuana?" Individuals provided a number response between 0 and 30. Current marijuana use was defined as self-reported 100+ lifetime uses and at least 1 day of use in the past month. Individuals were not asked about their daily quantity or frequency of use. For tobacco cigarette use, individuals were asked, "Have you smoked at least 100 cigarettes in your entire life," and "How many cigarettes have you smoked in the past 5 days?" Current tobacco use was defined as self-reported lifetime history of smoking 100+ tobacco cigarettes and current use as an average of 1 or more tobacco cigarettes per day. The criterion of 100+ lifetime uses for both marijuana and tobacco was implemented to exclude experimental users of either substance. Nonsmokers had never used marijuana and had not smoked tobacco cigarettes more than 100 times. The total sample consisted of 6,728 individuals: 4,789 nonsmokers, 1,525 tobacco-only smokers, and 414 marijuana smokers (320 also smoked tobacco).

Outcome Measures

Respiratory symptoms were asked about as part of the general household survey. The following respiratory symptoms were examined: chronic bronchitis, frequent phlegm, shortness of breath, frequent wheezing, chest sounds without a cold, and pneumonia (see Table 1 for the specific questions used to determine these symptoms). In addition, the medical exam provided an overall chest finding and spirometry measures. The overall chest finding summarized whether the physician noted any respiratory abnormality such as decreased breath or adventitious sounds in either lung. For the spirometry data, we calculated the FEV1/FVC ratio and used a cutoff of <70% as an indicator of obstruction.[19] Height was also controlled in the analysis of the FEV1/FVC ratio cutoff.

Table 1. NHANES III Questions for Respiratory Symptoms

Has a doctor ever told you that you had chronic bronchitis?
Do you usually cough on most days for 3 consecutive months or more during the year?
Do you bring up phlegm on most days for 3 consecutive months or more during the year?
Are you troubled by shortness of breath when hurrying on level ground or walking up a slight hill?
Have you had wheezing or whistling in your chest at any time in the past 12 months?
Apart from when you have a cold, does your chest ever sound wheezy or whistling?
During the past 12 months, have you had pneumonia?

NHANES III, third National Health and Nutrition Examination Survey.

Data Analysis

All analyses were completed using SAS, version 8.2 (SAS Institute, Cary, NC) with callable SUDAAN, version 8.0 (Research Triangle Park, NC). SUDAAN was used to adjust the standard errors in accordance with the variable selection probabilities including noncoverage and nonresponse associated with the survey sampling frame.[18] For demographics, χ^2 tests were used to examine weighted proportional differences among categorical variables and ANOVAs were used for continuous measures. Demographic variables available in the NHANES III dataset included gender, age, race, education, marital status, and income. Logistic regression was employed to compare marijuana users to nonsmokers with each respiratory symptom while controlling for gender, age, and tobacco cigarettes smoked per day. Although marijuana users differed on other demographic variables in addition to gender and age, these variables were highly correlated with age and gender, such that marijuana users did not differ on the other demographic variables when age and gender were controlled. The analysis of respiratory symptoms also controlled for current asthma. Current asthma was statistically controlled because it is more likely to be a preexisting condition, and marijuana smokers may have used marijuana to treat or control their asthma. For individuals who reported that a doctor had told them they had asthma, current asthma was defined by whether participants reported that they still had asthma.

RESULTS

Marijuana smokers reported smoking on an average of 10.2 days (standard error [SE], 0.84) of the previous 30 days, with 16% ($n = 68$) reporting daily or near daily use (28 or more days). Marijuana smokers were more likely to be male, white, younger, and single than nonsmokers (see Table 2). They were also more likely to have lower education levels and earn less income than nonsmokers. Seventy-seven percent of marijuana smokers also smoked tobacco. Among marijuana smokers, the mean number of tobacco cigarettes smoked per day (19.22; SE, 1.05) did not differ significantly from that of tobacco-only smokers (19.27; SE, 0.64). Tobacco-only smokers were more likely to be male, white, older, have less education, and earn less income than nonsmokers.

Table 3 presents the unadjusted comparisons of the marijuana and tobacco users and nonusers on respiratory symptoms. Compared to nonusers, both marijuana and tobacco users had higher rates of chronic bronchitis (odds ratio [OR], 2.68, 95% confidence interval [CI], 1.47 to 4.89 for marijuana users and OR, 2.69, 95% CI, 1.87 to 3.86 for tobacco users, respectively), cough on most days (OR, 7.05, 95% CI, 4.84 to 10.26 and OR, 6.17, 95% CI, 4.54 to 8.38), phlegm production (OR, 5.54, 95% CI, 3.70 to 8.30, and OR, 4.67, 95% CI, 3.19 to 6.82), shortness of breath (OR, 1.79, 95% CI, 1.14 to 2.81, and OR, 2.89, 95% CI, 2.36 to 3.54), wheezing (OR, 6.24, 95% CI, 4.51 to 8.62, and OR, 3.13, 95% CI, 2.42 to 4.05), and chest sounds (OR, 4.96, 95% CI, 3.41 to 7.21, and OR, 3.88, 95% CI, 3.01 to 5.01). A significantly higher proportion of tobacco users were found to report pneumonia in the past year (OR, 2.06, 95% CI, 1.15 to 3.72). Tobacco users were also more likely to

Table 2. Characteristics of Nonsmokers, Tobacco-only Smokers, and Marijuana Smokers: NHANES III, 1988 to 1994

Variable	Nonsmokers (n=4,789)	Tobacco Smokers (n=1,525)	Marijuana Smokers (n=414)
Gender, % male*†	36.6	50.0	77.0
Race, % white*†	65.3	73.6	78.8
Education*†			
<12 years	22.0	34.9	27.6
12 years	32.4	39.2	39.2
>12 years	45.6	25.9	33.1
Mean age, y (± SE)*†	34.7 (0.31)	41.5 (0.52)	31.2 (0.65)
Marital status, % married*†	63.7	75.0	29.8
Income, %*†			
<$10,000	15.8	22.3	17.6
$10,000 to $29,000	34.2	37.7	49.7
$30,000 to $59,000	23.1	19.6	18.2
>$59,000	26.9	20.3	14.5

*Nonsmokers versus marijuana smokers, P<.05.
†Nonsmokers versus tobacco smokers, P<.05.
NHANES III, third National Health and Nutrition Examination Survey. SE, standard error.

Table 3. Percent of Nonsmokers, Tobacco-only Smokers, and Marijuana Smokers with Respiratory Symptoms: NHANES III, 1988 to 1994

Variable	Nonsmokers	Tobacco Smokers		Marijuana Smokers	
	(n=4,789)	(n=1,525)		(n=414)	
	%	%	NNH	%	NNH
Current asthma*	3.8	6.5	37.0	5.8	50.0
Chronic bronchitis*†	3.2	8.2	20.0	8.1	20.4
Cough: most days*†	3.8	19.5	6.4	21.7	5.6
Phlegm*†	3.5	14.6	9.0	16.9	7.5
Shortness of breath*†‡	14.8	33.4	5.4	23.7	11.2
Wheezing*†‡	9.7	25.2	6.5	40.1	3.3
Chest sounds*†	5.8	19.4	7.4	23.5	5.6
Pneumonia*	1.7	3.5	55.6	2.8	90.9
Overall chest finding*†	1.1	9.0	12.7	3.1	50.0
FEV1/FVC ratio<70%*†‡	3.8	20.0	6.2	9.1	19.8

*Nonsmokers versus tobacco smokers, P<.05.
†Nonsmokers versus marijuana smokers, P<.05.
‡Tobacco smokers versus marijuana smokers, P<.05.
NHANES III, third National Health and Nutrition Examination Survey. NNH, number needed to harm.

have some respiratory abnormality as indicated by the physician's overall chest finding (OR, 8.94, 95% CI, 4.91 to 16.29), while marijuana users did not differ significantly from nonusers (OR, 2.89, 95% CI, 0.95 to 8.75). Compared to nonusers, both marijuana and tobacco users had a higher proportion of individuals with an FEV1/FVC ratio <70% (OR, 2.56, 95% CI, 1.54 to 4.35 and OR, 6.25, 95% CI, 4.76 to 8.33, respectively). Direct comparisons between tobacco and marijuana users indicated that a greater proportion of tobacco users had shortness of breath, chest findings, and evidence of airway obstruction as indicated by an FEV1/FVC ratio <70%, while marijuana users evidenced greater wheezing.

In general, marijuana smokers showed increased rates of respiratory symptoms similar to those of tobacco smokers. For example, 16.9% of marijuana users reported frequent phlegm production, which corresponds to a national estimate of 1,084,000 individuals. Table 3 also presents the number needed to harm (NNH) for both marijuana and tobacco users. This measure indicates how many users would be expected for each case that exhibited the symptom. For marijuana users, NNH values ranged from 3.3 (wheezing) to 20.3 (chronic bronchitis). For tobacco users, NNH values ranged from 5.4 (shortness of breath) to 37.0 (current asthma).

Because a large number of marijuana users also used tobacco, and marijuana and tobacco users differed on demographic characteristics, odds ratios for respiratory symptoms were computed comparing marijuana users to controls, controlling for gender, age, current asthma, and tobacco cigarettes used per day (Table 4). The odds of respiratory symptoms of chronic bronchitis, coughing on most days, phlegm production, wheezing, and chest sounds without a cold were greater for marijuana users. However, marijuana use was not associated with greater odds of shortness of breath, pneumonia, or objective measures of respiratory functioning, including the physician's respiratory findings and the FEV1/FCV ratio. Tobacco use was associated with increased odds of all respiratory variables (all P<.0001) with one exception. Tobacco use was not associated with greater odds of pneumonia when age, gender, and current asthma were controlled.

Direct comparisons of marijuana and tobacco users with tobacco-only users were also conducted controlling for age, gender, and current asthma. The pattern of findings was the same as the results examining marijuana use while controlling for cigarettes per day. Although both groups smoked a similar number of tobacco cigarettes, smoking both marijuana and tobacco was associated with greater odds of chronic bronchitis (OR, 2.10, 95% CI, 1.07 to 4.15; P=.03), coughing on most days (OR, 1.87, 95% CI, 1.24 to 2.83; P=.004), phlegm production (OR, 1.60, 95% CI, 1.02 to 2.50; P=.04), wheezing (OR, 2.38, 95% CI, 1.57 to 3.61; P=.0001), and chest sounds without a cold (OR, 1.90, 95% CI, 1.06 to 3.39; P=.03), but not shortness of breath (OR, 1.10, 95% CI, 0.72 to 1.69; P=.65), pneumonia (OR, 2.66, 95% CI, 0.79 to 8.98; P=.11), the overall chest finding (OR, 0.49, 95% CI, 0.21 to 1.10; P=.08), or the FEV1/FVC ratio (OR, 0.89, 95% CI, 0.40 to 2.00; P=.78).

DISCUSSION

In a nationally representative sample, marijuana use was associated with a variety of respiratory problems including chronic bronchitis, coughing on most days, phlegm production, wheezing, and chest sounds without a cold, even when gender, age, tobacco use, and current asthma were controlled. When examined categorically, marijuana users had similar rates of respiratory symptoms as tobacco cigarette users even though they were 10 years younger. These rates of respiratory problems constitute a potentially large national public health burden. For example, based on the current analyses, an estimated 1 million marijuana users had phlegm production on most days for 3 consecutive months or more during the year.

These findings, replicated in a nationally representative sample, are consistent with other studies examining respiratory symptoms between marijuana and tobacco smokers.[10,13,15,20] However, rates of specific respiratory symptoms were generally lower in the current study. This may be due to our inclusion of all marijuana users rather than the restriction to marijuana dependence as was done in the Taylor et al. study.[13] Taken together, these findings suggest that marijua-

Table 4. Odds Ratios and 95% Confidence Intervals for Respiratory Symptoms for Marijuana Users and Tobacco Users Versus Nonsmokers Controlling for Gender, Age, and Current Asthma

Respiratory Variable	Marijuana Users*	Tobacco Users
Chronic bronchitis	2.17 (1.11 to 4.26), $P = .02$	2.44 (1.66 to 3.57), $P < .0001$
Cough: most days	2.00 (1.32 to 3.01), $P = .001$	5.02 (3.58 to 7.04), $P < .0001$
Phlegm	1.89 (1.35 to 2.66), $P = .0005$	3.71 (2.45 to 5.62), $P < .0001$
Shortness of breath	1.29 (0.81 to 2.03), $P = .26$	2.70 (2.16 to 3.37), $P < .0001$
Wheezing	2.98 (2.05 to 4.34), $P < .0001$	3.39 (2.54 to 4.53), $P < .0001$
Chest sounds	2.06 (1.18 to 3.61), $P = .02$	4.25 (3.06 to 5.91), $P < .0001$
Pneumonia	1.47 (0.54 to 3.97), $P = .44$	1.57 (0.98 to 2.51), $P = .06$
Overall chest finding	0.67 (0.22 to 1.99), $P = .46$	6.48 (3.82 to 10.99), $P < .0001$
FEV1/FVC ratio < 70%	1.01 (0.51 to 1.94), $P = .99$	4.17 (3.03 to 5.68), $P < .0001$

*For marijuana users, the number of cigarettes per day was also controlled.

na use is associated with a range of respiratory problems that are likely greater with marijuana dependence.

Of note, although unadjusted comparisons indicated that marijuana users evidenced increased airway obstruction as indicated by an FEV1/FVC ratio < 70%, marijuana use was not associated with the objective indicators of respiratory functioning when age, gender, current asthma, and cigarette use were controlled. While the analyses were intended to control for group differences and examine the contribution of marijuana use, the sample of marijuana users was significantly younger and reported only an average of 10 days of use in the past 30 days. The current findings may be indicative of an earlier stage of respiratory problems for which self-reported symptoms are more sensitive. Thus, it may be important for physicians to ask marijuana-using patients about symptoms such as wheezing or cough in addition to a physical respiratory exam in order to provide a more complete picture of respiratory functioning.

Smoking both marijuana and tobacco was common among marijuana users (77%). This prevalence was higher than that noted in other studies of marijuana and tobacco use, which may be due to different definitions of marijuana and tobacco use across studies.[3,21] However, individuals who smoked both marijuana and tobacco were found to have greater prevalence of respiratory symptoms than those who smoked only tobacco. Unfortunately, information regarding the amount of marijuana smoked per day or week was not available. A more detailed analysis of the incremental impact of marijuana smoking on respiratory health is still needed. Nonetheless, the generally high prevalence of tobacco use among marijuana smokers appears to pose increased risk for respiratory illness due to potential additive effects of smoking both substances.[15,22]

Four methodological limitations warrant mention regarding the marijuana use information available from NHANES III. First, only three questions about marijuana use were included in the survey. No information was available regarding the frequency and amount used per day, nor are there specific questions on the history of marijuana use, such as the total number of years of use. Although we attempted to exclude casual users by limiting the sample to individuals who used marijuana more than 100 times, the current measure of days used in the past month provides only an estimate of an individual's marijuana use. Although there is no evidence that the measure is biased, the measure lacks the detail and specificity of measures of tobacco use. The fact that the 1 or more days of use in the past month alone was significantly associated with so many respiratory symptoms is somewhat surprising, and suggests that a more detailed assessment of use is needed to provide an optimal dose-response relationship. Second, the illegal nature of marijuana use may have led to underreporting, as these data were based on self-report. However, this would result in a greater number of marijuana users being classified as nonusers and tobacco users, and thus decrease the chance of finding differences between marijuana users and the comparison groups. Third, no information was available on the modality of marijuana use. Although the method of use of marijuana is overwhelmingly smoking, it is possible that in the current sample marijuana was used in other manners (e.g., ingestion). Finally, the sample was restricted to adults age 20 to 59 because NHANES III did not ask individuals 60 and older drug use questions. Thus, the marijuana-related respiratory effects correspond to a relatively young population, particularly for the marijuana-smoking groups who were found to be younger than the tobacco-only smokers and nonusers. Although the current analyses controlled for age, rates of respiratory problems would be expected to be higher for an older population of marijuana users. As a whole, these limitations suggest that the findings are conservative estimates of marijuana's respiratory effects.

In summary, marijuana use was associated with increased risk of many respiratory symptoms that are associated with disorders common to tobacco use such as chronic bronchitis, chronic obstructive pulmonary disease, and cancer.[20,23,24] In addition, marijuana smoking may increase risk of respiratory exposure by infectious organisms, such as fungi and molds, as cannabis plants are contaminated with a range of fungal spores.[25,26] Because more than 2 million adult Americans are heavy marijuana smokers,[3] these risks represent a potentially large health burden. Marijuana smokers use more medical services for respiratory problems, and such demands are likely to increase as the population of heavy marijuana smokers ages.[14] Efforts to prevent and reduce marijuana use, such as advising patients to quit and providing referrals for support and assistance, may have substantial public health benefits.[27]

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REFERENCES

1 **Hall W, Johnston L, Donnelly N.** Epidemiology of cannabis use and its consequences. In: Kalant H, Corrigal WA, Hall H, Smart R, eds. The

Health Effects of Cannabis. Toronto, Ontario: Centre for Addiction and Mental Health; 1999:69–126.
2. **SAMHSA.** Summary of Findings from the 1998 National Household Survey on Drug Abuse. Rockville, MD: U.S. Department of Health and Human Services; 1999.
3. **SAMHSA.** National Household Survey on Drug Abuse, 1998 [computer file]. 2nd ICPSR version. Research Triangle Park, NC: Research Triangle Institute, Inter-university Consortium for Political and Social Research; 2000.
4. **Hoffmann D, Brunnemann KD, Gori GB, Wynder EL.** On the carcinogenicity of marijuana smoke. In: Runeckles VC, ed. Recent Advances in Phytochemistry. New York, NY: Plenum Press; 1975.
5. **Sparacino CM, Hyldburg PA, Hughes TJ.** Chemical and biological analysis of marijuana smoke condensate. In: Chiang CN, Hawks RL, eds. Research Findings on Smoking of Abused Substances (NIDA Research Monograph No. 99). Washington, DC: US Government Printing Office; 1990:121–40.
6. **Matthias P, Tashkin DP, Marques-Magallanes JA, Wilkins JN, Simmons MS.** Effects of varying marijuana potency on deposition of tar and delta9-THC in the lung during smoking. Pharmacol Biochem Behav. 1997;58:1145–50.
7. **Simmons MS, Tashkin DP.** The relationship of tobacco and marijuana smoking characteristics. Life Sci. 1995;56:2185–91.
8. **Tashkin DP, Gliederer F, Rose J, et al.** Effects of varying marijuana smoking profile on deposition of tar and absorption of CO and delta 9 THC. Pharmacol Biochem Behav. 1991;40:651–6.
9. **Wu TC, Tashkin DP, Djahed B, Rose JE.** Pulmonary hazards of smoking marijuana as compared with tobacco. N Engl J Med. 1988;318:347–51.
10. **Tashkin DP, Coulson AH, Clark VA, Simmons M, Bourque LB, Duann S.** Respiratory symptoms and lung function in habitual heavy smokers of marijuana alone, smokers of marijuana and tobacco, smokers of tobacco alone, and nonsmokers. Am Rev Respir Dis. 1987;135:209–16.
11. **Sherrill DL, Krzyzanowski M, Bloom JW, Lebowitz MD.** Respiratory effects of non-tobacco cigarettes: a longitudinal study in general population. Int J Epidemiol. 1991;20:132–7.
12. **Tashkin DP.** Cannabis effects on the respiratory system. In: Kalant H, Corrigal WA, Hall H, Smart R, eds. The Health Effects of Cannabis. Toronto, Ontario: Centre for Addiction and Mental Health; 1999:311–46.
13. **Taylor DR, Poulton R, Moffitt TE, Ramankutty P, Sears MR.** The respiratory effects of cannabis dependence in young adults. Addiction. 2000;95:1669–77.
14. **Polen MR, Sidney S, Tekawa IS, Sadler M, Friedman GD.** Health care use by frequent marijuana smokers who do not smoke tobacco. West J Med. 1993;158:596–601.
15. **Fligiel SG, Roth MD, Kleerup ED, Barsky SH, Simmons MS, Tashkin DP.** Tracheobronchial histopathology in habitual smokers of cocaine, marijuana, and/or tobacco. Chest. 1997;112:319–26.
16. **Roth MD, Arora A, Barsky SH, Kleerup EC, Simmons M, Tashkin DP.** Airway inflammation in young marijuana and tobacco smokers. Am J Respir Crit Care Med. 1998;157:928–37.
17. **Gong H Jr, Fligiel S, Tashkin DP, Barbers RG.** Tracheobronchial changes in habitual, heavy smokers of marijuana with and without tobacco. Am Rev Respir Dis. 1987;136:142–9.
18. **National Center for Health Statistics.** Plan and Operation of the Third National Health and Nutrition Examination Survey, 1988–94. Vital Health Stat 1. 1994; No. 32:1–407.
19. **Pauwels RA, Buist S, Calverley PMA, Jenkins CR, Hurd SS, GOLD Scientific Committee.** Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. Am J Respir Crit Care Med. 2001;163:1256–76.
20. **Bloom JW, Kaltenborn WT, Paoletti P, Camilli A, Lebowitz MD.** Respiratory effects of non-tobacco cigarettes. Br Med J. 1987;295:1516–8.
21. **Moore BA, Budney AJ.** Tobacco smoking in marijuana dependent outpatients. J Subst Abuse. 2001;13:585–98.
22. **Barsky SH, Roth MD, Kleerup EC, Simmons M, Tashkin DP.** Histopathologic and molecular alterations in bronchial epithelium in habitual smokers of marijuana, cocaine, and/or tobacco. J Natl Cancer Inst. 1998;90:1198–205.
23. **Mao L, Oh Y.** Does marijuana or crack cocaine cause cancer? J Natl Cancer Inst. 1998;90:1182–4. Editorial.
24. **Zhang ZF, Morgenstern H, Spitz MR, et al.** Marijuana use and increased risk of squamous cell carcinoma of the head and neck. Cancer Epidemiol Biomarkers Prev. 1999;8:1071–8.
25. **Verweij PE, Kerremans JJ, Voss A, Meis JF.** Fungal contamination of tobacco and marijuana. JAMA. 2000;284:2875.
26. **Marks WH, Florence L, Lieberman J, et al.** Successfully treated invasive pulmonary aspergillosis associated with smoking marijuana in a renal transplant recipient. Transplantation. 1996;61:1771–4.
27. **Fagerstrom K.** The epidemiology of smoking: health consequences and benefits of cessation. Drugs. 2002;62(suppl 2):1–9.

BRITISH LUNG FOUNDATION

A SMOKING GUN?

CONTENTS

THE IMPACT OF CANNABIS SMOKING ON RESPIRATORY HEALTH

INTRODUCTION

Cannabis is the most widely consumed illegal drug in the UK. Recent media coverage has focussed on the public and political debate around issues such as reclassification of cannabis and how the police should deal with those who sell or are found to be in possession of varying amounts of the substance.

What has been consistently missing from the public debate on the safety or otherwise of cannabis as compared to other illegal drugs is the impact of smoking cannabis on respiratory health and the possible link with nicotine addiction in the form of tobacco smoking.

This report sets out to identify existing scientific and medical research on cannabis smoking and respiratory health. It identifies what conclusions it is possible to draw from the existing evidence and highlights gaps in our knowledge which require further research.

The aim of this report is to ensure that those taking part in the debate on cannabis and those engaged in promoting health education to our young people have the fullest possible information on the medical and scientific evidence of the impact of cannabis smoking on respiratory health.

Many young people will make decisions about whether they wish to use cannabis or not – regardless of its legal status. We have a duty to ensure that they do so with full knowledge of the risks associated with smoking cannabis.

Cannabis sativa leaf
Image by LPX, © 2002 Erowid.org

SUMMARY OF FINDINGS AND RECOMMENDATIONS

While there is a wealth of research into the health impact of tobacco smoking, there is relatively little on the effects of cannabis smoking.

Research investigating whether the inhalation of cannabis smoke causes damage to the lungs and airways focuses on whether this effect is independent of the effects of tobacco smoke or not. In general, the studies indicate that there is an increased negative health impact on those who smoke cannabis compared to those who do not smoke at all. When cannabis is smoked together with tobacco then the effects are additive. However, what is not clear is whether it is the addition of the cannabis or the tobacco which is more harmful or whether this is the result of the combined effects of equally harmful substances.

Some key findings emerge from the research:

• The cannabis smoked today is much more potent that that smoked in the 1960s. The average cannabis cigarette smoked in the 1960s contained about 10mg of tetrahydrocanabinol (THC), the ingredient which accounts for the psychoactive properties of cannabis, compared to 150mg of THC today. This means that longitudinal studies carried out in the 1960s and 1970s may not be indicative of the effects of cannabis cigarettes smoked today.

• Studies comparing the clinical effects of habitual cannabis smokers versus non-smokers demonstrate a significantly higher prevalence of chronic and acute respiratory symptoms such as chronic cough and sputum production, wheeze and acute bronchitis episodes.

• 3-4 Cannabis cigarettes a day are associated with the same evidence of acute and chronic bronchitis and the same degree of damage to the bronchial mucosa as 20 or more tobacco cigarettes a day.

• Cannabis tends to be smoked in a way which increases the puff volume by two-thirds and depth of inhalation by one-third. There is an average fourfold longer breath-holding time with cannabis than with tobacco. This means that there is a greater respiratory burden of carbon monoxide and smoke particulates such as tar than when smoking a similar quantity of tobacco.

• Cannabis smoking is likely to weaken the immune system. Infections of the lung are due to a combination of smoking-related damage to the cells lining the bronchial passage (the fine hair-like projection on these cells filter out inhaled micro-organisms) and impairment of the principal immune cells in the small air sacs caused by cannabis.

• The evidence concerning a possible link between cannabis smoking and Chronic Obstructive Pulmonary Disease (COPD) has not yet been conclusively established. A number of studies indicate a causal relationship between the two whereas others contradict these findings.

• Research linking cannabis smoking to the development of respiratory cancer exists although there have also been conflicting findings. Not only does the tar in a cannabis cigarette contain many of the same known carcinogens as tobacco smoke but the concentrations of these are up to 50% higher in the smoke of a cannabis cigarette. It also deposits four times as much tar on the respiratory tract as an unfiltered cigarette of the same wieght. Smokers of cannabis and tobacco have shown a greater increase in cellular abnormalities indicating a cumulative effect of smoking both.

• The THC in cannabis has been shown to have a short term bronchodilator effect. This has lead to suggestions that THC may have therapeutic benefits in asthma. However, the noxious gases, chronic airway irritation or malignancy after long term use associated with smoking would seem likely to negate these benefits.

RECOMMENDATIONS

From a clinical perspective the main effects of smoking cannabis on the lungs are increased risk of pulmonary infections and respiratory cancers. Benzpyrene, a known constituent of the tar of cannabis cigarettes has been shown to promote alterations in one of the most common tumour suppressor genes, p53, hence facilitating the development of respiratory cancer. Gene p53 is thought to play a role in 75% of all lung cancers.

The British Lung Foundation recommends a public health education campaign aimed at young people to ensure that they are fully aware of the increased risk of pulmonary infections and respiratory cancers associated with cannabis smoking.

The increased potency of the cannabis smoked today compared to the cannabis smoked twenty-thirty years ago suggests that earlier studies may underestimate the effects of cannabis smoking. In addition the lack of conclusive evidence concerning the link between cannabis smoking and Chronic Obstructive Pulmonary Disease (COPD) underlines the need for further research.

The British Lung Foundation recommends that further research is undertaken to take into account the increased potency of today's cannabis and to establish what link (if any) there is between COPD and cannabis smoking.

THE EFFECT OF CANNABIS SMOKING ON RESPIRATORY HEALTH

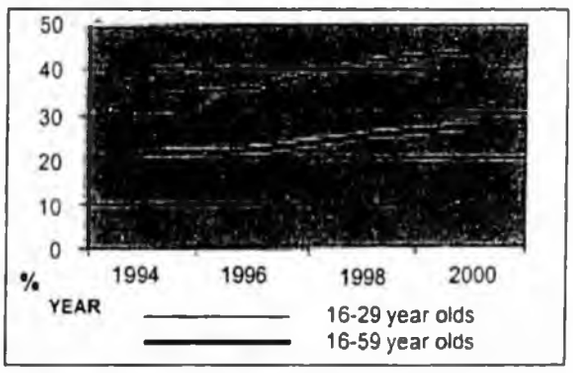
1. SCOPE OF THIS REPORT AND BACKGROUND

This report surveys the current medical and scientific research into the direct effects of smoking cannabis – both alone and in combination with tobacco – on the smoker's respiratory health. The report is divided into two parts the first part outlines the constituents of cannabis, the amount of cannabis smoked and the dynamics of smoking cannabis compared with tobacco. The second part surveys the findings of the existing published research into the biological effects on respiratory health of cannabis which is smoked, both in the short-term and long-term. Full references to the individual publications are included at the end of the report.

Prevalence of cannabis smoking in UK

Cannabis is the most widely consumed illegal drug in the UK by gross weight (it is estimated that 486,224kg were consumed in 1998 – this is roughly the weight of 7,000 people put together)[1]. It is often smoked together with tobacco although it can also be ingested in the form of 'hash cookies' or taken as cannabis oil.

Percentage of people in England and Wales to have 'ever' taken cannabis



Source: Annual Report on the UK Drug Situation 2001, Drug Scope, London

Constituents of cannabis

The smoke of the same quantity of cannabis and tobacco smoke contains the same constituents and quantities of chemicals known to be toxic to respiratory tissue as tobacco smoke, apart from nicotine[2,3]. This includes carbon monoxide, bronchial irritants, tumour initiators, tumour promoters and cancer-producing agents[4]. Tar from cannabis cigarettes contains up to 50% higher concentrations of the carcinogens benzanthracenes and benzpyrenes[5] than tobacco smoke[6,7,8].

There are three main species of cannabis, Cannabis sativa, Cannabis indica and Cannabis ruderalis. The plant is also known as hemp. As a drug of abuse it is either taken in the form of herbal cannabis (marijuana) which consists of the dried leaves and female flower heads or as cannabis resin (hashish) which is the resin secreted by the leaves and flower heads and may be compressed into blocks.

Cannabis contains over 400 compounds including 60 different cannabinoids (plant derivatives unique to cannabis) the most abundant of which is tetrahydrocanabinol (THC). This accounts for the psychoactive properties of cannabis. It is highly soluble in fats and rapidly absorbed in the respiratory and gastrointestinal tract lining. The intoxicating effects depend on the way in which cannabis is taken – blood concentrations after oral ingestion are only about 25-30% to those obtained when cannabis is smoked[9]. About 50% of the THC in a cigarette of herbal cannabis is inhaled in the mainstream smoke, nearly all of which is absorbed through the lungs, rapidly entering the bloodstream and reaching the brain within minutes.

A greater amount of tar is inhaled from the cannabis cigarette butt rather than its tip. There is also a higher concentration of carbon monoxide and THC in the smoke from the butt end. The effect of the carbon monoxide is to produce high concentrations of carboxyhaemoglobin in the blood[10], which interferes with the transport of oxygen around the body. This is likely to be due to decreased filtration of insoluble particles and differential burn rates. The clinical implication of this is that smoking cannabis cigarettes down to the butt is more harmful than smoking a similar quantity of cannabis cigarettes to a longer butt length.

Other cannabinoids which interact with THC although are not actually psychoactive in themselves are cannabidiol and cannabinol. The amounts and proportions of the various cannabinoids in each plant vary from strain to strain, and can be adjusted by breeding.

Caption

Amount of Cannabis smoked

THC is present in varying concentrations in the stalks, leaves, flowers and seeds of the plant as well as the resin secreted by the female plant. This has an impact on the potency of different cannabis preparations. Furthermore, sophisticated cultivation has increased the potency of cannabis products over the last 20 years. Whereas the average cannabis cigarette of the 1960s and 1970s contained about 10mg of THC today it may contain up to 150mg of THC, or 300mg if laced with hashish oil[11]. This means that the modern cannabis smoker may be exposed to greater doses of THC than in the 1960s and 1970s[12 13], which in turn means that studies investigating the long-term effects of smoking cannabis have to be interpreted cautiously.

Cannabis and tobacco

Cannabis resin, the most commonly used form of cannabis in the United Kingdom, is often smoked mixed with tobacco. Although this can confound research on the respiratory effects of smoking pure cannabis, the well-documented consequences of smoking tobacco need therefore also be considered in the evaluation of the effects of cannabis smoking on respiratory health.

It has been calculated that smoking 3-4 cannabis cigarettes a day is associated with the same evidence of acute and chronic bronchitis and the same degree of damage to the bronchial mucosa as 20 or more tobacco cigarettes a day[14 15].

Dynamics of smoking cannabis vs tobacco

Significant differences have been noted in the dynamics of smoking cannabis and tobacco including an approximately two-thirds larger puff volume, a one-third greater depth of inhalation and a fourfold longer breath-holding time with cannabis than with tobacco[16]. This means that there is a greater respiratory burden of carbon monoxide and smoke particles than when smoking a similar quantity of tobacco. Similarly with tar, it has been estimated that smoking a cannabis cigarette results in a fourfold greater amount of tar inhaled and retention in the respiratory tract or one-third more tar than smoking a tobacco cigarette[17] (due to the longer breath holding time for cannabis and differences in filtering characteristics of the two types of cigarette).

2. EFFECTS OF SMOKING CANNABIS ON RESPIRATORY HEALTH

The British Medical Association estimates that smoking a cannabis cigarette containing only herbal cannabis leads to an approximately fivefold increase in blood carboxyhaemoglobin concentration (which is formed by carbon monoxide reacting with the oxygen carrying particle haemoglobin in red blood cells, thereby reducing the transport of oxygen.)[18].

Within minutes of smoking cannabis significant decreases in airway resistance and increases in specific airway conductance have been observed in healthy individuals, which persist for at least one hour[19]. This is caused by THC which has subsequently been investigated for its possible therapeutic use in diseases such as asthma (see below).

From a clinical perspective, the main effects of smoking cannabis on the lungs are pulmonary infections and respiratory cancer.

Immune responses

Several studies indicate that smoking cannabis has a negative effect on the immune system. THC has been shown to decrease the function of several white blood cells (T cells, natural killer cells and macrophages) that help protect the lungs against micro-organisms[20]. Alveolar macrophages in particular are important in regulating lung immunity and their central location in the lung's air sacs means that they are exposed to very large amounts of cannabis smoke.

Twice as many alveolar macrophages as normal have been found to be produced in the lungs of cannabis smokers and three times as many in cannabis & tobacco smokers[21]. These macrophages have been found to be considerably larger and contain more ingested particles than is the case in non-smokers[22]. They are also functionally impaired in that they are less likely to kill tumour target cells[23] and a variety of common fungal organisms and bacteria such as *Candida albicans*[24] and *Candida pseudotropicalis*[25] (can cause thrush), *Legionella pneumophila*[26] (can cause pneumonia) and *Staphylococcus aureus*[27] (can cause food poisoning). Macrophagal ability to produce a variety of chemicals that play a key role in the immune response to infection and malignancy has also shown to be impaired[28].

A decreased immune function may explain why there appears to be an association between cannabis use and opportunistic bacterial and fungal pneumonias in patients with cancer[29] and transplant[30, 31] patients as well as those with human immunodeficiency virus (HIV) infection[32].

Inflammation

Visual inspection of the central airway of cannabis smokers has shown increased redness, swelling and mucous secretion by comparison to non-smokers[33]. Smoking tobacco in conjunction with cannabis appears to have an additive effect[34, 35]. An increase in the number and size of small blood vessels and replacement of the normal ciliated surface lining cells (with hair-like projections) by mucus-secreting cells have also been observed. This may explain why cannabis smokers tend to suffer from chronic cough and phlegm as there may not be sufficient ciliated cells to remove the mucus from the airways.

Caption

Chronic Obstructive Pulmonary Disease, COPD

COPD is an umbrella term for conditions such as emphysema and chronic bronchitis. The evidence that COPD is mostly smoking related is already well established. Currently more than 32,000 people die from COPD every year in the UK.