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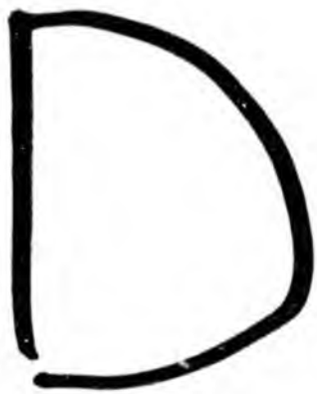

MARIJUANA AND PUBLIC HEALTH

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.*

AMERICAN JOURNAL OF
Respiratory Cell and
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

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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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Introduction

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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)

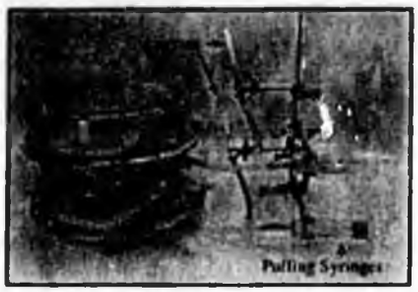
and monochlorobimane (MCB) were from Molecular Probes (Eugene, OR). Propidium iodide, ascorbic acid, and pyrrolidinedithiocarbamate (PDTC) were from Sigma (St. Louis, MO). The Promega (Madison, WI) Apoptosis Assay Kit was used for cytotoxicity evaluation.

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).

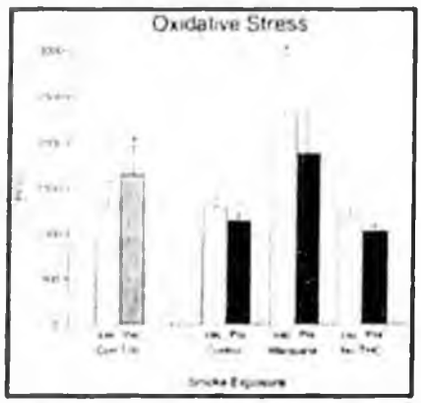

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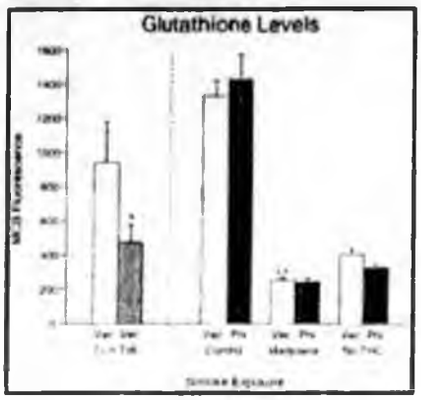
Figure 2. Accumulation of ROS in cultured endothelial ECV 304 cells exposed to smoke from tobacco (Tob) or MJ cigarettes. Cells transfected with either hygromicin-resistance vector DNA (Vec) or human peroxiredoxin-B (Prx) DNA were loaded with DCF before smoke exposure. After exposure to smoke from two 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.

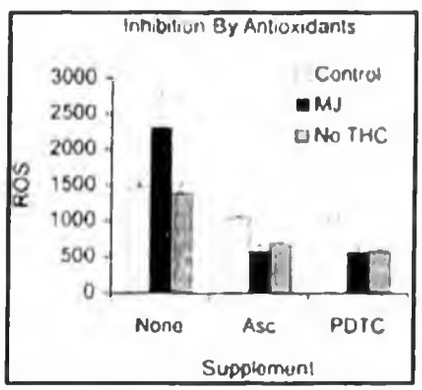

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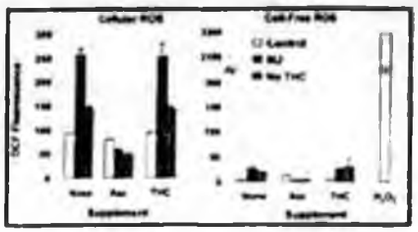
Figure 4. ROS accumulation (expressed as relative normalized DCF fluorescence) inhibited by 1 mM Asc or 1 mM PDTC. Values are means of five determinations ± SEM. *P* values were < 0.05 comparing ascorbate- and PDTC-treated samples with corresponding untreated samples by Student's *t* test.

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.

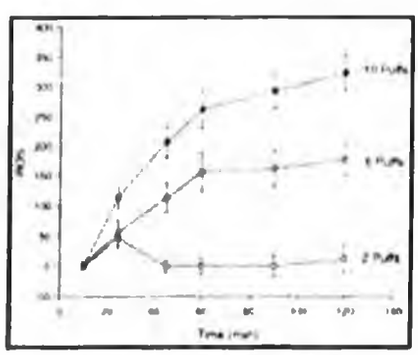

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Figure 6. Time course and dose-response for MJ smoke-induced ROS accumulation. ECV 304 cells were exposed to indicated number of 50-ml smoke puffs and chamber was then sealed. Total time for smoke exposure was 10 min for each sample. Normalized DCF 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

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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.)

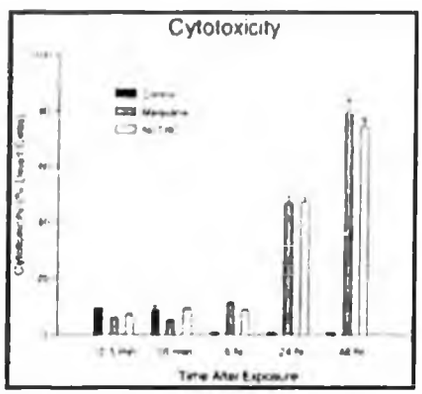

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Figure 7. Time course for ECV 304 cell death following 10 min exposure to smoke from a single MJ cigarette. Cytotoxicity was quantitated as described in MATERIALS AND METHODS. Values represent means of six determinations ± SEM. The experiment was repeated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

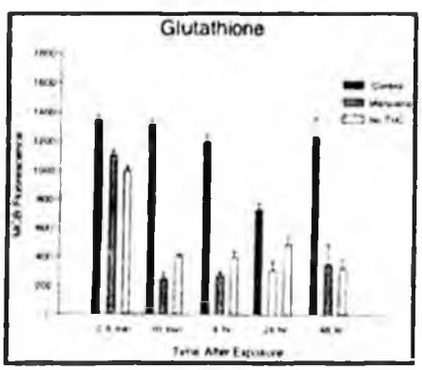

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Figure 8. Time course for GSH levels measured as MCB fluorescence following 10 min exposure to smoke from a single cigarette. Values represent means of six determinations ± SEM. Experiments were repeated twice with similar results.

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.

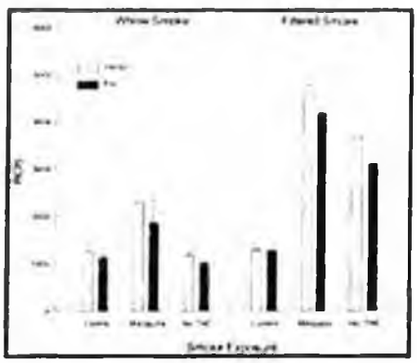

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Figure 9. ROS accumulation following exposure to gaseous-phase MJ cigarette smoke. Smoke from two cigarettes was filtered through Cambridge filters to remove particulates before exposure to ECV 304 cells. Values represent means of 34 determinations ± 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

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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

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

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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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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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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

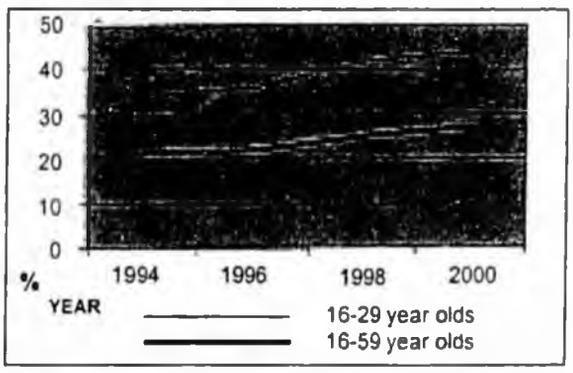
1. SCOPE OF THIS REPORT AND BACKGROUND

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.

There is a lot of evidence that the long-term effects of habitual cannabis smoking include a significantly higher prevalence of chronic and acute respiratory symptoms such as chronic cough, chronic sputum production, wheeze and acute bronchitis episodes[36 37 38 39] by comparison to non-smokers. There is evidence of a cumulative effect of smoking cannabis and tobacco in two studies[40 41] although not in another[42].

Some studies indicate that young cannabis smokers may be at risk of developing obstructive airway disease in later life[43 44]. This is supported by animal studies in which dogs[45], monkeys[46] and rats[47 48] have been exposed to varying doses of cannabis for 12-30 months and suffered damage to the smaller airway which is a major site of injury in tobacco-related COPD as well as acute and chronic pneumonia. However, other studies contradict a causal relationship between smoking cannabis and COPD[49 50 51]. Regular cannabis smoking has been associated with emphysema in some studies[52 53] but not so in others[54 55]. These studies are, however non-conclusive as they did not distinguish between smoking only cannabis and smoking cannabis together with tobacco. They also only involved a relatively small number of participants. A further study involving rats exposed to increasing doses of cannabis for 6 months did not display any evidence of emphysema although this was the case in rats exposed to tobacco smoke[56].

Further research in this area is necessary to provide more conclusive results.

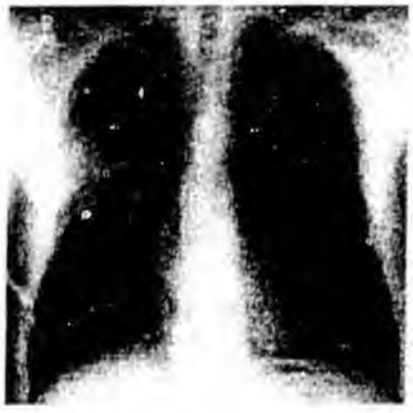
Respiratory cancer

More people die of lung cancer in the UK than from any other cancer – more than 34,000 people die every year in the UK.

As already mentioned, the tar from a cannabis cigarette contains many of the same (and even higher concentrations of) carcinogenic compounds found in cigarette smoke and deposits four times as much tar on the respiratory tract in comparison to an unfiltered cigarette of the same weight. This amplifies the exposure of cannabis smokers to particles that are known to be involved in the development of lung cancer.

There are a number of case studies (over 75) reporting cancers of the aero-digestive tract in young adults with a history of cannabis use [57 58 59 60 61 62 63] which are rare in adults under the age of 60 although the exact cause of these cancers is not clearly identifiable as many of the cases also used alcohol and tobacco. A retrospective study undertaken in the United States[64] did not find a link between smoking cannabis and tobacco-related cancers but it has been suggested that the time span investigated may not have been sufficient to study the long-term effects[65]. There is clearly a need for more epidemiological research in this area.

As it is, the development of cancer is a multistep process comprised of sequential alterations in genomic DNA (the genetic material contained in



Caption

cells) which are promoted and/ or interact with environmental and genetic factors. It is therefore often not clear what the exact cause of a particular cancer may be.

Research suggests that cannabis might contribute to cancer by manipulating the genetic makeup of cells. For lung cells to transform into cancerous cells, a specific combination of genes that regulate cell growth must be activated (in the case of oncogenes) and/ or mutate (in the case of tumour suppressor genes). THC has been shown to increase the production of a chemical particle (CYP1A1) that is responsible for causing benzpyrene (a constituent of cannabis smoke) to promote alterations in one of the most common

tumour suppressor genes, p53 thereby facilitating the development of respiratory cancer[66 67]. The gene p53 is thought to play a role in 75% of all lung cancers[68] and has been found to be expressed in 11% of individuals who smoke cannabis and tobacco[69]. Other studies looking at the effect of tar in cannabis smoke on animals[70 71 72] also indicate a correlation between cannabis and respiratory cancer.

An increase in cellular abnormalities has also been observed in cannabis smokers by comparison to non-smokers[73 74]. Abnormalities include an increase in the production of mucus producing cells (goblet cells) and reserve cells, transformation of ciliated cells into cells that resemble skin (squamous metaplasia), an accumulation of inflammatory cells and abnormalities in the cell nuclei. Nuclear alterations and squamous metaplasia have been described as precursors to the development of lung cancer in tobacco smokers[75]. In addition, smokers of cannabis and tobacco have shown a greater increase in cellular abnormalities indicating an additive effect.

Oral soft tissues

The effects of tobacco smoking on oral soft tissues have been well documented but there is little data available on the effects of cannabis smoking. However, there are some case reports that heavy cannabis use is associated with cancer of the tongue[76 77], larynx[78] and lung[79].

Other lung conditions

There have been isolated reports of spontaneous pneumothorax (breaches of the lungs causing gas in the lung cavity leading to compression of the lungs) and pneumomediastinum (breaches of the lungs causing gas in the cavities of the respiratory tract) associated temporally with the use of cannabis[80 81 82] which are thought to be caused by deep inhalation of cannabis smoke to enhance absorption of THC and hence the intoxication caused by it[83]. Deep inhalation coupled with direct pulmonary toxicity from components in cannabis in susceptible smokers has also been implicated with the formation of large lung bullae (watery blisters) in the upper respiratory area[84].

Contamination of cannabis

There has been a report of chronic cannabis smoking leading to necrotizing pulmonary granulomata (these are changes in the lungs at cellular level which may prevent the lungs from working as they should)[85] as a result of possible fungal contamination of cannabis.

Health care utilization by cannabis smokers

This has been assessed in an epidemiological study in which cannabis smokers who had never smoked tobacco were compared with non-smokers[86]. Frequent cannabis smokers showed a slight increase in outpatient visits for respiratory and other illnesses compared with non-smokers as well as a small increased risk of hospitalization.

Potential therapeutic benefits

The bronchodilator effects of THC in cannabis have also been found in the case of asthmatics with mild to moderate airway obstruction although not to the same extent as in healthy people[87]. This has led to suggestions that THC might 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 over the long term. Oral intake of THC has also shown to cause unwanted side-effects such as central nervous system intoxication and an excessive increase in heart rate[88 89]. Furthermore, tolerance to the bronchodilator effects of THC has been demonstrated after several weeks of use[90].

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Pulmonary hazards of smoking marijuana as compared with tobacco.

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To compare the pulmonary hazards of smoking marijuana and tobacco, we quantified the relative burden to the lung of insoluble particulates (tar) and carbon monoxide from the smoke of similar quantities of marijuana and tobacco. The 15 subjects, all men, had smoked both marijuana and tobacco habitually for at least five years. We measured each subject's blood carboxyhemoglobin level before and after smoking and the amount of tar inhaled and deposited in the respiratory tract from the smoke of single filter-tipped tobacco cigarettes (900 to 1200 mg) and marijuana cigarettes (741 to 985 mg) containing 0.004 percent or 1.24 percent delta 9-tetrahydrocanabino As compared with smoking tobacco, smoking marijuana was associated with nearly fivefold greater increment in the blood carboxyhemoglobin level, an approximately threefold increase in the amount of tar inhaled, and retention i the respiratory tract of one third more inhaled tar (P less than 0.001). Significant differences were also noted in the dynamics of smoking marijuan and tobacco, among them an approximately two-thirds larger puff volume, a one-third greater depth of inhalation, and a fourfold longer breath-holding tir with marijuana than with tobacco (P less than 0.01). Smoking dynamics and the delivery of tar during marijuana smoking were only slightly influenced b the percentage of tetrahydrocanabinol. We conclude that smoking marijuana, regardless of tetrahydrocannabinol content, results in a substantially greater respiratory burden of carbon monoxide and tar than smoking a similar quanti of tobacco.

PMID: 3340105 [PubMed - indexed for MEDLINE]

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Pulmonary complications of smoked substance abuse.

Tashkin DP.

Department of Medicine, University of California, School of Medicine, Los Angeles 90024.

After tobacco, marijuana is the most widely smoked substance in our society Studies conducted within the past 15 years in animals, isolated tissues, and humans indicate that marijuana smoke can injure the lungs. Habitual smokin of marijuana has been shown to be associated with chronic respiratory tract symptoms, an increased frequency of acute bronchitic episodes, extensive tracheobronchial epithelial disease, and abnormalities in the structure and function of alveolar macrophages, key cells in the lungs' immune defense system. In addition, the available evidence strongly suggests that regularly smoking marijuana may predispose to the development of cancer of the respiratory tract. "Crack" smoking has become increasingly prevalent in our society, especially among habitual smokers of marijuana. New evidence is emerging implicating smoked cocaine as a cause of acute respiratory tract symptoms, lung dysfunction, and, in some cases, serious, life-threatening act lung injury. A strong physician message to users of marijuana, cocaine, or bc concerning the harmful effects of these smoked substances on the lungs and other organs may persuade some of them, especially those with drug-related respiratory complications, to quit smoking.

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Concurrent tobacco and marijuana use may hamper cigarette smoking cessation

Tobacco smokers who also smoke marijuana may be less likely to quit smoking tobacco and less likely to try to quit than those who do not smoke marijuana, according to a study by researchers at The Johns Hopkins University. Dr. Daniel Ford and colleagues interviewed 431 adults who had reported being current tobacco smokers in a study conducted 13 years earlier. In the baseline interview, more than 40 percent of the participants reported having smoked marijuana, with more than 25 percent reporting using it within the previous 30 days (recent use) and nine percent reported daily use for two weeks or more. At the 13-year follow-up, 79 percent of participants who had reported smoking tobacco at baseline were still smoking it.

Recent and daily use of marijuana at baseline were more predictive of continued tobacco smoking than use of marijuana more than a month prior to baseline. Participants who reported recent use were about twice as likely to continue to smoke tobacco 13 years later compared those who did not use marijuana within the preceding 30 days. Those who reported daily marijuana use were over three times more likely to still smoke tobacco. About 66 percent of recent marijuana users reported trying to quit tobacco during the following 13 years compared to 80 percent of those who had never used marijuana.

WHAT IT MEANS: These findings suggest that marijuana use may interfere with tobacco cessation attempts. However, there is no evidence that marijuana use can substitute for tobacco use.

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This study, funded by the National Institute on Drug Abuse, was published in the August 2002 issue of Drug and Alcohol Dependence.

The National Institute on Drug Abuse (NIDA) is a component of the National Institutes of Health, U.S. Department of Health and Human Services. NIDA supports more than 85 percent of the world's research on the health aspects of drug abuse and addiction. The Institute carries out a large variety of programs to ensure the rapid dissemination of research information and its implementation in policy and practice. Fact sheets on the health effects of drugs of abuse and other topics are available in English and Spanish. These fact sheets and further information on NIDA research and other activities can be found on the NIDA home page at http://www.drugabuse.gov.

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Science Blog

April 2003

From NIH/National Institute on Drug Abuse

Concurrent tobacco and marijuana use may hamper cigarette smoking cessation

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The pharmacological activity of inhalation exposure to marijuana smoke in mice

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Abstract

Although the majority of cannabinoid users smoke marijuana, the preponderance of laboratory animal research is based on administration of Δ^9-tetrahydrocannabinol (Δ^9-THC) or other cannabinoid agents via injection. The aim of the present study was to evaluate the impact of inhaling marijuana, or ethanol-extracted placebo smoke in the mouse model of cannabinoid activity by assessing inhibition of spontaneous activity, antinociception, catalepsy, and body temperature. In order to determine dosimetry, blood levels of Δ^9-THC were obtained following either marijuana exposure or intravenous injection of Δ^9-THC. Inhalation exposure to marijuana produced dose-related increases in antinociception and catalepsy, with estimated ED_{50} doses of Δ^9-THC of 2.4 and 3.8 mg/kg, respectively. However, hypothermia and locomotor depression occurred in both the placebo- and marijuana-exposed mice. The CB_1 receptor antagonist, SR 141716A antagonized the antinociceptive effects of marijuana (AD_{50}=0.6 mg/kg), but only slightly decreased marijuana-induced catalepsy, and failed to alter either the hypothermic or locomotor depressive effects. In contrast, SR 141716A antagonized the antinociceptive, cataleptic, and hypothermic effects of intravenously administered Δ^9-THC in mice that were exposed to air alone, though all subjects exhibited locomotor depression, possibly related to the restraint. In accordance with reports of others, these data suggest that exposure to smoke alone has

pharmacological consequences. Our findings also indicate that marijuana-induced antinociception is mediated through a CB_1-receptor mechanism of action and are consistent with the notion that Δ^9-THC is mainly responsible for this effect.

Author Keywords: Marijuana smoking; Cannabinoid; Δ^9-THC; SR 141716A; Antinociception; Analgesia; Catalepsy; Hypothermia

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Researchers At UCLA's Jonsson Cancer Center Report Smoking Marijuana May Increase Risk Of Head And Neck Cancers

Researchers at UCLA's Jonsson Cancer Center are reporting, for the first time, that smoking marijuana may increase the risk of head and neck cancers.

Results of a . epidemiological study of more than 340 people are outlined in an article published in today's (Dec. 17) edition of the peer-reviewed journal Cancer Epidemiology Biomarker and Prevention.

Previous laboratory and clinical studies have indicated that marijuana use may be related to molecular alterations in the respiratory tract, changes that may lead to cancer. This is the first study to examine whether smoking marijuana increases risk of head and neck cancers, said Dr. Zuo-Feng Zhang of UCLA's Jonsson Cancer Center, a professor in the Department of Epidemiology in the UCLA School of Public Health and director of the cancer epidemiology training program at UCLA.

"Most people don't think about marijuana in relationship to cancer," said Zhang, lead author of the journal ar' le. "The carcinogens in marijuana are much stronger than those in tobacco. The big message here is that marijuana, like tobacco, can cause cancer."

Zhang studied the relationship between marijuana use and head and neck cancers in 173 patients diagnosed with those diseases. He compared those findings to 176 cancer-free control patients, and found that those who habitually smoked marijuana were at higher risk for head and neck cancers.

The epidemiological data was collected using a structured questionnaire, which queried patients about their histories of tobacco smoking, marijuana smoking and alcohol use. Zhang said researchers were able to evaluate the data on marijuana smoking independently from data on tobacco smoking and alcohol use, which also increase the risk of certain cancers.

The results of the study are particularly important now, Zhang said, as habitual marijuana smokers from the 1960s reach older ages. Because head and neck cancers -- cancers of the mouth, tongue, larynx and pharynx -- take many years to develop, people who smoked large amounts of marijuana in the 1960s may just now be contracting head and neck cancers, Zhang said.

"In the '60s, we had very high numbers of people in their 20s smoking marijuana," Zhang said. "These people are just now getting to the ages at which they will get head and neck cancers. This is the time to study a risk like this."

The more times per day a person smokes marijuana, the greater his or her risk of head and neck cancers, according to the study. Additionally, people who use marijuana habitually for many years also increase their risk of head and neck cancers, Zhang said.

Congressional - M. Moustakas Cerebrovascular disease

"If you smoke a little, your risk increases a little," Zhang said. "If you smoke a lot, your risk increases a lot."

Marijuana is the most commonly used illegal drug in the United States, Zhang said. It is estimated that about 31 percent of the U.S. population 12 years or older has used marijuana, according to the journal article.

Zhang's research builds on previous studies of marijuana and cancer risk. An article by UCLA cancer researchers published in the Aug. 19, 1998, issue of the Journal of the National Cancer Institute stated that habitual smoking of marijuana and crack cocaine causes the same kinds of molecular changes that precede the development of lung cancer in cigarette smokers.

"Now we have evidence that may link marijuana smoking to head and neck cancers," Zhang said. "Many people may think marijuana is harmless, but it's not."

In addition, the epidemiological study and the subsequent journal article also touch on the interplay between marijuana smoking and the genetic defect that prevents DNA from repairing itself. Some marijuana smokers with this genetic defect might not have the ability to repair DNA damage prompted by the habit. Zhang said these people are about 16 times more likely to develop head and neck cancers than non-marijuana smokers whose DNA repair function is operating normally.

Zhang said larger epidemiological studies are needed to replicate the results obtained by UCLA cancer researchers. One such study, funded by the National Institutes of Health, is being conducted now at UCLA.

This story has been adapted from a news release issued by University Of California, Los Angeles Health Sciences.

Cancer Epidemiology Biomarkers & Prevention Vol. 8, 1071-1078, December 1999

Marijuana Use and Increased Risk of Squamous Cell Carcinoma of the Head and Neck[1]

Zuo-Feng Zhang[2], Hal Morgenstern, Margaret R. Spitz, Donald P. Tashkin, Guo-Pei Yu, James R. Marshall, T. C. Hsu and Stimson P. Schantz

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Abstract

Marijuana is the most commonly used illegal drug in the United States. In some subcultures, it is widely perceived to be harmless. Although the carcinogenic properties of marijuana smoke are similar to those of tobacco, no epidemiological studies of the relationship between marijuana use and head and neck cancer have been published. The relationship between marijuana use and head and neck cancer was investigated by a case-control study of 173 previously untreated cases with pathologically confirmed diagnoses of squamous cell carcinoma of the head and neck and 176 cancer-free controls at Memorial Sloan-Kettering Cancer Center between 1992 and 1994. Epidemiological data were collected by using a structured questionnaire, which included history of tobacco smoking, alcohol use, and marijuana use. The associations between marijuana use and head and neck cancer were analyzed by Mantel-Haenszel methods and logistic regression models. Controlling for age, sex, race, education, alcohol consumption, pack-years of cigarette smoking, and passive smoking, the risk of squamous cell carcinoma of the head and neck was increased with marijuana use [odds ratio (OR) comparing ever with never users, 2.6; 95% confidence interval (CI), 1.1–6.6]. Dose-response

relationships were observed for frequency of marijuana use/day (P for trend < 0.05) and years of marijuana use (P for trend < 0.05). These associations were stronger for subjects who were 55 years of age and younger (OR, 3.1; 95% CI, 1.0–9.7). Possible interaction effects of marijuana use were observed with cigarette smoking, mutagen sensitivity, and to a lesser extent, alcohol use. Our results suggest that marijuana use may increase the risk of head and neck cancer with a strong dose-response pattern. Our analysis indicated that marijuana use may interact with mutagen sensitivity and other risk factors to increase the risk of head and neck cancer. The results need to be interpreted with some caution in drawing causal inferences because of certain methodological limitations, especially with regard to interactions.

Introduction

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Marijuana is the second most commonly smoked substance in the United States after tobacco (1 , 2) . It is estimated that 31% of the United States population 12 years or older in 1992 had ever used marijuana (3) . Studies conducted within the past two decades in experimental animals and humans indicate that marijuana smoke can injure the lung and respiratory tract (4) . In humans, habitual smoking of marijuana has been shown to be associated with symptoms of chronic bronchitis, an increased frequency of acute bronchitic episodes, extensive tracheobronchial epithelial histopathology including alterations correlated with the subsequent development of malignancy in tobacco smokers (5) , DNA injury (6) , and abnormalities in the structure and function of alveolar macrophages, key cells in the immune defense system of the lung (7 , 8) . Further evidence also suggests that marijuana may predispose to the development of cancer of the respiratory tract (9) . For example, the tar phase of marijuana smoke contains some of the same carcinogenic compounds found in tobacco smoke, such as phenols and polycyclic aromatic hydrocarbons, including benzo[*a*]pyrene, which is present in ≈50% higher concentration in marijuana tar than in the tar from a comparable amount of unfiltered tobacco (10) . In addition, a single marijuana cigarette deposits four times as much tar in the respiratory tract as that deposited from a single filtered tobacco cigarette of approximately the same weight (11) . The higher content of carcinogenic polycyclic aromatic hydrocarbons in marijuana smoke and the greater deposition of marijuana tar in the lung act together to amplify exposure of the marijuana smoker to carcinogens in the particulate phase. Finally, preliminary *in vitro* studies involving mixed reactions of antigen-presenting dendritic cells and T lymphocytes (12) and *in vivo* studies using a murine model of an immunogenic carcinoma of the lung (12 , 13) suggest that Δ9-tetrahydrocannabinol, the major psychoactive ingredient in marijuana smoke, impairs immune responses to tumor antigens. A recent paper reported that habitual marijuana (and/or cocaine) smokers exhibited more molecular genetic abnormalities than nonsmokers (14) . The study suggested that smoking marijuana and or cocaine, like tobacco smoking, exerts field cancerization effects on bronchial epithelium, which may place marijuana/cocaine smokers at increased risk for the subsequent development of lung cancer.

The above-cited biological evidence pointing to a carcinogenic role for marijuana is supported by several case-series reports, indicating an unexpectedly large proportion of marijuana users among

selected cases of upper aerodigestive tract cancer. Since 1986, a total of 74 anecdotal cases of head and neck cancer with a history of marijuana use have been reported in medical literature (15, 16, 17, 18, 19, 20, 21, 22, 23, 24) . The characteristics of these marijuana-exposed malignancies of the upper aerodigestive tract include young age at diagnosis (<55 years old), extensive field cancerization, and aggressive biological behavior. Although causal inference cannot be made directly from uncontrolled case-series studies, these case reports suggest a need for in-depth epidemiological investigations of the relationship between marijuana use and the risk of cancers of the upper aerodigestive tract.

In the only published epidemiological study of marijuana use and cancer incidence, the authors reported positive associations between lifetime marijuana use (six or more occasions) and both prostate and perhaps cervical cancer among nonsmokers of tobacco cigarettes. No association was observed between marijuana use and all tobacco-related cancers (25) . Unfortunately, the specific relationship between marijuana use and cancers of the head and neck, those sites most likely to be affected by marijuana use along with lung, was not explored independently. Moreover, subjects in the latter study (25) may not have been followed long enough for adequate assessment of an effect of marijuana on cancer risk. In addition, there may not have been enough exposure to marijuana to observe an effect in this population.

The aim of the present case-control study was to examine the association between marijuana use as derived from questionnaire data and head and neck cancers, controlling for other known risk factors for the disease, including cigarette smoking and alcohol drinking. We also examined the possible gene-environment interaction between marijuana use and mutagen sensitivity, as well as interactions with other known risk factors for head and neck cancer. Mutagen sensitivity is considered a predisposition marker of cancer risk (26, 27, 28, 29) . Defects in one or more steps of the DNA repair process may play a significant role in environmental carcinogenesis, and the extent of such defects may be partially responsible for susceptibility or resistance to environmental mutagens (30) . Mutagen sensitivity tests are indirect indicators of DNA repair competence. Bleomycin, a radiomimetic agent, was used as the test mutagen to evaluate the rates of induced chromosome breakage as a crude indicator of the response to a genotoxic agent (31 , 32) .

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Cases and Controls.

Untreated new patients with a histologically confirmed diagnosis of first primary squamous cell carcinoma of the head and neck, seen at Memorial Sloan-Kettering Cancer Center from 1992 to 1994, were considered as cases in this study. We approached 192 patients, and 173 agreed to participate. Sites of disease were classified by the American Joint Committee on Cancer criteria and coded by the International Classification of Diseases Version 9 (ICD-9). The tumor sites included lip (ICD-9, 140; n = 2), tongue (ICD-9, 141; n = 52), salivary glands (ICD-9, 142; n = 1, metastatic lesion, squamous cell carcinoma), gum (ICD-9, 143; n = 13), floor of mouth (ICD-9, 144; n = 15), other parts of the mouth (ICD-9, 145; n = 11), oropharynx (ICD-9, 146; n = 12), nasopharynx (ICD-9, 147; n = 2, squamous cell carcinomas), hypopharynx (ICD-9, 148. n = 13), other oral cavity (ICD-9, 149; n = 2), esophagus (ICD-

9, 150; $n = 1$), nasal cavities (ICD-9, 160; $n = 1$), and larynx (ICD-9, 161; $n = 48$). Age- and sex-frequency matched controls were identified for this study. Controls were without a history of cancer and were identified from the Blood Bank Center of Memorial Sloan-Kettering Cancer Center during the same period. We approached 196 blood donors, and 176 agreed to participate in the study.

Data Collection.

The study was approved by the Institutional Research Board on Human Subjects of Memorial Sloan-Kettering Cancer Center. All cases and controls were asked to sign an informed consent form if they agreed to participate in the study, to complete a structured questionnaire, and to donate a sample of blood. The questionnaire requested information on the following variables: age, gender, race, year and place of birth, religion, family income, and education; average number of tobacco cigarettes smoked/day, years of smoking, age at initiation of smoking; exposure to environmental tobacco smoking (at home and at work); alcohol consumption, types and frequency of alcohol consumption; occupational and environmental exposures; family history of cancer; sexual history; medical history; and oral hygienic history. In addition, all subjects were asked if they had ever used marijuana. If they responded yes, subjects were asked the average number of times they smoked/day and the number of years of marijuana use.

Mutagen-Sensitivity Assay.

A total of 91 patients and 131 controls provided a blood specimen for the assessment of mutagen sensitivity. The mutagen-sensitivity assay used in this study has been described in detail previously (33) . A peripheral blood sample (10 ml or less) was collected from cases and controls in a heparinized tube prior to initiation of lymphocyte culture. The standard lymphocyte culture procedure used RPMI 1640, supplemented with 15% FCS and phytohemagglutinin, in a ratio of blood:medium of 1:9. At 67 h of incubation, one set of cultures was treated with bleomycin (0.03 unit/ml) for 5 h. Colcemid (0.04 mg/ml) was added in the last hour to induce mitotic arrest prior to harvesting. A conventional cell-harvesting procedure followed. The cells were treated with hypotonic KCl (0.975 M KCl) solution for 15–20 min, fixed, washed with a freshly prepared mixture of methanol:acetic acid (3:1), and air-dried on wet slides. The slides were stained with Giemsa solution without banding. Fifty well-spread metaphases were examined from coded slides. Chromatid aberrations recorded were frank chromatid breaks or exchanges. Bleomycin tends to induce few chromatid exchanges (which, if present, are considered as two breaks). Chromatid gaps or attenuated regions were disregarded. The frequency of breakage was expressed as breaks/cell. The reliability of cytogenetic scoring has been evaluated previously by comparing four separate blood samples from a respective donor with a minimum interval between samples of 1 week. Mutagen sensitivity appeared to be stable and representative in a random-effect, one-way ANOVA model (30) .

Statistical Analysis.

The effects of marijuana use on the risk of head and neck cancer were estimated with ORs[3] and their 95% CIs, derived from logistic regression analysis (34) . Continuous variables, such as years of marijuana use and frequency of use, were first analyzed as continuous variables and then divided into three groups according to their marginal distributions: frequency of use (marijuana use/day) was categorized as never, less or equal to once per day, and more than once per day; and years of use was

categorized as never use, 1–5 years, and >5 years. For eight cases and nine controls who reported previous marijuana use but failed to report frequency of use, the median value of once per day was used to replace the missing values for the continuous variable and for the categorical variable. For five cases and five controls who reported previous use but provided no information on years of use, the median value of 5 years was used for the continuous variable and 1–5 years category for the categorical variable. Results of both replacing missing data with median values and excluding missing data are presented in the results. Dummy variables were used in logistic regression analysis to estimate ORs for each category of exposure. Trend tests for ordered variables were performed by assigning the score j to the jth exposure level of a categorical variable (where $j = 1, 2, \ldots$) and treating the categorical variable as an interval predictor in unconditional logistic regression. Three models were used to assess marijuana effects: (*a*) no covariates (crude analysis); (*b*) statistical adjustment for pack-years of cigarette smoking (continuous variable); (*c*) statistical adjustment for pack-years of cigarette smoking plus age (continuous variable), sex (male, female), race (white, nonwhite), education (≤high school, college, >college), passive smoking (no, yes), and heavy alcohol drinking (<100 drinks/month; ≥100 drinks/month). Stratified analysis was used to assess departures from additive effects between marijuana use and other known risk factors for head and neck cancer, including cigarette smoking, alcohol drinking, and mutagen sensitivity.

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The overall prevalence of lifetime marijuana use was 9.7% in controls and 13.9% in cases. The highest prevalence of marijuana use was found in cases with squamous cell carcinoma of the larynx ($n = 48$; 22.9%) and tongue ($n = 52$; 19.2%). The distributions of marijuana use among cases and controls, stratified by demographic characteristics, cigarette smoking, alcohol drinking, and mutagen sensitivity, are shown in Table 1⊡. Age was strongly associated with marijuana use; large proportions of marijuana smokers were found in younger age groups for both cases and controls. No obvious differences in marijuana use were found between categories of gender, race, or education. Tobacco cigarette smoking was generally independent of marijuana use in both cases and controls, except for those variables related to age such as pack-years of tobacco cigarette smoking, years of smoking, and age at smoking initiation in cases. Heavy alcohol drinking and mutagen hypersensitivity were not related to marijuana use in cases or controls. Passive smoking, not associated with marijuana use in controls, was related to marijuana use in cases.

View this table: [in this window] [in a new window] Table 1 The distribution of marijuana use (number and percentage of users and nonusers) in cases and controls, by category of selected demographic factors, smoking, alcohol, and mutagen sensitivity

The estimated crude OR for the effect of lifetime marijuana use (ever *versus* never) on the risk of head and neck cancer was 1.5 (95% CI, 0.8–2.9). Adjusting for age, gender, race, education, heavy alcohol

drinking, pack-years of tobacco cigarette smoking, and passive smoking increased the OR to 2.6 (95% CI, 1.1–6.6; Table 2). Strong dose-response relationships were observed for the effects of frequency of marijuana use and years of use. The adjusted ORs were 2.1 for those who smoked marijuana once per day and 4.9 for those who smoked marijuana more than once per day (P for trend = 0.0358) when missing values were replaced by median values. After excluding those with missing information on frequency of marijuana use, the adjusted ORs were 4.0 (0.9–2.4) and 5.4 (0.9–33) for those who smoked once per day and more than once per day, respectively (P for trend = 0.0214). Of those who smoked marijuana for 1–5 years, the adjusted OR was 1.9 (0.6–5.9); for individuals who smoked marijuana >5 years, the adjusted OR was 4.3 (0.99–19) when missing values were replaced by median values (P for trend = 0.0325; Table 2). After excluding those with missing information on years of marijuana use, the adjusted ORs were 3.9 (0.99–15) and 4.9 (0.8–29) for those who smoked 1–5 years and >5 years, respectively (P for trend = 0.0134).

View this table: [in this window] [in a new window] Table 2 Estimated effects of marijuana use (OR and 95% CI) on the risk of head and neck cancer, by covariates selected for adjustment[a]

The observed association between marijuana use and head and neck cancer was stronger among younger subjects. When the analyses were restricted to 55 cases and 65 controls <55 years, the adjusted OR increased to 3.1 (95% CI, 1.0–9.7; Table 3). Dose-response relationships were also stronger for the effects of frequency of marijuana use and years of use, controlling for the same covariates. When the analysis was further restricted to those between the ages of 40 and 55, the magnitudes of the estimated effects were still persistent. No association was observed between marijuana use and head and neck cancer for those 55 years or older.

View this table: [in this window] [in a new window] Table 3 Estimated effects of marijuana use (OR and 95% CI) on the risk of head and neck cancer for individuals <55 years by covariates selected for adjustment[a]

Table 4 shows the combined effects of lifetime marijuana use (ever *versus* never) and each of three potential effect modifiers: tobacco cigarette smoking, alcohol use, and mutagen sensitivity. For these analyses, we used >1.0 breaks/cell as the cutoff value to define hypersensitivity and having 100 or more drinks per month as a cutoff point for heavy drinking, and we categorized tobacco cigarette smoking into never smoking, former smoking, and current smoking. These variables were further stratified by marijuana use. The effects of marijuana use and cigarette smoking were more than multiplicative; the adjusted OR for the joint category of current tobacco cigarette smokers and marijuana users was greater than the product of the two component effects for those two exposures, *i.e.*, $36.1 > 3.6 \times 2.6 = 9.4$. Similar interaction effects (greater than multiplicative) were found for marijuana use and mutagen sensitivity. The adjusted OR for joint category of marijuana use and mutagen sensitivity was greater than the product of two component effects, *i.e.*, $77.1 > 6.1 \times 1.1 = 6.7$. The effects of marijuana use and

alcohol consumption appeared more than additive but less than multiplicative, *i.e.*, 4.3 (alcohol only) + 2.7 (marijuana only) - 1 = 6.0 < 9.6 (both exposures) < 4.3 x 2.7 = 11.6. In each case, however, power for testing each null hypothesis (effects are additive or multiplicative) and for comparing the fits of additive *versus* multiplicative models was low.

View this table: [in this window] [in a new window] Table 4 Estimated combined effects (OR and 95% CI) of lifetime marijuana use (ever *versus* never) and each of three potential modifiers (cigarette smoking, heavy alcohol use, and mutagen hypersensitivity) on the risk of head and neck cancers by covariates selected for adjustment

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This study has several possible limitations. One limitation is potential selection bias, which might have resulted in an overestimate of the marijuana effect (bias away from null). The controls for this study were blood donors and possibly less likely to be substance abusers. If use of marijuana were inversely associated with blood donation, the selection bias would lead to an overestimate of the marijuana effect. The blood donors at Memorial Sloan-Kettering Cancer Center had to be between the ages of 17 and 75, weigh 110 pounds or more, and be in good health. The prospective donors were asked to give a health history and take a physical examination to ensure the greatest possible safety for both donors and recipients. Nevertheless, the only question directly related to drug abuse was: "Have you used illegal drugs with a needle?" Although marijuana is not generally injected, marijuana use and injected drug use could be positively associated, which might lead to an overestimate of the marijuana effect. Nevertheless, because the observed prevalence in our controls was similar to the expected prevalence based on national data, the selection of blood donors as controls probably did not affect the association under study (Table 5).

View this table: [in this window] [in a new window] Table 5 Lifetime prevalence (%) of marijuana use in the study controls (no. of user /total) and the United States population, 12 years and older, from 1991 to 1993, by birth cohort[a]

When we evaluated the interaction between marijuana smoking and mutagen sensitivity (Table 4), the possible selection bias might exist because those with blood samples for mutagen assay may be different from individuals without blood samples. A total of 26.1% of controls and 46.8% of cases refused to provide a blood sample for the bleomycin in this study. We have compared the differences between those with and without blood samples on selected variables. This attempt is crucial to show whether there is selection bias attributable to missing samples that may threaten the validity of the interaction between marijuana smoking and mutagen sensitivity. No obvious difference was found between those with and without blood samples in terms of age, gender, race, education, and marijuana smoking. Only a board-line difference for cigarette smoking between those with and without blood samples in head and

neck cases was detected ($P = 0.05$), which indicates that the subjects with blood samples might not be a selected group for smoking habits from the original study population. The association between tobacco smoking and risk of head and neck squamous cell cancer was stronger in people with mutagen data then those without mutagen data, which might lead to a stronger confounder effects on the association between marijuana smoking and head and neck cancer. However, when the interaction between mutagen sensitivity and marijuana use was evaluated, the point estimates of the crude ORs were pretty similar to those after controlling for pack-years (Table 4).

A second limitation is differential misclassification of marijuana use, which may also bias the estimated marijuana effect. Because marijuana smoking is illegal, cases and controls might tend to underreport their history of marijuana use, but the degree of underreporting might have been greater for controls than cases who might want to rationalize their disease. Thus, the estimates of marijuana effects could be positively biased. On the other hand, cancer patients, under some duress because of their illness, could underreport their history of marijuana use more than controls, which would negatively bias the estimated marijuana effects. To address this potential source of bias, we compared the reported lifetime prevalence of marijuana use in controls with the corresponding prevalence in the United States population during the same period, stratified by gender and year of birth (Table 5; Ref. 3). We found that the overall (crude) lifetime prevalence of marijuana use in each gender of the controls was approximately equal to the corresponding prevalence in the United States population standardized to the birth-cohort distribution of the controls. For the majority of controls born before 1951 ($n = 152$; 86%), the lifetime prevalence of marijuana use was similar to estimates for the United States population. For a small fraction of those controls born since 1951 ($n = 24$; 14%), however, there is some indirect evidence for systematically underreporting of marijuana use. When we reanalyzed the data by excluding those cases and controls born since 1951, we found little change in the estimated marijuana effects. Because we cannot address issues of either over- or underreporting by cases, it is difficult to evaluate the direction of bias by differential misclassification of past marijuana use on the association under study. The possible limitation of using mutagen sensitivity assays in case-control study was discussed by Caporaso (29) . Cultured cells obtained from patients with cancer or control subjects in a hospital setting can differ for abnormal nutrition, secondary metabolic alterations of neoplastic disease, and effect of treatment, hospitalization, inactivity, or stress, which will allow bias attributable to differential misclassification. However, a recent paper by Cloos *et al.* (28) reported a high heritability estimate of the susceptibility to bleomycin-induced chromatid breaks, which indicates that a clear genetic basis for mutagen sensitivity-related cancer susceptibility may exist in the general population. If the mutagen sensitivity is highly inherited, the differential misclassification bias for this assay might be minimal.

The third limitation is low power and precision. The relatively small sample size and low frequency of marijuana use limits our ability to estimate the effects precisely, especially when analyzing specific sites or when assessing interaction effects with other risk factors.

A fourth possible source of bias is no differential error in measuring confounders of the association under study. It has been shown, for example, that no differential misclassification of a strong confounder will cause the investigator to underestimate both the impact of the confounder on effect estimate and the

association of the confounder with the factor under study (35 , 36) . However, even if the association of major confounders, such as alcohol and tobacco with marijuana, are stronger than they appear, they appear so weak as to represent an unlikely source of bias.

Possible confounding effects also need to be addressed. We have evaluated the possible confounding effects to identify the potential confounders that induced the large changes in point estimates of ORs and *P*s. Our results showed that age was a major confounder, which causes the largest changes in point estimates of OR and *P* for marijuana smoking after controlling for it. In addition, passive smoking and pack-years of smoking are positive confounders, and alcohol drinking is a negative confounder on the association between marijuana and head and neck cancer.

This is the first epidemiological study to report an effect of marijuana use on the risk of head and neck cancer. Not only did we find an elevated cancer risk among marijuana users, but we also observed dose-response associations for frequency and years of marijuana use, adjusting for several potential confounders.

Marijuana use in the United States increased dramatically among teenagers and young adults in the mid-to-late 1960s, *i.e.*, among persons born between 1941 and 1955. Assuming marijuana use is associated with cancer risk with an induction/latency period of 20–30 years, this cohort will be the earliest possible group to experience and clinically manifest elevated risks of head and neck cancer. This suggests that observed risks should be greater among subjects younger than 55 years. Our analyses, restricted to the younger population (<55 years old) with only 32% of our cases (n = 55) and 36% of controls (n = 63) suggested a stronger marijuana effect in the subpopulation of younger subjects than in the population as a whole. The dose-response relationships were also stronger in younger subjects. No association was observed for subjects 55 years or older.

Others have speculated that the uniquely characteristic technique of smoking marijuana might influence the tumor site of development (19 , 20) . The more rapid and deeper inhalation technique of marijuana smoking may lead to earlier and more pronounced deposition of carcinogens in the particulate phase of the smoke at relatively narrow sites in the upper airway, such as the larynx, as well as in the central portions of the tracheobronchial tree, because of turbulence and inertial impaction (11 , 37) . At the same time, the prolonged inhalation time might permit larger particles in the tar phase to deposit in the oral cavity, especially on the tongue. Because of the limited sample size, we would not be able to analyze marijuana use and head and neck cancer stratified by tumor site. Future studies with larger sample size are warranted to explore this aspect.

Possible interaction effects were suggested between marijuana use and other risk factors for head and neck cancer. The interplay between carcinogens and intrinsic host susceptibility is an important factor in environmental carcinogenesis. Mutagen hypersensitivity, an indirect marker for DNA repair, interacts with tobacco smoking in head and neck cancer risk (38, 39, 40, 41) . Synergy between mutagen hypersensitivity and marijuana use was suggested in this study because the effects were more than additive, which suggests that the development of the upper aerodigestive cancers may be affected by gene-environment interaction. Synergy (greater than additive effects) was also suggested between

marijuana use and tobacco smoking. These results suggest that the carcinogenic properties of marijuana may include not only the carcinogens present in tobacco but also other potential carcinogens and/or other factors that might particularly predispose marijuana smokers to cancer development, such as the Δ9-tetrahydrocannabinol-related impairment of antitumor immunity (12) . Because of the low power for testing these interactions, however, the present findings will need to be replicated in future studies.

In summary, this is the first epidemiological report that marijuana smoking is associated with a dose-dependent increased risk of head and neck cancer. This association is supported by a series of case reports and by experimental studies that provide a biologically plausible basis for the hypothesis that marijuana is a risk factor for human head and neck cancer. Given the long induction/latency period of head and neck cancer and the first wave of marijuana use in the 1960s in the United States, it is now time to examine the association between marijuana use and cancer risk. Large epidemiological studies are needed to replicate our results, to examine the relationships between marijuana use and increased risk of cancer, and to assess potential interactions between marijuana use and other risk factors.

Footnotes

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[3] The abbreviations used are: OR, odds ratio; CI, confidence interval.

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Δ-9-Tetrahydrocannabinol Enhances Breast Cancer Growth and Metastasis by Suppression of the Antitumor Immune Response[1]

Robert J. McKallip,[2]* Mitzi Nagarkatti,* and Prakash S. Nagarkatti†

In the current study, we tested the central hypothesis that exposure to Δ-9-tetrahydrocannabinol (Δ^9-THC), the major psychoactive component in marijuana, can lead to enhanced growth of tumors that express low to undetectable levels of cannabinoid receptors by specifically suppressing the antitumor immune response. We demonstrated that the human breast cancer cell lines MCF-7 and MDA-MB-231 and the mouse mammary carcinoma 4T1 express low to undetectable levels of cannabinoid receptors, CB1 and CB2, and that these cells are resistant to Δ^9-THC-induced cytotoxicity. Furthermore, exposure of mice to Δ^9-THC led to significantly elevated 4T1 tumor growth and metastasis due to inhibition of the specific antitumor immune response in vivo. The suppression of the antitumor immune response was mediated primarily through CB2 as opposed to CB1. Furthermore, exposure to Δ^9-THC led to increased production of IL-4 and IL-10, suggesting that Δ^9-THC exposure may specifically suppress the cell-mediated Th1 response by enhancing Th2-associated cytokines. This possibility was further supported by microarray data demonstrating the up-regulation of a number of Th2-related genes and the down-regulation of a number of Th1-related genes following exposure to Δ^9-THC. Finally, injection of anti-IL-4 and anti-IL-10 mAbs led to a partial reversal of the Δ^9-THC-induced suppression of the immune response to 4T1. Such findings suggest that marijuana exposure either recreationally or medicinally may increase the susceptibility to and/or incidence of breast cancer as well as other cancers that do not express cannabinoid receptors and are resistant to Δ^9-THC-induced apoptosis. *The Journal of Immunology*, **2005, 174: 3281–3289.**

Marijuana is one of the most common drugs of abuse and it medicinal use is the subject of current debate. Δ-9-tetrahydrocannabinol (Δ^9-THC),[3] the major psychoactive component in marijuana (1), and other synthetic cannabinoids have been used as potential therapeutic agents in alleviating such complications as intraocular pressure in glaucoma, cachexia, nausea, and pain (2). Interest in the potential medicinal use of cannabinoids grew with the discovery of two cannabinoid receptors, CB1 and CB2 (3, 4). CB1 is predominantly expressed in the brain, whereas CB2 is primarily found in the cells of the immune system (1, 4). Furthermore, endogenous ligands for these receptors capable of mimicking the pharmacological actions of Δ^9-THC have also been discovered. Such ligands were designated endocannabinoids and include anandamide and 2-arachidonoyl glycerol (5–7). The physiological function of endocannabinoids and cannabinoid receptors remains unclear. Recent work from our laboratory and others suggest that cannabinoids, including Δ^9-THC, may be effective in treating a variety of cancers including lymphomas, leukemias, and gliomas (8–10).

In contrast to these potentially beneficial properties, the use of marijuana has been associated with unwanted effects such as increased susceptibility to infections (11–13), and increased incidence of head and neck cancers in humans (14) and lung cancer in mice (15). Δ^9-THC possesses significant immunomodulatory properties. For example, exposure of macrophages to Δ^9-THC led to decreased production of TNF-α and NO in response to LPS (16). Additionally, exposure of macrophages to Δ^9-THC caused an impairment of their Ag-presenting capabilities (17). Exposure to cannabinoids can also lead to significant reductions in the proliferative and cytolytic response of T lymphocytes and Ab production by B cells (18–21). In addition, other studies conducted in vivo have shown that exposure to Δ^9-THC can lead to increased susceptibility to infections with various pathogens including *Herpes simplex* and Friend leukemia virus (12, 13). Furthermore, exposure to Δ^9-THC has been shown to suppress the immune response to lung cancers in mice (15).

Both the innate and adaptive immune responses are believed to be involved in controlling the growth of many cancers. Coordination of the two arms of the immune system is largely controlled by cytokines produced by cells such as dendritic cells. In addition, T regulatory cells and NKT cells have been implicated in the control of the antitumor immune response (22–24). In general, it is believed that a Th1 response is necessary for an effective immune response to be mounted against most tumors (25). IL-2 and IFN-γ are two cytokines that promote a Th1 response, while IL-4 and IL-5 promote a Th2 response. In addition, a number of cytokines possess suppressive activity. For example, IL-10 has been shown to suppress the Th1 response. In previous work, it was demonstrated that exposure to Δ^9-THC could lead to alterations in cytokine production which resulted in suppression of the immune response to *Legionella pneumophila* (26) as well as a lung cancer cell line (15).

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[3] Abbreviations used in this paper: Δ^9-THC, Δ-9-tetrahydrocannabinol; SOCS, suppressor of cytokine signaling; MMTV, mouse mammary tumor virus.

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Current work examining the potential use of Δ^9-THC and other cannabinoids for the treatment of cancers relies on the expression of CB1 and/or CB2 by the targeted tumor. However, little is known about the effect of Δ^9-THC exposure on the generation, growth, or response to tumors with low to no expression of CB1 and/or CB2. Because CB1 and CB2 are primarily expressed by tumor of neural and immune origins, respectively, it is possible that the majority of tumors originating in other tissues would be significantly less sensitive to Δ^9-THC-mediated killing and because Δ^9-THC is highly immunosuppressive, such tumors may find a favorable environment for growth and progression.

The immune system is suggested to play a key role in controlling the development of cancers as suggested by the findings that immunosuppressed individuals are at a higher risk for developing cancer. For example, there is an increased incidence of Karposi sarcoma, non-Hodgkins lymphoma, Burkitt lymphoma, and cervical cancer in AIDS patients (27). In addition, there have been reports of increased susceptibility to various lymphomas and cutaneous neoplasms following organ transplantation (28–30). Interestingly, there is evidence that de novo breast cancer incidence may increase following liver transplantation (31), suggesting the possibility that the immune system can play an important role in the development of this type of cancer. Therefore, in the current study, using a breast cancer model, we examined the effect of Δ^9-THC exposure on the immune response to and the growth of cancer cells that expresses low to undetectable levels of cannabinoid receptors.

Materials and Methods

Mice

Adult female BALB/c mice were purchased from the National Institutes of Health. SCID-NOD mice were purchased from The Jackson Laboratory. The mice were housed in polyethylene cages and given rodent chow and water ad libitum. Mice were housed in rooms maintaining a temperature of 74 ± 2°F and on a 12-h light/dark cycle.

Reagents

Δ^9-THC was obtained from the National Institute on Drug Abuse and was initially dissolved in DMSO (Sigma-Aldrich) to a concentration of 20 mM and stored at −20°C. Δ^9-THC was further diluted with tissue culture medium for in vitro studies and PBS for in vivo studies. SR141716A and SR144528 were obtained from Sanofi Recherche. Anti-IL-4 mAbs (11B.11) were obtained from the Biological Resources Branch, National Cancer Institute-Frederick Cancer Research and Development Center. Anti-IL-10 mAbs were obtained from BD Pharmingen.

Cell lines

The murine mammary cell carcinomas 4T1 and EMT6 syngeneic to BALB/c mice, the human breast cancer cell lines, MCF-7 and MDA-MB-231, the human T lymphoblastic leukemia cell line, Jurkat, and the human glioma U87 were maintained in RPMI 1640 (Life Technologies Laboratories) supplemented with 5% FCS, 10 mM HEPES, 1 mM glutamine, 40 μg/ml gentamicin sulfate, and 50 μM 2-ME.

RNA isolation and RT-PCR

RNA was isolated from ~1×10^7 cells using the RNeasy Mini kit (Qiagen). As CB1 and CB2 are encoded by single exons, a DNase digestion was included in the isolation procedure to limit the possibility of PCR amplification of CB1 and CB2 from genomic DNA. cDNA was prepared with the Qiagen OmniScript RT kit using 1 μg of RNA as template for first strand synthesis. Mouse and human CB1 was amplified using primers H CB1 U (5′-CGTGGGCAGCCTGTTCCTCA-3′) and H CB1 L (5′-CATGCGGGCTTGGTCTGG-3′), which yield a product of 403 bp. Human CB2 was amplified using primers H CB2 U (5′-CGCCGGAAGCCCTCATACC-3′) and H CB2 L (5′-CCTCATTCGGGCCATTCCTG-3′), which yield a product of 522 bp. Mouse CB2 was amplified using M CB2 (5′-CCGGAAAAGAGGATGGCAATGAAT-3′) and M CB2 (5′-CTGCTGAGCGCCCTGGAGAAC-3′) which yields a product of 479 bp. β-Actin was used as a positive control (primers M BA U (5′-AAGGCCAACCGTGAAAAGATGACC-3′) and M BA L (5′-ACCGCTCGTTGCCAATAGTGATGA-3′), product size of 427 bp). PCR were conducted using the following parameters: 95°C for 15 s, 58°C for 15 s, and 72°C for 30 s for 35 cycles, followed by a final 5 min at 72°C in an Applied Biosystems GeneAmp 9700. The resulting PCR products were separated on a 1% agarose gel.

Detection of Δ^9-THC-mediated cell death in vitro

Tumor cells or splenocytes (1×10^6 cells/well) were cultured in 24-well plates in the presence or absence of various concentrations of Δ^9-THC for 24 h. Next, the cells were harvested, washed twice in PBS and analyzed for cell viability by trypan blue dye exclusion.

Quantification of the effect of Δ^9-THC exposure on 4T1 tumor growth and metastasis in vivo

Groups of BALB/c or SCID-NOD mice were injected s.c. with 3×10^5 4T1 tumor cells. Three days later, the mice then were exposed every other day for ~3 wk to various doses of Δ^9-THC (12.5, 25, or 50 mg/kg body weight) or vehicle (DMSO) control. The tumor volume was observed, recorded, and calculated using the following equation: tumor volume = length × width^2 × 0.52. In addition, the level of metastasis was determined by directly quantifying the number of metastatic nodules located in the lungs, by H&E staining of lung sections, and by assessing tumor burden by determining the increase in lung weight.

In vivo antitumor immune response

BALB/c mice were first sensitized to 4T1 by injecting them i.p. with 1×10^6 irradiated 4T1 tumor cells twice at 2-wk intervals. Two weeks following the final sensitization, the mice were injected s.c. into their rear footpads with 1×10^5 irradiated 4T1 tumor cells or 1×10^5 irradiated EMT6 tumor cells (negative control). Groups of mice were then treated i.p. with various doses of Δ^9-THC (0, 12.5, 25, or 50 mg/kg) daily for 4 days. Four days following the challenge with the irradiated tumor cells the immune response was determined by aseptically removing the draining lymph node and quantifying the increase in lymph node mass, cell number, and lymphocyte DNA synthesis. In experiments examining the role of anti-IL-4 mAbs and anti-IL-10 mAbs, mice received a single injection of 5 mg or 5 mg/kg of mAbs, respectively, which was previously shown to effectively reduce IL-4 and IL-10 concentrations (15, 32).

In vitro proliferation assay

The spleens and lymph nodes from control or Δ^9-THC-treated mice were placed into 10 ml of RPMI 1640 (Life Technologies Laboratories) supplemented with 10% FCS, 10 mM HEPES, 1 mM glutamine, 40 μg/ml gentamicin sulfate, and 50 μM 2-ME, referred to as complete medium. The spleens and lymph nodes were prepared into a single cell suspension using a laboratory homogenizer, washed twice, and adjusted to 5×10^6/ml in complete medium. The splenocytes and lymph node cells (5×10^5 in 100 μl/well) were cultured in 96-well flat-bottom plates and stimulated with various concentrations of irradiated 4T1 tumor cells for 4 days. During the final 8 h of culture, the cells were pulsed with 2 μCi of [^{3}H]thymidine. DNA synthesis was determined by beta scintillation counting (33, 34).

Cytokine detection

BALB/c mice were first sensitized to 4T1 by injecting them i.p. with 1×10^6 irradiated 4T1 tumor cells twice at 2-wk intervals. Two weeks following the final sensitization injection the mice were injected s.c. into their rear footpads with 1×10^5 irradiated 4T1 tumor cells. Groups of mice were then treated daily for 4 days with vehicle control or Δ^9-THC (50 mg/kg i.p.). Four days following the challenge with the irradiated tumor cells the draining lymph node were removed and adjusted to 2.5×10^6/ml in RPMI 1640 containing 10% FCS. The lymph node cells were cultured in a 96-well flat-bottom plate (200 μl/well) for 24 h, after which the levels of IFN-γ, TGF-β, IL-4, IL-10, and TNF were determined using the methods described in the Quantikine M ELISA kits (R&D Systems).

Microarray analysis of gene expression

Total RNA was isolated from lymph node cells isolated from 4T1-immunized mice that were stimulated in their rear footpads with irradiated 4T1 tumor cells (1×10^5 s.c.) and treated i.p. for 4 days with vehicle or 50 mg/kg Δ^9-THC using the RNeasy Mini kit (Qiagen). Labeled cDNA probes were synthesized from the RNA samples using the Ampolabeling-LPR kit (SuperArray). The labeled cDNA probes were hybridized to individual GEArray Q series mouse Th1, Th2, Th3 array membranes overnight at 60°C with continuous agitation at 5–10 rpm. The membranes were washed twice for 10 min at 60°C with 2× SSC, 1% SDS solution, and twice for 10

min at 60°C with 0.1× SSC, 0.5% SDS. Nonspecific binding was blocked by incubating the membranes with GEAblocking solution for 40 min. The membranes were labeled with alkaline phosphatase-conjugated streptavidin alkaline phosphatase for 10 min. Excess alkaline phosphatase was removed by washing the membranes four times with Buffer F (SuperArray) for 5 min and rinsing the membranes with Buffer G. Gene expression was detected using CDP-Star chemiluminescent substrate and exposing the membranes to x-ray film. The data were analyzed by converting the x-ray image into a grayscale TIFF file and using the ScanAlzye software program to convert the data into numerical data. Finally, data analysis was performed using the GEArray Analyzer data analysis software (SuperArray). Data was normalized using housekeeping genes including β-actin, GAPDH, cyclophilin A, and ribosomal protein L13a.

Statistical analysis

Student's *t* test or Tukey Kramer test was used to compare vehicle and Δ^9-THC-treated groups. $p < 0.05$ was considered to be statistically significant.

Results

Expression of CB1 and CB2 in human and murine breast cancer cells

The expression of CB1 and CB2 mRNA was determined by RT-PCR. The results showed that splenocytes expressed both receptors, while in the 4T1 breast cancer cells, CB1 and CB2, mRNA was not detectable (Fig. 1*A*). Similar results were seen when we examined the expression of CB1 and CB2 in the human breast cancer cell lines MCF-7 and MDA-MB-231 (Fig. 1*C*). In this experiment, Jurkat cells were used as a positive control for CB2 expression and the human glioma U87 was used as a positive control for CB1 expression. The results demonstrated that in both human breast cancer cell lines there was very low detectable expression of CB1 while CB2 expression was not detected.

Sensitivity of 4T1 and MCF-7 to Δ^9-THC-induced cell death

Next we examined whether 4T1 or MCF-7 were sensitive to Δ^9-THC-induced cytotoxicity compared with other cells reported to be sensitive to Δ^9-THC. To this end, 4T1 breast cancer cells and splenocytes from BALB/c mice were cultured for 24 h in RPMI 1640 containing 5% FCS in the presence of various concentrations of Δ^9-THC (0, 5, 10, or 20 μM). The viable cell number was determined by trypan blue dye exclusion (Fig. 1*B*). The results demonstrated that although the splenocytes were highly sensitive to Δ^9-THC-induced killing, the 4T1 cells were relatively resistant. No decrease in viable cell number in the 4T1 breast cancer cells was observed even at the highest concentration of Δ^9-THC tested. In contrast, splenic culture showed a significant reduction in viable cell number following exposure to concentration of Δ^9-THC as low as 5 μM. In addition, we examined whether the human breast cancer cell line MCF-7 was sensitive to Δ^9-THC-mediated cell death. To this end, MCF-7 and Jurkat cells were cultured for 24 h in RPMI 1640 containing 5% FCS in the presence of various concentrations of Δ^9-THC (0, 5, 10, or 20 μM) and the viable cell number was determined by trypan blue dye exclusion (Fig. 1*D*). The results showed that while the Jurkat cells were sensitive to Δ^9-THC-mediated killing at concentrations as low as 5 μM, the MCF-7 cells were resistant to Δ^9-THC-induced toxicity. Together, these data suggested that both the murine 4T1 and the human MCF-7 human breast cancer cell lines are resistant to killing mediated by Δ^9-THC exposure.

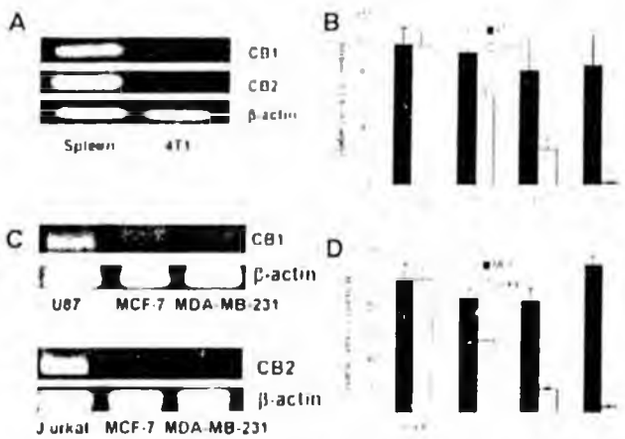

FIGURE 1. Human and murine breast cancer cells expression of CB1 and CB2 and sensitivity to Δ^9-THC-induced cytotoxicity. The expression of CB1 and CB2 mRNA was determined by RT-PCR analysis. Total RNA was isolated from mouse spleen cells, 4T1, Jurkat, MCF-7, MDA-MB-231, and U87 tumor cells. mRNA was reverse transcribed and amplified by PCR with primers specific for CB1, CB2, and β-actin. A photograph of ethidium bromide-stained amplicons is depicted (*A* and *C*). The effect of Δ^9-THC on cell viability was determined by culturing the cells with various concentrations of Δ^9-THC for 24 h in medium containing 5% FCS. The cell viability was determined by trypan blue dye exclusion. The data were expressed as percent of control viable cell number (*B* and *D*).

Δ^9-THC-exposure leads to increased growth of the 4T1 breast cancer in vivo

Next, we examined whether exposure to Δ^9-THC had any effect on the local growth of the 4T1 tumor (Fig. 2*A*). To this end, BALB/c mice were injected s.c. with 3×10^5 4T1 tumor cells. Three days following the tumor injection, the mice were exposed every other day for 18–21 days to either vehicle or various doses of Δ^9-THC (12.5, 25, or 50 mg/kg). Tumor growth was monitored and the data revealed that exposure to 25 mg/kg Δ^9-THC led to a significant increase in tumor mass. This effect was even more pronounced in mice treated with 50 mg/kg Δ^9-THC.

Δ^9-THC-exposure leads to increased metastasis of 4T1 tumor to the lung

In addition to examining the effects of Δ^9-THC on the local growth of the 4T1 tumor, we examined whether exposure to Δ^9-THC would have any effect on the level of metastasis in the lungs. To this end, BALB/c mice were injected s.c. with 3×10^5 4T1 tumor cells. Three days following the tumor injection, the mice were exposed every other day to either vehicle control or various doses of Δ^9-THC (12.5, 25, or 50 mg/kg). The lungs from the tumor-bearing mice were harvested 18–21 days following tumor injection and the level of metastasis was quantified (Fig. 2, *B* and *C*). The results showed that exposure to 25 or 50 mg/kg Δ^9-THC led to a significant increase in the number of tumor nodules located in the lungs. H&E staining of lung sections revealed that Δ^9-THC-treatment led to a dose-dependent increase in the size of the metastatic nodules (Fig. 2*D*). In addition, tumor burden in the lungs was quantified by determining the increase in lung mass in tumor bearing mice vs control mice and the results show that Δ^9-THC-treatment led to a significant increase in lung mass (Fig. 2*E*). Together, these results suggested that Δ^9-THC-exposure increased the metastasis of 4T1 tumor to the lungs.

The effect of Δ^9-THC exposure on 4T1 tumor growth in SCID-NOD mice

Next, the role of the immune system in the observed increase in 4T1 tumor growth and metastasis following Δ^9-THC was evaluated using the SCID-NOD model. SCID-NOD mice are devoid of an antitumor immune response. Therefore, any effect of Δ^9-THC

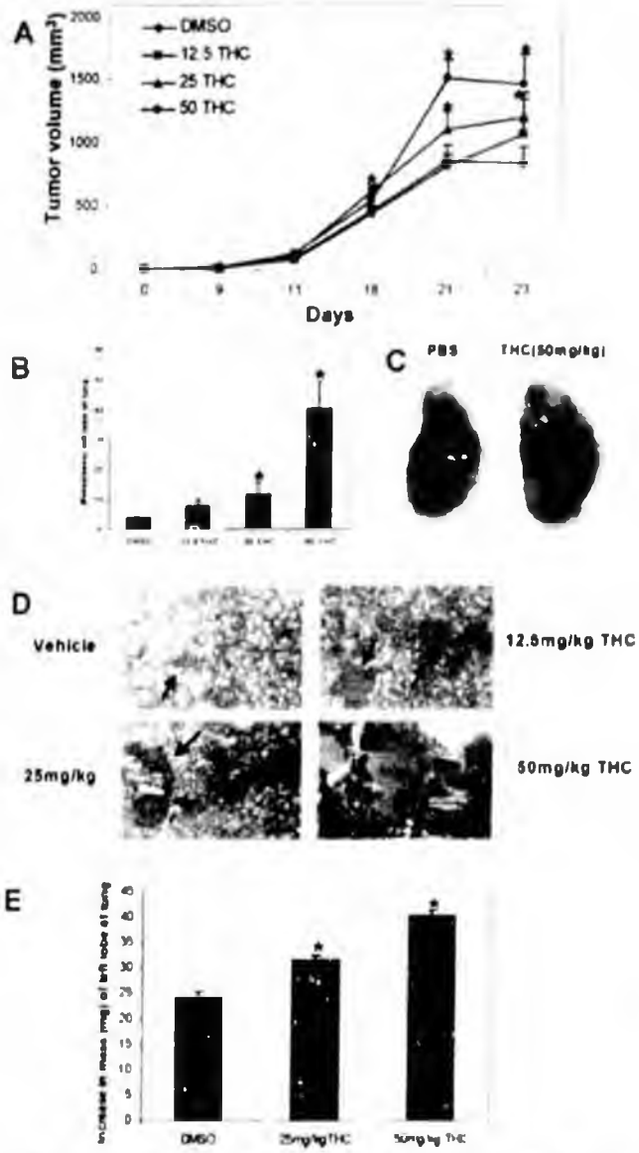

FIGURE 2. Δ⁹-THC exposure leads to an increase in number and size of 4T1 tumors metastasizing to the lungs in vivo. Mice injected s.c. with 3×10^5 4T1 tumor cells were treated with various concentration of Δ⁹-THC every other day for 21 days. Local tumor volume was determined (*A*). The lungs were harvested and the metastases were quantified (*B* and *C*). Sections of the lungs were stained with H&E (*D*). The arrows indicate the sites of tumor growth. •, Statistically significant difference ($p < 0.05$) when compared with the controls. The results are representative data of experimental groups containing four mice. The experiment has been repeated three times with similar results. Tumor burden was quantified by determining the increase in the weight of the lungs from tumor bearing mice compared with control mice (*E*).

on tumor growth in these mice would be independent of an effect on the immune response. To this end, SCID-NOD mice were injected s.c. with 4T1 tumor cells. The mice were then treated with the vehicle or 25 mg/kg Δ⁹-THC every other day for 19 days. Local tumor growth and metastasis were recorded. The results revealed that Δ⁹-THC exposure did not result in a significant increase in tumor growth (Fig. 3*A*) or metastasis (Fig. 3*B*), suggesting that the effects of Δ⁹-THC on the growth of the 4T1 tumor in immunocompetent mice may be directly related to an effect on the immune system.

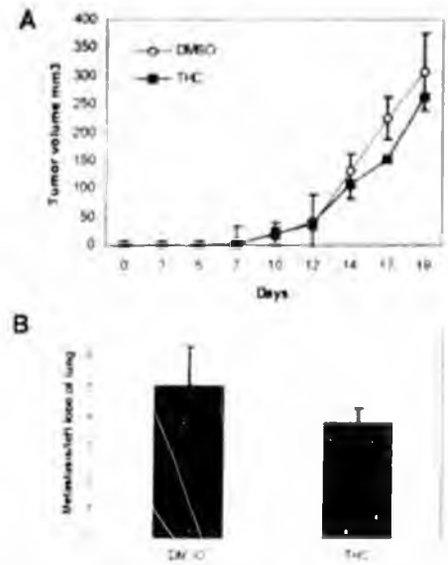

FIGURE 3. The effect of Δ⁹-THC exposure on 4T1 tumor growth in SCID-NOD mice. SCID-NOD mice were injected s.c. with 3×10^5 4T1 tumor cells. The mice were then treated i.p. with the vehicle control or 25 mg/kg Δ⁹-THC every other day for 19 days. Local tumor growth (*A*) and metastasis were recorded (*B*). The results are representative data of experimental groups containing four mice. The experiment was repeated three times with similar results.

Δ⁹-THC exposure directly suppresses the immune response to 4T1 in vivo

To directly examine the effect of Δ⁹-THC exposure on the antitumor immune response, we used a modified version of the popliteal lymph node assay. More specifically, mice were first sensitized to 4T1 by injecting them twice, separated by 2 wk, with irradiated 4T1 tumor cells. Two weeks following the final sensitization injection, the mice were rechallenged in their rear footpads with irradiated 4T1 tumor cells and either received daily i.p. injections of Δ⁹-THC (25 or 50 mg/kg) or vehicle. The immune response was determined 4 days following rechallenge by harvesting the lymph nodes, draining the site of tumor injection, and assessing the increase in lymph node mass (Fig. 4*A*) and cell number (Fig. 4*B*) compared with the same lymph nodes from mice not receiving the rechallenge. The results showed that rechallenge with 4T1 led to a significant and measurable immune response and that exposure to Δ⁹-THC at concentrations as low as 25 mg/kg significantly suppressed the antitumor immune response against 4T1. In addition, groups of mice sensitized against 4T1 received a challenge with an unrelated syngeneic mammary carcinoma (EMT6), and such mice showed no significant immune response (data not shown), demonstrating that the immune response in the sensitized mice was specific for 4T1. Next, the effect of Δ⁹-THC exposure on the growth and metastasis of 4T1 tumor cells in 4T1-sensitized mice was examined and the data showed that exposure to Δ⁹-THC led to quicker appearance of detectable tumors (Fig. 4*C*), an increase in tumor size (Fig. 4*D*), and an increase in the level of metastatic lesions in the lungs (Fig. 4*E*). Together, the results from these experiments demonstrated 4T1 tumor can be immunogenic and that exposure to Δ⁹-THC can suppress the immune response against 4T1 tumor, which may account for enhanced tumor growth and metastasis.

Δ⁹-THC exposure leads to suppression of the tumor-specific proliferative response

To further examine the effect of Δ⁹-THC on the antitumor immune response, we determined the effect of Δ⁹-THC exposure on the

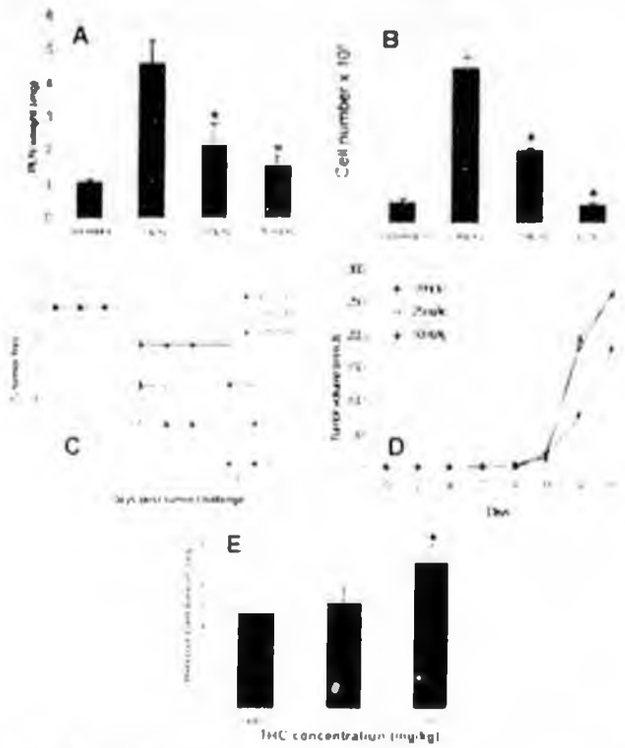

FIGURE 4. Δ^9-THC exposure directly suppresses the immune response to 4T1 in vivo. 4T1-sensitized mice were challenged s.c. in their footpads with irradiated 4T1 (1×10^5 cells). After which, the mice were treated daily for 4 days with CB1 (SR141716A), CB2 (SR144528) antagonists, or vehicle 1 h before exposure to Δ^9-THC (25 mg/kg). The immune response was assayed by determining the increase in lymph node mass (*A*) and cell number (*B*) compared with unchallenged mice. *, Statistically significant difference ($p < 0.05$) when compared with the controls. The effect of Δ^9-THC exposure on the growth and metastasis of 4T1 tumor cells in 4T1-sensitized mice was examined. To this end, 4T1-sensitized mice were injected s.c. with 1×10^5 live 4T1 cells. The mice were treated every other day for 16 days with vehicle or Δ^9-THC (25 or 50 mg/kg). The tumor incidence (*C*), tumor mass (*D*), and number of metastatic lesions in the lungs were determined (*E*). The results are representative data of experimental groups containing four mice. The experiment was repeated three times with similar results.

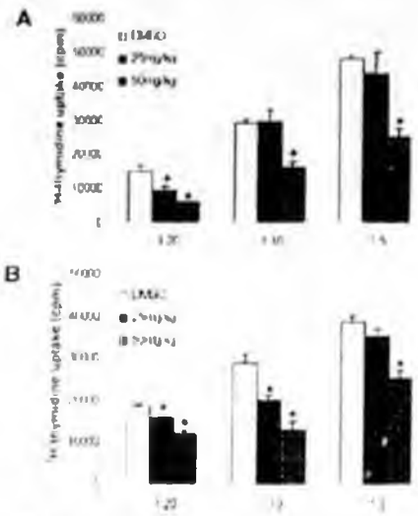

FIGURE 5. Δ^9-THC exposure leads to suppression of the tumor-specific proliferative response. 4T1-sensitized mice were treated for 4 days with vehicle or Δ^9-THC (25 or 50 mg/kg). Next, spleens (*A*) and lymph nodes (*B*) were harvested and cultured in vitro for 4 days with irradiated 4T1 tumor cells. Various responder (splenocytes or lymph node cells) to stimulator (irradiated 4T1 tumor cells) were tested. The proliferative response was determined by [^{3}H]thymidine uptake. The experiment was repeated three times with similar results. *, Statistically significant difference ($p < 0.05$) when compared with the controls.

proliferative response to 4T1. To this end, sensitized mice were treated for 4 days with various concentrations of Δ^9-THC (0, 25, and 50 mg/kg). Next, the splenocytes and lymph node cells were harvested and cultured in vitro for 4 days with irradiated 4T1 tumor cells. The proliferative response was determined by [^{3}H]thymidine uptake and the results revealed that in vivo exposure to Δ^9-THC led to a significant suppression of the proliferative response of splenocytes (Fig. 5*A*) and lymph nodes cells (Fig. 5*B*) to 4T1.

The effect of CB1 and CB2 antagonist on Δ^9-THC-induced suppression of the immune response to 4T1 in vivo

To investigate the role of CB1 and CB2 in Δ^9-THC-induced suppression of the antitumor immune response to 4T1, sensitized mice were challenged s.c. in their footpads with irradiated 4T1. Next, the mice were treated daily for 4 days with CB1 (SR141716A), CB2 (SR144528) antagonists (20 mg/kg), or vehicle 1 h before exposure to Δ^9-THC (25 mg/kg). The immune response was assayed by determining the increase in lymph node mass (Fig. 6*A*), cell number (Fig. 6*B*), and proliferation (Fig. 6*C*) compared with unchallenged mice. The results demonstrated that treatment with the CB2 antagonist, but not the CB1 antagonist, could significantly reverse the Δ^9-THC-induced suppression of the immune response against 4T1, suggesting a prominent role for CB2 in the observed Δ^9-THC-mediated suppression of the antitumor immune response.

Δ^9-THC exposure alters cytokine production

Previous reports have indicated that exposure to Δ^9-THC can alter the production of various cytokines (35, 36). Because the antitumor immune response is primarily mediated by Th1-directed immune response, we examined whether exposure to Δ^9-THC had any effect on the production of Th1 vs Th2 cytokines. To this end, 4T1-sensitized mice were challenged s.c. with irradiated 4T1 tumors and then received daily injection with various doses of Δ^9-THC (vehicle, 25, and 50 mg/kg). Four days following the challenge with 4T1, the lymph node cells draining the site of injection were harvested, counted, and cultured (1×10^6 cells/well) for 24 h in 96-well plates. Next, the supernatants were tested for the presence of various Th1 and Th2 cytokines (Fig. 7*A*). The results showed that exposure to 25 mg/kg Δ^9-THC led to a dramatic increase in the Th2 cytokines IL-4 and IL-10, suggesting that at this concentration, Δ^9-THC enhances the Th2 response. In addition, levels of IFN-γ were found to be elevated following exposure to Δ^9-THC. Interestingly, exposure to 50 mg/kg Δ^9-THC led to a significant reduction in IL-4, IFN-γ, and IL-10 compared with the vehicle or 25 mg/kg Δ^9-THC groups, suggesting the possibility that at a higher concentration, Δ^9-THC was leading to a more generalized suppression of the antitumor immune response, possibly due to the induction of apoptosis (21).

Anti-IL-4 and anti-IL-10 mAbs partially prevent Δ^9-THC-induced suppression of the immune response to 4T1

Next, we examined the effects of Abs against IL-4 or IL-10 on the Δ^9-THC-induced suppression of the immune response to 4T1. To this end, 4T1-sensitized mice were first challenged in their rear footpads with irradiated 4T1 cells. Groups of mice were then treated with vehicle + isotype control mAbs, Δ^9-THC (25 mg/kg/day) + isotype control mAbs, Δ^9-THC (25 mg/kg/day) + anti-

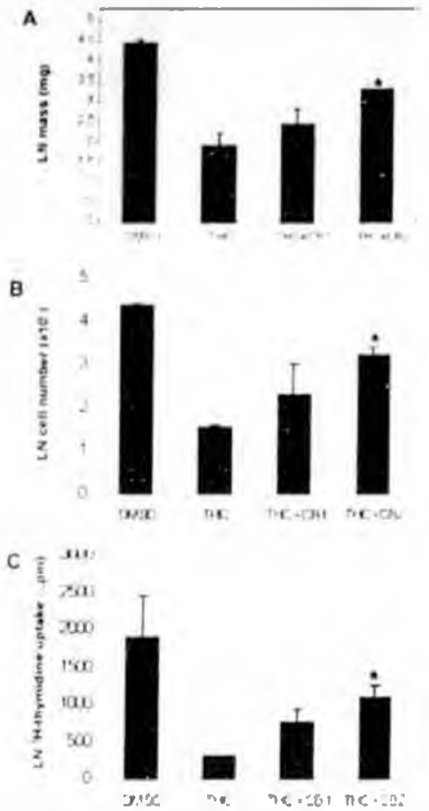

FIGURE 6. The effect of CB1 and CB2 antagonist on Δ⁹-THC-induced suppression of the immune response to 4T1 in vivo. 4T1-sensitized mice were challenged s.c. in their footpads with irradiated 1×10^5 irradiated 4T1 cells. Next, the mice were treated daily for 4 days with CB1 (SR141716A), CB2 (SR144528) antagonists (20 mg/kg), or vehicle 1 h before exposure to Δ⁹-THC (25 mg/kg). The immune response was assayed by determining the increase in lymph node mass (*A*), cell number (*B*), and DNA synthesis (*C*) compared with lymph nodes from unchallenged mice. The results are representative data of experimental groups containing four mice. The experiment was repeated three times with similar results. •, Statistically significant difference ($p < 0.05$) when compared with the controls.

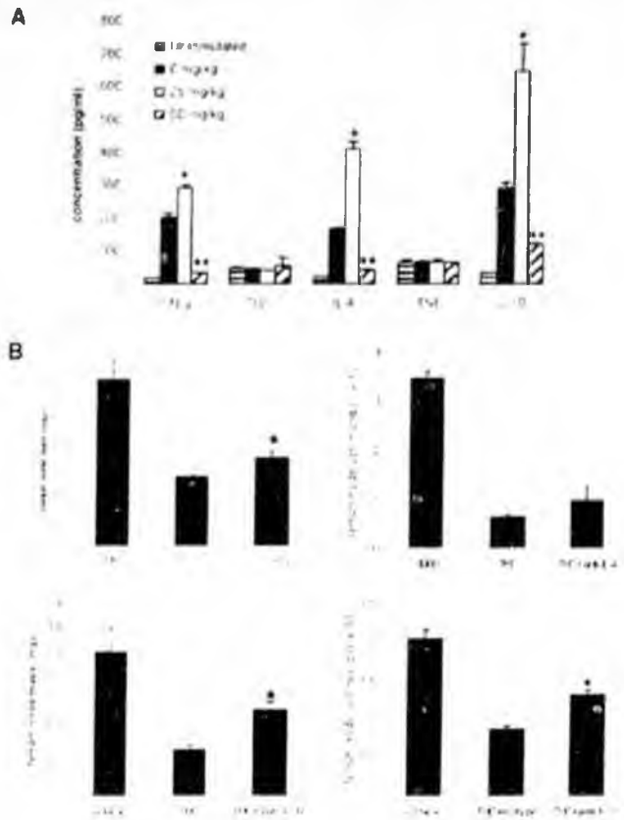

FIGURE 7. Δ⁹-THC exposure leads to alteration in cytokine production. 4T1-sensitized mice were challenged s.c. with 1×10^5 irradiated 4T1 cells and then received daily injection with various doses of Δ⁹-THC (vehicle, 25, and 50 mg/kg). Four days following the challenge with 4T1, the lymph node cells draining the site of injection were harvested, counted and cultured (1×10^6 cells/well) for 24 h in 96-well plates. Next, the supernatants were tested for the presence of various Th1 and Th2 cytokines (*A*). •, Statistically significant increase ($p < 0.05$) when compared with the untreated control. **, Statistically significant decrease ($p < 0.05$) when compared with the untreated control. To examine the effects of Abs against IL-4 or IL-10 on Δ⁹-THC-induced suppression of the immune response, 4T1-sensitized mice were first challenged in their rear footpads with irradiated 4T1 cells (1×10^5 cells). Groups of mice were then were treated with vehicle control + isotype control mAbs, Δ⁹-THC (25 mg/kg/day) + isotype control mAbs, Δ⁹-THC (25 mg/kg/day) + anti-IL-4 mAbs, or Δ⁹-THC (25 mg/kg/day) + anti-IL-10 mAbs. The immune response was assayed 4 days later by determining the mass and cell number of the lymph nodes draining the site of 4T1 injection (*B*). •, Statistically significant differences ($p < 0.05$) when compared with mice treated with Δ⁹-THC alone.

IL-4 mAbs, or Δ⁹-THC (25 mg/kg/day) + anti-IL-10 mAbs. The immune response was assayed 4 days later by determining the mass and cell number of the lymph nodes draining the site of 4T1 injection (Fig. 7*B*). The results showed that exposure to Δ⁹-THC led to a significant reduction in the lymph node mass. However, if the mice were treated with anti-IL-10 mAbs, or to a lesser extent, anti-IL-4 mAbs, the Δ⁹-THC-induced reduction in lymph node mass could be partially reversed. Together, these results further suggested a role for IL-4 and IL-10 in the Δ⁹-THC-induced suppression of the immune response to 4T1.

The effect of Δ⁹-THC exposure of gene expression in lymph node cells draining the site of 4T1 injection

Next, using cDNA array analysis, we screened for alterations in the expression of genes involved in the Th1 and Th2 response in lymph node cells draining the site of 4T1 injection following exposure of 4T1-sensitized mice to 25 mg/kg Δ⁹-THC. Of the 96 genes screened, the expression of 18 genes was significantly (>2-fold) altered in the lymph nodes cells from the Δ⁹-THC-treated mice. The expression of 6 genes was reduced, while the expression of 12 was increased in the lymph node cells isolated from the Δ⁹-THC-treated mice (Table 1). Included in the group of down-regulated genes were the Th1-associated genes, IL-1R, and the TNFR superfamily members DR6 and 4-1BB. In addition, the expression of a number of transcriptional regulators was reduced. Analysis of the genes that were up-regulated following exposure to Δ⁹-THC revealed several Th2-associated genes, including C2ta, eotaxin, IL-13R, IL-4, IL-4R, IL-5, GATA binding protein 3, and growth factor independent 1. In addition, the expression of a number of transcriptional regulators including, suppressor of cytokine signaling (SOCS)2, SOCS5, SOCS7, and Fos-like Ag 2 was increased. Taken together, the results from the cDNA analysis further suggested that exposure to Δ⁹-THC leads to suppression of genes regulating Th1 response and an increase in the Th2 response genes leading to an inefficient immune response against the 4T1 tumor in vivo.

Discussion

In the current study, we demonstrated that exposure to Δ⁹-THC can enhance the growth and metastasis of the 4T1 mammary

Table I. *cDNA array analysis of Th1/Th2-associated gene expression in 4T1-stimulated lymph node cells from vehicle- or Δ^9-THC-treated 4T1-sensitized mice*[a]

Gene Name	Description	Function	Accession Number	Fold Change[b] vs Vehicle
C2ta	Class II transactivator	Th2	NM_007575	+2.1
Scya11/eotaxin	Small chemokine ligand 11	Th2	U26426	+19.4
IL13RA2	Interleukin-13 receptor, α2	Th2	U65747	+4.4
IL-4	Interleukin-4	Th2	M25892	+4.8
IL-4ra	Interleukin-4 receptor, α	Th2	NM_010557	+4.4
IL-5	Interleukin-5	Th2	NM_010558	+2.9
GATA3	GATA binding protein 3	Th2	NM_008091	+2.9
Gfi1	Growth factor independent 1	Th2	NM_010278	+3.5
SOCS2	SOCS2	Trans. reg.	NM_007706	+2.0
SOCS5	SOCS5	Trans. reg.	NM_019654	+6.8
SOCS7	SOCS7	Trans. reg.	NM_080843	+2.6
Fosl2	Fos-like antigen 2	Trans. reg.	NM_008037	+3.2
IL-1R	Interleukin-1 receptor	Th1	U43673	−14.6
DR6	TNF receptor superfamily member	Th1	AF322069	−5.3
4-1BB	TNF receptor superfamily member	Th1	J04492	−5.7
Jund1	Jun proto-oncogene related gene d1	Trans. reg.	NM_010592	−11.7
JNKK2	MAP kinase kinase MKK7	Trans. reg.	U74463	−2.5
JNK1	Mitogen-activated protein kinase 8	Trans. reg.	AB005663	−2.9

[a] Summary of gene expression that was found to be increased or decreased in splenic cells isolated from Δ^9-THC-treated preimmunized mice following stimulation with irradiated 4T1 cells mice compared to the gene expression in splenic cells isolated from vehicle-treated preimmunized mice following stimulation with irradiated 4T1.

[b] Fold change represents the change in gene expression following normalization with β-actin gene expression.

[c] Trans. Reg., Transcriptional regulator.

carcinoma. This is in contrast to our previous finding in which we demonstrated that treatment with Δ^9-THC led to the elimination of the EL-4 leukemia in vivo (8). This stark contrast suggests that some tumors may be more resistant to Δ^9-THC-mediated killing and that the effects of Δ^9-THC on the immune system may play an important role in tumor growth and host survival in such tumor models. More specifically, we hypothesize that the degree of sensitivity of a tumor to Δ^9-THC may be directly related to the level of CB1 and CB2 expression. Importantly, these results would suggest that, although Δ^9-THC may be effective at killing tumors that express cannabinoid receptors, Δ^9-THC-exposure may actually lead to increased growth and metastasis of tumors with low to no expression of cannabinoid receptors due to suppression of the antitumor immune response.

The use of cannabinoids for the treatment of a number of cancers is currently under investigation (8, 10, 37, 38). However, little is known about the relationship between the level of cannabinoid expression and the sensitivity to Δ^9-THC killing. In the current study, we proposed that tumors that express little to no cannabinoid receptors would be relatively resistant to the cytotoxic effects of Δ^9-THC. This was shown in both a mouse and human breast cancer cell line. However, previous studies have shown that exposure to cannabinoids can lead to a decrease in the growth of some breast cancer cell lines in vitro. For example, exposure to anandamide inhibited the proliferation of the MCF-7 and EFM-19 human breast cancer cell line in vitro (38). It should be noted that although the use of CB1 antagonists led to the partial reversal of the anandamide-induced suppression of the proliferation of the EFM-19 cell line, the expression of CB1 or CB2 was not directly examined. To date, little has been reported about the expression and/or role of cannabinoid or vanilloid receptors in either human or mouse breast cancer cell lines. In this report, we demonstrated that the human breast cancer cell lines MCF-7 and MDA-MB-231 express only low levels of CB1 and undetectable levels of CB2 and that neither receptor was detectable in the mouse 4T1 mammary cell carcinoma. In addition, we demonstrated that 4T1 cells express high levels of vanilloid receptor 1 (data not shown). Therefore, because anandamide is also know to act as potent agonist for the vanilloid receptor 1 (39–41), it is possible that the breast cancer cells may be more sensitive to anandamide compared with Δ^9-THC due to the expression of vanilloid receptors. In addition, most previous studies did not directly examine the effects of anandamide on the growth of tumors in an in vivo setting. Therefore, depending on the role of the immune system in the control of growth of the specific tumor tested, it is still possible that the antitumor effects of anandamide and other cannabinoids may be offset by their immunosuppressive properties, ultimately leading to increased tumor growth as seen in our study.

In the current study, we used doses of Δ^9-THC up to 50 mg/kg. Importantly, there is evidence to suggest that the doses of Δ^9-THC used in the current study are pharmacologically relevant. Azorlosa et al. showed that levels as high as 1 μM could be obtained in the plasma of humans (42), and in separate report it was shown that Δ^9-THC can be concentrated 15- to 20-fold in some tissues (43). Therefore, it might be possible to reach levels as high as 20 μM in some tissues after recreational use. In an earlier study, Chan et al. showed that rats injected with 50 mg/kg body weight of Δ^9-THC led to a serum concentration of 10 μM of Δ^9-THC within 10 h of administration (44). Moreover, it has been proposed that the use of higher doses may be necessary in order for Δ^9-THC to be effective medicinally. Therefore, use of up to 50 mg/kg of Δ^9-THC should lead to physiologically relevant concentrations that correlate to the potential concentrations following recreational use and may also correlate with the concentrations necessary for some of the proposed clinical uses.

The immune response to tumors is believed to be mediated primarily by the Th1 response. Skewing of the immune response from the cell-mediated Th1 response to the humoral-mediated Th2 response may lead to a positive environment for tumor growth and development. In the current study, we showed that exposure to Δ^9-THC led to increased production of IL-4 and IL-10, and importantly, administration of Abs against these cytokines reversed the Δ^9-THC-mediated suppression of antitumor immunity. Increased levels of these cytokines have been associated with a number of cancers. For example, increased levels of IL-4 and IL-10 have been reported in patients with breast cancer and this was directly correlated to suppression of the immune response (45). In a separate study examining the immune response in patients with

breast and lung cancer, a shift toward the Th2 immune response was observed (46). Furthermore, increased levels of IL-10 secreting T-regulatory cells have been associated with the inability to mount an effective immune response to Hodgkins lymphoma (47). These studies highlight the potential involvement of the immune system in the development and progression of various tumors, including breast cancer, and suggest that skewing of the immune response to the Th2 phenotype may enhance the tumor's chances of survival. Therefore, the induction of a Th2 response following Δ^9-THC exposure may significantly increase tumor cell survival and ultimately facilitate tumor growth. Interestingly, in this study we also observed an increase in IFN-γ following Δ^9-THC exposure. This may suggest that, in the current study, Δ^9-THC led to an incomplete Th2 skewing of the response as seen in other tumor models (48) or to the activation of cells such as NKT or T regulatory cells (49, 50).

A number of other reports suggest that exposure to cannabinoids may affect the immune system by altering cytokine production in mice (35). For example, exposure to Δ^9-THC leads to inhibition of the Th1 response following *L. pneumophila* infection (26). Exposure of mice to cannabinoids in the concanavalin A-induced hepatitis model led to increased production of Th2-associated cytokines IL-10 and IL-6 and a reduction in the Th1-associated cytokines IL-2 and IFN-γ (51). Similar results were seen when examining the immune response to a murine lung cancer in which it was shown that the Δ^9-THC-induced suppression of the antitumor immune response was due to a Δ^9-THC-mediated shifting of cytokine production (15). Also, a recent study demonstrated that individuals who smoked marijuana on an occasional (eventual to monthly use) or regular basis (weekly to daily use) had abnormal T cell and NK cell functions and increased levels of TGF-β and IL-10 (52), suggesting a possible Th2 bias in humans, similar to what we reported in the current study. In addition, previous studies from our laboratory have shown that Δ^9-THC at doses of 50 mg/kg can lead to the induction of apoptosis in the thymus and spleen of naive mice. Previously, we demonstrated that concanavalin A-activated splenocytes and LPS-activated dendritic cells are relatively resistant to Δ^9-THC-induced apoptosis when compared with their naive counterparts and that the sensitivity correlated with the level of cannabinoid receptor expression (21, 53). Little is know about the expression of cannabinoid receptors in cells involved in the immune response to tumors or the effect of Δ^9-THC on their viability. Therefore, it is possible that Δ^9-THC may suppress the tumor-specific immune response by inducing apoptosis in Th1-associated cells reacting to the tumor challenge, resulting in the observed shift to the Th2 response.

Work using the 4T1 has shown that the immune response to this tumor is primarily mediated by $CD8^+$ cells (54). Additional studies suggested that NKT cells may play a negative role in the response to this tumor (55). For example, $CD1d^{-/-}$ mice had a significantly elevated response to the 4T1 tumor in vivo (55). Following stimulation, NKT can rapidly produce large quantities of IL-4 and IL-10 and have been implicated as possible negative or positive regulators of the antitumor immune response. Another cell that may play an important role in controlling the immune response is the $CD4^+CD25^+$ regulatory T cell. Interestingly, $CD4^+CD25^+$ regulatory T cells have been reported to suppress the antitumor immune response and this suppression was associated with the increased production of IL-10 (47, 56). To date, little is known about the effect of cannabinoids on NKT or $CD4^+CD25^+$ regulatory T cell functions. However, it is possible that Δ^9-THC exposure may directly lead to altered NKT and/or $CD4^+CD25^+$ regulatory T cell activity, resulting in the observed suppression of the antitumor immune response. In addition, it is possible that the observed suppression of the tumor-specific immune response may be mediated through alterations in dendritic cell function. This possibility is supported by work from our laboratory in which we demonstrated that dendritic cells are sensitive to Δ^9-THC-mediated apoptosis (53). The exact role of these cells in the Δ^9-THC-induced suppression of the antitumor immune response is currently being investigated in our laboratory.

Although, the importance of the immune system in protection against many of the common epithelial cancers remains controversial, it is becoming clear that the immune system plays a considerable role in the protection against virally induced or virus-associated tumors. For example, there is an increased rate of Karposi sarcoma, non-Hodgkins lymphoma, Burkitt lymphoma, and cervical cancer in AIDS patients (27). In addition, there have been reports of increased incidences of various lymphomas, cutaneous neoplasms, and de novo breast cancers following organ transplantation (28–31). Although, the immune response to 4T1 has not been fully elucidated, it has been postulated that the immune response may be directed against mouse mammary tumor virus (MMTV) Ags expressed by the tumor (57). Interestingly, a number of studies suggest a possible role of an MMTV-like virus in the etiology of a large proportion of human breast cancers (58, 59). Although direct epidemiological data linking marijuana exposure to increased incidence of breast cancers is not currently available, it is intriguing to speculate that immunocompromised individuals may become increasingly susceptible to MMTV-like infection and to the subsequent development of breast cancers. Therefore, the possibility exists that exposure to marijuana, either through recreational or medicinal use, may lead to increased incidence of immunogenic tumors.

Disclosures

The authors have no financial conflict of interest.

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Prenatal tobacco and marijuana use among adolescents: effects on offspring gestational age, growth, and morphology.

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OBJECTIVE. This longitudinal study examined the effects of tobacco and marijuana use during pregnancy on the gestational age, growth, and morphology of 310 offspring of adolescents. Data were collected during 199 through 1993. METHODOLOGY. The adolescents were drawn from a prena clinic in Pittsburgh, PA. They were interviewed at mid-pregnancy and at delivery to obtain information on tobacco, marijuana, and other substance us before and during pregnancy. Infants were examined 24 to 36 hours after birt RESULTS. The average maternal age was 16.1 (range 12 to 18 years); 70% were African-American. Prenatal tobacco use was associated with reduced birth weight, length, head and chest circumferences, and ponderal index, but not gestational age or the number of morphological abnormalities. Prenatal marijuana exposure was associated with reduced gestational age. Among whites, first trimester marijuana exposure was associated with an increased r of minor physical anomalies. Prenatal marijuana exposure was not associated with any growth outcomes. CONCLUSIONS. These effects of prenatal tobac and marijuana use were prominent despite lower levels of prenatal exposure the offspring of adolescent mothers as compared with the offspring of adult mothers from the same clinic. Young maternal age may increase the offsprin risk of negative effects from prenatal tobacco and marijuana exposure.

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Pharmacology

Prenatal exposure to a cannabinoid agonist produces memory deficits linked to dysfunction in hippocampal long-term potentiation and glutamate release

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Abstract

To investigate the possible long-term consequences of gestational exposure to cannabinoids on cognitive functions, pregnant rats were administered with

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the CB1 receptor agonist WIN 55,212-2 (WIN), at a dose (0.5 mg/kg) that causes neither malformations nor overt signs of toxicity. Prenatal WIN exposure induced a disruption of memory retention in 40- and 80-day-old offspring subjected to a passive avoidance task. A hyperactive behavior at the ages of 12 and 40 days was also found. The memory impairment caused by the gestational exposure to WIN was correlated with alterations of hippocampal long-term potentiation (LTP) and glutamate release. LTP induced in CA3-CA1 synapses decayed faster in brain slices of rats born from WIN-treated dams, whereas posttetanic and short-term potentiation were similar to the control group. In line with LTP shortening, *in vivo* microdialysis showed a significant decrease in basal and K^+-evoked extracellular glutamate levels in the hippocampus of juvenile and adult rats born from WIN-treated dams. A similar reduction in glutamate outflow was also observed in primary cell cultures of hippocampus obtained from pups born from mothers exposed to WIN. The decrease in hippocampal glutamate outflow appears to be the cause of LTP disruption, which in turn might underlie, at least in part, the long-lasting impairment of cognitive functions caused by the gestational exposure to this cannabinoid agonist. These findings could provide an explanation of cognitive alterations observed in children born from women who use marijuana during pregnancy.

Introduction

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Even though marijuana is the most widely used illegal drug among women at reproductive age, reports dealing with the effects of prenatal exposure to this substance of abuse on the length of gestation, fetal growth, and offspring behavior are still controversial (1-4). Confounding factors, such as possible impurities in the drug and concomitant tobacco smoking, may be responsible for inconsistencies in the results reported in studies to date (4, 5). It is likely that many of these conflicting results are due to methodological problems such as the measurement of neonatal outcomes and the context in which the research is conducted. More complex and less understood is the scenario concerning the possible long-term consequences of *in utero* exposure to cannabis derivatives on cognitive functions. In fact, data on this issue are sparse, and the identification of alterations in brain development and adult expression of cognitive and behavioral functions is far from definitive. These inconclusive results may depend on ethical, practical, and interpretative difficulties surrounding research with human subjects (4). In this regard, animal models provide a useful tool for examining the possible developmental and long-term effects of prenatal exposure to cannabinoids (CBs).

Studies performed in adult rats have demonstrated the involvement of a specific CB receptor (CB1) highly expressed in many brain regions (6) in the reinforcing effects of CBs (7) and also in the disruptive effects of either Δ^9-tetrahydrocannabinol (Δ^9-THC) or the synthetic agonist WIN 55,212-2 (WIN) (8) on cognitive processes (9).

In particular, it has been reported that deficits of cognitive functions induced by marijuana use during adulthood could be mainly attributable to the activation of CB1 receptors located in the hippocampus (6, 10, 11), a brain region crucial for certain forms of learning and memory. In this regard, it has been

shown that CBs decrease excitatory postsynaptic currents and disrupt hippocampal long-term potentiation (LTP) (12-14), which is considered the cellular and molecular model for learning and memory (15, 16).

Accordingly, the CB1 receptor-mediated LTP disruption seems to be associated with an inhibition of hippocampal glutamatergic transmission (14, 17), a finding that could be relevant in elucidating the possible electrophysiological and neurochemical mechanisms underlying the effects of CBs on cognitive functions (11, 18).

The aim of the present study was to determine the effect of long-term prenatal exposure to WIN on cognitive function, hippocampal LTP, and hippocampal glutamate release in juvenile and adult rats. Cognitive function, evaluated with a passive avoidance task, was tested 40 and 80 days after birth. LTP was studied in hippocampal slices obtained from 40-day-old rats. Glutamate release was measured by microdialysis in 40- and 80-day-old rats as well as in hippocampal primary cell cultures obtained from pups born from dams exposed to WIN.

Furthermore, because previous clinical findings have reported abnormal motor activity in children of mothers who used marijuana during pregnancy (3, 19), the effect of prenatal WIN exposure on spontaneous motility was analyzed in infant (12-day-old), juvenile (40-day-old), and adult (80-day-old) offspring.

Materials and Methods

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Animal Care.

Experiments were performed in accordance with the guidelines issued by the Italian Ministry of Health (Decreto Legislativo 116/92) and (Decreto Legislativo 111/94-B), the Declaration of Helsinki, and the Guide for the Care and Use of Laboratory Animals as adopted and promulgated by the National Institutes of Health.

Animals and Exposure Conditions.

Primiparous Wistar female rats (Harlan SRC, Milan) weighing 250-280 g were housed for 1 week before exposure to males at constant room temperature (20 ± 1°C) and humidity (60%) with lights on 12 h/day (0800 to 2000 h) and food and water available ad libitum. Pairs of females were then placed with single male rats in the late afternoon. Vaginal smears were taken the following morning at 0900 h. The day on which sperm were present was designated as the gestation day 0 (GD 0).

Pregnant rats were treated daily with WIN (0.5 mg/kg) from GD 5 to GD 20. This dose was chosen on the basis of our pilot studies, which showed that prolonged prenatal exposure to a higher WIN dose (1.0 mg/kg) significantly affected reproduction parameters such as dam and pup weight gain as well as litter size at birth. The drug was suspended in 0.3% Tween 80/saline and injected s.c. at the volume of 1.0 ml/kg. Control rats were injected with the vehicle.

Litters were reduced to a standard size of six male pups (when possible) within 24 h after birth. Litters from both control and WIN-exposed groups were then assigned to nonexposed mothers whose pups were born on the same day.

One pup per litter from different litters per treatment group was used in each experiment. Pups were weaned at 21 days of age. Each male pup was used only for a single test and tested once.

Reproduction Data.

Body weights of the dams were taken on GD 0 and GD 20. The number of dams giving birth and the length of pregnancy were determined. Litter size at birth and postnatal mortality (the number of male pups that died before weaning) were evaluated. Body weights of male rats (one pup per litter from 12 control litters and 10 WIN-exposed litters) were recorded.

Behavioral Studies. *Motor activity.*

Motor activity was recorded in an Opto-Varimex apparatus linked to an IBM PC (Columbus Instruments, Columbus, OH) according to the method described by Wedzony *et al.* (20). The apparatus consisted of a cage (42 × 42 × 30 cm) equipped with 15 infrared emitters (spaced at 2.65-cm intervals) located on the *x* and *y* axes 2-3 cm above the floor of the cage (depending on the size of the animal) and an equivalent number of receivers located on the opposite walls. A further line of emitter/receiver pairs was located ≈5 cm (depending on the size of the animal) above the floor of the cage to detect vertical movements (i.e., rearings). Each interruption of a beam generates an electric impulse scored by a digital counter.

Procedure.

The amount of time spent in ambulatory activity was analyzed by using AUTO-TRACK software (Columbus Instruments, Columbus, OH). Ambulatory activity was defined as a trespass of three consecutive photo-beams, whereas other movements (e.g., repeated interruption of the same photo-beams) were regarded as stereotypic movements. Resting time was calculated as the amount of time during which there were neither ambulatory nor stereotypic movements. Furthermore, vertical activity was measured by recording the number of horizontal beams that were broken by the rearings of the animal.

Tests (5-min sessions) were carried out in a 1 × 1 × 2 m sound-attenuating cabin (Amplifon G-type cabin) illuminated by a 20-W white light source suspended 2 m above the apparatus. Background noise of 42 dB sound pressure level was produced by a fan. Different groups of animals were tested at 12, 40, and 80 days of age. Experimental groups: (*i*) vehicle-treated groups (10 animals) and (*ii*) WIN-treated groups (8 animals). Tests were carried out between 0900 and 1400 h.

Passive avoidance behavior.

A "step-down" apparatus was used according to the method extensively described by Trabace *et al.* (21). It consisted of a compartment (25 × 24 × 24 cm) constructed of black Plexiglas and equipped with a grid

floor to which an elevated compartment (13 × 24 × 16 cm) with a solid Plexiglas floor was attached. A guillotine door (9 × 10 cm) separated the opening between the elevated compartment and the large compartment. A 25-W lamp illuminated the elevated compartment while the large compartment remained dark. Scrambled foot shocks were delivered from a Letica shock generator (LI 2750 Unit, Barcelona). The experiments were performed in a sound-attenuating chamber (Amplifon G-type cabin) that was dark except for illumination of the elevated compartment of the apparatus.

Procedure.

Each animal was removed from the home cage and placed in a holding cage adjacent to the apparatus. Two minutes later, the rat was placed in the illuminated compartment, and, after a 10-s delay, the guillotine door was raised. The time taken by the animal to completely enter into the dark compartment was measured (approach latency) and taken as an index of emotional, nonassociative behavior.

A single 2-s inescapable scrambled foot shock (0.8 mA) was delivered immediately after the rat entered the dark compartment. Twenty-four hours after this session (acquisition trial), each animal was tested for memory retention. The animal was placed in the elevated compartment and latency to re-enter (avoidance latency) the dark compartment was recorded and assumed to be a measure of memory retention. Both acquisition and retention trials lasted for a maximum observation time of 180 s. The experiments were conducted in 40- and 80-day-old male offspring of either control or WIN-exposed mothers, each group consisting of eight rats.

Electrophysiological Studies.

The electrophysiological experiments (see ref. 22 for details) were performed in 40-day-old offspring of either vehicle-exposed ($n = 10$) or WIN-exposed ($n = 9$) mothers. Transverse hippocampal slices were prepared following standard methods. Briefly, rats were decapitated under deep anesthesia by halothane (4.0% in O_2), and the brain was rapidly removed. Slices (350 μm thick) were cut in chilled Ringer solution with a vibroslicer (VSL, WPI, Sarasota, FL), incubated at room temperature (20 ± 2°C) for at least 60 min, and then individually transferred to the recording (submerged) chamber. At least two slices from each animal were tested. Ringer medium contained 124 mM NaCl, 3.5 mM KCl, 1.25 mM NaH_2PO_4, 22.0 mM $NaHCO_3$, 10.0 mM dextrose, 1.0 mM $MgCl_2$, 2.0 mM $CaCl_2$. The solution was maintained at pH 7.4 by continuous bubbling with 5% CO_2 in O_2.

The procedure was as follows. Field-excitatory postsynaptic potentials (f-EPSPs) were recorded from stratum radiatum of CA1 pyramidal cells in response to monopolar stimuli (20 μs-duration) delivered to the Schaffer collateral/commissural pathway via platinum electrodes. Recording electrodes were filled with the medium (1-2 MΩ). Synaptic responses were sampled at 5-10 kHz. Acquisition and analysis were performed by a pCLAMP 5.5/Digidata 1200 system (Axon Instruments Inc., Foster City, CA). The evoked f-EPSPs were measured as the slope of their rising phase after the presynaptic volley. An *I/O* curve was constructed for each slice by plotting increasing single stimulus intensity (scan: 50 to 1,000 μA) vs. the evoked f-EPSP. The current intensity required to produce 50% of maximal response (EC_{50}) was used to assess the synaptic excitability and was used for test stimulation and tetanization.

Samples of f-EPSP were taken every 5 min, averaging 10 consecutive responses (22). Tetanization consisted of two trains of stimuli (100 Hz for 1.0 s at 25-s intervals) delivered after at least 30 min of baseline. Responses were followed up to 180 min and were considered potentiated if their slope was ≥20% of baseline.

The three temporal phases of f-EPSP changes, i.e., posttetanic potentiation (PTP), short-term potentiation (STP), and LTP expression (or maintenance) were distinguished as indicated (15, 16, 22, 23).

Neurochemical Studies. *Microdialysis.*

In vivo experiments were performed in the offspring of WIN-treated and vehicle-treated dams, at the age of 40 and 80 days. Under halothane anesthesia (1.5% mixture of halothane/air), animals were mounted in a David Kopf stereotaxic apparatus, and a microdialysis probe (1 mm dialyzing membrane length) was implanted into the hippocampus. The coordinates relative to bregma were as follows: anteroposterior, −5.2; mediolateral, ±4.0; and dorsoventral, −3.8 mm (24). After the implantation, the probe was secured to the skull with methacrylic cement. Microdialysis measures were performed after at least 36 h of recovery.

Procedure.

On the day of the experiment, the probe was perfused with an artificial cerebrospinal fluid (148 mM NaCl/2.7 mM KCl/1.2 mM $CaCl_2$/0.85 mM $MgCl_2$/2.7 mM glucose) at a constant flow rate (2 μl/min) via a microinfusion pump. At least 300 min later, dialysates were collected every 20 min, and glutamate content was measured by HPLC. The average concentration of three successive stable samples (variation ≤10%) was considered as baseline glutamate outflow. Thereafter, the probe was perfused (10 min) with an isotonic artificial cerebrospinal fluid containing 50 mM KCl. This medium was then replaced with the original one, and further four samples were collected.

Histology.

At the end of each experiment, the probe location was verified in 30-μm-thick coronal cryostat sections. Only those animals in which the probe was correctly located were included in the study.

Hippocampal cell cultures.

Hippocampal cells were prepared from 1-day-old rats (25) born from mothers that had received the WIN-vehicle (control) or WIN during pregnancy. Briefly, neurons were plated on poly-L-lysine (5 μg/ml)-coated dishes at a density of 2.5×10^6 cells per dish and cultured in Eagle's Basal Medium supplemented with inactivated FCS, 25 mM KCl, 2 mM glutamine, and 100 μg/ml gentamycine. Cultures were grown at 37°C in a humidified atmosphere, 5% CO_2/95% air. Cytosine arabinoside (10 μM) was added within 24 h of plating to prevent glial cell replication. The cultures were used in experiments after 8 days *in vitro*.

Procedure.

On the day of the experiment, the cells were rinsed twice by replacing the culture medium with Krebs-Ringer bicarbonate buffer (37°C). Thereafter, five consecutive fractions were collected renewing this solution (400 μl) every 30 min. The first three samples were used to assess basal glutamate levels while, to evoke endogenous glutamate, cells were treated with an isotonic Krebs solution containing 20 mM KCl, applied 20 min before the end of the fourth fraction.

Endogenous glutamate assay.

Endogenous glutamate was quantified by using an HPLC/fluorimetric detection system, including precolumn derivatization *o*-phtaldialdeihyde reagent and a Chromsep 5 (C18) column. The mobile phase consisted of 0.1 M sodium acetate, 10% methanol, and 2.5% tetrahydrofurane, pH 6.5 (0.75 ml/min; ref. 26).

Statistical Analysis.

The reproduction data were analyzed by overall one-way or two-way ANOVAs followed by post hoc tests (Tukey's test) for individual comparisons between groups. Fisher's exact test was used where appropriate.

The analysis of motor activity data were based on overall two-way ANOVAs followed by post hoc tests (Tukey's test).

Mann-Whitney *U* test was used to analyze the passive avoidance data. The electrophysiological results were evaluated by a two-way ANOVA for repeated measures followed by Tukey's test or Student's *t* test, where appropriate. Data obtained from neurochemical studies were analyzed by Student's *t* test for grouped data.

Substances.

WIN mesylate {(R)-(+)-[2,3-dihydro-5-methyl-3-(4-morpholinyl-methyl)pyrrolo (1,2,3-de)-1,4-benzoxazin-6-yl]-1-naphthalenylmethanone} was obtained from Tocris Cookson (Bristol, U.K.). The culture dishes were purchased from Nunc. FCS and basal Eagle's medium were obtained from GIBCO. Poly-L-lysine, trypsin, soybean trypsin inhibitor, DNase, cytosine arabinoside, gentamycine sulfate, and glutamine were obtained from Sigma.

Results

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General Reproduction Data.

General reproduction data are reported in Table 1. Overall one-way ANOVAs showed that prenatal treatment with WIN did not significantly affect dam weight gain [$F = 3.65$, $df = 1/20$, not significant (n.s.)], pregnancy length ($F = 0.33$, $df = 1/20$, n.s.), and litter size at birth ($F = 1.71$, $df = 1/20$, n.s.). Moreover, an overall two-way ANOVA for repeated measures showed that prenatal exposure to

the CB1 receptor agonist did not influence male pup weight gain: ($F_{treatments} = 0.01$, $df = 1/20$, n.s.; $F_{ages} = 1638$, $df = 2/4^{\prime}$, $P < 0.001$; $F_{treatments \times ages} = 0.52$, $df = 2/40$, n.s.). Finally, Fisher's exact test revealed that WIN treatment caused neither hypothermia, catatonia, or hypomotility in dams, nor postnatal toxicity or teratogenesis in male pups (data not shown).

Table 1. Reproduction data

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Behavioral Studies. *Motor activity.*

An overall two-way ANOVA for repeated measures of the ambulatory time (Fig. 1) showed the following effects: $F_{treatments} = 12.72$, $df = 1/16$, $P < 0.005$; $F_{ages} = 100.18$, $df = 2/32$, $P < 0.001$; $F_{treatments \times ages} = 7.80$, $df = 2/32$, $P < 0.001$. Individual comparisons (Tukey's test) revealed that prenatal treatment with WIN significantly increased the ambulatory time of the offspring at both postnatal day (PND) 12 ($P < 0.05$) and 40 ($P < 0.01$). No significant differences were observed in ambulatory activity between the two groups at 80 days of age.

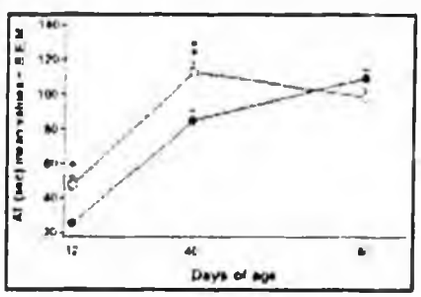

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Fig. 1. Effects of prenatal treatment with WIN on motor activity in 12-, 40-, and 80-day-old rats (●, vehicle; ○, WIN). Each point represents the mean ± SEM of the ambulatory time (AT) spent by rats in 5-min trials. *n* was 10 and 8 for vehicle- and WIN-exposed rats, respectively. *, $P < 0.05$; **, $P < 0.01$ (vs. controls; Tukey's multiple comparison test).

Furthermore, overall two-way ANOVAs for repeated measures of both stereotypic time and rearings did not reveal any significant change between controls and WIN-exposed offspring at all ages (PND 12, 40, and 80) considered in the present study (data not shown).

Passive avoidance behavior.

As shown in Fig. 2, during the first (acquisition) trial 40- and 80-day-old rats from the control group showed approach latencies that did not differ significantly with respect to animals prenatally exposed to WIN. However, when the trial was repeated 24 h later (retention trial), the avoidance latencies of the WIN-exposed group were significantly shorter than those of control animals ($P < 0.01$, Mann-Whitney

U test).

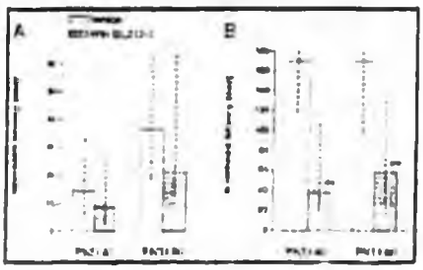

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Fig. 2. Effect of prenatal WIN exposure on approach latency (*A*) and avoidance latency (*B*) measured 24 h later (retention) of 40- and 80-day-old offspring in a passive avoidance task. Data represent median values and interquartiles (dashed line). **, $P < 0.01$ with respect to relative control (Mann-Whitney *U* test).

Electrophysiological Studies. *Synaptic excitability.*

Changes in basal synaptic excitability in hippocampal slices from 40-day-old rats were investigated, comparing the current intensity required to produce 50% of maximal response (excitatory current 50) before tetanization in both groups and by the evaluation of the number of slices exhibiting PTP.

Although the EC_{50} in slices from WIN-treated rats (WIN-slices) was found to be slightly higher than it was in controls, no statistical significance was reached (Student's *t* test). This result indicates that the responsiveness of CA3-CA1 synapses to electrical stimuli was not affected by the treatment.

Moreover, the first potentiation, which immediately follows tetanization (PTP), was found to be comparable in the two groups [255.90 ± 18.07 and 229.18 ± 23.43% for vehicle- and WIN-treated animals, respectively (Student's *t* test)]. Furthermore, the occurrence of slices showing a PTP of at least 200% was similar [22/22 and 21/21 in slices from control and WIN-treated group, respectively (Table 2)].

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Table 2. Number of slices from 30- to 40-day-oid offspring showing PTP, STP, and LTP of f-EPSP

Taken together, these results indicate that no alterations in basal synaptic excitability were evident in slices from prenatally WIN-exposed rats.

Time course of STP and LTP.

In control slices the decay of f-EPSP potentiation after tetanization followed a typical biphasic curve (Fig. 3*A*). Thus, in agreement with previous studies (15, 16, 23, 27), the f-EPSP slope in control slices showed a first fast decremental phase lasting 15 to 20 min (STP), which then slowly decayed over the

observation time (180 min).

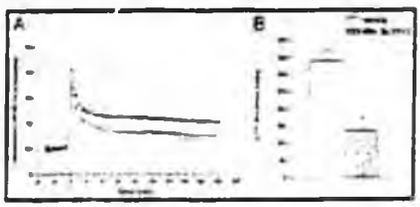

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Fig. 3. Prenatal WIN selectively suppresses LTP maintenance but not its induction. (*A*) Time course of the averages of f-EPSP slopes from slices obtained from 40-day-old offspring of vehicle-treated (●) and WIN-treated dams (○). Values of f-EPSP slopes have been normalized to the pretetanus period. Each point represents the average ± SEM of 10 consecutive responses taken every 5 min. Just after tetanization (given at time −5 min), the values of f-EPSP first potentiation (i.e., the PTP) were 255.90 ± 18.07 and 229.18 ± 23.43% for vehicle- and WIN-treated groups, respectively (not significant, Student's *t* test). (*B*) Duration of LTP. Evoked f-EPSPs were considered potentiated until their slope was ≥20% with respect to baseline. For the vehicle group, LTP duration was estimated by fitting analysis of the curve in *A* to calculate the interception point where this curve asymptotically subsided to a value of +20%. It occurred at 334.45 ± 25.36 min after tetanus. However, the curve describing LTP expression of the WIN-treated group (data from *A*) returned to +20% of baseline in 136.87 ± 12.18 min. Bars represent the mean ± SEM obtained from 22 and 21 slices from vehicle- and WIN-exposed rats, respectively. *, $P < 0.001$ vs. vehicle (Student's *t* test).

in line with the PTP results (see above), the time course of the early phase of f-EPSP de-potentiation (STP) was similar in both treated and control groups (Fig. 3*A*). Indeed, a two-way ANOVA showed no significant deviation between the two curves ($P < 0.09$) in the STP interval (from 5 to 20 min).

Thereafter, however, the averaged curve describing the LTP-expression phase decayed faster in slices from WIN-treated than in vehicle-treated offspring (Fig. 3*A*). Accordingly, the deviation between the two curves, in the 20- to 180-min interval after tetanization, was statistically significant ($P < 0.01$, two-way ANOVA).

Moreover, whereas a typical time course of LTP was seen in 20/22 tested slices from control animals, the potentiation remained above +20% for >60 min in only 3 of 21 slices from the WIN group (Table 2).

As shown by fitting analysis, the interception points at which the averaged curves of LTP, asymptotically subsided to a value of +20%, with respect to the baseline, were at 334.45 ± 25.36 and 136.87 ± 12.18 min, after tetanus, in control and WIN slices, respectively (Fig. 3*B*).

Neurochemical Studies. *Hippocampal cell cultures experiments.*

Basal extracellular glutamate levels were measured in hippocampal cell cultures obtained from 1-day-old pups. As shown in Fig. 4*A*, glutamate levels were found to be significantly lower ($P < 0.01$; Student's *t* test) in animals born from mothers exposed to WIN during pregnancy than in those born from

vehicle-treated mothers.

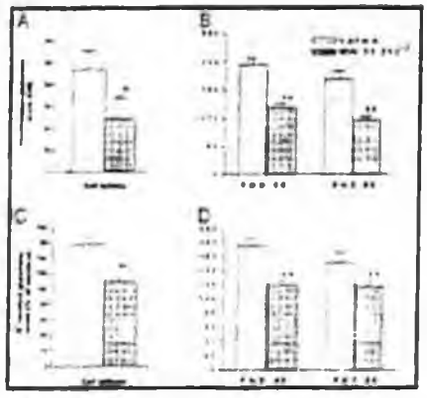

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Fig. 4. Effect of prenatal exposure to WIN on basal (*A* and *B*) and K^+-evoked (*C* and *D*) extracellular hippocampal glutamate levels in cell cultures (*A* and *C*) and *in vivo* at 40 and 80 days of age (*B* and *D*). Each column represents the mean ± SEM obtained from 22 and 11 replications for *in vitro* and *in vivo* experiments, respectively. **, $P < 0.01$ vs. vehicle (Student's *t* test).

Bath application of KCl (20 mM) increased glutamate extracellular levels in both cell cultures. However, the increase was significantly lower ($P < 0.01$; Student's *t* test) in cultures of rats born from WIN-treated mothers than in those obtained from control pups (Fig. 4*C*).

Microdialysis in vivo.

Basal extracellular hippocampal glutamate levels, evaluated as the mean of three stable dialysates, were significantly lower ($P < 0.01$; Student's *t* test) in both 40- and 80-day-old rats born from mothers treated with WIN during pregnancy than in those born from mothers treated with the vehicle (Fig. 4*B*).

A 10-min pulse of high K^+ (50 mM) solution significantly increased glutamate efflux in both groups of animals. However, the K^+-evoked glutamate efflux from the hippocampus of rats born from mothers exposed to WIN during pregnancy, was significantly lower ($P < 0.01$; Student's *t* test) than the enhancement observed in rats born from mothers treated with vehicle during pregnancy (Fig. 4*D*).

Discussion

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The present study, by combining different methodological approaches, provides evidence that maternal exposure to the CB1 receptor agonist WIN induces impairment of memory retention capacities in the offspring. This impairment is associated with alterations of hippocampal LTP and glutamate outflow.

WIN-exposed offspring were also characterized by motor hyperactivity during infantile and juvenile, but not adult, periods.

Memory impairment in prenatally WIN-exposed rats, assessed by the disruption in the retention of a passive avoidance task, seems to be a persistent condition, present at both 40 and 80 days of age.

Memory impairment does not appear to be attributable to alterations of a nonassociative nature, because approach latency, measured during the acquisition trials of the learning task, remained unchanged.

WIN-treated dams did not show hypothermia, catatonia, or hypomotility, which are typically induced by the high and/or moderate exposure to CBs (8). Moreover, the dose of WIN used in the present study (0.5 mg/kg/die s.c.) produced neither gross malformations nor overt signs of toxicity, and it failed to alter reproductive parameters, such as dam and pup weight and weight gain. Furthermore, litters of WIN-treated dams were assigned to untreated dams to avoid confounding factors generated during lactation as well as malnutrition.

However, memory deficit produced by prenatal WIN may be dissociated from the hyperactivity, which has been reported to be caused postnatally by WIN (28), because the latter was present at 40 but not at 80 days of age, whereas the former was present at both periods.

Memory impairment observed in offspring exposed prenatally to WIN was correlated to alterations in both hippocampal LTP, a widely accepted cellular and molecular model for learning and memory (15, 16), and hippocampal glutamate release.

LTP was assessed in brain slices from 40-day-old rats, whereas spontaneous and K^+-evoked glutamate release was measured *in vivo* at 40 and 80 days of age, as well as in cell cultures obtained from 1-day-old pups.

Slices from WIN-treated animals showed a reduced ability to maintain LTP over time, whereas basal synaptic excitability and LTP induction phases (PTP and STP) were normal.

These results are in agreement with previous observations made in brain slices from adult rats showing that bath application of low concentrations of Δ^9-THC selectively reduced LTP duration but not the extent of PTP (12).

However, other authors have reported that CB1 receptor activation by WIN, in slices from adult rodent brain, suppressed both early (induction) and late (maintenance/expression) phases of LTP in hippocampal CA3-CA1 synapses (11, 14, 29). The inhibitory effect of CBs on hippocampal LTP has been attributed to the reduction in presynaptic glutamate release and the consequent suppression of *N*-methyl-D-aspartate-mediated entry of postsynaptic Ca^{2+}, necessary for LTP induction, rather than to a direct modulation of postsynaptic ionic channels (11, 14, 30).

According to this hypothesis, the microdialysis data have shown that basal and K^+-stimulated extracellular hippocampal glutamate release was significantly lower in animals born from WIN-treated dams than in control animals.

Therefore, it might be suggested that in rats exposed prenatally to WIN, glutamate release is sufficiently preserved to activate *N*-methyl-D-aspartate receptors responsible for LTP induction, but it is not

sufficiently sustained to stimulate postsynaptic metabotropic and α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptors involved in LTP maintenance (15).

The reduced glutamate outflow seems to be a precocious and persisting consequence of prenatal exposure to the CB agonist: it is already present in cell cultures, obtained from 1-day-old WIN-exposed pups, and persists unmitigated at 40 and 80 days of age.

Although the reduction of glutamate outflow could explain the disruption of LTP induced by gestational exposure to the CB1 receptor agonist, the electrophysiological alterations may, in turn, represent a neuronal substrate responsible for the selective retention deficit (reduction of avoidance latencies in a passive avoidance task) that was observed in the offspring of mothers treated with WIN during pregnancy.

Thus, it may be hypothesized that gestational exposure to the CB produces an irreversible alteration to endogenous CB1 systems in the developing brain (29, 31), possibly leading to a long-term disruption of hippocampal function. Accordingly, CB1 receptors are already measurable at GD 14 in a variety of brain structures including hippocampus (32).

Additional studies are needed to clarify whether the effects caused by WIN are reproduced by Δ^9-THC and whether they may be prevented by CB1 receptor antagonists such as SR 141716.

Concerning the clinical relevance of the present study, it is important to estimate, by extrapolation, whether the dose of WIN administered compares with that of Δ^9-THC absorbed by cannabis users.

Previous studies have estimated that 5 mg/kg Δ^9-THC in rats corresponds to a moderate exposure of the drug in humans, correcting for the differences in route of administration and body weight surface area (33, 34, 35).

However, WIN has been found to be 3-10 times more potent than Δ^9-THC, depending on the administration route and the endpoints considered (8, 36, 37). This estimate is consistent with the relative K_i of each compound for CB1 receptors in brain membranes, i.e., 2-12 nM vs. 35-80 nM for WIN and Δ^9-THC, respectively (38). Based on these considerations, the dose of WIN used in the present study might correspond to a moderate, or even to a low, exposure to cannabis in humans.

The present results are in line with clinical data showing that the consumption of marijuana by women during pregnancy has negative consequences on the cognitive functions of their children. In particular, memory has been reported to be negatively associated with daily marijuana use, and this statistical association remained after checking for confounding variables (39).

Moreover, the increased motor activity observed in both infant and juvenile offspring of WIN-treated dams is consistent with data showing that children prenatally exposed to marijuana were rated, at a prepuberty age, as hyperactive, inattentive, and particularly impulsive (3, 19).

Whatever the mechanism of action of prenatal exposure to WIN, our results suggest that alterations of

hippocampal glutamategic function may underlie, at least in part, the subtle impairment of cognitive processes induced by gestational marijuana exposure (1, 4, 39).

Acknowledgements

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Abbreviations

CB, cannabinoid; f-EPSP, field excitatory postsynaptic potential; LTP, long-term potentiation; PTP, posttetanic potentiation; STP, short-term potentiation; GD, gestation day; PND, postnatal day; WIN, WIN 55,212-2; Δ^9-THC, Δ^9-tetrahydrocannabinol.

Footnotes

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Marijuana Use and Birth Defects

When parents abuse alcohol or drugs, the consequences can be devastating for their children. Children of alcoholic or drug-dependent parents can suffer neglect, developmental hindrances, and emotional and physical abuse. However, people who abuse substances can also damage the health of their unborn children. For example, a woman who smokes marijuana during pregnancy can put the fetus at risk for a host of dangerous problems, such as low birthweight, developmental difficulties, and even drug addiction. Similarly, a woman who drinks alcohol while pregnant—perhaps before she even realizes she's pregnant—can cause heart defects, growth retardation, and serious neurological injury to the fetus (commonly known as fetal alcohol syndrome, or FAS).

Much research has shown that alcohol and drug use on the part of men and women can impair fertility and/or lead to birth defects in their children. Despite these known risks, a National Institute on Drug Abuse study on alcohol and other drug use among pregnant women found that 5.5 percent of the study participants used illicit drugs while pregnant, 18.8 percent used alcohol, and 20.4 percent used tobacco.[1] These figures are even higher for teen mothers. In another study, one-third of mothers between the ages of 12 and 18 used marijuana before their pregnancies, and of those, over half used it at some time during their pregnancies.[2] With statistics like these, it's important that teens understand the additional risks of alcohol and drug use, particularly if they are sexually active.

Specifically, how does marijuana affect the fetus? Like alcohol and tobacco, marijuana use has been linked to low birth weight and premature babies. One study showed that marijuana use by the mother is associated with slow embryo growth and spontaneous abortion in the early stages of pregnancy. Other studies have shown that marijuana causes FAS-like symptoms in newborns, such as abnormally shaped heads, small size, and nervous-system difficulties. Research also suggests that the fetuses of teen mothers, as opposed to those of adult mothers, may be especially vulnerable to the damage marijuana causes, especially during the first trimester (when the teen may not even know she's pregnant).[2] Symptoms such as excessive trembling and withdrawal-like irritability in newborns have also been associated with heavy marijuana use by the mother.

In addition, THC, the active component in marijuana, can be passed from mother to infant through breastfeeding.[1] This chemical is more concentrated in the mother's breastmilk than it is in her blood, and use of marijuana by breastfeeding mothers has been linked to motor development problems in newborns.

In general, it is important to remember that the fetus can be exposed to anything that enters the mother's body. THC can pass freely through the placenta. If marijuana poses a health risk to the mother's body, it also poses a potential risk to the fetus she carries in her body.

For males, studies have established that marijuana can lower sperm count, but the drug can also cause slow-moving or abnormally-shaped sperm, which can ultimately lead to miscarriages, low fetal birth weight, or other health problems. [3] Also, simply smoking marijuana around a pregnant woman could endanger both the woman and the fetus if she inhales the secondhand smoke.

Does your teen want to be a parent someday? She may feel that she's too young to worry about children right now, but if she becomes addicted to drugs or alcohol, her addiction could last well into her adult years. Studies indicate that female drug users usually reduce their drug intake after they discover they are pregnant, but they often do not or cannot quit completely.[4] This is a testament to just how addictive drugs can be, even at a time when it is especially important to stay healthy. When your teen finally decides she does want to be a parent, she may have a very difficult time quitting.

Make sure your teen knows that substance abuse can permanently damage the life chances of his future children. The National Council on Alcoholism and Drug Dependence established National Alcohol- and Other Drug-Related Birth Defects Awareness Week (May 13-19) to recognize and help educate others about the dangers of prenatal exposure to alcohol and drugs. This is one kind of birth defect that is highly preventable, so take this opportunity to talk to your teen about these and other serious risks of substance abuse.

For more information, see the following sites:

The National Council on Alcoholism and Drug Dependence, "Alcohol- and Other Drug-Related Birth Defects."

Marijuana Interferes With Early Pregnancy

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In utero marijuana exposure associated with abnormal amygdal dopamine D2 gene expression in the human fetus.

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Department of Clinical Neuroscience, Psychiatry Section, Karolinska Institut 171-76 Stockholm, Sweden.

BACKGROUND: Marijuana (Cannabis sativa) is the illicit drug most used b pregnant women, and behavioral and cognitive impairments have been documented in cannabis-exposed offspring. Despite the extensive use of marijuana, very limited information exists as to the consequences of prenatal cannabis exposure on the developing human brain. METHODS: We optimiz an in situ hybridization histochemistry technique to visualize mRNA expression in midgestation (weeks 18-22) human fetal specimens from moth with and without documented evidence of cannabis use during pregnancy. Tl cannabinoid receptor type 1 (CB(1)) and major dopamine receptor subtypes, (1) and D(2), were examined in the striatum and mesocorticolimbic structure (amygdala and hippocampus). RESULTS: Adjusting for various covariates, found a specific reduction, particularly in male fetuses, of the D(2) mRNA expression levels in the amygdala basal nucleus in association with maternal marijuana use. The reduction was positively correlated with the amount of maternal marijuana intake during pregnancy. No significant cannabis-related alterations were detected in the hippocampus or caudal striatum for the D(2), (1), and CB(1) mRNA levels, although alcohol showed significant contributi to striatal D(1)/D(2) expression. CONCLUSIONS: These human fetal findin suggest that in utero cannabis exposure may impair distinct mesocorticolimb neural systems that regulate emotional behavior.

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Marijuana impairs growth in mid-gestation fetuses.

Hurd YL, Wang X, Anderson V, Beck O, Minkoff H, Dow-Edwards D.

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Karolinska University Hospital, Stockholm, Sweden.

Marijuana (Cannabis sativa) is the most commonly used illicit drug by pregnant women, but information is limited about the effects of prenatal cannabis exposure on fetal development. The present study evaluated the influence of early maternal marijuana use on fetal growth. Women electing voluntary saline-induced abortions were recruited at a mid-gestational stage (pregnancy (weeks 17-22), and detailed drug use and medical histories were obtained. Toxicological assays (maternal urine and fetal meconium) were us(in conjunction with the maternal report to assign groups. Subjects with documented cocaine and opiate use were excluded. Main developmental outcome variables were fetal weight, foot length, body length, and head circumference; ponderal index was also examined. Analyses were adjusted f(maternal alcohol and cigarette use. Marijuana (n=44)- and nonmarijuana (n=95)-exposed fetuses had similar rates of growth with increased age. However, there was a 0.08-cm (95% CI -0.15 to -0.01) and 14.53-g (95% CI 28.21 to 0.86) significant reduction of foot length and body weight, respectively, for marijuana-exposed fetuses. Moreover, fetal foot length development was negatively correlated with the amount and frequency of marijuana use reported by the mothers. These findings provide evidence of a negative impact of prenatal marijuana exposure on the mid-gestational fetal growth even when adjusting for maternal use of other substances well knowr to impair fetal development.

PMID: 15734273 [PubMed - in process]

[redacted]

Drug Abuse Warning Network

The DAWN Report

AUGUST 2003

Marijuana-related Emergency Department Visits by Youth

In Brief

- According to the Drug Abuse Warning Network (DAWN), marijuana is the most frequently reported drug in emergency department (ED) visits related to drug abuse in youth age 12 to 19.
- In 2001, youth age 12 to 19 made an estimated 26,706 ED visits related to the abuse of marijuana or marijuana with other substances.[1] More than 60 percent (16,516) of these visits involved youth age 12 to 17.
- From 1994 to 2001, youth age 18 to 19 had the highest rates of marijuana-related ED visits per 100,000 population; adults age 35 and over had the lowest rates. Rates for youth age 12 to 17 fell between these two extremes.
- The rate of marijuana-related ED visits[2] among youth has been increasing. For youth age 12 to 17, the rate of marijuana-related ED visits rose 126 percent from 1994 to 2001, while their overall rate of drug-related ED visits was stable. For youth age 18 to 19, the rate of marijuana-related visits increased 149 percent over this time period.
- More than half of marijuana-related ED visits among youth age 12 to 17 involve other drugs,[3] particularly alcohol, cocaine, and amphetamines.
- When marijuana alone was implicated in the ED visit, *psychic effects* was the most commonly cited motive for using the drug (in 60% of cases for youth age 12 to 17), and *unexpected reaction* was the most commonly cited reason for the ED visit (40% of cases).

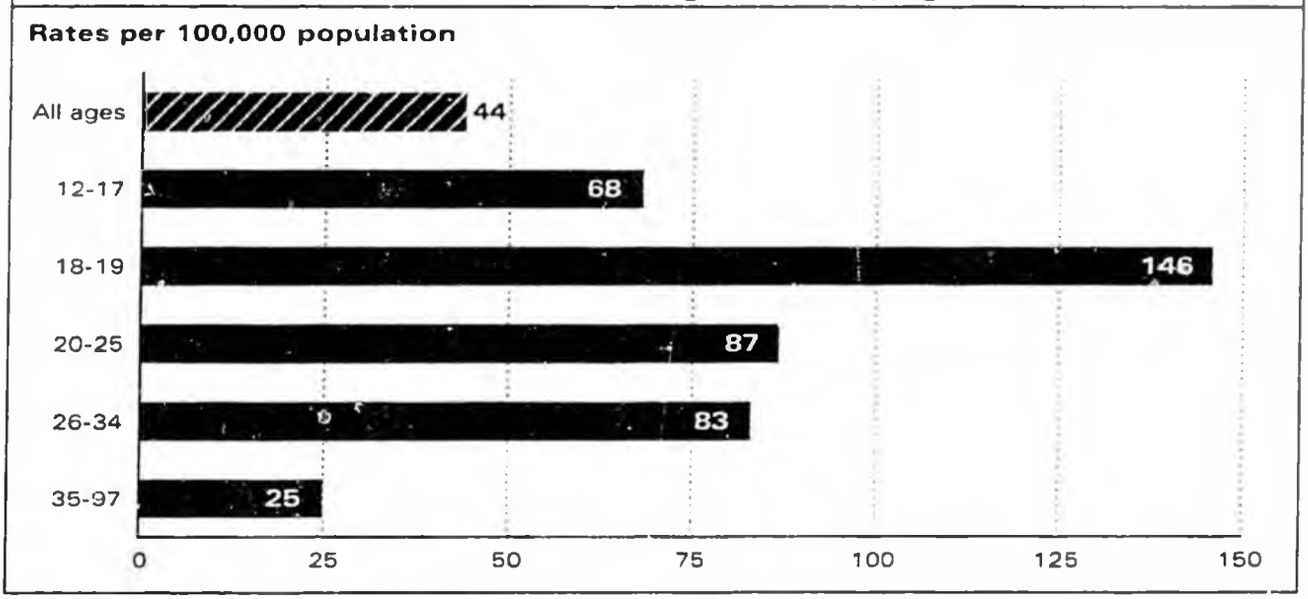
[1] The number of DAWN visits does not represent individuals because a patient may make multiple visits to an ED.

[2] Rates are expressed as the number of ED visits per 100,000 population in the age group.

[3] Up to 4 drugs plus alcohol may be reported for a single visit.

FIGURE 1

Marijuana in ED visits related to drug abuse, by age: 2001



Marijuana is more frequently reported than other drugs in ED visits among youth.

Marijuana abuse by youth is a major and growing problem in the U.S. An estimated 3.6 million youth age 12 to 17 reported using marijuana in 2001,[4] an increase of 14 percent since 2000.

Patients who present to hospital EDs for problems related to marijuana abuse represent only a small fraction of users. Still, in ED visits related to drug abuse, DAWN finds that marijuana is reported more frequently than any other drug for youth age 12 to 19.

In 2001, youth age 12 to 17 made an estimated 16,516 ED visits related to the abuse of marijuana or marijuana with other substance(s).[5] Youth age 18 to 19 added another 10,190 ED visits involving marijuana.

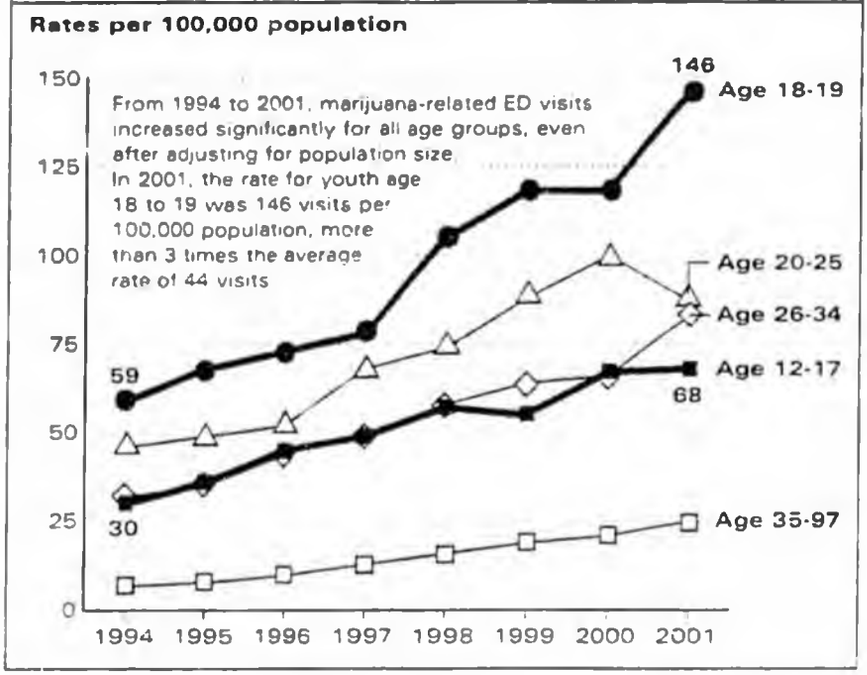
Overall, marijuana was a factor in more than 1 in 4 drug-related ED visits among youth (27% of 61,695 visits for age 12 to 17, and 29% of 34,578 visits for age 18 to 19).

Youth account for a disproportionate number of marijuana-related ED visits.

In 2001, youth age 12 to 17 made up 15 percent of marijuana-related ED visits and 28 percent of marijuana-only visits. By contrast, they were 10 percent of the population and 10 percent of all DAWN ED visits.

FIGURE 2

Marijuana-related ED visits, by age group: 1994 to 2001



Youth age 18 to 19 accounted for 9 percent of marijuana-related visits and 14 percent of marijuana-only visits. This age group was only 3 percent of the population and 5 percent of DAWN ED visits overall.

Marijuana-related ED visits are highest for youth age 18 to 19.

In 2001, there were 68 marijuana-related visits per 100,000 youth age 12 to 17. For youth age 18 to 19, the rate was 146 visits per 100,000, the highest of all age groups (**Figure 1**). By contrast, the rate across all age groups was 44 visits per 100,000.

Since 1994, youth age 18 to 19 have had the highest rates of marijuana-related ED visits, and adults age 35 and over have had the lowest. Rates for youth age 12 to 17 fell between these two extremes (**Figure 2**).

Marijuana-related ED visits are increasing faster than drug-related visits overall.

Marijuana-related ED visits have been increasing much faster than drug-related visits overall, with increases evident in every age group. The rate of marijuana-related visits for all ages increased 151 percent, from 17 to 44 per 100,000 population, from 1994 to 2001. By contrast, the rate of drug abuse-related ED visits overall increased a mere 12 percent, with many age groups showing no increase at all.

Among youth age 12 to 17, the rate of marijuana-related visits increased 126 percent from 1994 to 2001, while the rate of drug abuse visits overall did not increase at all.

Among youth age 18 to 19, the rate of marijuana-related visits increased 149 percent from 1994 to 2001, while the rate of drug abuse visits overall increased only 20 percent.

[4] Office of Applied Studies, Substance Abuse and Mental Health Services Administration (8/2002) *Results From the 2001 National Household Survey on Drug Abuse (NHSDA): Volume III Detailed Tables.* Rockville, MD.

[5] Up to 4 drugs plus alcohol may be reported for a single visit.

Marijuana is often reported with other drugs.

Why do individuals go to EDs as a result of marijuana abuse? In many cases, marijuana is present along with other drugs.

In 2001, almost half (46%) of marijuana-related visits among youth age 12 to 17 involved marijuana as the only drug reported. In 1994, this number was 35 percent[6] (**Figure 3**).

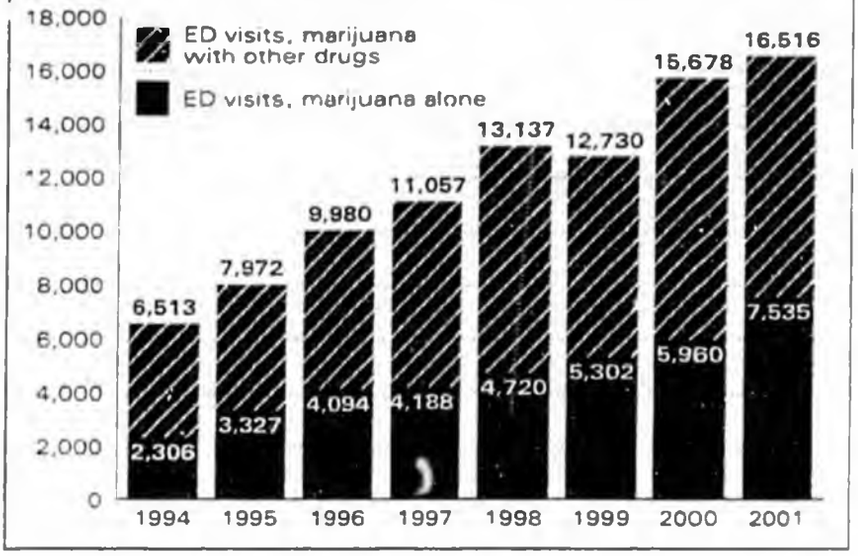
Despite this growth in marijuana-only visits, over half of the marijuana-related ED visits continue to involve more than one drug.

In 2001, alcohol was reported most often with marijuana for all age groups. Among youth age 12 to 17, alcohol was present in more than a quarter (26%) of marijuana-related ED visits. In this group, 14 percent involved only marijuana and alcohol, and 12 percent involved marijuana, alcohol, and other drug(s). Alcohol was present in nearly half of all marijuana visits that involved multiple drugs.

In terms of numbers, 4,313 ED visits by youth age 12 to 17 involved marijuana with alcohol. Marijuana also was reported frequently with cocaine (1,711), amphetamine (760), unnamed benzodiazepines (668), unnamed narcotic analgesics (626), LSD (519), and methamphetamine (444) (**Table 1**, page 4).

FIGURE 3

Marijuana-related ED visits, age 12 to 17: 1994 to 2001



These combinations appear to be changing. For youth age 12 to 17, unnamed narcotic analgesics (626), heroin (282), and unnamed tricyclic antidepressants (264) were among the top 10 drugs reported with marijuana in 2001. None of these drugs appeared in the top 20 in 1994.

Why marijuana leads to ED visits is unclear.

When multiple drugs are involved, it is not possible to know which drug (or combination) precipitated the ED visit. Only one reason for the ED visit and one motive for abusing the drug are recorded for each ED visit, regardless of the number of drugs involved.

However, the reason for the visit can be determined in cases where marijuana is the only drug. Among youth age 12 to 17 in 2001, where marijuana was the only drug reported, *psychic effects* (60%) was the most frequently cited motive for the marijuana use. *Dependence* was cited in 15 percent of cases.

Unexpected reaction (40%) was the most frequently reported reason for these ED visits. *Overdose* (10%), *chronic effects* (6%), *accident/injury* (4%), *seeking detoxification* (3%), and *withdrawal* (2%) were less frequent reasons.

These patterns differ somewhat for the multi-drug visits. For motive, multi-drug visits tended to include more suicide attempts and overdoses, with proportionately fewer psychic effects and unexpected reactions.

[6] The proportion for youth age 18 to 19 did not change; it was 31 percent in 1994 and 2001.

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TABLE 1

Top 20 drugs mentioned with marijuana in ED visits, youth age 12 to 17: 1994 and 2001

Substance mentioned with marijuana	1994
alcohol-in-combination	1,936
LSD (lysergic acid diethylamide)	783
cocaine	699
methamphetamine	528
amphetamine	276
PCP (phencyclidine)	229
acetaminophen-diphenhydramine	198
diazepam	159
datura sauveolens	126
psilocybin	114
benzodiazepines-NOS	99
anxiolytics, sedatives, and hypnotics-NOS	82
acetaminophen	77
paroxetine	76
hydrocodone	72
mescaline	70
clonazepam	69
sertraline	66
caffeine	64
amitriptyline	60

Substance mentioned with marijuana	2001
alcohol-in-combination	4,313
cocaine	1,711
amphetamine	760
benzodiazepines-NOS	668
narcotic analgesics-NOS	626
LSD (lysergic acid diethylamide)	519
methamphetamine	444
heroin	282
tricyclic antidepressants-NOS	264
PCP (phencyclidine)	252
acetaminophen	234
psilocybin	212
barbiturates-NOS	208
MDMA (Ecstasy)	198
alprazolam	181
sertraline	154
clonazepam	152
acetaminophen-chlorpheniramine	134
flunitrazepam	119
drug unknown	111

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Emergency Department Trends From the Drug Abuse Warning Network, Final Estimates 1995–2002

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TRENDS IN MAJOR SUBSTANCES OF ABUSE

This section presents annual estimates from DAWN for total drug-related ED episodes and mentions of major substances of abuse.

"Major substances of abuse" include the most common illicit drugs reported to DAWN, alcohol reported in combination with any other substance reported to DAWN, and lower frequency drugs of particular policy interest (e.g., club drugs such as MDMA (Ecstasy), and GHB). The specific terms (including street names) reported to DAWN for each drug category are listed, with corresponding mentions from 1995 to 2002, in Table 2.4.0 (full-year estimates) and Table 12.4.0 (full-year rates per 100,000 population). Corresponding half-year tables are Tables 2.3.0 and 12.3.0, respectively.

One ED episode can include mentions of one drug alone or mentions of multiple drugs. Major substances of abuse, such as cocaine, heroin, and marijuana, are often reported in combination with other drugs. Alcohol is reportable to DAWN only when present in combination with another reportable drug. Therefore, the total number of drug mentions exceeds the number of episodes. Mentions for individual drugs, which may be recorded only once per episode, are equivalent to episodes. For example, the number of cocaine mentions is equivalent to the number of episodes in which cocaine was mentioned.

The following discussion focuses primarily on comparisons of final estimates for 2002 with 2001. Tables also show statistical tests comparing 2002 estimates with those for 2000 and, for long-term trends, 2002 estimates with those for 1995 (the earliest year shown in the tables). In addition, long-term trends in drug-related ED episodes overall and for those involving the most frequently mentioned illicit drugs and alcohol-in-combination are shown in Figure 3.

DAWN estimates for 2002 are based on data from a nationally representative sample of 437 responding hospitals (Table 1.1).

TOTAL DRUG-RELATED ED EPISODES

- In 2002, there were 670,307 drug abuse-related ED episodes in the coterminous U.S., with 1,209,938 drug mentions (on average, 1.8 drugs per episode) (Table 2.2.0).
- There were no significant increases from 2001 to 2002 in total drug-related ED episodes or in ED drug mentions (Table 2.2.0). Total ED visits (that is, ED visits for any reason) increased 2 percent (from 100.5 million to 102.8 million) during this period.
- In 2002, drug abuse-related ED visits occurred at the rate of 261 ED episodes per 100,000 population in the coterminous U.S. (Table 12.2.0).
- From 2001 to 2002, among the most common major substances of abuse, only amphetamines showed a significant increase (17%, from 18,555 to 21,644). Mentions of alcohol-in-combination (207,395 in 2002), cocaine (199,198), marijuana (119,472), heroin (93,519), and methamphetamine (17,696), were all statistically unchanged. There were no significant decreases among these substances (Table 2.2.0).

- Among the less frequently mentioned major substances of abuse, only 2 had significant increases from 2001 to 2002. Mentions of inhalants rose 187 percent (from 522 to 1,496), returning to the level observed in 2000, and mentions of PCP rose 25 percent (from 6,102 to 7,648). Mentions of LSD decreased (-68%, from 2,821 to 891). MDMA (Ecstasy) (4,026), GHB (3,330), miscellaneous hallucinogens (1,428), and Ketamine (260), were statistically unchanged from 2001 to 2002. Mentions of flunitrazepam (Rohypnol) and illicit combinations NTA were too imprecise for publication (Table 2.2.0).
- Among the major substances of abuse, the highest rates of ED drug mentions in 2002 occurred for the following substances (Table 12.2.0):
  - Alcohol-in-combination (81 mentions per 100,000 population),
  - Cocaine (78),
  - Marijuana (47), and
  - Heroin (36).

ALCOHOL-IN-COMBINATION

- Alcohol-in-combination was mentioned in 31 percent of ED drug episodes in 2002 (207,395 mentions) and remains the most common substance reported in drug-related ED visits (Table 2.2.0 and Figure 3). Alcohol is reported to DAWN only when present in combination with another reportable drug, so the actual number of alcohol-related ED visits is higher than the DAWN estimate for alcohol-in-combination episodes.
- Mentions of alcohol-in-combination were statistically unchanged from 2001 to 2002, but have increased 24 percent (from 166,897 mentions) since 1995 (Table 2.2.0 and Figure 3).

COCAINE, HEROIN, MARIJUANA

- Cocaine continues to be the most frequently mentioned illicit substance, present in 30 percent of ED episodes (199,198 mentions) in 2002. Cocaine was followed in frequency by marijuana (18%, 119,472 mentions), and heroin (14%, 93,519 mentions) (Table 2.2.0 and Figure 3).
- Cocaine, heroin, and marijuana mentions were statistically unchanged from 2001 to 2002 (Table 2.2.0).
- About one-fifth of the cocaine mentions in 2002 (21%, 42,146 mentions) were attributed to "crack." This number has been stable since 1995. Most cocaine mentions (78%, 155,381) were reported to DAWN simply as "cocaine," and it is not possible to determine what proportion of these might be crack. Mentions that were reported simply as "cocaine" increased 54 percent from 1995 to 2002 (from 101,043 to 155,381), but did not increase from 2000 to 2002, or 2001 to 2002 (Table 2.4.0).
- Taking changes in population into account, from 1995 to 2002, cocaine mentions increased 33 percent (from 58 to 78 mentions per 100,000 population). Also during

this period, heroin mentions increased 22 percent (from 30 to 36), and marijuana mentions increased 139 percent (from 19 to 47) (Table 12.2.0).

AMPHETAMINES AND METHAMPHETAMINE

- In 2002, amphetamines and methamphetamine were each mentioned in 3 percent of drug abuse-related ED episodes (21,644 mentions of amphetamines; 17,696 mentions of methamphetamine) (Table 2.2.0). Only rarely were they reported together in the same ED visit, and it is not possible to know the accuracy of distinctions between them. Most mentions of amphetamines (93%) are reported simply as "amphetamine," while methamphetamine mentions are most frequently identified as "methamphetamine" (66%) or "speed" (13%) (Table 2.4.0). Together amphetamines and methamphetamine accounted for 39,340 mentions in 2002.

- From 1995 to 2002, mentions of amphetamines increased 126 percent (from 9,581 to 21,644), and the rate of amphetamine mentions increased 105 percent (from 4 to 8 mentions per 100,000 population). From 2001 to 2002, mentions of amphetamines rose 17 percent (from 18,555), and the rate of mentions of amphetamines increased 15 percent (from 7 to 8 mentions) (Table 12.2.0). Methamphetamine mentions were statistically unchanged from 2001, 2000, or 1995. This stability masks a period of great fluctuation in methamphetamine ED mentions during the late 1990s.

CLUB DRUGS

- No significant changes from 2001 to 2002 were evident for the club drugs MDMA (Ecstasy) (4,026 mentions in 2002), GHB (3,330), or Ketamine (260) (Table 2.2.0).

- The percentage changes in MDMA and GHB mentions from 1995 to 2002 are very large because of very small numbers in 1995 (Table 2.2.0). Both drugs remain relatively infrequent in ED visits, with no more than 2 mentions per 100,000 population in 2002 (Table 12.2.0).

- Estimates for flunitrazepam (Rohypnol) have been too imprecise for publication every year from 1995 through 2002 (Table 2.2.0 and Figure 4).

OTHER TRENDS

- Among the less frequently mentioned major substances of abuse (Table 2.2.0):
  - Mentions of inhalants increased 187 percent (from 522 in 2001 to 1,496 in 2002), returning to the level observed in 2000.
  - Mentions of PCP increased 25 percent (from 6,102 to 7,648) from 2001 to 2002.
  - Mentions of LSD continued to decline, with a 68 percent decrease from 2001 to 2002 (from 2,821 to 891).
  - No significant changes were evident for miscellaneous hallucinogens from 2001 to 2002 (from 1,788 to 1,428).

- For the 15 major substances of abuse (displayed in Figure 4), relative standard errors (RSEs) in 2002 range from a low of 10.0 for alcohol-in-combination to a high of 78.9 for combinations NTA. Any DAWN estimate with an RSE exceeding 50 percent is considered too imprecise for publication and is therefore suppressed in the tables. In 2002, estimates for methamphetamine, Ketamine, miscellaneous hallucinogens, flunitrazepam (Rohypnol), GHB, inhalants, and combinations NTA all had RSEs greater than 20 percent. Only the RSE for flunitrazepam (Rohypnol) exceeded 50 percent (66%) (Table RSE-2.4.0).

Figure 3
ED drug-related episodes and alcohol-in-combination, cocaine, heroin, and marijuana mentions: 1995 through 2002

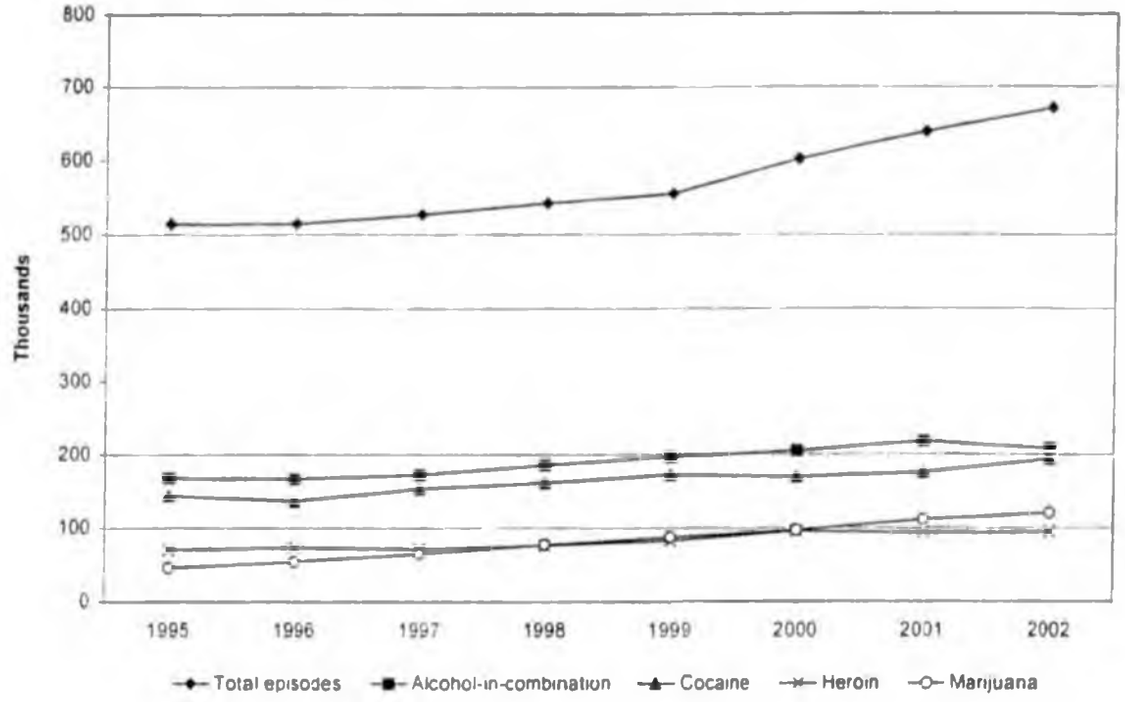
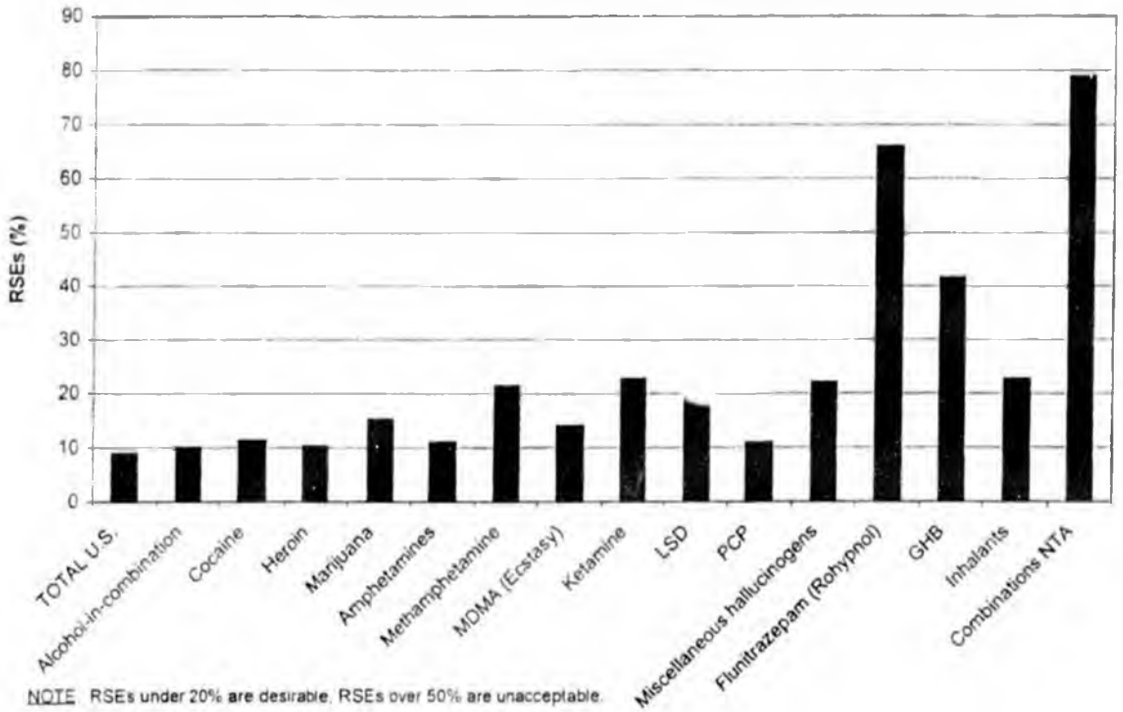


Figure 4
Relative standard errors (RSEs) for major substances of abuse: 2002



NOTE: RSEs under 20% are desirable. RSEs over 50% are unacceptable.

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TRENDS IN OTHER SUBSTANCES OF ABUSE

DAWN also receives reports of ED episodes involving the nonmedical use of legal drugs. These can involve deliberate abuse of prescribed or legally obtained over-the-counter (OTC) medications or of pharmaceuticals diverted for abuse. Accidental overdoses or adverse reactions to OTC or prescription drugs taken as directed are not reportable to DAWN unless they were present in combination with an illicit drug.

These "other substances of abuse" are tabulated first by categories composed of similar substances (Tables 2.2.0 and 12.2.0 for full-year estimates and rates, respectively) and then by generic drug name for the largest categories: psychotherapeutic agents (Tables 2.6.0 and 12.6.0), central nervous system (CNS) agents (Tables 2.8.0 and 12.8.0), respiratory agents (Tables 2.10.0 and 12.10.0), and cardiovascular agents (Tables 2.12.0 and 12.12.0). Corresponding half-year tables (2.5.0, 2.7.0, 2.9.0 and 2.11.0 for estimates and 12.5.0, 12.7.0, 12.9.0 and 12.11.0 for rates) are reported in this publication as well.

By design, all drug mentions in DAWN are tabulated either as major substances of abuse or as other substances of abuse. There is no double counting, and the deliberate assignment of drugs into major substances is the result of specific interest in such substances.

Drugs are presented in DAWN publications by generic names (e.g., acetaminophen, rather than Tylenol), and DAWN estimates should not be attributed to drugs marketed under particular brand (trade) names. DAWN data are extracted from medical records produced in the course of health care delivery (no patient is ever interviewed), so DAWN case reports contain information about particular substances as that information was documented in the ED medical record. Any prescription or OTC drug may be reported to DAWN by its brand (trade) name, generic name, or chemical name, depending on what was documented in the source record. There is no way to discern whether the brand names in the medical record are always accurate or how frequently particular brands might have been recorded by generic name. Therefore, brand names are recoded into generic names, and we do not publish estimates by brand. An index linking brand to generic names is available online at http://DAWNinfo.samhsa.gov/. The index is provided solely as an aid to readers who may be unfamiliar with generic names.

This discussion focuses mainly on comparisons of estimates from 2001 to 2002.

OTHER SUBSTANCES OF ABUSE

- DAWN estimates that other substances of abuse (527,981 mentions) comprised 44 percent of total ED drug mentions in 2002 (Table 2.2.0). Although the vast majority of these other substances are marketed legally by prescription or OTC, it is impossible to know from DAWN the number of ED visits related to the abuse of prescription drugs by patients with a legitimate prescription.

- ED mentions of other substances of abuse in 2002 were most concentrated in 2 categories—CNS agents (227,342 mentions) and psychotherapeutic agents (223,481

mentions)—in nearly equal proportions (19% and 18% of total ED mentions, respectively) (Table 2.2.0).

- The particular drugs involved in ED visits are sometimes unknown or unknowable. In 2002, there were 30,544 such mentions (3% of total mentions) (Table 2.2.0).

PSYCHOTHERAPEUTIC AGENTS

- Overall, mentions of psychotherapeutic agents were statistically unchanged from 2001 to 2002 (Table 2.2.0).
- Mentions of psychotherapeutic agents were up 9 percent since 2000 (from 204,527 to 223,481) and 18 percent since 1995 (from 190,270) (Table 2.2.0).
- Psychotherapeutic agents in DAWN are broken into 4 subcategories: antidepressants; antipsychotics; anxiolytics, sedatives, and hypnotics; and CNS stimulants.

Antidepressants

- Antidepressants (5% of total ED mentions, 62,635 mentions) were the second most frequent psychotherapeutic agents mentioned in drug-related ED visits in 2002, and as a category have remained statistically unchanged in recent years (Table 2.2.0). This category includes:
  - MAO inhibitors (14 mentions),
  - SSRI antidepressants (27,914),
  - Tricyclic antidepressants (11,546), and
  - Miscellaneous antidepressants (23,161).

MAO Inhibitors

- From 1995 to 2002, mentions of MAO inhibitors overall decreased 95 percent (from 303 to 14), but no significant change was evident from 2000 to 2002, or from 2001 to 2002 (Table 2.6.0).

SSRI Antidepressants

- From 1995 to 2002, mentions of SSRI antidepressants overall increased 29 percent (from 21,585 to 27,914), but no significant change was evident from 2000 to 2002 (Table 2.6.0).
- From 2001 to 2002, no significant changes were evident for any of the SSRI antidepressants. In 2002, the most frequently mentioned SSRIs (Table 2.6.0) were:
  - Citalopram (5,313 mentions), which rose 54 percent from 2000 to 2002,
  - Fluoxetine (5,770), down 39 percent from 1995 to 2002, and down 27 percent from 2000 to 2002,

- Paroxetine (9,443), up 67 percent from 1995 to 2002, and
- Sertraline (7,214), which has remained relatively stable in recent years.

Tricyclic Antidepressants

- Overall, mentions of tricyclic antidepressants decreased 41 percent (from 19,429 to 11,546) from 1995 to 2002, but have remained stable in the last 3 years (Table 2.6.0).
- From 2001 to 2002, no significant changes were evident for any of the SSRI antidepressants, and from 2000 to 2002, only amitriptyline mentions changed significantly. In 2002, the most frequently mentioned tricyclic antidepressants (Table 2.6.0) were:
  - Amitriptyline (4,436 mentions), down 50 percent from 1995 and down 31 percent from 2000 to 2002,
  - Doxepin (868), down 68 percent since 1995,
  - Imipramine (242), down 90 percent since 1995,
  - Nortriptyline (424), down 82 percent since 1995, and
  - Tricyclic antidepressants not identified by name (noted as "not otherwise specified" or "-NOS") (5,397), with no change from 1995, 2000 or 2001.

Miscellaneous Antidepressants

- Overall, mentions of miscellaneous antidepressants increased 86 percent (from 12,447 to 23,161) from 1995 to 2002, but remained stable from 2000 to 2002, and from 2001 to 2002 (Table 2.6.0).
- Among the miscellaneous antidepressants, only venlafaxine mentions changed significantly during the 3 years from 2000 to 2002. In 2002, the category of miscellaneous antidepressants (Table 2.6.0) included:
  - Buproprion (4,074 mentions), up 226 percent since 1995,
  - Mirtazapine (2,222),
  - Nefazodone (923), up 294 percent since 1995,
  - Trazadone (9,560),
  - Venlafaxine (5,501), up 345 percent since 1995, up 48 percent since 2000, and up 38 percent since 2001; and
  - Unnamed antidepressants (antidepressants-NOS) (875), up 508 percent from 1995 to 2002.

Antipsychotics

- Mentions of substances classified as antipsychotics were statistically unchanged from 1995, 2000 and 2001. In 2002, this category included 4 subcategories, but more than 90 percent of mentions fell into the single subcategory of miscellaneous antipsychotic agents.

- In 2002, there were 18,492 ED mentions of miscellaneous antipsychotic agents. This estimate was statistically unchanged from 2000 but 67 percent higher than in 1995 (Table 2.6.0). However, the trends for the individual antipsychotic agents in this category varied considerably; they include:

  - Haloperidol (911 mentions), down 67 percent since 1995,
  - Lithium (2,231), down 67 percent since 1995, down 40 percent since 2000, and down 35 percent since 2001,
  - Olanzapine (4,207), unchanged over the periods 1995, 2000 and 2001 to 2002,
  - Quetiapine (6,508), up 116 percent since 2000 and up 50 percent since 2001, and
  - Risperidone (3,566), up 248 percent since 1995.

- Other significant long-term trends in antipsychotics included thioridazine which declined 98 percent (from 2,566 to 48 mentions), fluphenzaine, which declined 95 percent (from 792 to 42), prochlorperazine, which declined 66 percent (from 555 to 191), and chlorpromazine, which declined 64 percent (from 2,202 to 795 mentions) from 1995 to 2002 (Table 2.6.0). Thioridazine also significantly decreased from 2000 to 2002, down 94 percent from 782.

Anxiolytics, Sedatives, and Hypnotics

- Anxiolytics, sedatives, and hypnotics (137,350, or 11% of total ED mentions) were the most frequent psychotherapeutic agents mentioned in drug-related ED visits in 2002 (Table 2.2.0). This category includes 3 subcategories, none of which posted significant changes from 2001 to 2002:

  - Barbiturates (1%, 9,783 mentions), with an increase of 38 percent from 2000 to 2002,
  - Benzodiazepines (9%, 105,752), with a 16 percent increase from 2000 to 2002, and
  - Miscellaneous anxiolytics, sedatives, and hypnotics (2%, 21,816), which were statistically unchanged since 2000.

Barbiturates

- From 2001 to 2002, ED mentions of the barbiturates, individually and as a class, were statistically unchanged (Table 2.2.0).

- From 1995 to 2002, barbiturate mentions rose 44 percent (from 6,793 to 9,783) (Table 2.2.0).

- In 2002, the most frequently mentioned barbiturates were unnamed (barbiturates-NOS, with 7,579 mentions) (Table 2.6.0). Mentions of barbiturates-NOS increased 56 percent from 2000 to 2002, and 110 percent from 1995 to 2002.
- Phenobarbital, the second most frequently mentioned barbiturate in 2002 with 1,217 mentions, decreased 58 percent from 1995 to 2002 (Table 2.6.0).

Benzodiazepines

- In 2002, mentions of benzodiazepines (105,752) accounted for 9 percent of all ED drug mentions. Overall, mentions of benzodiazepines increased 16 percent (from 91,078) from 2000 to 2002 (Table 2.2.0 and Figure 5). Since 1995, mentions of benzodiazepines have risen 38 percent (from 76,548).
- From 2001 to 2002, ED mentions of the benzodiazepines, individually and as a class, were statistically unchanged.
- In 2002, the most frequently mentioned benzodiazepines (Table 2.6.0 and Figure 6) were:
  - Alprazolam (27,659 mentions),
  - Clonazepam (17,042),
  - Diazepam (11,193),
  - Lorazepam (11,042),
  - Temazepam (2,219), and
  - Unnamed benzodiazepines (i.e., benzodiazepines-NOS, 34,697).
- From 1995 to 2002, among the most frequently mentioned benzodiazepines (Table 2.6.0 and Figure 6):
  - Mentions of benzodiazepines-NOS rose 199 percent, alprazolam rose 62 percent, and clonazepam 33 percent, while
  - Mentions of diazepam, lorazepam, and temazepam remained stable.
- From 2000 to 2002, all the benzodiazepines except alprazolam and benzodiazepines-NOS were statistically unchanged (Table 2.6.0).
  - Mentions of alprazolam rose 25 percent (from 22,105 to 27,659),
  - Mentions of benzodiazepines-NOS increased 55 percent (from 22,376 to 34,697).
- Mentions of 2 of the less frequently mentioned benzodiazepines decreased from 1995 to 2002 (Table 2.6.0):
  - Chlordiazepoxide (-74%, from 2,661 to 696), and
  - Triazolam (-77%, from 776 to 175).

Figure 13
ED mentions of alcohol-in-combination, cocaine, heroin, and marijuana: 1995 through 2002

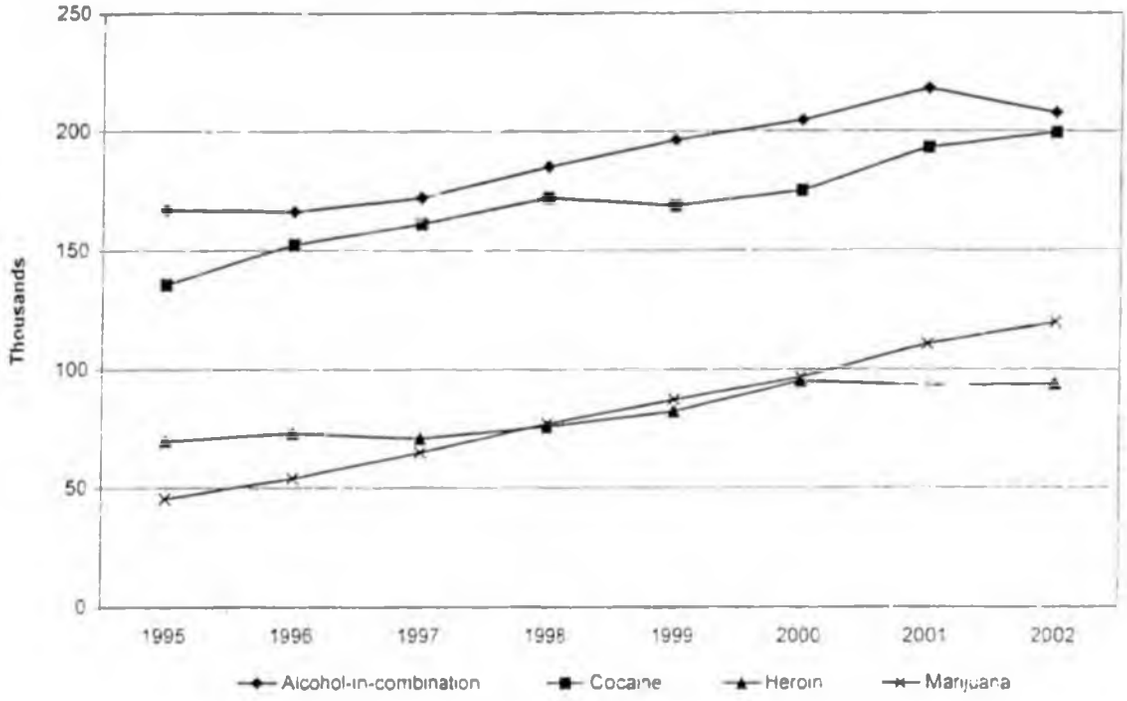
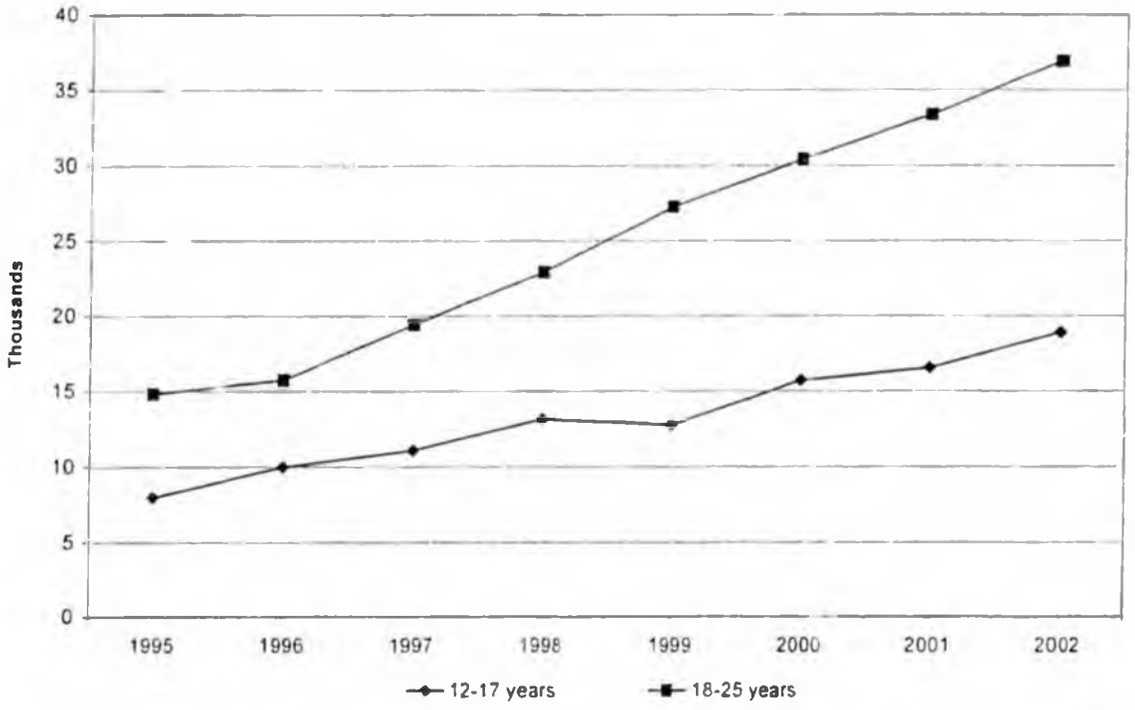


Figure 14
ED mentions of marijuana among patients age 12 to 17 and age 18 to 25: 1995 through 2002



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Acute cardiovascular fatalities following cannabis use

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Abstract

We report six cases of possible acute cardiovascular death in young adults, where very recent cannabis ingestion was documented by the presence of tetrahydrocannabinol (THC) in postmortem blood samples. A broad toxicological blood analysis could not reveal other drugs. Similar cases have been reported in the literature, but the toxicological analysis has been absent or limited to urine samples, which represent a much broader time window for cannabis intake. This paper presents six case reports, where cannabis alone was detected in blood. Further, an overview over previously published cases, clinical trials and possible patho-physiological mechanisms are presented.

Keywords: Cannabis; Toxicity; Tetrahydrocannabinol; Cardiovascular

1. Introduction

Different preparations of the plant *Cannabis sativa* are widely used around the world for their euphoric effects, making cannabis the most frequent drug of abuse, second only to alcohol in the western world. The most commonly used preparations are marijuana and hashish, which in this paper will be referred to as cannabis. Cannabis toxicity is regarded to be low [1]. By extrapolation from animal experiments, the ratio of lethal to effective (intoxicating) dose is estimated to be in the order of thousands to one [2]. Acute cannabis toxicity is briefly, if at all, mentioned in comprehensive textbooks about drug abuse. However, several case reports of both coronary and cerebral ischaemia related to cannabis intake have been published, since the seventies [3–8]. Many studies reported in the literature lack the determinations of tetrahydrocannabinol (THC) or THC metabolites in blood, actually demonstrating the recent intake of cannabis.

After smoking a "regular" dose of cannabis (usually containing about 20 mg THC), blood concentration of THC rises quickly and reaches peak levels before the end of the smoking period. The immediate distribution from blood to tissues is also fast and blood THC levels quickly drop to <10% within 2 h. As a consequence, THC can only be detected in blood by standard methods, depending on dose and analytical cut-off, for 4–12 h after intake. Subjective feeling of euphoria is associated with whole blood levels from 2 μg/l and higher. Whole blood levels 1 h after smoking 20–25 mg THC will typically be in the range 5–10 μg/l [9].

2. Case reports

2.1. Case 1

A 39-year-old male was found dead sitting in his living room with the TV-set on. He did not have any previous record of heart disease, but had a recent sick leave from his job as a fisherman because of shoulder pain. On the day of his death, a co-worker had driven him home from work because of worsening of his shoulder pain. The autopsy revealed findings compatible with an older and a recent heart infarction as well as hypertrophied heart. There was widespread atheromatosis in the coronary arteries and aorta. No information about use of drugs of abuse was available. Toxicological analysis revealed 22 μg/l THC in whole blood and the presence of THC acid in urine. No other drugs or alcohol were found.

2.2. Case 2

A 40-year-old male was found dead after the car he drove slid off the road. There was no record of any illness and he

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was not taking any medication. A witness perceived him as normal shortly before the time of death. The autopsy revealed sparse signs of atheromatosis in the coronary arteries and insinuated narrowing in the left coronary artery next to the aorta. Toxicological analysis revealed 4 μg/l THC in whole blood. THC acid was not detected in urine. There were no other toxicological findings.

2.3. Case 3

A 43-year-old male with a previous coronary heart condition was found dead in his home. He had a myocardial infarction at age 38. He was currently using several drugs for his heart condition (metoprolol (a β-blocker), doxazosine (an α-blocker) and diltiazem (a calcium antagonist)), but there was no record of use of illicit drugs. The autopsy showed widespread atheromatosis enlarged heart and signs of an earlier infarction. Toxicological analysis revealed 2 μg/l THC in whole blood. Urine was not available. There were no other toxicological findings.

2.4. Case 4

A 37-year-old male was found dead at a friend's home. There was no record of use of illicit drugs and no information of previous heart conditions. The autopsy revealed widespread atheromatosis, narrowing of coronary arteries and signs of emphysema. Toxicological analysis revealed 5 μg/l THC in whole blood and 0.04‰ ethanol. There were no other toxicological findings, except THC acid in urine.

2.5. Case 5

A 17-year-old male was found dead on his bed in the morning at his parent's house. He had a record of illicit drug use, without further details about type or types of drugs consumed. There was no record of any illness other than pollen allergy or any record of family heart conditions. The autopsy revealed a slightly enlarged heart. No signs of atheromatosis were found. Toxicological analysis revealed 3 μg/l THC in whole blood. Urine was not available for analysis. There were no other toxicological findings.

2.6. Case 6

A 42-year-old male died suddenly in a hotel. Cardiac resuscitation was started immediately, but was unsuccessful. He had a record of illicit drug use. Needle marks in both arms were ascribed to medical treatment. The autopsy revealed slight atheromatosis in the coronary blood vessels and also narrowing of a coronary artery. The autopsy conclusion was an acute coronary event. Toxicological analysis revealed 7 μg/l THC in whole blood. Urine was not available for analysis. There were no other toxicological findings.

Table 1
Classification of death cause in cases having cannabis as the major toxicological finding

Cause of death	Cases
Suicide (excluding poisoning)	9
Accident	9
Somatic illness (any type)	7
Unknown cause (sudden death)	6
Murder	3
Missing data	1
Total	35

3. Materials and methods

The National Institute for Forensic Toxicology (NIFT) is the national laboratory for forensic pharmacological and toxicological analyses in Norway. Blood, urine and other biological samples from almost every medicolegal autopsies performed in Norway, are sent to NIFT together with the preliminary results from the autopsies. Illegal drugs, including cannabis, are part of the standard analytical program for all autopsy samples. Postmortem blood is screened for amphetamines, benzodiazepines, cannabis, cocaine and opiates with immunological methods (EMIT II) and further with GC-headspace for alcohol and with GC and/or HPLC for a broad spectrum of drugs. Confirmatory analysis of THC and THC acid are performed by GC–MS [10,11].

4. Results

In the period from 1995 to 1999, cannabis was detected in a total of 180 blood samples out of almost 10,000 autopsy cases analysed. In 145 cases, there were also other toxicological findings (prescribed medication or illicit drugs) that could have contributed to the death. The remaining samples (35) contained THC as the major toxicological finding, although low alcohol concentrations (below 0.05‰) or benzodiazepines in the therapeutic concentration range were present in some cases. These 35 samples were classified according to the information from the pathologist (Table 1). Six cases were classified as sudden death of unknown cause and are described in our case reports.

5. Discussion

Cardiovascular effects are the most consistent physiological findings after acute cannabis administration. Significant tachycardia, conjunctival injection and increased limb blood flow with postural hypotension have been reported. These effects are likely to be mediated via β-adrenergical stimulation and possibly also a parasympathetic nervous system blockade [12–15]. A catecholamine increase will

lead to an increased oxygen demand in the myocardium, constituting a potential threat to patients with an ischaemic heart condition [1,12,16].

One controlled cross-over study has compared effects of smoking tobacco and cannabis on angina pectoris [17] and demonstrated that smoking one marijuana cigarette significantly decreased the exercise time until angina more than smoking of one high-nicotine cigarette. Exercise time until angina showed a reduction of 50% after smoking a marijuana cigarette versus 23% reduction after smoking one high-nicotine cigarette, indicating that smoking of cannabis might have a more pronounced effect on triggering angina than nicotine in coronary patients.

Several cases of acute coronary ischaemia related to cannabis smoking have been published. One case report described a previously fit 25-year-old man that presented a sudden onset of pulmonary oedema 30 min after smoking marijuana [3]. Enzymatic, X-ray and electrocardiographical alterations indicated an acute myocardial infarction. Cardiac catheterisation and angiography 3 months after admission were normal. Another case report presented a 32-year-old male with a sudden onset of chest pain after cannabis smoking [5]. He died before the ambulance arrived. The autopsy revealed widespread coronary atheromatosis, focal stenosis and thrombosis in the left coronary artery. Also, one case report presented a previously fit 33-year-old woman with an acute myocardial infarction while smoking marijuana [4]. Shortly after admission to hospital, she developed ventricular fibrillation, which responded to electroconversion. Toxicological analyses of urine showed the presence of cannabinoids. She recovered completely and 3 months later a treadmill test was normal.

With respect to cerebral ischaemia, there are published cases of stroke or transient ischaemic attacks while smoking cannabis in young, previous fit individuals [6,8,18–21]. Two of the individuals had records of alcohol or amphetamine abuse, but had not been using these drugs at the time those episodes occurred.

Interference with the integrity of the peripheral vascular reflex responses is considered to be an important patho-physiological mechanism for the cardiac events during cannabis smoking [15,22,23]. This reflex normally provides a compensatory vasoconstriction in hypotension and can be of capital importance in a myocardial hypoxic situation, where an increase of the pre-load can be essential to preserve adequate perfusion. Vasospasm is another patho-physiological mechanism that has been suggested, especially to explain those cases of coronary or cerebral ischaemia where blood vessels have shown normal conditions in the affected areas after the episode [20].

Several studies have investigated electrocardiographic effects that follow cannabis intake [16,17,24,25]. A common finding mentioned in these studies is different types of arrhythmia, notably ventricular extrasystoles [17,24,26]. In contrast, others have reported lower incidence of arrhythmia when cannabis, compared to diazepam, was used as a pre-medication before surgery. Other electrocardiographic effects reported include changes in ST-segment and T-wave as in epicardial lesion and flattening of P-wave. Possible mechanisms for cannabis-induced cardiovascular events are summarised in Fig. 1.

The use of cannabis in the western world became popular among youngsters in the sixties. Many individuals have continued their drug-using patterns and the age range among cannabis users today is probably broader than it was some years ago. Due to this age-shift, a higher incidence of atheromatosis and coronary heart disease is expected among cannabis users today. The older individuals would presumably have a higher frequency of cardiovascular side effects than younger and healthier cannabis users.

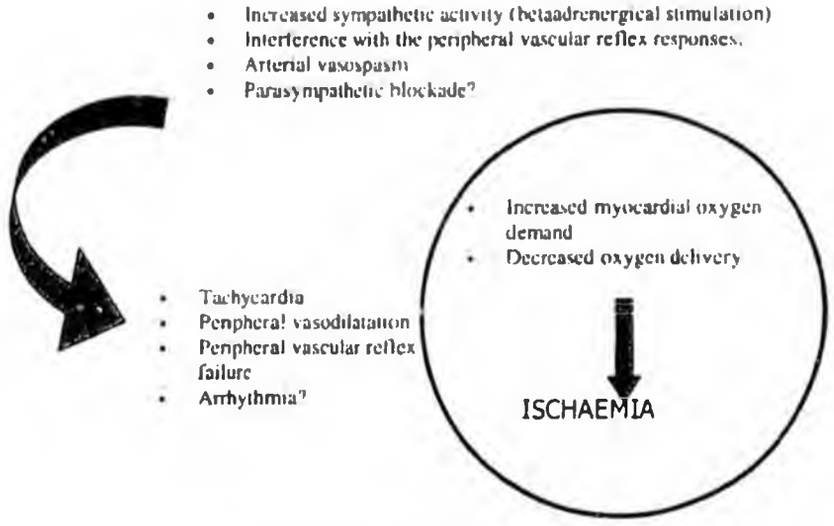

Fig. 1. Cardiovascular mechanisms of cannabis.

6. Conclusions

Several reports of acute cardiovascular episodes associated to cannabis use have been published in the last 20 years and underlying patho-physiological mechanisms have been discussed. Cannabis is generally considered to be a drug with very low toxicity. In this paper, we report six cases where recent cannabis intake was associated with sudden and unexpected death. An acute cardiovascular event was the probable cause of death. In all cases, cannabis intake was documented by blood analyses. To our information there were no heavy drug addicts in our material and the deceased individuals seemed to be occasional cannabis users. Coronary pathology was revealed by the autopsies in some cases. Further investigations of clinical, toxicological and epidemiological aspects are needed to enlighten causality between cannabis intake and acute cardiovascular events.

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March 29, 2002

Marijuana and Cardiovascular death in young adults

An Associated Press story in March of 2000, reported on the findings of Dr. Murray Mittleman of the Harvard School of Public Health and Boston's Beth Israel Deaconess Medical Center that smoking "Marijuana Raises Heart Risks." The study on which this was based was also published in July of 2001 in the medical journal Circulation Magazine and reported by ABCNews.com as "Pot Boosts Heart Attack Risk." The proponents of pot smoking and medical excuse marijuana were not happy. They demanded to know who asked for the study, who funded the study, and insisted that the methodology was flawed and that the researcher was biased

Now, a report in Forensic Science International, by researchers Bachs & Mørland, of the National Institute of Forensic Toxicology in Oslo, Norway, report on six cases of "cardiovascular death in young adults" where THC and no other drugs, were reported in postmortem blood samples. Although only these six cases are detailed in the report, the authors reference several other cases of cardiovascular incidents related to cannabis use.

None of the research done on cannabis to date has shown it to be benign. It should be noted that autopsies are not always done following death, and that because of patient confidentiality laws deaths caused by illicit substances are typically not made public. Therefore, it is likely that there have been far more cardiovascular deaths caused by marijuana than have been reported to date. With these data, acute cardiac deaths from marijuana can not longer be denied.

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The Curse of Cancer

Diana Campbell

Story in .rtf

Kevin Webster couldn't go outside to play in the snow, his favorite thing to do. A fever and lung congestion kept the active two-year old inside.

Cathy Webster, who admits she is overprotective, thought it was just a routine January cold as her eight-year old daughter Chloe was sick, too.

But when Kevin didn't get any better after Cathy gave him children's cold medicine and pain reliever, she took him to the health clinic.

The doctors said asthma, and while prescribed medicine eased his breathing, he still didn't seem right.

"My sister and I were noticing his hands were really white," she said of the little boy. "He kept running a fever."

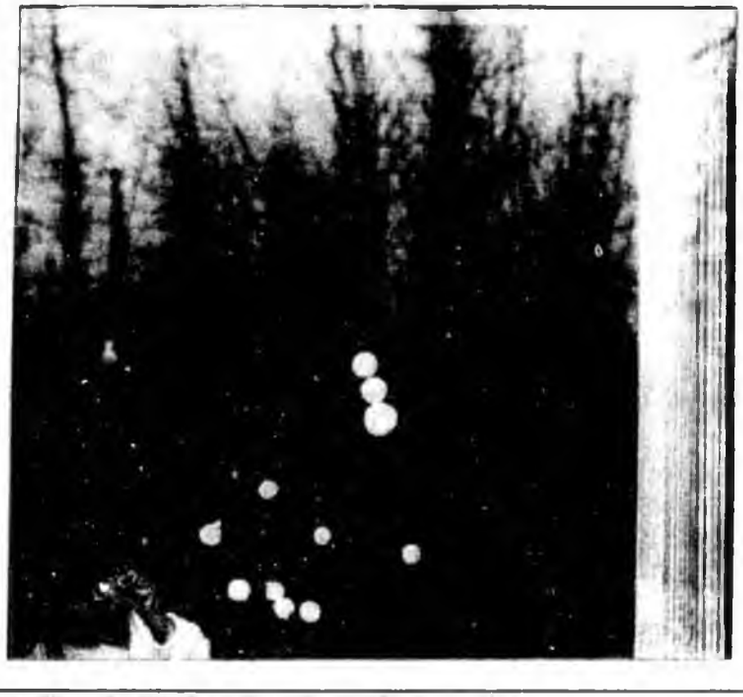
Cathy Webster pressed the doctors for answers and within days, Kevin, his parents, grandmother and sister were at Childrens Hospital and Regional Center in Seattle, about 1,200 miles away the family's hometown of Fairbanks, Alaska.

Leukemia, the doctors said this time, and immediately they put the cooperative little boy on an aggressive regimen of powerful drugs and tests. He will survive, doctors predict, but must endure three and a half years of treatment.

The Websters are Athabascan Indian, and their ordeal is not new to the Athabascan community of Fairbanks. Friends and family hosted a February fundraiser to help the Webster family with expenses. In the past year, fundraisers for for seven other Alaska Native cancer patients, including relatives of Kevin's, have been held.

Cancer is now the leading cause of death for Alaska Natives, a rate that has doubled in the last 30 years, according to the latest reports from the Alaska Native Tumor Registry, a National Cancer Institute-sanctioned monitoring of cancer. Alaska Natives, of which there are just under 100,000 Eskimos, Indians and Aleuts, now face a 30 percent higher risk than U.S. whites of dying from cancer, the registry data shows.

Kevin Webster, a two-year old



Athabascan boy, looks at a suction dart stuck to his grandmother's living room window. Kevin had just come back home to Fairbanks, Alaska after undergoing his first round of chemotherapy at Childrens Hospital and Regional Center in Seattle.

Photo by Eric Engman, Fairbanks Daily News-Miner.

The number of Alaska Natives with can er is now seven percent higher than U.S. whites and past trends show that number has climbed.

The statistics have changed dramatically over the last 40 years, said Dr. Anne Lanier, a founder of the registry, and director of Alaska Native Health Research with the Alaska Native Tribal Health Consortium. The consortium operates an Indian Health Service funded hospital in Anchorage.

In 1950, cancer was rare and tuberculosis was the leading cause of death for Alaska Natives, she said.

But by the mid-1970's, Lanier and others began studying cancer rates by reviewing Alaska Native death certificates on the advice of doctors who noticed an increase of cancer among their patients, she said.

"Experienced clinicians working in the Alaska Native health system have often reported unusual patterns of disease which were later confirmed by special studies," Lanier said.

At first the studies showed Alaska Natives had a lower overall cancer death rate from U.S. whites, but not significantly different, she said. But what the studies did show was that rates for specifics types of cancer were higher than U.S. whites.

Now about 250 Alaska Natives are diagnosed yearly with cancer, a rate that has tripled from those early days, according to registry data.

Lanier is the principal investigator for the registry. National Cancer Institute officials, who funded the initial Alaska Native cancer studies in the 1970's, have since sanctioned grants to further more cancer study and data collection, Lanier said.

"Early on the National Ca ncer Institute was also interested in what was going on in this population," she said. The registry is now part of NCI's Surveillance, Epidemiology and End Result program, a

nationwide system that uses standard methodology for collecting and reporting cancer data.

Those subsequent NCI-funded studies have yielded alarming trends.

Lung cancer in Alaska Natives now exceeds the national average by 48 percent and according to the study Cancer Mortality Among Alaska Natives, 1994-1998, lung cancer is 30 percent of all Alaska Native cancer deaths, making it the leading cause of cancer deaths.

It's tobacco, Lanier has said repeatedly over the years.

According to the a 1997 study by the Behavioral Risk Factor Surveillance System, a statewide telephone health survey, at least 47 percent of Alaska Native men smoked compared to 39 percent of Alaska Native women. The U.S. tobacco use average is 26 percent for males and 21 percent for females.

Smoking among Alaska Natives has shown no signs of slowing down, according to the behavior surveys, which lead Lanier and others at the tribal health consortium to believe that lung cancer rates will likely exceed U.S. whites for years to come.

Tobacco isn't the only factor contributing to the high rates of Alaska Native cancer.

According to the Alaska Native Tumor Registry 30-year report, Alaska Native men had thirty times the death rate risk of U.S. whites from a particular type of nasopharyngeal cancer, a disease that occurs in the back of the throat and nose. This type of cancer is so rare that little is known about the disease except that is it also found among Chinese, Filipino and Vietnamese populations and may be associated with Epstein Barr Virus, the virus that can cause mononucleosis, the National Cancer Institute reports.

Alaska Natives are five times more likely to die from stomach cancer than U.S. whites; twice as likely from esophagus cancer; and one and half times from liver cancer, according to the 30-year report. The reason for the high number is also unknown, but low fruit and vegetable consumption along with alcohol and tobacco use are suspect causes for those types of cancer, according to the American Cancer Society.

A recent study by the Centers for Disease Control suggested that Helicobactor pylori, an infectious agent, may be a source in stomach cancers. Hepatitis B has been linked to liver cancer.

On the flip side, some cancers rates are still low. Data has shown that prostate cancer rates in Alaska Native men, uterine cancer in women, leukemia, and lymphoma are lower than U.S. whites. The reasons are unclear, the 30-year report said.

Both the mortality study and the 30-report suggest a plan of action.

Alaska Natives are a young population, said Gretchen Ehrsam, an epidemiologist with the Alaska Native Tribal Health Consortium and an author of the mortality study .

The median age of Alaska Natives is 23, while the U.S. median age is 36, she said. Since chances of getting cancer increase as people age and Alaska Natives are living longer, it is likely a greater number of Alaska Natives will get cancer as they get older, placing a greater burden on families, health care and society, she said.

"Cancer is an old person's disease," Ehrsam said. "We need to do something now."

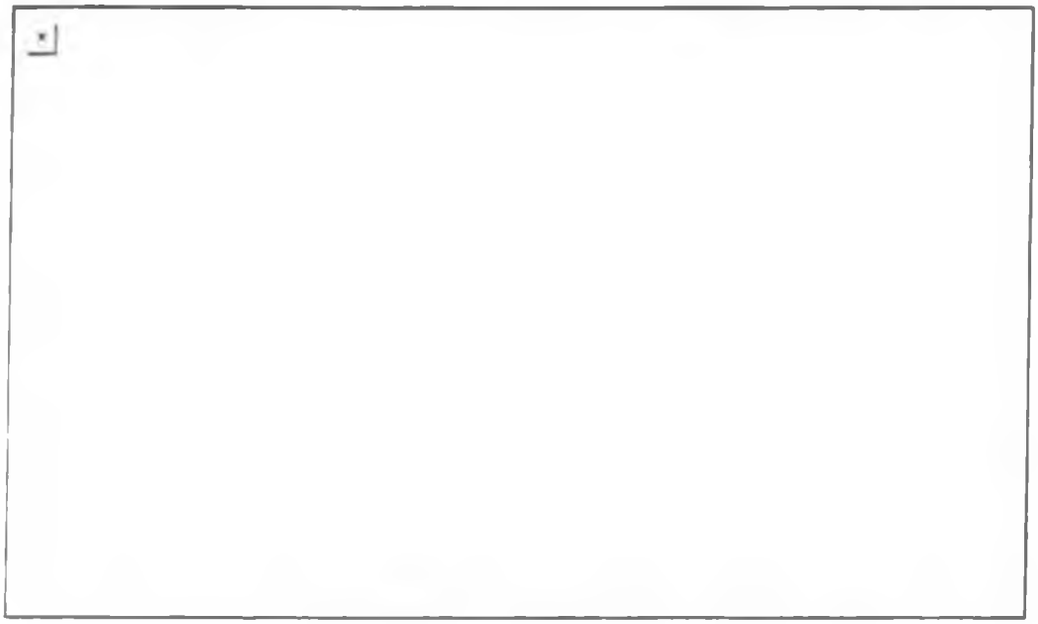


Table 1. Average Annual Age-Adjusted† Cancer Mortality Rates per 100,000 for Alaska Natives and U.S. Whites. Males and Females combined,1994-1998.

	# of cases	AK Rate	US Rate	Odds Ratio		Lower C.I.	Upper C.I.
All Sites	597	224.5	166.7	1.3	*	1.2	1.4
Oral Cavity and Pharynx	20	7.8	2.4	2.9	*	1.9	4.6
Salivary Gland	0	-	0.2	-		-	-
Gum and Other Mouth	2	-	0.4	-		-	-
Nasopharynx	12	4.8	0.2	20.4	*	11.5	36.2
Digestive System	209	77.6	37.5	2.2	*	1.7	2.3
Esophagus	18	7.2	3.4	1.9	*	1.2	3.1
Stomach	51	17.1	3.6	4.9	*	3.7	6.4
Colon and Rectum	84	31.9	17	1.7	*	1.4	2.2
Colon	66	25.5	14.5	1.6	*	1.3	2.1
Rectum & Rectosigmoid Jxn.	18	6.4	2.5	2.5	*	1.6	4
Liver	17	6.4	3.4	1.8	*	1.1	2.9
Gallbladder	4	-	0.6	-		-	-
Other Biliary	1	-	0.5	-		-	-
Pancreas	34	12.7	8.2	1.5	*	1.1	2.1

Respiratory System	184	73.9	50.2	1.4	*	1.2	1.6
Larynx	5	1.9	1.2	1.6		0.7	3.8
Lung and Bronchus	179	72	48.6	1.4	*	1.2	1.6
Bones and Joints	1	-	0.4	-		-	-
Soft Tissue	0	-	1.3	-		-	-
Skin	3	-	3.3	-		-	-
Melanomas of the Skin	3	-	2.6	-		-	-
Other Non-Epithelial Skin	0	-	0.7	-		-	-
Breast	35	11.2	13.6	0.9		0.6	1.2
Female Genital System	17	11.1	14	0.8		0.5	1.2
Cervix	3	1.8	2.4	-		-	-
Corpus and Uterus, NOS	0	-	3.2	-		-	-
Ovary	14	9.2	7.7	1.2		0.7	2
Male Genital System	13	12	22.5	0.5	*	0.3	0.8
Prostate	13	12	22.1	0.5		0.3	0.8
Testis	0	-	0.3	-		-	-
Urinary System	25	10.2	7.2	1.2		0.8	1.8
Urinary Bladder	4	-	3.5	-		-	-
Kidney and Renal Pelvis	21	8.4	3.6	2	*	1.3	3.1
Eye and Orbit	0	-	0.1	-		-	-
Brain and Other Nervous System	5	1.4	4.5	0.3	*	0.1	0.8
Brain	4	-	4.4	-		-	-
Endocrine System	0	-	0.7	-		-	-
Thyroid	0	-	0.4	-		-	-
Lymphoma	11	4	7.8	0.5	*	0.3	0.8
Hodgkin's Disease	0	-	0.5	-		-	-
Non-Hodgkin's	11	4	7.4	0.5		0.1	1.9
Multiple Myeloma	6	2.2	2.9	0.7		0.3	1.7
Leukemia	13	3.7	6.5	0.6		0.4	1.1
Ill Defined	53	19.2	11.5	1.6	*	1.2	2.1

†All rates age-adjusted 1970 U.S. population;

* 95% confidence intervals for odds ratios do not include 1.

Table 2. Average Annual Age-Adjusted+ Cancer Mortality Rates per 100,000 for Alaska Natives and U.S. White Males 1994-1998.

	# of cases	AK Rate	US Rate	Odds Ratio		Lower C.I.	Upper C.I.
All Sites	323	261.8	201.8	1.3	*	1.1	1.4
Oral Cavity and Pharynx	16	12.7	3.5	3.4	*	2.1	5.5
Salivary Gland	0	-	0.3	-		-	-
Gum and Other Mouth	1	-	0.6	-		-	-
Nasopharynx	11	9	0.3	27.1	*	14.8	49.4
Digestive System	108	85.2	47	1.8	*	1.5	2.2
Esophagus	11	9.2	5.9	1.4		0.8	2.6
Stomach	35	25.3	5.1	5.2	*	3.8	7.3
Colon and Rectum	34	27.7	20.1	1.4	*	1	2
Colon	26	22	16.9	1.2		0.8	1.8
Rectum & Rectosigmoid Jxn.	8	5.7	3.2	3.3	*	2	5.6
Liver	10	8.1	4.8	1.6		0.9	3
Gallbladder	3	-	0.4	-		-	-
Other Biliary	1	-	0.6	-		-	-
Pancreas	14	11.1	9.4	1.4		0.9	2.3
Respiratory System	124	104.4	69.6	1.4	*	1.2	1.7
Larynx	5	3.8	2.1	1.9		0.8	4.5
Lung and Bronchus	119	100.6	66.9	1.4	*	1.2	1.7
Bones and Joints	0	-	0.5	-		-	-
Soft Tissue	0	-	1.4	-		-	-
Skin	1	-	4.7	-		-	-
Melanomas of the Skin	1	-	3.6	-		-	-

Other Non-Epithelial Skin	0	-	1	-	-	-
Breast	0		0.2	-	-	-
Male Genital System	13	12	22.5	0.5 *	0.3	0.8
Prostate	13	12	22.1	0.5 *	0.3	0.8
Testis	0	-	0.3	-	-	-
Urinary System	11	10.2	11.1	0.8	0.4	1.4
Urinary Bladder	2	-	5.7	-	-	-
Kidney and Renal Pelvis	9	8.1	5.1	1.3	0.7	2.5
Eye and Orbit	0	-	0.1	-	-	-
Brain and Other Nervous System	3	-	5.4	-	-	-
Brain	3	-	5.3	-	-	-
Endocrine System	0	-	0.7	-	-	-
Thyroid	0	-	0.3	-	-	-
Lymphoma	7	5.2	9.5	0.5	0.1	2.7
Hodgkin's Disease	0	-	0.5	-	-	-
Non-Hodgkin's	7	5.2	8.9	0.6	0.3	1.2
Multiple Myeloma	2	-	3.5	-	-	-
Leukemia	7	4.8	8.4	0.6	0.3	1.2
Ill Defined	31	23.8	13.8	1.7 *	1.2	2.4

†All rates age-adjusted 1970 U.S. population;

* 95% confidence intervals for odds ratios do not include 1.

Table 3. Average Annual Age-Adjusted† Cancer Mortality Rates per 100,000 for Alaska Natives and U.S. White Females 1994-1998.

	# of cases	AK Rate	US Rate	Odds Ratio	Lower C.I.	Upper C.I.
All Sites	274	187.2	141.6	1.3 *	1.1	1.4
Oral Cavity and Pharynx	4	-	1.4	-	-	-

Salivary Gland	0	-	0.1	-		-	-
Gum and Other Mouth	1	-	0.3	-		-	-
Nasopharynx	1	-	1.4	-		-	-
Digestive System	101	70	29.9	2.2	*	1.8	2.7
Esophagus	7	5.3	1.4	3.4	*	1.6	7.2
Stomach	16	8.8	2.5	4	*	2.5	6.6
Colon and Rectum	50	36.2	13.6	2.2	*	1.7	2.9
Colon	40	29.1	14.6	2.1	*	1.5	2.8
Rectum and Rectosigmoid Jxn.	10	7.1	2	3.2	*	1.7	6
Liver	7	4.7	2.3	2	*	1	4.2
Gallbladder	1	-	0.8	-		-	-
Other Biliary	0	-	0.4	-		-	-
Pancreas	20	14.2	7.2	1.8	*	1.2	2.8
Respiratory System	60	43.3	35.6	1.2		0.9	1.5
Larynx	0	-	0.5	-		-	-
Lung and Bronchu	60	43.3	34.9	1.2		0.9	1.5
Bones and Joints	1	-	0.3	-		-	-
Soft Tissue	0		1.2	-		-	-
Skin	2	-	2.2	-		-	-
Melanomas of the Skin	2	-	1.8	-		-	-
Other Non-Epithelial Skin	0	-	0.4	-		-	-
Breast	35	22.4	24.4	0.9		0.7	1.3
Female Genital System	17	11.1	14	0.8		0.5	1.2
Cervix	3	1.8	2.4	-		-	-
Corpus and Uterus, NOS	0	-	3.2	-		-	-
Ovary	14	9.2	7.7	1.2		0.7	2
Urinary System	14	10.2	4.4	2.1	*	1.2	3.5
Urinary Bladder	2	-	1.8	-		-	-
Kidney and Renal Pelvis	12	8.6	2.4	3.3	*	1.9	5.8
Eye and Orbit	0	-	0.1	-		-	-
Brain and Other Nervous System	2	-	3.7	-		-	-

Brain	1	-	3.6	-	-	-
Endocrine System	0	-	0.7	-	-	-
Thyroid	0	-	0.4	-	-	-
Lymphoma	4	-	6.5	-	-	-
Hodgkin's Disease	0	-	0.4	-	-	-
Non-Hodgkin's	4	-	6.1	-	-	-
Multiple Myeloma	4	-	2.4	-	-	-
Leukemia	6	2.6	5.1	0.7	0.3	1.5
Ill Defined	22	14.6	9.7	1.6 *	1.1	2.5

†All rates age-adjusted 1970 U.S. population:

* 95% confidence intervals for odds ratios do not include 1.

Web Resources include:

Military biological and chemical weapons testing:
www.deploymentlink.osd.mil/current_issues/shad/shad_intro.shtml

Alaska Native Tribal Health Consortium
www.anthc.org

Native Village of Tanacross
www.nativevillageoftanacross.com

St. Lawrence Island
www.akaction.net

 A business reporter for the *Fairbanks Daily News-Miner*, Diana Campbell is looking at the incidence of cancer among Alaska natives.

DEMOGRAPHICS OF MARIJUANA USE IN ALASKA

I. Marijuana Use In Alaska.

- A national study estimated that Alaska led the nation in 1999 and 2000 in average annual rates of first use of marijuana by persons 12 and older. *Gfroerer, J., et.al., Initiation of Marijuana Use: Trends, Patterns, and Implications, Department of Health and Human Services, Substance Abuse and Mental Health Services Administration, Office of Applied Studies, 2002.*
- The same study estimated that 4,000 of the 5-7,000 new initiates in Alaska were aged 12-17. *Gfroerer, J., et.al.*
- One in eight Alaska high school students reports using marijuana before age 13. *2003 Alaska Youth Risk Behavior Survey.*
- In 1995 and again in 1999, 29% of middle school students reported having smoked marijuana. *Health Risks, 1995 Youth Risk Behavior Survey Summary, 1999 Youth Risk Behavior Survey Results.*
- In a regional survey, over 10% of middle school students reported using marijuana even before the age of 11. *2003 Youth Risk Behavior Results for the Northwest Arctic Borough School District, Middle School Survey.*

- Alaska native students were significantly more likely (69.7%) to have used marijuana than non-Natives (41.2%). *2003 Alaska Youth Risk Behavior Survey.*
- Alaska native students were significantly more likely to be current users (use within past 30 days) (35.5%) than non-natives (20.6%) in 2003. *2003 Alaska Youth Risk Behavior Survey.*
- In a survey of Alaska Native preschool parents, the use of marijuana by the preschool parents in the preceding 30 days was self-reported to be 3 times higher than the national estimates. (19% vs, 6.7%) *Stillner, V, et.al., Drug Use in Very Rural Alaska Villages, Substance Use and Misuse, 1999.*

Initiation of Marijuana Use: Trends, Patterns, and Implications

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Michael A. Penne

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Substance Abuse and Mental Health Services Administration
Office of Applied Studies

Table 4.1 Estimated Numbers (in Thousands) of Average Annual Marijuana Initiates, by Age Group and State: 1999 and 2000

	Total		Age Group (Years)					
			12-17		18-25		26 or Older	
State	Estimate	Prediction Interval	Estimate	Prediction Interval	Estimate	Prediction Interval	Estimate	Prediction Interval
Total	2,268		1,230		898		139	
Alabama	34	(29 - 39)	17	(13 - 21)	15	(12 - 19)	2	(1 - 4)
Alaska	6	(5 - 7)	4	(3 - 4)	2	(2 - 3)	0	(0 - 1)
Arizona	45	(39 - 52)	29	(24 - 35)	13	(10 - 17)	2	(1 - 4)
Arkansas	21	(18 - 24)	11	(9 - 14)	8	(6 - 10)	1	(1 - 2)
California	246	(226 - 267)	135	(123 - 148)	93	(79 - 109)	17	(11 - 26)
Colorado	38	(32 - 44)	22	(18 - 27)	14	(10 - 18)	2	(1 - 4)
Connecticut	26	(22 - 30)	15	(12 - 18)	10	(7 - 12)	2	(1 - 3)
Delaware	7	(6 - 8)	4	(4 - 5)	3	(2 - 3)	0	(0 - 1)
District of Columbia	4	(4 - 5)	2	(2 - 3)	2	(1 - 2)	0	(0 - 1)
Florida	105	(95 - 115)	59	(53 - 67)	38	(32 - 44)	7	(4 - 12)
Georgia	65	(56 - 74)	33	(28 - 39)	28	(22 - 35)	4	(2 - 7)
Hawaii	10	(8 - 11)	6	(5 - 7)	3	(2 - 4)	0	(0 - 1)
Idaho	11	(10 - 13)	6	(5 - 7)	5	(4 - 7)	1	(0 - 1)
Illinois	99	(90 - 108)	53	(47 - 60)	40	(34 - 46)	6	(4 - 9)
Indiana	49	(42 - 56)	26	(22 - 32)	19	(15 - 24)	3	(2 - 5)
Iowa	26	(22 - 29)	14	(11 - 17)	10	(8 - 13)	1	(1 - 3)
Kansas	25	(22 - 29)	13	(11 - 16)	11	(9 - 14)	1	(1 - 2)
Kentucky	37	(32 - 42)	19	(16 - 23)	16	(13 - 19)	2	(1 - 4)
Louisiana	36	(31 - 42)	20	(17 - 25)	13	(10 - 17)	2	(1 - 4)
Maine	11	(10 - 13)	6	(5 - 7)	4	(3 - 6)	1	(0 - 1)
Maryland	42	(36 - 48)	21	(17 - 26)	18	(14 - 22)	3	(1 - 4)
Massachusetts	60	(51 - 68)	36	(30 - 43)	20	(15 - 26)	3	(2 - 6)
Michigan	92	(84 - 101)	51	(46 - 57)	36	(31 - 42)	5	(3 - 8)
Minnesota	48	(42 - 55)	24	(20 - 28)	22	(18 - 27)	2	(1 - 4)
Mississippi	25	(21 - 29)	12	(10 - 15)	11	(9 - 14)	1	(1 - 3)
Missouri	46	(40 - 53)	25	(20 - 30)	19	(15 - 24)	3	(1 - 4)
Montana	9	(8 - 10)	5	(4 - 6)	3	(3 - 4)	0	(0 - 1)

Table 4.2 Average Annual Rates of First Use of Marijuana, by Age Group and State: 1999 and 2000

State	Total		Age Group (Years)					
			12-17		18-25		26 or Older	
	Estimate	Prediction Interval	Estimate	Prediction Interval	Estimate	Prediction Interval	Estimate	Prediction Interval
Total	1.52		6.08		5.47		0.12	
Alabama	1.28	(1.08 - 1.51)	5.19	(4.09 - 6.56)	5.35	(4.18 - 6.81)	0.10	(0.06 - 0.20)
Alaska	2.32	(1.96 - 2.74)	7.29	(5.96 - 8.89)	6.48	(4.95 - 8.46)	0.17	(0.09 - 0.32)
Arizona	1.82	(1.54 - 2.15)	8.16	(6.69 - 9.92)	4.69	(3.53 - 6.19)	0.13	(0.07 - 0.25)
Arkansas	1.32	(1.12 - 1.55)	5.75	(4.65 - 7.09)	4.58	(3.58 - 5.84)	0.10	(0.06 - 0.19)
California	1.46	(1.33 - 1.61)	5.57	(5.05 - 6.15)	4.50	(3.83 - 5.29)	0.14	(0.09 - 0.22)
Colorado	2.01	(1.69 - 2.40)	7.68	(6.19 - 9.47)	7.03	(5.34 - 9.20)	0.15	(0.08 - 0.29)
Connecticut	1.59	(1.32 - 1.92)	6.83	(5.45 - 8.53)	6.47	(4.84 - 8.60)	0.13	(0.07 - 0.25)
Delaware	1.90	(1.61 - 2.24)	8.32	(6.83 - 10.10)	7.01	(5.33 - 9.17)	0.13	(0.07 - 0.25)
District of Columbia	1.48	(1.24 - 1.77)	5.54	(4.34 - 7.05)	5.28	(4.06 - 6.83)	0.13	(0.07 - 0.26)
Florida	1.21	(1.09 - 1.34)	5.76	(5.06 - 6.55)	4.67	(3.96 - 5.50)	0.11	(0.06 - 0.18)
Georgia	1.50	(1.28 - 1.76)	5.61	(4.67 - 6.71)	5.47	(4.25 - 7.00)	0.13	(0.07 - 0.23)
Hawaii	1.65	(1.38 - 1.97)	7.63	(6.16 - 9.41)	5.50	(4.01 - 7.50)	0.11	(0.04 - 0.26)
Idaho	1.58	(1.33 - 1.87)	4.91	(3.93 - 6.11)	5.39	(4.20 - 6.88)	0.13	(0.07 - 0.24)
Illinois	1.56	(1.41 - 1.73)	6.17	(5.45 - 6.97)	5.61	(4.80 - 6.55)	0.12	(0.08 - 0.20)
Indiana	1.44	(1.23 - 1.69)	5.88	(4.82 - 7.15)	5.27	(4.11 - 6.74)	0.12	(0.07 - 0.23)
Iowa	1.47	(1.26 - 1.73)	6.17	(5.03 - 7.56)	5.24	(4.11 - 6.66)	0.11	(0.06 - 0.22)
Kansas	1.68	(1.42 - 1.98)	6.17	(4.96 - 7.64)	6.54	(5.12 - 8.32)	0.12	(0.06 - 0.22)
Kentucky	1.62	(1.39 - 1.89)	6.74	(5.52 - 8.21)	6.46	(5.15 - 8.06)	0.12	(0.06 - 0.23)
Louisiana	1.39	(1.18 - 1.65)	5.51	(4.49 - 6.75)	4.26	(3.25 - 5.55)	0.12	(0.07 - 0.22)
Maine	1.74	(1.47 - 2.05)	7.12	(5.81 - 8.70)	8.07	(6.17 - 10.48)	0.11	(0.06 - 0.22)
Maryland	1.52	(1.28 - 1.81)	5.92	(4.77 - 7.32)	6.14	(4.80 - 7.84)	0.12	(0.07 - 0.23)
Massachusetts	2.03	(1.71 - 2.41)	8.75	(7.17 - 10.65)	7.55	(5.73 - 9.88)	0.15	(0.08 - 0.29)
Michigan	1.83	(1.66 - 2.03)	7.10	(6.31 - 7.98)	6.90	(5.88 - 8.07)	0.13	(0.08 - 0.21)
Minnesota	1.91	(1.63 - 2.24)	6.42	(5.24 - 7.84)	7.63	(6.05 - 9.59)	0.13	(0.07 - 0.25)
Mississippi	1.49	(1.27 - 1.76)	5.26	(4.22 - 6.54)	5.32	(4.22 - 6.69)	0.12	(0.06 - 0.22)
Missouri	1.51	(1.28 - 1.79)	5.85	(4.76 - 7.17)	5.91	(4.60 - 7.56)	0.11	(0.06 - 0.21)
Montana	1.73	(1.48 - 2.03)	7.33	(5.98 - 8.96)	6.58	(5.17 - 8.34)	0.1[illegible]	(0.06 - 0.24)

Table 4.2 (continued)

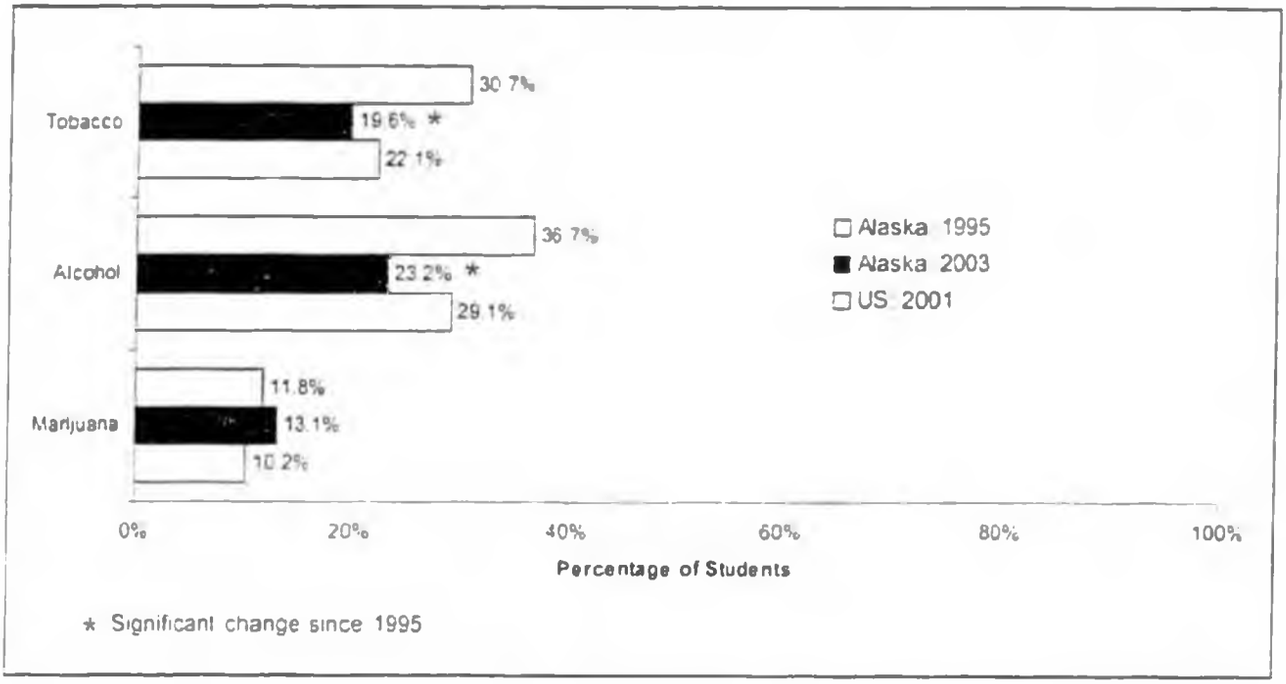
State	Total		Age Group (Years)					
			12-17		18-25		26 or Older	
	Estimate	Prediction Interval	Estimate	Prediction Interval	Estimate	Prediction Interval	Estimate	Prediction Interval
Nebraska	1.51	(1.29 - 1.77)	5.71	(4.63 - 7.03)	5.48	(4.29 - 6.98)	0.11	(0.06 - 0.20)
Nevada	1.66	(1.39 - 1.98)	7.63	(6.18 - 9.37)	5.47	(4.07 - 7.32)	0.13	(0.07 - 0.26)
New Hampshire	1.92	(1.62 - 2.27)	7.52	(6.16 - 9.15)	7.49	(5.65 - 9.88)	0.13	(0.07 - 0.24)
New Jersey	1.39	(1.18 - 1.64)	5.50	(4.53 - 6.67)	6.45	(4.96 - 8.33)	0.13	(0.07 - 0.24)
New Mexico	1.99	(1.68 - 2.35)	7.66	(6.24 - 9.37)	5.99	(4.54 - 7.86)	0.14	(0.07 - 0.27)
New York	1.43	(1.28 - 1.59)	5.64	(4.94 - 6.44)	5.93	(5.01 - 7.00)	0.12	(0.07 - 0.19)
North Carolina	1.50	(1.28 - 1.75)	6.67	(5.59 - 7.94)	5.35	(4.16 - 6.86)	0.12	(0.07 - 0.22)
North Dakota	1.89	(1.64 - 2.19)	7.31	(6.04 - 8.81)	6.53	(5.21 - 8.17)	0.10	(0.05 - 0.20)
Ohio	1.49	(1.35 - 1.65)	5.94	(5.25 - 6.72)	5.91	(5.09 - 6.86)	0.10	(0.06 - 0.17)
Oklahoma	1.47	(1.24 - 1.76)	6.58	(5.26 - 8.20)	4.14	(3.16 - 5.41)	0.12	(0.06 - 0.23)
Oregon	1.70	(1.42 - 2.03)	6.50	(5.27 - 7.99)	7.10	(5.48 - 9.13)	0.15	(0.07 - 0.29)
Pennsylvania	1.32	(1.19 - 1.46)	5.32	(4.71 - 5.99)	5.85	(5.03 - 6.79)	0.10	(0.06 - 0.18)
Rhode Island	1.69	(1.43 - 1.99)	7.34	(5.95 - 9.03)	6.57	(5.01 - 8.56)	0.13	(0.07 - 0.26)
South Carolina	1.47	(1.25 - 1.74)	6.43	(5.24 - 7.87)	4.95	(3.82 - 6.39)	0.12	(0.06 - 0.24)
South Dakota	1.60	(1.37 - 1.88)	6.16	(5.02 - 7.53)	5.43	(4.22 - 6.96)	0.10	(0.05 - 0.19)
Tennessee	1.49	(1.26 - 1.76)	6.34	(5.17 - 7.76)	5.46	(4.22 - 7.03)	0.12	(0.06 - 0.24)
Texas	1.47	(1.33 - 1.63)	5.49	(4.88 - 6.18)	4.55	(3.89 - 5.30)	0.13	(0.08 - 0.20)
Utah	1.60	(1.34 - 1.91)	4.67	(3.71 - 5.87)	3.88	(3.00 - 5.02)	0.14	(0.07 - 0.27)
Vermont	2.25	(1.91 - 2.66)	8.30	(6.89 - 9.98)	8.22	(6.33 - 10.61)	0.15	(0.07 - 0.29)
Virginia	1.40	(1.17 - 1.66)	5.09	(4.15 - 6.23)	5.68	(4.35 - 7.39)	0.13	(0.07 - 0.25)
Washington	1.61	(1.37 - 1.90)	6.78	(5.58 - 8.21)	5.17	(3.99 - 6.66)	0.13	(0.07 - 0.24)
West Virginia	1.28	(1.09 - 1.50)	6.27	(5.10 - 7.70)	4.98	(3.86 - 6.41)	0.10	(0.05 - 0.19)
Wisconsin	1.88	(1.61 - 2.19)	7.34	(6.15 - 8.74)	6.46	(5.03 - 8.28)	0.15	(0.06 - 0.37)
Wyoming	1.83	(1.56 - 2.14)	6.51	(5.33 - 7.94)	6.18	(4.84 - 7.86)	0.12	(0.07 - 0.23)

Note: Estimates are based on a survey-weighted hierarchical Bayes estimation approach, and the 95 percent prediction (credible) intervals are generated by Markov Chain Monte Carlo techniques.

Source: SAMHSA, Office of Applied Studies, National Household Survey on Drug Abuse, 1999 and 2000.

Use of Tobacco, Alcohol or Marijuana Before the Age of 13

Among Alaska high school students, 23.2% report having had a first drink of alcohol before age 13, a decrease from 36.7% in 1995. Alaska students reporting use of marijuana before age 13 has risen from 11.8% in 1995 to 13.1% in 2003. Alaska boys are more likely than Alaska girls to report use alcohol, tobacco or marijuana before age 13.



Healthy Alaskans 2010 Objective:

- ***Increase the average age of first use of marijuana among adolescents grades 9-12 to 17.4 years of age (mean age in years, based on students using marijuana at least once in lifetime).***
- ***Reduce to 4% the proportion of adolescents who have used illegal steroids (percentage of students grades 9-12 who have ever used steroids pills or shots).***
- ***Reduce to 2% inhalant use among high school students (percentage of students grades 9-12 who sniffed glue, breathed the contents of aerosol spray cans, or inhaled any paints or sprays to get high 1 or more times in past month).***
- ***Increase to 60% the proportion of adolescents not using alcohol or illicit drugs during the past 30 days (percentage of students grades 9-12 who have not used alcohol, marijuana or cocaine in the past 30 days).***
- ***Increase the average age of first use of alcohol among adolescents grades 9-12 to 16.1 years (mean age in years, based on students reporting having at least one drink of alcohol in life)***

Computed Marijuana Use: "How Many Times Have You Used Marijuana?" and "In the Past 30 Days, How Many Times Did You Use Marijuana?"

1995	Total	Current Marijuana Users (Within past 30 days)				Former Marijuana Users (More than 30 days ago)				Never Used Marijuana			
Combined Race Category	Respondents	Estimated	Percentage	Lower 95% CL	Upper 95% CL	Estimated	Percentage	Lower 95% CL	Upper 95% CL	Estimated	Percentage	Lower 95% CL	Upper 95% CL
American Indian / Alaska Native	178	1,253.52	29.72%	22.49%	38.13%	1,369.67	32.48%	27.87%	37.48%	1,594.28	37.80%	31.38%	44.71%
Asian / Pacific Islander	74	396.14	31.63%	21.01%	45.32%	139.91	11.28%	5.74%	20.99%	703.82	56.77%	46.73%	67.17%
Black	83	307.03	21.17%	13.11%	32.33%	157.22	10.84%	5.44%	20.43%	986.17	67.99%	56.85%	78.04%
[redacted] (include multi-hispanic)	51	81.83	6.91%	3.73%	19.81%	269.18	29.39%	16.70%	46.35%	584.86	61.70%	44.36%	76.48%
[redacted]-Hispanic	1,132	5,851.50	29.71%	26.86%	32.70%	3,445.74	17.50%	15.28%	19.87%	10,398.19	52.79%	48.51%	56.99%
[redacted]	69	260.70	35.64%	20.85%	53.63%	182.14	17.05%	9.85%	27.65%	505.41	47.31%	27.77%	67.71%
Total	1,578	8,270.52	28.93%	26.32%	31.69%	5,563.84	19.46%	17.16%	21.99%	14,752.83	51.61%	48.58%	54.61%

2003	Total	Current Marijuana Users (Within past 30 days)				Former Marijuana Users (More than 30 days ago)				Never Used Marijuana			
Combined Race Category	Respondents	Estimated	Percentage	Lower 95% CL	Upper 95% CL	Estimated	Percentage	Lower 95% CL	Upper 95% CL	Estimated	Percentage	Lower 95% CL	Upper 95% CL
American Indian / Alaska Native	269	2,620.44	35.78%	29.62%	42.44%	2,423.46	33.09%	25.60%	41.64%	2,280.45	31.13%	25.14%	37.83%
Asian / Pacific Islander	100	404.19	14.85%	9.19%	23.13%	494.94	18.19%	11.63%	27.30%	1,822.23	66.96%	54.61%	77.35%
Black	41	120.81	18.80%	9.83%	32.96%	181.50	28.24%	15.36%	46.09%	340.43	52.97%	35.76%	69.49%
Hispanic (include multi-hispanic)	81	253.37	25.70%	15.68%	39.15%	130.30	13.22%	6.57%	24.81%	602.28	61.08%	47.61%	73.06%
White	882	4,430.84	21.29%	18.31%	24.61%	4,293.35	20.63%	17.10%	24.69%	12,082.76	58.07%	53.62%	62.21%
Multi-Non-Hispanic	62	159.35	17.09%	9.47%	28.89%	263.78	28.29%	15.89%	45.54%	509.30	54.62%	37.10%	71.07%
Total	1,415	7,988.96	23.91%	21.34%	26.66%	7,787.33	23.31%	19.99%	26.98%	17,637.44	52.78%	49.12%	56.42%

Italics - Results based upon less than 100 respondents.

SOURCE: Alaska Youth Risk Behavioral Survey, High Schools, 1995 and 2003

Computed Marijuana Use: "How Many Times Have You Used Marijuana?" and "In the Past 30 Days, How Many Times Did You Use Marijuana?"
2003

American Indian / Alaska Native	Total Respondents	Current Marijuana Users (Within past 30 days) Estimated	Percentage	Lower 95% CL	Upper 95% CL	Former Marijuana Users (More than 30 days ago) Estimated	Percentage	Lower 95% CL	Upper 95% CL	Never Used Marijuana Estimated	Percentage	Lower 95% CL	Upper 95% CL
9th Grade	77	640.65	37.47%	25.43%	51.30%	286.51	16.76%	7.91%	32.06%	782.30	45.77%	33.11%	58.99%
10th Grade	82	1,078.46	41.28%	30.77%	52.64%	867.12	33.20%	23.96%	44.13%	662.78	25.44%	17.77%	35.00%
11th Grade	57	411.83	28.28%	16.70%	43.60%	677.28	46.45%	33.80%	59.58%	368.89	25.30%	16.48%	36.77%
12th Grade	40	365.53	28.73%	16.45%	46.48%	81.12	36.41%	19.47%	63.84%	400.19	30.86%	19.14%	45.70%
[redacted]	284	2,561.36	35.49%	29.31%	42.20%	2,383.88	33.17%	25.61%	41.71%	2,282.16	31.34%	25.30%	38.10%

White	Total Respondents	Current Marijuana Users (Within past 30 days) Estimated	Percentage	Lower 95% CL	Upper 95% CL	Former Marijuana Users (More than 30 days ago) Estimated	Percentage	Lower 95% CL	Upper 95% CL	Never Used Marijuana Estimated	Percentage	Lower 95% CL	Upper 95% CL
9th Grade	311	850.96	13.54%	10.42%	17.40%	785.84	12.50%	9.82%	16.09%	4,649.98	73.96%	68.43%	78.83%
10th Grade	174	1,133.80	22.99%	17.05%	30.25%	989.89	20.07%	12.13%	31.37%	2,807.45	56.93%	46.82%	66.50%
11th Grade	215	1,357.17	28.66%	20.45%	38.56%	1,126.45	23.78%	17.36%	31.65%	2,252.63	47.56%	39.46%	56.80%
12th Grade	182	1,088.90	22.44%	17.32%	28.55%	1,391.17	28.67%	21.57%	37.00%	2,372.81	48.89%	40.81%	57.04%
Total	882	4,430.84	21.29%	18.31%	24.61%	4,293.35	20.63%	17.10%	24.69%	12,082.76	58.07%	53.82%	62.21%

Italics - Results based upon less than 100 respondents
SOURCE: Alaska Youth Risk Behavior Survey, High Schools, 2003

Computed Marijuana Use: "How Many Times Have You Used Marijuana?" and "In the Past 30 Days, How Many Times Did You Use Marijuana?"
2003

Native	Total Respondents	Current Marijuana Users (Within past 30 days) Estimated	Percentage	Lower 95% CL	Upper 95% CL	Former Marijuana Users (More than 30 days ago) Estimated	Percentage	Lower 95% CL	Upper 95% CL	Never Used Marijuana Estimated	Percentage	Lower 95% CL	Upper 95% CL
9th Grade	77	640.55	37.47%	25.43%	51.30%	286.81	16.78%	7.91%	32.06%	782.30	45.77%	33.11%	58.99%
10th Grade	82	1,075.48	41.26%	30.77%	52.64%	867.12	33.28%	23.98%	44.13%	662.78	25.44%	17.77%	35.00%
11th Grade	57	41.83	28.29%	16.70%	43.60%	677.28	46.45%	33.80%	59.58%	368.89	25.30%	16.48%	36.77%
12th Grade	40	385.52	26.73%	15.45%	41.48%	51.12	35.41%	19.47%	53.84%	400.19	30.86%	19.14%	45.70%
	264	2,561.36	35.49%	29.91%	42.20%	2,383.88	33.17%	29.61%	41.71%	2,262.18	31.34%	25.30%	38.10%

Non-Native	Total Respondents	Current Marijuana Users (Within past 30 days) Estimated	Percentage	Lower 95% CL	Upper 95% CL	Former Marijuana Users (More than 30 days ago) Estimated	Percentage	Lower 95% CL	Upper 95% CL	Never Used Marijuana Estimated	Percentage	Lower 95% CL	Upper 95% CL
9th Grade	412	1,116.59	13.46%	10.68%	16.82%	978.22	11.79%	9.36%	14.75%	6,202.21	74.75%	69.98%	79.00%
10th Grade	217	1,264.33	21.69%	16.31%	28.25%	1,269.17	21.77%	14.60%	31.19%	3,347.07	56.53%	47.55%	65.10%
11th Grade	288	1,584.29	26.55%	20.12%	34.14%	1,421.47	23.82%	18.18%	30.58%	2,962.48	49.64%	42.70%	56.59%
12th Grade	226	1,365.38	23.47%	18.18%	29.75%	1,643.16	28.25%	21.36%	36.33%	2,808.51	48.28%	40.66%	55.96%
Total	1,144	5,368.55	20.81%	17.99%	23.50%	5,348.05	20.53%	17.29%	24.19%	15,335.30	58.86%	54.96%	62.66%

Italics - Results based upon less than 100 respondents.
Native = American Indian / Alaska Native; Non-Native = Asian, Black or African American, Hispanic or Latino, Native Hawaiian or Pacific Islander, White, Multiple-Hispanic, Multiple-Non-Hispanic
SOURCE: Alaska Youth Risk Behavioral Survey, High Schools, 2003.

Ever Used Marijuana: "How Many Times Have You Used Marijuana?"

1995	Total	Used Marijuana				Never Used Marijuana			
Combined Race Category	Respondents	Estimated	Percentage	Lower 95% CL	Upper 95% CL	Estimated	Percentage	Lower 95% CL	Upper 95% CL
American Indian / Alaska Native	180	2,679.70	62.70%	56.15%	68.81%	1,594.26	37.30%	31.19%	43.85%
[redacted] / Pacific Islander	*74*	*536.05*	*43.23%*	*32.83%*	*54.27%*	*703.82*	*56.77%*	*45.73%*	*67.17%*
[redacted]	*83*	*464.26*	*32.01%*	*21.96%*	*44.05%*	*986.17*	*67.99%*	*55.95%*	*78.04%*
[redacted]anic (include multi-hispanic)	*51*	*350.78*	*38.30%*	*23.52%*	*55.62%*	*564.99*	*61.70%*	*44.38%*	*76.48%*
White	1,137	9,397.38	47.47%	44.15%	50.81%	10,398.19	52.53%	49.19%	55.85%
Multi-Non-Hispanic	*59*	*579.57*	*53.42%*	*33.21%*	*72.56%*	*505.41*	*46.58%*	*27.44%*	*66.79%*
Total	1,584	14,007.73	48.70%	45.67%	51.75%	14,752.83	51.30%	48.25%	54.33%

2003	Total	Used Marijuana				Never Used Marijuana			
Combined Race Category	Respondents	Estimated	Percentage	Lower 95% CL	Upper 95% CL	Estimated	Percentage	Lower 95% CL	Upper 95% CL
American Indian / Alaska Native	280	5,332.20	69.90%	63.45%	75.65%	2,295.76	30.10%	24.35%	36.55%
Asian / Pacific Islander	101	924.19	33.65%	23.25%	45.92%	1,822.23	66.35%	54.08%	76.75%
Black	*41*	*302.31*	*47.03%*	*30.51%*	*64.24%*	*340.43*	*52.97%*	*35.76%*	*69.49%*
Hispanic (include multi-hispanic)	*61*	*383.67*	*38.91%*	*26.94%*	*52.39%*	*602.28*	*61.09%*	*47.61%*	*73.06%*
White	886	8,774.10	41.95%	37.83%	46.19%	12,140.24	58.05%	53.81%	62.17%
Multi-Non-Hispanic	*62*	*423.12*	*45.38%*	*28.93%*	*62.90%*	*509.30*	*54.62%*	*37.10%*	*71.07%*
Total	1,433	16,139.59	47.68%	44.12%	51.27%	17,710.24	52.32%	48.73%	55.88%

Italics - Results based upon less than 100 respondents

SOURCE: Alaska Youth Risk Behavioral Survey, High Schools, 1995 and 2003

Ever Used Marijuana: "How Many Times Have You Used Marijuana?"
2003

American Indian / Alaska Native	Total Respondents	Used Marijuana Estimated	Percentage	Lower 95% CL	Upper 95% CL	Never Used Marijuana Estimated	Percentage	Lower 95% CL	Upper 95% CL
9th Grade	*80*	*969.19*	*54.86%*	*42.13%*	*66.98%*	*797.63*	*45.14%*	*33.02%*	*57.87%*
[redacted] Grade	*86*	*2,063.14*	*75.69%*	*66.60%*	*82.93%*	*662.78*	*24.31%*	*17.07%*	*33.40%*
[redacted]rade	*60*	*176.99*	*76.14%*	*65.53%*	*84.20%*	*368.89*	*23.86%*	*15.80%*	*34.37%*
[redacted] Grade	*41*	*934.37*	*70.01%*	*55.54%*	*81.36%*	*400.19*	*29.99%*	*18.64%*	*44.46%*
Total	275	5,243.56	69.72%	63.22%	75.52%	2,277.51	30.28%	24.48%	36.78%

White	Total Respondents	Used Marijuana Estimated	Percentage	Lower 95% CL	Upper 95% CL	Never Used Marijuana Estimated	Percentage	Lower 95% CL	Upper 95% CL
9th Grade	315	1,668.96	26.28%	21.32%	31.92%	4,682.15	73.72%	68.08%	78.68%
10th Grade	174	2,123.69	43.07%	33.50%	53.18%	2,807.45	56.93%	46.82%	66.50%
11th Grade	217	2,501.38	52.34%	44.06%	60.50%	2,277.83	47.66%	39.50%	55.94%
12th Grade	182	2,480.07	51.11%	42.96%	59.19%	2,372.81	48.89%	40.81%	57.04%
Total	888	8,774.10	41.95%	37.83%	46.19%	12,140.24	58.05%	53.81%	62.17%

Italics - Results based upon less than 100 respondents.
SOURCE: Alaska Youth Risk Behavioral Survey, High Schools, 2003

Ever Used Marijuana: "How Many Times Have You Used Marijuana?"
2003

Native	Total Respondents	Used Marijuana Estimated	Percentage	Lower 95% CL	Upper 95% CL	Never Used Marijuana Estimated	Percentage	Lower 95% CL	Upper 95% CL
9th Grade	*80*	*969.19*	*54.86%*	*42.13%*	*66.08%*	*797.63*	*45.14%*	*33.02%*	*57.87%*
[illegible] Grade	*86*	*2,063.14*	*75.69%*	*66.60%*	*82.93%*	*662.78*	*24.31%*	*17.07%*	*33.40%*
[illegible]rade	*60*	*176.99*	*76.14%*	*65.63%*	*84.20%*	*368.89*	*23.86%*	*15.80%*	*34.37%*
[illegible]Grade	*41*	*934.37*	*70.01%*	*55.54%*	*81.36%*	*400.19*	*29.99%*	*18.64%*	*44.46%*
Total	275	5,243.56	69.72%	63.22%	75.52%	2,277.51	30.28%	24.48%	36.78%

Non-Native	Total Respondents	Used Marijuana Estimated	Percentage	Lower 95% CL	Upper 95% CL	Never Used Marijuana Estimated	Percentage	Lower 95% CL	Upper 95% CL
9th Grade	416	2,126.97	25.44%	21.13%	30.28%	6,234.38	74.56%	69.72%	78.87%
10th Grade	217	2,573.49	43.47%	34.90%	52.45%	3,347.07	56.53%	47.55%	65.10%
11th Grade	288	3,023.51	50.30%	43.28%	57.31%	2,987.78	49.70%	42.69%	56.72%
12th Grade	227	3,033.60	51.93%	44.38%	59.39%	2,808.51	48.07%	40.61%	55.62%
Total	1,151	10,791.57	41.21%	37.43%	45.10%	15,392.78	58.79%	54.90%	62.57%

Italics - Results based upon less than 100 respondents.
Native = American Indian / Alaska Native; Non-Native = Asian, Black or African American, Hispanic or Latino, Native Hawaiian or Pacific Islander, White, Multiple-Hisp
SOURCE: Alaska Youth Risk Behavioral Survey, High Schools, 2003.

Current Marijuana User: "In the Past 30 Days, How Many Times Did You Use Marijuana?"

1995	Total	Current Marijuana Users (Within past 30 days)				No Marijuana Use in Past 30 Days			
Combined Race Category	Respondents	Estimated	Percentage	Lower 95% CL	Upper 95% CL	Estimated	Percentage	Lower 95% CL	Upper 95% CL
American Indian / Alaska Native	180	1,253.52	29.35%	22.34%	37.50%	3,017.01	70.65%	62.50%	77.66%
[redacted] / Pacific Islander	*74*	*396.14*	*31.95%*	*21.01%*	*45.32%*	*843.73*	*68.05%*	*54.68%*	*78.99%*
[redacted]	*84*	*307.03*	*20.95%*	*12.94%*	*32.09%*	*1,158.49*	*79.05%*	*67.91%*	*87.06%*
Hispanic (include multi-hispanic)	*51*	*81.83*	*8.91%*	*3.73%*	*19.81%*	*834.14*	*91.09%*	*80.19%*	*96.27%*
White	1,135	5,864.72	29.71%	26.87%	32.72%	13,874.71	70.29%	67.28%	73.13%
Multi-Non-Hispanic	*58*	*380.70*	*35.64%*	*20.95%*	*53.63%*	*687.55*	*64.36%*	*46.37%*	*79.05%*
Total	1,582	8,283.74	28.86%	26.24%	31.63%	20,415.64	71.14%	68.37%	73.76%

2003	Total	Current Marijuana Users (Within past 30 days)				No Marijuana Use in Past 30 Days			
Combined Race Category	Respondents	Estimated	Percentage	Lower 95% CL	Upper 95% CL	Estimated	Percentage	Lower 95% CL	Upper 95% CL
American Indian / Alaska Native	276	2,681.57	35.73%	30.19%	41.67%	4,824.31	64.27%	58.33%	69.81%
Asian / Pacific Islander	101	404.19	14.77%	9.13%	23.00%	2,333.28	85.23%	77.00%	90.87%
Black	*42*	*120.81*	*18.39%*	*9.66%*	*32.19%*	*536.06*	*81.61%*	*67.81%*	*90.34%*
Hispanic (include multi-hispanic)	*61*	*253.37*	*25.70%*	*15.68%*	*39.15%*	*732.58*	*74.30%*	*60.85%*	*84.32%*
White	886	4,445.69	21.30%	18.31%	24.62%	16,425.86	78.70%	75.38%	81.69%
Multi-Non-Hispanic	*62*	*159.35*	*17.09%*	*9.47%*	*28.89%*	*773.08*	*82.91%*	*71.11%*	*90.53%*
Total	1,428	8,064.98	23.94%	21.42%	26.65%	25,629.17	76.06%	73.35%	78.58%

Italics - Results based upon less than 100 respondents

SOURCE: Alaska Youth Risk Behavioral Survey, High Schools, 1995 and 2003.

Current Marijuana User: "In the Past 30 Days, How Many Times Did You Use Marijuana?"
2003

American Indian / Alaska Native	Total Respondents	Current Marijuana Users (Within past 30 days) Estimated	Percentage	Lower 95% CL	Upper 95% CL	No Marijuana Use in Past 30 Days Estimated	Percentage	Lower 95% CL	Upper 95% CL
9th Grade	*78*	*640.55*	*36.96%*	*25.12%*	*50.82%*	*1,092.35*	*63.04%*	*49.38%*	*74.88%*
[redacted]Grade	*84*	*112.45*	*41.77%*	*31.92%*	*52.31%*	*1,551.06*	*58.23%*	*47.69%*	*68.08%*
[redacted]ade	*60*	*435.98*	*28.36%*	*16.83%*	*43.63%*	*1,101.38*	*71.64%*	*56.37%*	*83.17%*
[redacted] Grade	*40*	*385.52*	*29.73%*	*15.45%*	*49.48%*	*911.31*	*70.27%*	*50.52%*	*84.55%*
Total	270	2,622.53	35.54%	29.97%	41.54%	4,755.97	64.46%	58.46%	70.03%

White	Total Respondents	Current Marijuana Users (Within past 30 days) Estimated	Percentage	Lower 95% CL	Upper 95% CL	No Marijuana Use in Past 30 Days Estimated	Percentage	Lower 95% CL	Upper 95% CL
9th Grade	314	865.81	13.66%	10.48%	17.62%	5,470.93	86.34%	82.38%	89.52%
10th Grade	174	1,133.80	22.99%	17.05%	30.25%	3,797.34	77.01%	69.75%	82.95%
11th Grade	216	1,357.17	28.54%	20.38%	38.40%	3,397.61	71.46%	61.60%	79.62%
12th Grade	182	1,088.90	22.44%	17.32%	28.55%	3,763.97	77.56%	71.45%	82.68%
Total	886	4,445.69	21.30%	18.31%	24.62%	16,429.86	78.70%	75.38%	81.69%

Italics - Results based upon less than 100 respondents
SOURCE: Alaska Youth Risk Behavioral Survey, High Schools, 2003

Current Marijuana User: "In the Past 30 Days, How Many Times Did You Use Marijuana?"
2003

Native	Total Respondents	Current Marijuana Users (Within past 30 days) Estimated	Percentage	Lower 95% CL	Upper 95% CL	No Marijuana Use in Past 30 Days Estimated	Percentage	Lower 95% CL	Upper 95% CL
9th Grade	*78*	*640.55*	*36.96%*	*25.12%*	*50.82%*	*1,092.35*	*63.04%*	*49.38%*	*74.88%*
[redacted] Grade	*84*	*112.45*	*41.77%*	*31.92%*	*52.31%*	*1,551.06*	*58.23%*	*47.69%*	*68.08%*
[redacted] rade	*60*	*435.98*	*28.36%*	*16.83%*	*43.63%*	*1,101.38*	*71.64%*	*56.37%*	*83.17%*
[redacted] Grade	*40*	*385.52*	*29.73%*	*15.45%*	*49.48%*	*911.31*	*70.27%*	*50.52%*	*84.55%*
Total	270	2,622.53	35.54%	29.97%	41.54%	4,755.87	64.46%	58.46%	70.03%

Non-Native	Total Respondents	Current Marijuana Users (Within past 30 days) Estimated	Percentage	Lower 95% CL	Upper 95% CL	No Marijuana Use in Past 30 Days Estimated	Percentage	Lower 95% CL	Upper 95% CL
9th Grade	415	1,131.44	13.56%	10.73%	16.98%	7,215.54	86.44%	83.02%	89.27%
10th Grade	217	1,284.33	21.69%	16.31%	28.25%	4,636.24	78.31%	71.75%	83.69%
11th Grade	287	1,584.29	26.46%	20.06%	34.03%	4,402.58	73.54%	65.97%	79.94%
12th Grade	228	1,365.36	23.35%	18.09%	29.59%	4,481.93	76.65%	70.41%	81.91%
Total	1,150	5,383.41	20.59%	17.97%	23.48%	20,767.33	79.41%	76.52%	82.03%

Italics - Results based upon less than 100 respondents.

Native = American Indian / Alaska Native; Non-Native = Asian, Black or African American, Hispanic or Latino, Native Hawaiian or Pacific Islander, White, Multiple-Hisp.

SOURCE: Alaska Youth Risk Behavioral Survey, High Schools, 2003.

30-Day Prevalence of Use of Various Drugs by Grade

Percentage of students who smoke cigarettes on one or more of the past thirty day: Yes

	Total			1995		Total			2003	
Grades	Respondents	Estimated	Percentage	Lower 95% CL	Upper 95% CL	Respondents	Estimated	Percentage	Lower 95% CL	Upper 95% CL
[redacted]	482	3,018.80	35.36%	28.60%	42.76%	488	1,252.15	12.54%	9.25%	16.78%
[redacted]rade	379	2,512.77	33.24%	26.59%	40.64%	301	2,025.47	23.61%	19.05%	28.89%
[redacted]rade	468	2,654.26	39.68%	35.71%	43.80%	342	1,422.01	19.21%	13.74%	26.21%
12th Grade	265	2,373.01	38.68%	32.41%	45.35%	261	1,609.94	23.23%	17.32%	30.42%
Total	1,600	10,599.88	36.49%	32.59%	40.59%	1,403	6,373.60	19.26%	16.70%	22.11%

Percentage of students who chewing tobacco or snuff on one or more of the past thirty day: Yes

	Total			1995		Total			2003	
Grades	Respondents	Estimated	Percentage	Lower 95% CL	Upper 95% CL	Respondents	Estimated	Percentage	Lower 95% CL	Upper 95% CL
9th Grade	492	1,255.36	14.40%	10.39%	19.62%	502	881.22	8.59%	6.27%	11.65%
10th Grade	361	1,127.15	14.83%	10.73%	20.14%	308	1,305.96	14.89%	9.20%	23.16%
11th Grade	474	1,112.42	16.41%	12.15%	21.80%	358	1,079.69	13.92%	9.45%	20.03%
12th Grade	267	1,065.20	17.24%	12.39%	23.47%	267	464.05	6.54%	3.81%	11.01%
Total	1,620	4,572.53	15.55%	12.72%	18.88%	1,447	3,786.72	11.10%	8.64%	14.16%

Percentage of students who had at least one drink of alcohol on one or more of the past thirty day: Yes

	Total			1995		Total			2003	
Grades	Respondents	Estimated	Percentage	Lower 95% CL	Upper 95% CL	Respondents	Estimated	Percentage	Lower 95% CL	Upper 95% CL
9th Grade	477	3,857.70	45.73%	38.03%	53.64%	485	2,605.43	26.29%	21.99%	31.10%
10th Grade	366	3,077.65	42.64%	37.73%	47.70%	302	3,120.69	36.13%	29.78%	43.00%
11th Grade	465	3,271.09	49.19%	44.57%	53.83%	345	3,386.90	45.40%	39.22%	51.73%
12th Grade	256	3,256.05	54.68%	46.78%	62.34%	257	3,627.31	52.91%	45.46%	60.23%
Total	1,570	13,490.15	47.53%	43.61%	51.47%	1,398	12,756.34	38.63%	34.59%	42.82%

Percentage of students who used marijuana one or more times during the past thirty day: Yes

	Total			1995		Total			2003	
Grades	Respondents	Estimated	Percentage	Lower 95% CL	Upper 95% CL	Respondents	Estimated	Percentage	Lower 95% CL	Upper 95% CL
9th Grade	488	2,402.08	27.76%	23.70%	32.22%	495	1,772.00	17.48%	13.95%	21.68%
10th Grade	375	1,916.24	25.68%	20.59%	31.53%	303	2,396.77	27.73%	22.58%	33.56%
11th Grade	473	2,142.57	31.75%	26.85%	37.09%	353	2,046.50	26.84%	21.22%	33.33%
12th Grade	264	1,886.88	30.85%	25.39%	36.91%	269	1,750.88	24.35%	19.07%	30.54%
[redacted]	1,606	8,360.16	28.72%	26.14%	31.45%	1,431	8,034.16	23.77%	21.29%	26.45%

[redacted]ntage of students who used any form of cocaine, including powder, crack, or freebase one or more times during the past thirty day: Yes

	Total			1995		Total			2003	
Grades	Respondents	Estimated	Percentage	Lower 95% CL	Upper 95% CL	Respondents	Estimated	Percentage	Lower 95% CL	Upper 95% CL
9th Grade	494	186.64	2.13%	1.25%	3.62%	502	209.10	2.04%	1.16%	3.57%
10th Grade	381	141.75	1.87%	0.86%	4.02%	310	166.57	1.88%	0.83%	4.24%
11th Grade	475	142.77	2.10%	0.84%	5.13%	360	274.03	3.52%	1.99%	6.14%
12th Grade	266	301.17	4.90%	2.70%	8.72%	268	220.96	3.08%	1.20%	7.65%
Total	1,622	772.34	2.62%	1.75%	3.93%	1,452	870.66	2.54%	1.69%	3.81%

Percentage of students who sniffed glue, breathed the contents of aerosol spray cans, or inhaled any paint or spray one or more times during the past thirty day: Yes

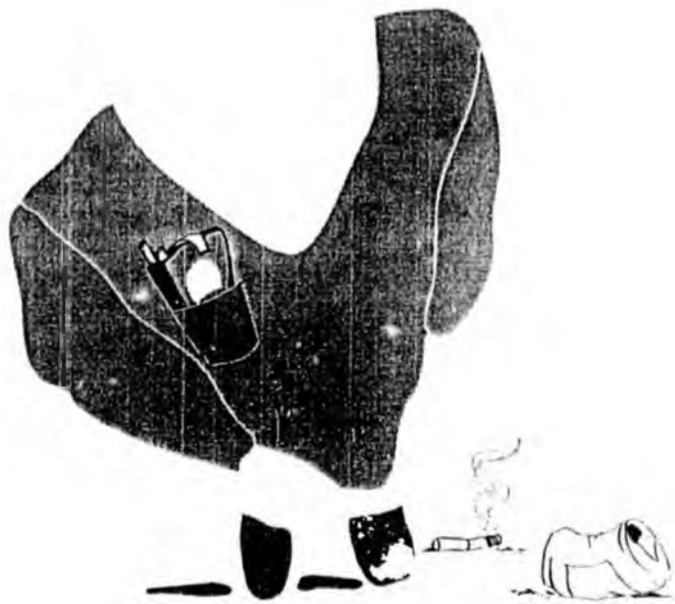
	Total			1995		Total			2003	
Grades	Respondents	Estimated	Percentage	Lower 95% CL	Upper 95% CL	Respondents	Estimated	Percentage	Lower 95% CL	Upper 95% CL
9th Grade	0					501	193.01	1.88%	0.96%	3.64%
10th Grade	0					310	176.30	2.00%	0.92%	4.28%
11th Grade	0					360	200.07	2.57%	1.48%	4.42%
12th Grade	0					269	261.44	3.63%	1.71%	7.57%
Total	0					1,451	830.82	2.42%	1.70%	3.44%

Italics - Results based upon less than 100 respondents

SOURCE: Alaska Youth Risk Behavioral Survey, High Schools, 2003.

Health Risks

Youth Risk Behavior Survey



Children have never been very good at listening to their elders, but they have never failed to imitate them.

James Baldwin,
American writer

Youth Risk Behavior Survey in Alaska

Since 1990, the federal Center for Disease Control and Prevention has sponsored several Youth Risk Behavior Surveys. These are national and state surveys of high school and middle school students, asking them how much they smoke, drink, carry weapons, and do other things that endanger their health and even their lives.

The first time Alaska schools took part in the survey was in 1995. The Alaska departments of Health and Social Services and Education and Early Development administered the survey to 1,634 students at 31 high schools and 1,265 students at 32 middle schools statewide. The adjacent table shows characteristics of the students surveyed and response rates.

The survey was conducted again in 1999, with 23 Alaska school districts taking part. Results of that survey are not yet available. But the Anchorage school district (Alaska's largest district, with more than a third of the state's high school students) did not take part in 1999. Parents objected to some of the questions, feeling that they infringed on students' and families' rights to privacy. So unlike the 1995 survey, the 1999 survey will not be a statewide sample.

Data from 1995 Youth Risk Behavior Survey in Alaska, a joint project of the departments of Health and Social Services and Education and Early Development

Youth Risk Behavior Survey in Alaska, 1995

	High Schools		Middle Schools
Number of Participating Schools	31		32
Response Rate from Sample of Schools	82%		80%
Total Respondents	**1,634***		**1,265***
Boys	821		651
Girls	807		608
Grade			
9	497	7	636
10	383	8	606
11	477		
12	269		
Unknown	8		
Race/Ethnicity			(No question about race/ethnicity)
White	1,147		
Black	87		
Hispanic or Latino	53		
Alaska Native	184		
Asian/Pacific Isl	75		
Other	62		

* *Numbers may differ slightly because not all respondents answered every question*

Source: *Alaska Departments of Health and Social Services and Education and Early Development*

Although information from the 1995 survey is now several years old, it is the best information available, as reported by the teenagers themselves. Many of the survey findings are worrisome—but on the brighter side, the survey also shows that most of Alaska's teenagers don't bring guns to school or drive drunk or do other things that make the headlines.

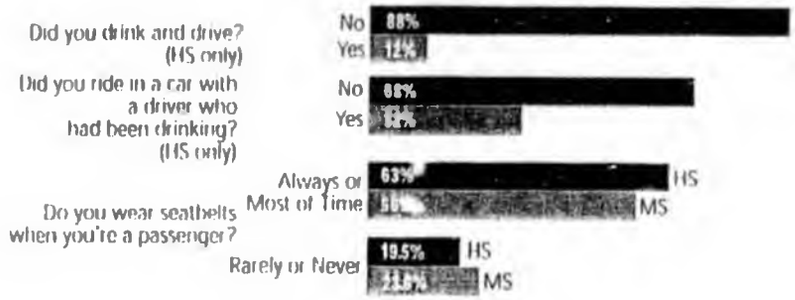
On the next few pages we provide a snapshot of some of the findings from the 1995 survey in Alaska. The published report of survey findings includes many more details.[1] Here we just provide a broad picture of survey findings, to help readers see the levels of health risks among Alaska's teenagers in the 1990s.

Youth Risk Behavior in Alaska (continued)

Car and other motor vehicle crashes cause 30 percent of the deaths among Alaska's young people every year—and we know many crashes involve drivers who have been drinking. Yet 20 percent of high school students and nearly 25 percent of middle school students say they seldom or never use seatbelts when riding in cars. And nearly one third of high school students report riding in cars with drivers who have been drinking.

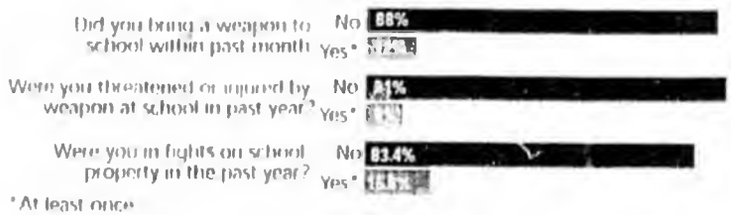
Drinking, Driving, and Seatbelts in Month Before Survey

(Middle and High School Students)



Weapons and Fighting at School

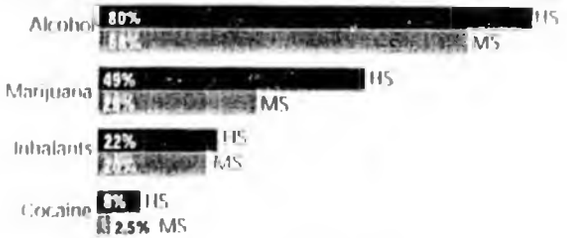
(High School Only)



*At least once

Alcohol or Drugs

(Middle and High School students who have used at least once)



Several times in the U.S. over the past few years—including once in Alaska—students have brought guns to school and murdered or wounded other students or teachers. But while we must stop this horrifying violence, it's useful to remember that the overwhelming majority of schools report no violence, and the overwhelming majority of students don't bring weapons to school. Still, more than one in ten of Alaska's high-school students reported bringing weapons (including guns, knives, or clubs) to school at least once in the month before the 1995 survey. Nearly one in ten reported being threatened or hurt by other students with weapons at school during the previous year. Close to one in five reported getting into one or more fights at school in the previous year.

Research has shown that teenagers who regularly use alcohol or drugs are more likely to fight, to smoke, to have sex, and even to consider suicide. We also know that alcohol and drugs not only impair judgement but can damage brain cells and even cause death. Most of Alaska's high school and even middle school students have at least tried alcohol. Nearly half of high school students and a third of middle school students have smoked marijuana. And one in five students—including those in middle school—have sniffed glue or used other inhalants that can kill.

Youth Risk Behavior Survey in Alaska (continued)

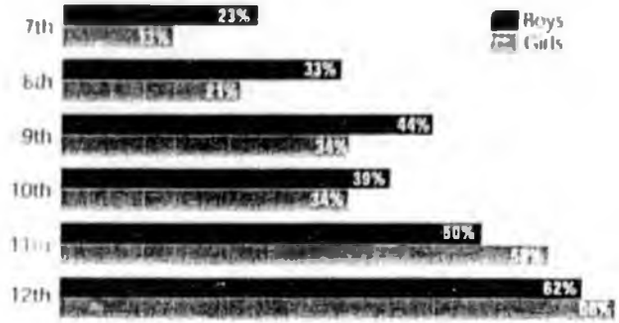
Share of Alaska Boys (15 and Older) Chewing Tobacco in Month Before Survey

We know that smoking cigarettes can cause lung cancer, emphysema, and heart disease, among other things. A growing body of evidence also shows that chewing tobacco and snuff can cause mouth and other cancers. One quarter of Alaska's high school students and nearly 10 percent of middle school students reported smoking cigarettes regularly—on at least 10 of the 30 days before the 1995 survey. And among boys—who are much more likely than girls to chew tobacco—chewing grows more common as they get older. About 16 percent of boys 15 or under reported chewing tobacco at the time of the survey, but nearly twice as many boys 18 and older chewed.

Higher Tobacco Taxes and Teenage Smoking

In 1997, Alaska tripled cigarette taxes, raising the tax on a pack of cigarettes from 29 cents to $1.00. Many health experts believe higher taxes reduce smoking by making cigarettes too expensive for some people—especially teenage smokers—to buy. Others, however, disagree about whether higher taxes actually cause people to quit smoking. The Alaska Department of Health and Social Services has commissioned a study of the effects of higher taxes on teenagers who smoke. The department also hopes the results of the 1999 Youth Risk Behavior Survey in Alaska will provide some information on the effects of the tax increase on teenage smoking. But since the survey was not conducted in the Anchorage school district, it will not provide a statewide sample.

Percentage of Alaska Students (Grades 7-12) Who Have Had Sexual Intercourse



Source: *State of Alaska Epidemiology Bulletin #23, 1997. Based on 1995 YRBS.*

Teenagers who have sexual intercourse not only risk becoming pregnant (or fathering children), they risk being infected with sexually transmitted diseases, including AIDS, which can kill them. And research has found that many younger teenage girls who have sex don't really want to but do so anyway because they feel pressured.[2]

In Alaska, nearly one quarter of boys and more than one in ten girls in the *seventh* grade—boys and girls who are most likely 12 years old—report having had sex. That share climbs steadily through the rest of middle and high school. The 1995 survey found that the younger teenagers are when they start having sex, the more likely they are to smoke, drink, and do other things that can hurt them. By the time they are seniors in high school, nearly two thirds of both boys and girls in Alaska have had sex. Fewer than half the sexually active Alaska teenagers reported using condoms regularly in 1995, and only 18 percent of sexually active girls said they were using birth control pills.

Notes for Health Risks Section

[1] Alaska Departments of Health and Social Services and Education, *Youth Risk Behavior Survey: Alaska Report 1995*. February 1996.

[2] K. A. Moore, A. K. Driscoll, and L. D. Lindburg, *A Statistical Portrait of Adolescent Sex, Contraception, and Childbearing*. The National Campaign to Prevent Teen Pregnancy.

Alaska Youth Risk Behavior Survey 1999

Alaska School Health Education Profile 1998

Methodology

The 1999 YRBS was intended to be an exact replica of the 1995 Alaska statewide survey so that data could be compared across several years. However, the Anchorage school district chose not to participate in the 1999 statewide survey. As a result, the 1999 statewide survey results for Alaska are not comparable to 1995. However, the 1999 YRBS survey results do provide representative prevalence data for the state's student population excluding Anchorage.

The samples were scientifically selected with each eligible student in the school population having an equal probability of being selected. This sampling process is most often referred to as probability sampling. The size of a sample is related directly to the size of the eligible population, the estimated student response rate, and the desired precision of the results. The eligible student population was determined from the official 1998 October enrollment counts reported by the Alaska State Department of Education & Early Development. The enrollment count was edited to include only students in grades 7 through 12. The school list was edited to remove correspondence, home study, alternative, and correctional schools. A sufficient number of students were selected to give a plus or minus five percent margin of error for each question.

A two-stage sample design was used to select the actual students for participation. The first stage consisted of selecting schools. Schools were selected with probability proportional to the size of their enrollment. Alaska has a large number of small schools, which means that more schools were needed to obtain the number of students required for the desired level of precision. Once a school was selected, classes were selected as the second stage. Eligible classes were those where a student would be enrolled in one, and only one, class at a time. (For example, second period, or required English). This gave each student an equal opportunity of being selected. At any time a school district, an individual school, a student's parents, or a specific student had the opportunity to decline to participate in the survey.

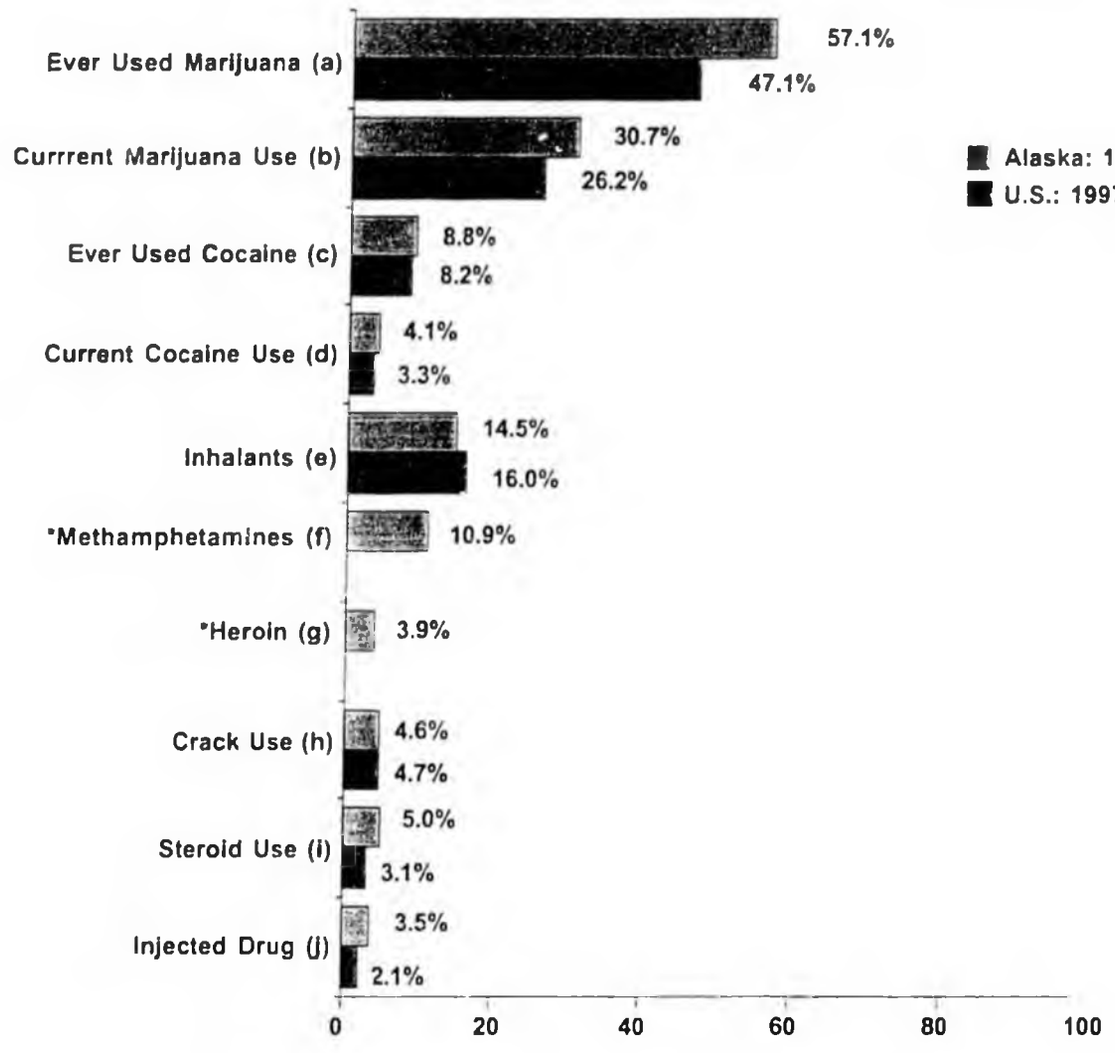
The numbers sampled in each stage were adjusted upward in anticipation that some schools and students would fail to participate. To ensure that sample results can be generalized to the total population, the overall participation rate (school participation rate multiplied by the student participation rate) must be equal to or greater than 60 percent.

At the classroom level, teachers were given a script to read to students that established guidelines for student privacy and anonymity, and the importance of the survey. Each student was given an unmarked envelope in which to seal his or her survey before turning it in. These survey envelopes remained sealed until received at a central state collection site.

The Centers for Disease Control and Prevention (CDC) and Westat, Inc., a CDC contractor, analyzed the state survey data. Analysis included the scanning of the surveys and performance of extensive edit checks to identify survey inconsistencies. When inconsistencies were found, responses were excluded from the analysis. For example, if a student reported in one question having never been in a physical fight, but then reported in another question being hurt in a physical fight, the data on that student was excluded for the two questions related to physical fighting.

Use of Drugs by High School Students

The most common drugs used by high school students in Alaska are marijuana, inhalants (glues, paints, and sprays), and methamphetamines (speed, crystal, crank, or ice). The prevalence of drug use is similar among Alaska students and U.S. students, with the exception of marijuana use, Alaska students are more likely to report marijuana use.

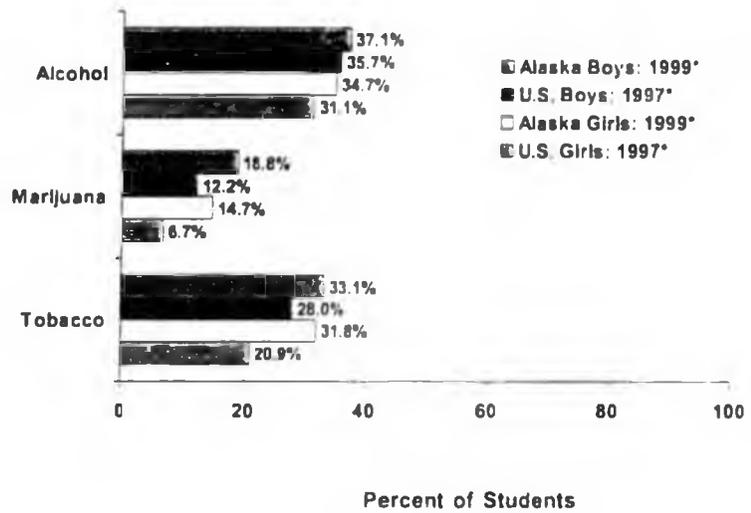


a) Ever used marijuana.
b) Used marijuana one or more times in the 30 days preceding the survey.
c) Ever tried any form of cocaine.
d) Used cocaine on one or more days in the 30 days prior to the survey.
e) Ever sniffed glue, breathed contents of spray cans or inhaled paints or sprays to get high.
f) Ever used methamphetamines (speed, crystal, crank, or ice).
g) Ever used heroin.
h) Ever used crack or freebase.
i) Ever used illegal steroids.
j) Ever used a needle to inject an illegal drug.

*U.S. Data not available

Use of Alcohol, Marijuana, or Tobacco Before the Age of 13 Years

Almost 40% of Alaska high school boys report having had a first drink of alcohol before age 13 years. Also by age 13 years, 18.8% of boys and 14.7% of girls report having tried marijuana for the first time, accounting for about a quarter of those who have ever used marijuana. Percentages of age at first use are higher for Alaska boys and girls than U.S. boys and girls in use of alcohol, tobacco, and marijuana.



*Use of alcohol, marijuana, or tobacco before the age of 13 years

Year 2000 Objectives:

- ***Increase by at least 1 year the average age of first use of cigarettes, alcohol, and marijuana by adolescents aged 12-17.***

Section III: Drug and Alcohol Use

Background

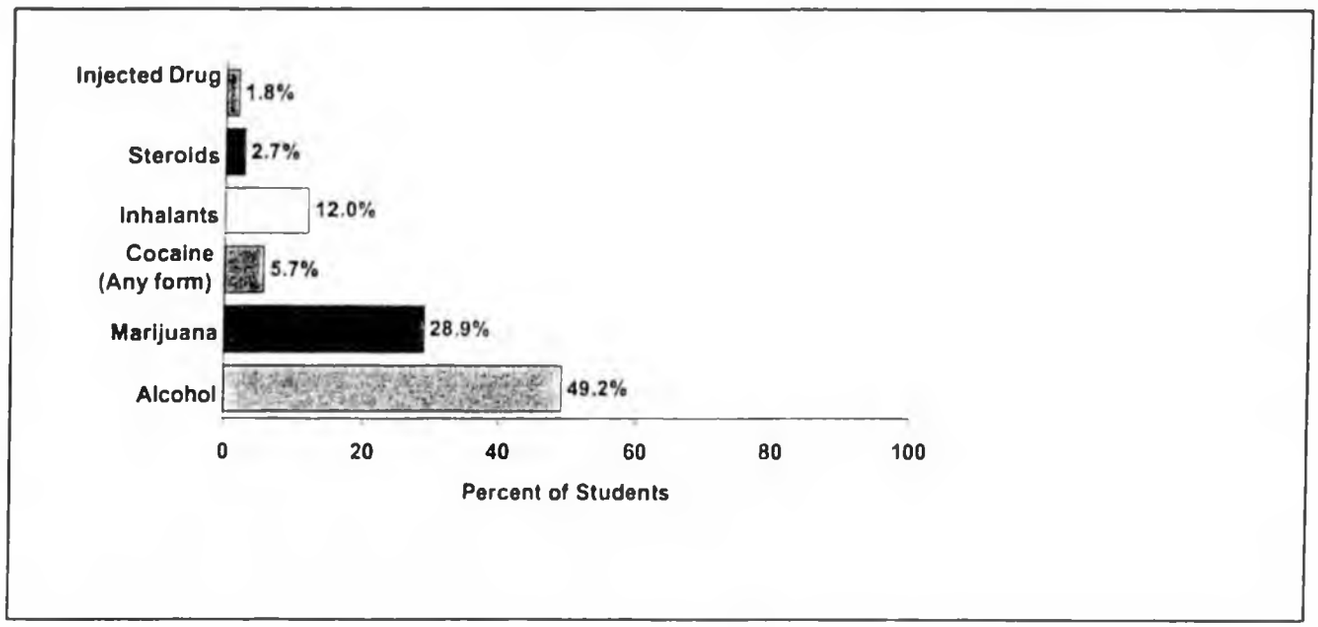
Alcohol and drug abuse are major contributing factors in homicides, suicides, and motor vehicle crashes, which are the leading causes of death and disability among young people in the U.S. and in Alaska. Heavy drinking and drug abuse among youth are linked to physical fights, destroyed property, job problems, school failure, delinquency, unwanted pregnancies, and transmission of sexually transmitted diseases.[8]

An estimated 19.2% of Alaska adults report binge drinking (having five or more drinks on an occasion, one or more time in the past month). Alaska's rate of adult binge drinking is among the highest in the U.S.[9]

YRBS Results

Alcohol and Drug Use (Ever Used)

Over 49% of middle school students report ever having had a drink of alcohol. The alcohol question excluded drinking wine for religious reasons. The next most common drugs are marijuana and inhalants (glue, paints, and sprays). Nearly 12% of students report ever having used inhalants and 28.9% report ever having used marijuana.



Health Risks

Youth Risk Behavior Survey

I broke out into the willows that grew around the edges of the cottonwoods. . . . A huge brown bear was coming head on, bounding through the willow clumps not fifty feet away! . . . I threw up my arms and yelled. That was all I could think to do. On he came . . . . I tripped and fell on my back. And then as he loomed over me, a strange thing happened. The air swooshed out of him as he switched ends. Off he went . . . . Never once did he look back. I was shouting, encouraging him in his flight.

Sam Keith, from the journals of Richard Proenneke
One Man's Wilderness
Published 1973; Reissued 1999
Anchorage: Alaska Northwest Books

DEFINITION AND SIGNIFICANCE

Since 1990, the U.S. Centers for Disease Control and Prevention have sponsored the Youth Risk Behavior Survey (YRBS) at both the national and state levels. The survey asks middle- and high-school students questions about a broad range of health issues: use of tobacco, alcohol, and drugs; sexual behavior; diet and physical activity; and behaviors (like fighting and carrying weapons) that could cause serious injury.

The survey is an excellent source of data on health risks among adolescents, allowing comparisons among states and with national averages and tracking changes over time.

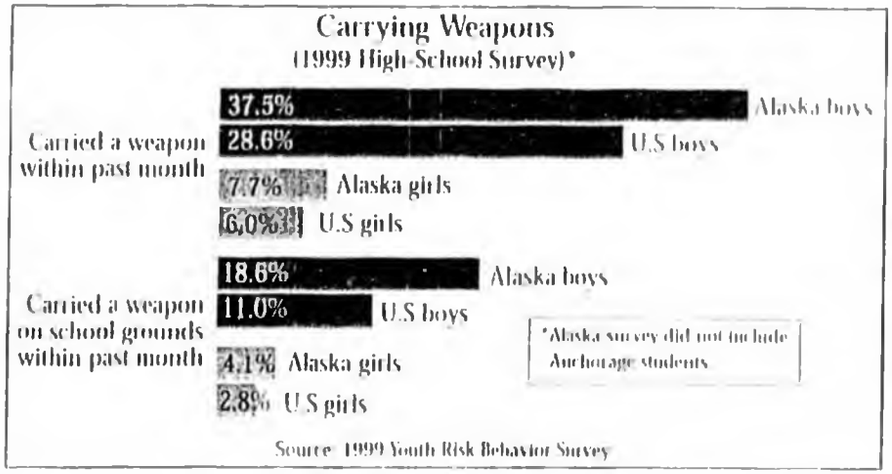
In Alaska, the survey is a joint project of the state departments of Health and Social Services and Education and Early Development. Alaska has conducted the survey only twice—in 1995 and 1999. However, in 1999 the Anchorage School District (by far the largest district in the state) decided not to take part in the survey.

Anchorage's decision not to take part means that we can't compare Alaska's 1995 and 1999 survey findings. The data reported here are from a sample of 1,427 high-school students throughout Alaska, except in Anchorage. Also, since the response from middle schools was below what is considered a reliable level, we report only the high-school results. When reading these results, keep in mind that Anchorage (with roughly 40 percent of the state's high-school students) did not take part in the survey.

The entire report is available online at: www.epi.hss.state.ak.us/publications.shtml

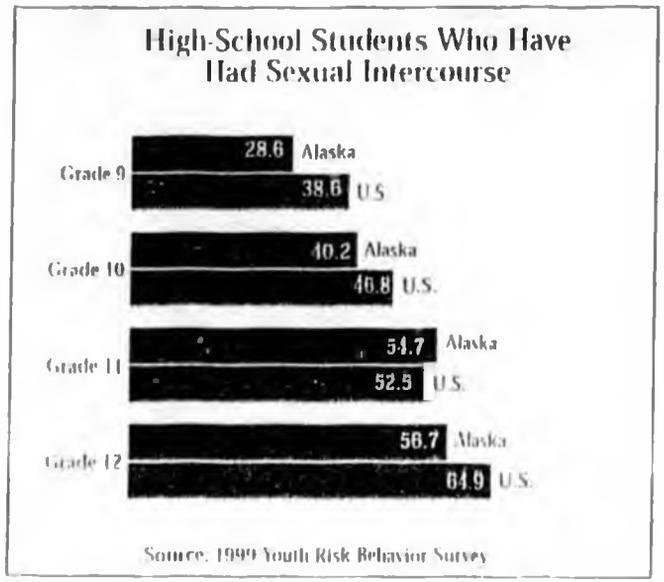
Carrying Weapons

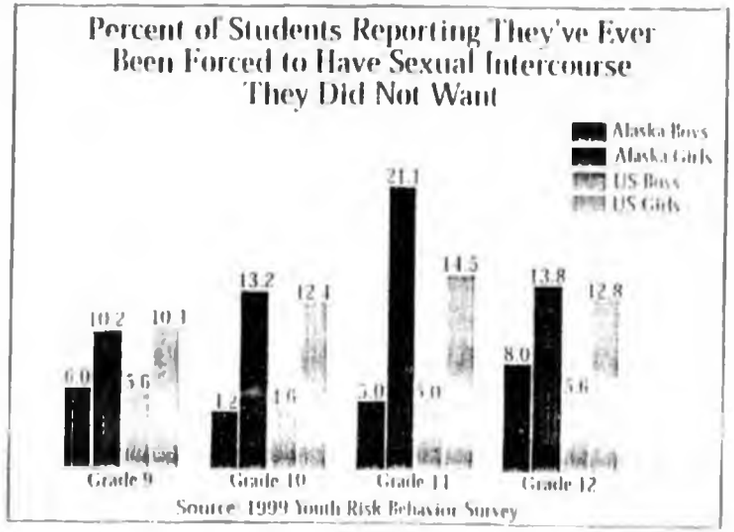
- High-school boys surveyed in Alaska were more likely to report carrying weapons in general and on school grounds in particular during the previous month. Nearly 38 percent of Alaska high-school boys said they had carried weapons and 18 percent said they had carried weapons on school grounds. That compares with 29 percent of boys nationwide carrying weapons in general and 11 percent on school grounds.
- High-school girls in Alaska were slightly more likely than girls nationwide to carry weapons in the previous month. About 8 percent of Alaska girls and 6 percent of girls nationwide reported carrying weapons; about 4 percent of Alaska girls and 3 percent of girls nationwide carried weapons to school.



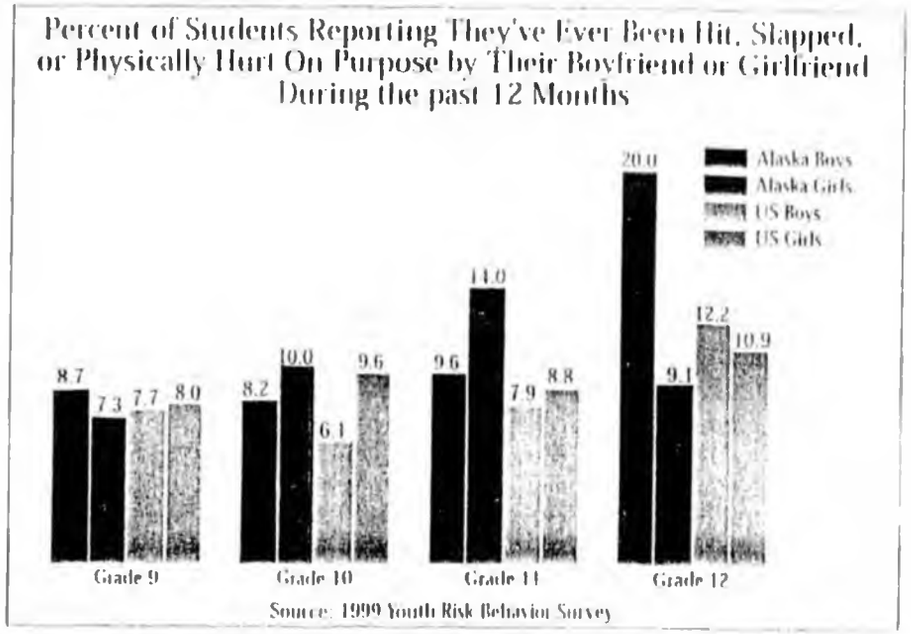
Sexual Intercourse and Violence

- By ninth grade, nearly 30 percent of Alaska high-school students report having sexual intercourse, and that share climbs to nearly 60 percent by twelfth grade. High-school students nationwide—especially younger students—are somewhat more likely to report having intercourse.
- A staggering number of high-school girls in both Alaska and the entire U.S. report being forced to have sexual intercourse at some time. Nearly one in 10 Alaska girls in ninth grade and one in five girls in eleventh grade report being forced to have sex.
- A significant but much smaller share of high-school boys in Alaska and nationwide also report having been forced to have sex—between 5 and 8 percent at different grade levels.
- About 10 percent of the girls and 12 percent of the boys surveyed in Alaskan high schools reported being hit, slapped, or otherwise hurt in the previous year by people they were dating. A figure that particularly stands out is that in twelfth grade, one in five Alaska boys surveyed said their girlfriends had purposefully hit them.





Alaska survey did not include Anchorage high-school students.



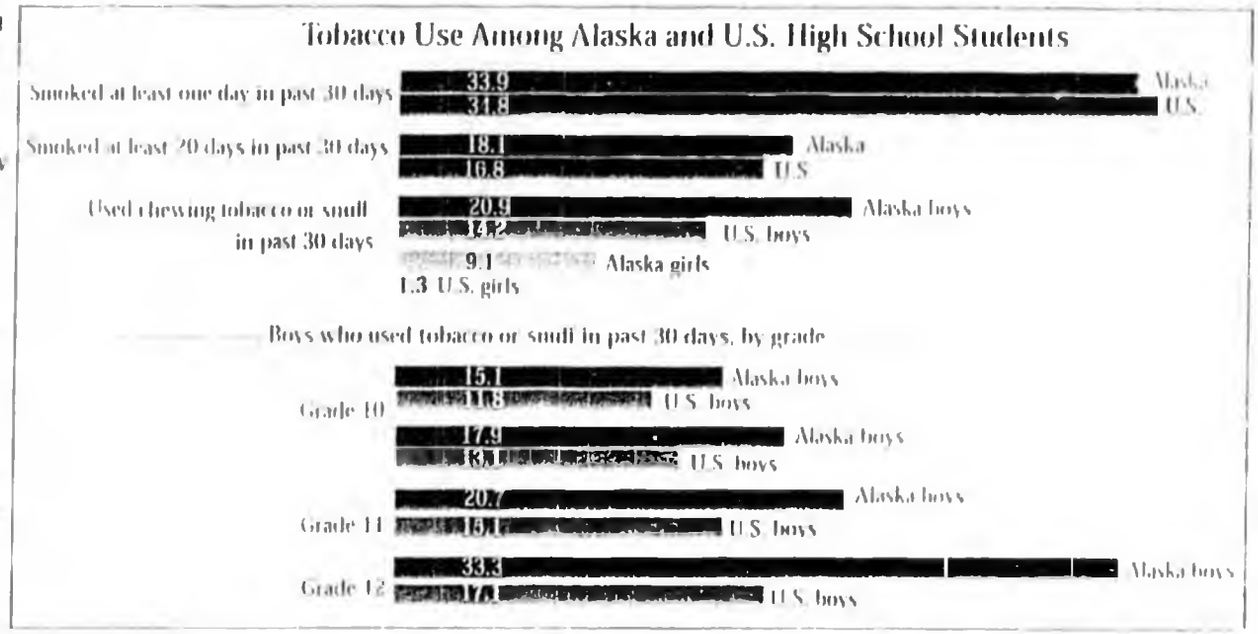
Tobacco Use

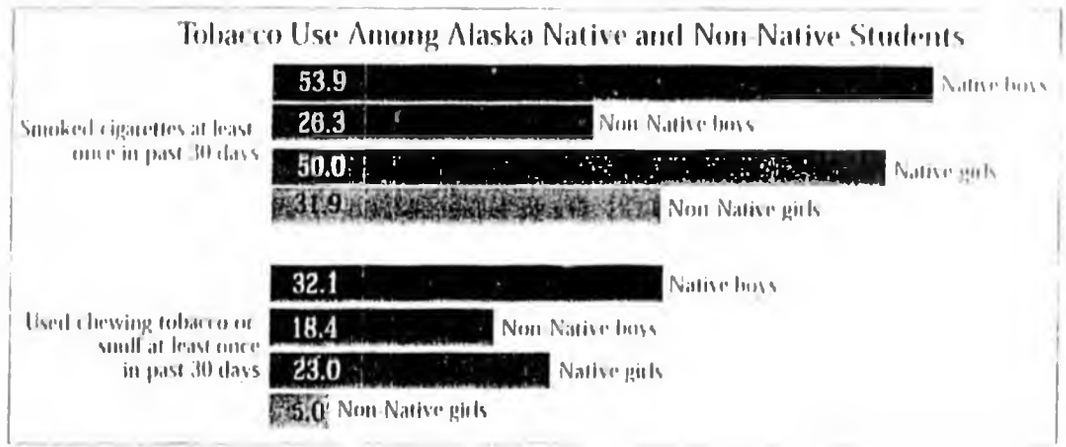
- Smoking is about equally common among Alaskan and U.S. high-school students, with roughly a third reporting they smoked at least once in the month before the survey.

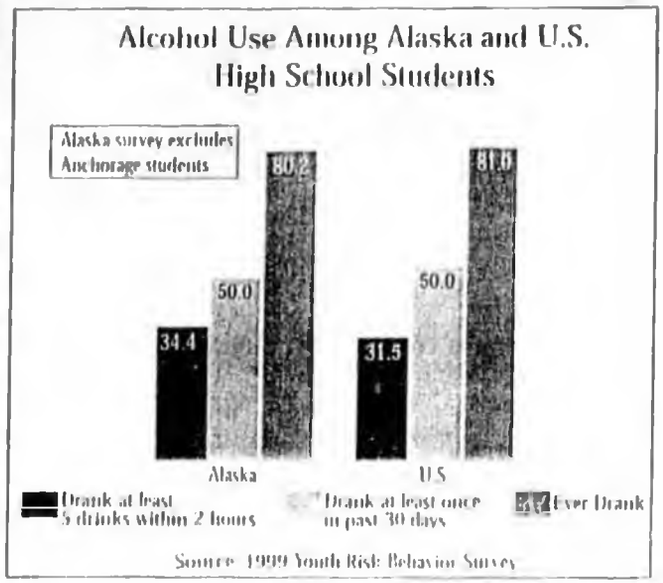
- Alaska's high school students are far more likely than other U.S. students to chew tobacco or use snuff. Alaskan girls in particular are more likely than other girls to chew tobacco. About 21 percent of Alaskan boys said they had used chewing tobacco in the month before the survey, compared with about 14 per cent nationwide. But nearly 10 percent of Alaskan high-school girls—almost 1 in 10—said they chewed tobacco, compared with just 1 percent—1 in 100—girls nationwide.

- The share of high-school boys nationwide and in Alaska who chew tobacco increases as they get older. But among Alaskan high-school boys surveyed, use increases much more—so that by the twelfth grade, a third of Alaska boys report chewing tobacco. That's nearly twice the rate among senior boys nationwide.

- Alaska Native students—both boys and girls—are far more likely to smoke or chew tobacco than are non-Natives. More than half of Native boys and girls reported that they currently smoked, compared with 26 percent of non-Native boys and 32 percent of non-Native girls. Nearly double the share of Native boys (32 percent) as non-Native boys (18 percent) chew tobacco. And the share of Native girls who chew (24 percent) is nearly five times the rate among non-Native girls (5 percent).

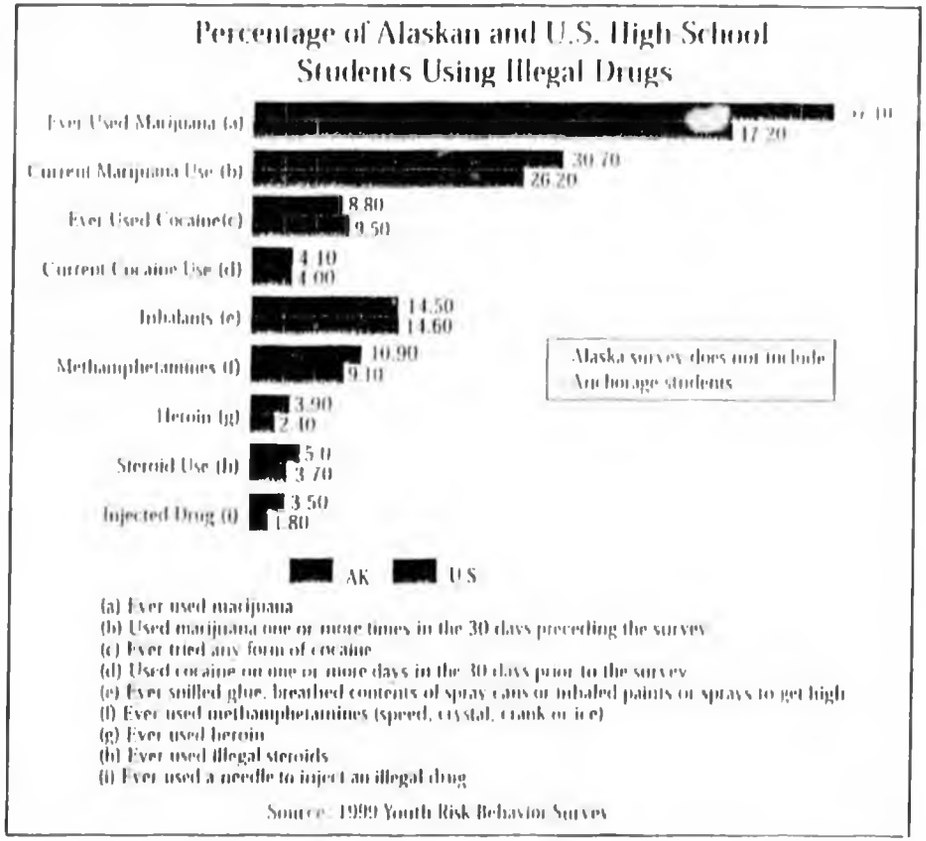






Drug and Alcohol Use

- About the same percentages of Alaskan and U.S. high school students drink alcohol. Eight out of 10 high school students surveyed in Alaska and the U.S. reported that they have tried alcohol at least once, and about half said they had drunk at least once in the month before the survey. A third reported binge drinking in the month before the survey.
- Marijuana is the most commonly used illegal drug among high school students in both Alaska and the U.S.—but a bigger share of Alaskan teenagers use marijuana. About 57 percent of Alaskan teens and 47 percent of U.S. teens report using marijuana at least once; 31 percent of Alaska students and 27 percent of U.S. teens reported using marijuana in the month before the survey.
- Close to one in six high-school students in both Alaska and the U.S. report sniffing glue or other inhalants at least once.
- After marijuana, methamphetamines and cocaine are the most widely-used illegal drugs among high-school students, with nearly 1 in 10 reporting at least one use.
- A bigger share of Alaskan high-school students than other U.S. students report trying herion—almost 4 in 100 Alaskan students, compared with just over 2 in 100 nationwide.
- Five in 100 Alaskan high-school students have used steroids, compared with fewer than 4 in 100 nationwide.
- More than 3 in 100 Alaskan students surveyed report using needles to inject drugs at least once—a share twice as large as among U.S. students in general.

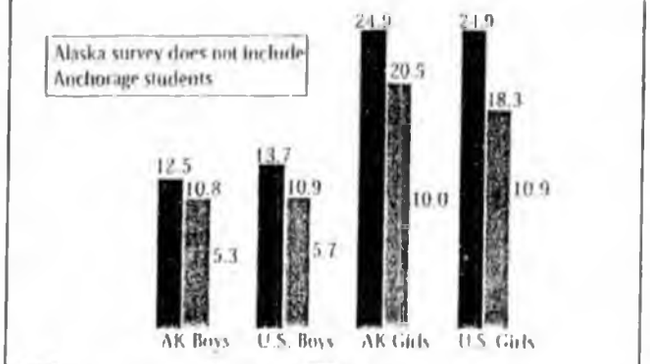


Suicide Thoughts and Attempts

As we saw in the section on injuries to children (pages 50-52), rates of suicide and attempted suicide are disconcertingly high among Alaska's teenagers, especially in northern and southwest Alaska. The Youth Risk Behavior Survey asked high-school students in Alaska and nationwide whether they had thought about or attempted suicide. The adjacent figure shows that:

- The shares of high-school students who have thought about, planned, or attempted suicide are remarkably similar in Alaska and across the country.
- High-school girls are far more likely than boys to report thinking about or attempting suicide. (However, Alaska statistics tell us that teenage boys—especially Alaska Native boys—are far more likely than girls to actually commit suicide.[1])
- A surprising one in four high school girls surveyed in both Alaska and the U.S. said they had thought seriously about committing suicide. Approximately one in five said they had made plans to kill themselves, and roughly one in ten had actually attempted suicide.
- Among Alaska boys, 12.5 percent said they had thought seriously about committing suicide, 11 percent said they had made plans, and 5 percent had attempted suicide. Rates are similar among U.S. boys, although slightly more (13.7 percent) reported having suicidal thoughts.

Alaska and U.S. Students Reporting Suicide Thoughts, Plans, and Attempts
(In Percentages)



Source: 1999 Youth Risk Behavior Survey

Discussion About Survey Results

The 1999 Youth Risk Behavior Survey in Alaska found that many high-school students are doing just fine, not putting their health or their lives at risk. But a significant number are doing dangerous things. And some report that fellow students have hurt them, scared them, or forced them to do things against their will.

A staggering one in five girls in the eleventh grade report being forced to have sexual intercourse they did not want. More than half of all Alaska Native students surveyed reported regularly smoking cigarettes. Nearly one in five high-school boys reported carrying weapons on school grounds. More than three in one hundred students surveyed said they had injected drugs with needles.

Parents, schools, and communities need to find better ways to keep teenagers safe. Alaska has taken steps to curb teenage smoking by sharply increasing cigarette taxes and better enforcing laws against selling cigarettes to minors. Preliminary research shows that these changes may be helping.[2]

In recent years Alaska schools have been more vigilant about trying to keep weapons out and to show that they won't tolerate fighting. Students who don't fight or carry weapons or intimidate other students need to be better protected from those who do. And violent students should not only be disciplined, but helped to change their behavior.

We need to find better ways of protecting teenagers—especially girls but boys as well—from being pressured or physically forced to have sexual relations they don't want. We need active efforts to prevent assaults and so called "date rape."

The good news from the survey is that most high-school students are on their way to being responsible, productive adults. We need to find more ways to help all students make the most of their lives.

Notes for Health Risks Section

[1] See Matthew Berman and Linda Leask, "Violent Death in Alaska," in *Alaska Review of Social and Economic Conditions*, University of Alaska Anchorage, Institute of Social and Economic Research, February 1994.

[2] See Alaska Department of Revenue and Health and Social Services, *Impact of the 1997 Tobacco Tax Rate Increase in Alaska*, June 2000. Available online at: www.hss.state.ak.us

2003 Youth Risk Behavior Survey Results

Northwest Arctic Borough School District Middle School Survey: Unweighted

V030D Percentage of students who tried marijuana for the first time before age 11

	Total			Males			Females		
	Percentage	95% Confidence Interval*	n	Percentage	95% Confidence Interval*	n	Percentage	95% Confidence Interval*	n
Total	10.2%	(9.8% - 10.5%)	128	(-)		62	(-)		66
Age									
11 or younger	(-)		3	(-)		3	(-)		0
12	(-)		20	(-)		14	(-)		6
13	(-)		60	(-)		22	(-)		37
14 or older	(-)		45	(-)		23	(-)		22
Grade									
6th	(-)		6	(-)		6	(-)		0
7th	(-)		75	(-)		34	(-)		41
8th	(-)		47	(-)		22	(-)		24
Race/Ethnicity**									
American Indian/Alaska Native	10.7%	(10.3% - 11.2%)	121	(-)		60	(-)		60
Asian	(-)		2	(-)		1	(-)		1
Black	(-)		1	(-)		0	(-)		1
Pacific Islander	(-)		0	(-)		0	(-)		0
Hispanic	(-)		1	(-)		0	(-)		1
White	(-)		8	(-)		1	(-)		7

Note: There were 4 students who were excluded from this analysis or who did not provide usable data for 030
Unweighted means that a 60% response rate was not obtained in selected classes. Data may not be representative of all district students.

n = Number of unweighted observations.

Blank = Fewer than 100 observations.

** A 95% confidence interval will contain the true mean 95 times out of 100 if additional samples of size n are drawn from this student population.*

*** An individual can be of more than one race/ethnicity.*

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Drug Use in Very Rural Alaska Villages

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ABSTRACT

The Alaska Native Preschool Project was centered in the Head Start Programs of two typical Alaska native villages near the Bering Sea. Data were collected over 5 years, 1990 to 1995, from preschool parents (N = 342) with surveys, a panel of villagers (N = 25 to 30) using qualitative interviews; villagers using participant observation; and a limited review of public records. The villages typify the changing life of Alaskan villagers who live in the Bering Straits area. Qualitative data indicated that a number of problems were associated with drug and alcohol use in the villages. The level of smokeless tobacco use from surveys in the previous month among preschool parents (41%) was self reported to be almost 10 times greater than the national level reported in the 1995 National Household Survey. The use of marijuana reported by preschool parents in the previous month was almost 3 times higher than the 1995 National Household Survey estimates (19 vs 6.7%). Tobacco use in the previous month was reported at over 56%, a level that was over 1½ times the level of use at 34.7% estimated from the 1995 National Household Survey. For 26–34 year olds, previous month alcohol use was lower for the village parents than estimated from the 1995 National Household Survey (38 vs 63%). The self-reported levels of other drug use among preschool parents were very low compared with overall United States

rates. [Translations are provided in the International Abstracts Section of this issue.]

Key words. Alaska; Native Alaskans; Substance abuse

INTRODUCTION

Alcohol and drug use are social and public health concerns in circumpolar areas like Alaska. In fact, Alaska Native leaders have characterized the alcohol problem among Alaskan Natives as a "plague" and as an "epidemic" (Alaska Federation of Natives, 1989). State officials also recognize this concern. However, like many other states and particularly rural states, there is a minimal systematic and statewide capability for collecting and reporting alcohol and drug data.

The purpose of this article is to describe the levels of self-reported drug use and related behaviors of Native Alaskans in two very rural Alaskan villages. Available data, qualitative data, and survey data are presented from a panel of key informants and a purposive sample of preschool parents of Head Start students. The data were collected as part of the Alaska Native Preschool Project. This educational approach to alcohol and drug use was funded by the Center for Substance Abuse Prevention (CSAP) and was concentrated in the Head Start Programs of two native villages in the Bering Strait area of Alaska which are typical of life in the Alaska bush.

According to the National Institute on Alcohol Abuse and Alcoholism (1994), the rates of alcohol use and "abuse" as well as related problems were highest among Native Americans. Brems (1996) recently reviewed selected substance use, mental health, and health data for Alaska and concluded that the high incidence of substance "abuse" appeared to be a reality across all of Alaska. More specifically, drug- and alcohol-use-associated problems were found in significant proportions in the Alaska population as a whole with specific drug and alcohol rates several times higher than the national average. For example, per capita alcohol consumption in Alaska, as measured in gallons per person per year, was the fourth highest in the United States—12% of Alaskan adults have alcohol-use-associated problems compared to 5.9% in the United States overall population (Brems, 1996). This population of Alaska was estimated by the Census Bureau to be only 599,200 in 1993 with 500,061 (83%) nonnative and 99,139 (17%) Native Alaskans.

The alcohol-related death rate among Alaska natives was 33.7 per 100,000 as compared to the overall United States rate of 14.0 per 100,000. Of particular concern were the high rates of alcohol use among Alaska Native women with rates up to twice as high as the United States general population and a lower age

of onset at 10 years of age compared with 15 to 19 years of age in the general United States population (Asbury et al., 1992).

In addition, Alaska Natives who comprise 17% of the Alaska population accounted for 47% of patients seen in state-funded alcohol and drug-user treatment centers (Brems, 1996). It should be noted that these data were limited since only publicly funded treatment centers were included. The drug of choice for Alaska Natives admitted to these treatment centers was alcohol at 92%. The second drug of choice for Alaskans was marijuana at 35%. Injection drug use was not limited to urban areas in Alaska, with one study reporting that almost three in ten rural drug users reported injecting (Fisher and Booker, 1990).

Data presented by the Alaska Native Commission (1994) and others pointed out that the alcohol mortality rate for natives during the 1980–1989 period was 3.5 times higher than the corresponding rate for Alaska non-Natives. Overwhelmingly, Native deaths occurred among young men and women, which is a reversal of the overall United States pattern. In addition, the homicide death rate among Alaska Natives was four times the United States rate for all race-ethnic groups with the majority of these deaths related to alcohol. Accidental deaths and injuries, the majority alcohol related, were also a major problem among Natives. These included snow machine accidents, gunshots, and freezings.

PARENT SURVEY DATA COLLECTION

Data were collected twice a year when the villages were visited from 1990 to 1995. The status of alcohol/drug use and related behaviors were assessed. The approach involved collecting survey data from Head Start parents, interviews with a panel of villagers, participant observation in public and private settings, and a limited records review. During the project's five years, there were changes in the prevention project staff. The Project Director changed three items. The two full-time project staff positions were filled by five different persons and the part-time position was filled by two different individuals.

After the study was described and explained, subjects were told that the study could provide culturally specific information that would be helpful in preventing substance misuse. In addition, subjects were informed that the information could be useful in their village in developing other prevention programs. Twenty-one percent refused to participate in the study.

Head Start parents filled out questionnaires on their own drug use at the Head Start Program before or after school. Respondents were given incentives for completing questionnaires which ranged from tee shirts to life preservers at each data collection time. Respondents were informed that their responses were confidential, that their names and answers to specific questions were separated—which respondents did after completing each questionnaire—and that their names on

specific identifying information would not be linked or identified with the study. Data were also collected from 25 to 30 key informants in each village. Selected key informants comprised an ongoing panel of villagers who were interviewed at each data collection time. Key informants were selected for their village leadership roles. Key informants included magistrates, school teachers, village police, clergy, village mayors, council members, village health aides, parents, store clerks, city managers, native corporation leaders, public officials in village offices, and village elders.

THE VILLAGES

At the start of the study, the villages were selected because of their similarities which included being almost the same size, their location near a major river, their close proximity to each other, being surrounded by tundra, and ordinances which prohibited alcohol in villages. However, one village grew about one-fourth faster than the other and the overall growth rate of Alaska. The large majority of inhabitants of both villages were natives who spoke one Eskimo dialect. There was continuous daylight in the summer and continuous darkness in midwinter. A major river was a central venue in the villagers' lives for it was a highway for boats in the summer and snowmobiles in the winter. The river regularly took the lives of natives in all seasons of the year from drownings and boating accidents.

Both villages were governed by a city council, and the Native Alaskan population was represented by a five-member Alaska Native Council. A state public health nurse and physician visited both villages periodically to provide medical services. According to the 1990 Census, the populations of the villages were 642 and 674, and had grown from 567 and 583, respectively, in the 1980 Census. The population was young with median ages of 21.9 and 20.1 years. Eighty-seven percent and 92% of the villages' populations were Alaska Natives.

There was seasonal cash employment, mostly associated with commercial fishing. Traditional subsistence activities helped provide additional income. These subsistence activities included hunting, fishing, gathering, and trapping. There were a small number of year-round wage positions in each village. Public jobs, mostly in the school system, were the main source of employment. A small number of year-round positions were also available in city government, law enforcement, health care, and the few local stores. Both villages had a seasonal fishing economy. Although the fish industry was cash based, the number of "openings" for the fishing decreased after the United States signed treaties with Canada. Over half the population was employed. It was estimated by a key informant that over 80% of the population received public assistance. The per capita income fell below the federal poverty level. Many of the village housing units were constructed within the past decade using Housing and Urban Development (HUD) funds. The water and sewer systems were associated with marked decreases in illnesses.

Based on interviews with school officials, the villages school dropout rates were high, with a little over one-fourth graduating from high school. School officials also indicated that drinking and tobacco use were common among children and adolescents, and children from alcoholic families contributed to many school behavior and disciplinary problems. A treatment center, about an hour away by air, provided residential treatment for drug and alcohol users. The treatment philosophy was founded on Native Eskimo traditions, and telephone follow-up treatment was provided to residents after they returned to the village.

The prevention program included two overall areas of interventions to enhance resiliency factors and to reduce risk factors. The first approaches targeted individuals and families with parent training classes, the Spirit of the Family Program, and the Healing Circle which were designed to strengthen the community and family unit culturally. The second approach focused on education and information which was village specific, including a newsletter and drug and alcohol information broadcast on village media.

It was extremely difficult to obtain official village-specific criminal activity and arrest data. Local Village Public Safety Officers indicated that the data were maintained in Anchorage by the State Police. These data were reported by region rather than by village due to the small numbers. Information from the Village Public Safety Officers, who do not retain copies of local arrest data, indicated that there were 1,100 to 1,200 police contacts per year per village. It was estimated that about one-fifth of these contacts were directly related to alcohol, or about 14 per month. It was also estimated that there were about two to eight suicide attempts per month, with the majority related to alcohol and drug misuse. Among adolescent suicide attempts, a majority were described as being associated with alcohol and drugs. Although substance misuse was described as being associated with suicide among youth, no other information was available. Violent deaths in the form of accidents, suicides, homicides, and others were directly attributable to alcohol as the leading cause of mortality in the villages. Major accidents were also frequently alcohol related.

Village Health Aides, who were part of the Native Health Service, estimated that there were over 300 contacts made by villagers each month. Major health problems were treated away from the village at the Regional Hospital and the Alaska Native Medical Center. Health Aides reported that many accidents, about 2 per month per village, were alcohol related. In addition, accidents associated with abuse and violence frequently involved alcohol. The Women's Shelter in one of the villages was used sporadically by women and their children. The Women's Shelter was established to provide a place for women and their children to reside

and obtain counseling related to physical and emotional abuse. Key informants indicated that much of the abuse was related to alcohol use.

VILLAGE SOCIAL CONTEXT

To understand the village context, a panel of interviewees which ranged from 20 to 30 villagers, depending on their availability, were followed over the five years. These "key informant" panel members were mostly natives, and interviews were conducted twice a year. Based on interviews and observations it was estimated that the majority of nonnatives were employed by the educational system, tended to live within their own social enclaves, and were disinterested in, and at times had distorted and even hostile views of, the native community. Over time it was possible to establish rapport with middle-aged and older Native women and men called elders who had a historical, generational view of their village and its strengths as well as its problems. The general status of alcohol/drug use and "abuse" was assessed through these panel interviews. Repeated inquires were made concerning certain behaviors held to be indicators of alcohol and drug-use-associated problems. Among these were suicides and suicide attempts, accidental deaths and injuries, homicides and related behaviors such as assaults, crime, family dysfunction, domestic violence, spouse and child abuse, and school or academic problems.

Several senior education officials and one clergyman with decades of experience in various Alaska Native communities suggested that, in terms of the severity of the alcohol and drug-use-associated problem, the villages selected for the study were somewhere in the midrange when compared to other villages in Alaska. A number of people did not drink and many drank only moderately. In the course of this study it was observed that respondents were keenly aware of the difficulty caused by alcohol in their village and were sincerely and constructively dedicated to its resolution. The discussion of drinking and drug-using behaviors in this article should be evaluated within the overall positive and constructive context of committed efforts to address these issues which includes the Alaska State-Wide Native Sobriety Movement.

PRACTICES AND ATTITUDES ABOUT ALCOHOL AND DRUG USE

The following practices and attitudes toward alcohol use and "abuse" were based on interview data from village key informants.

It is important to keep in mind that the formal structure of village governments with a mayor, city manager, village council, and budget was a template which was superimposed from the dominant Western culture. These roles and

names have no analog in the traditional native culture which is still active and which constitutes the informal level of governance. Traditionally, consensus was laboriously achieved through discussion among the elders of large, extended families. This continued to be the rule; however, the traditional values of cooperation, communalism, and prohibitions against aggression were attenuated. Based upon interviews, it was found that relationships between powerful extended families were very competitive and involved rivalries, particularly where scarce economic resources and competition for employment was concerned.

The role of the native leader in the formal structure was a complex and stressful one. Control was tenuous, power was limited, and the designated leader often found him/herself in the position of having to pass judgment on family members. Commitment was much stronger and more pressing to family than commitment to the governmental role. Added to this was the native attitudes toward a person who acted as through he/she were "the boss," since "boss" is a pejorative term in the Eskimo culture. The Eskimo concept of leadership related more to leadership by consensus and by example as opposed to the Western model of the leader who gets out front and gives directions. When one considers this, it was easier to see the multiple stresses that impinge on village leaders, and it helps explain, in part, the high rates of leadership attrition. This was also reflected in attitudes toward drinking and bootlegging. The village leader may himself or herself drink, and villagers involved in drinking or bootlegging may have been relatives to those he or she owed support and allegiance.

Within the context of village prohibition, attitudes toward alcohol and the enforcement of the law differed between the villages. One village had a history, dating back to the decade before the study, of active opposition to bootlegging under the leadership of a senior male. At that time, according to reports, bootleggers would come down the river in boats, land on the beach, and unload whole boatloads of illegal alcohol. The leader spearheaded resistance to this, and promoted a vigorous enforcement of the village's dry laws. This action involved some dramatic, and probably dangerous, physical confrontations between the bootleggers and villagers. The result was that bootlegging in that village was undesirable, against the law, and would be prosecuted. Thus, the attitude in that village tended to be one of outrage and active opposition to bootlegging. In that village, although bootlegging continued to occur, it was viewed negatively and arrests were made.

The other village did not have the tradition of active community opposition to bootlegging and indiscriminant drinking. Informants from the second village stated repeatedly that drinking and bootlegging had permeated the culture of the village and "the bootleggers were in control." Since bootlegging and alcohol appeared to permeate all levels of the government, there was an attitude of cynicism, powerlessness, and fatalism concerning the alcohol and drug problem.

The school system was a major institution in both villages. Its significance and impact upon the villages goes far beyond the provision of educational services. In both villages, schools were a major source of cash from salaries and investments. Through lunch programs, the schools made a major contribution to the nutrition of the young people. Schools also contained the only libraries. The athletic facilities were a major source of recreation for both boys and girls. It was a key area for meeting and socialization in both villages. School tended to be seen as the "safe" place to go and to socialize. Nonnative teachers' knowledge of the native culture, perception of it, and willingness and ability to work within it varied widely. A minority of natives were teachers. The majority of school staff were natives who tended to be viewed with mixed feelings by other villagers because of their cash employment.

It was difficult to gather specific, systematic data on substance use in the general school population. The nonnative faculty had a wide range of opinions which ranged from outrage and shock to minimization and bland denial. There was a consensus of concern about the use of snuff, tobacco, inhalants, marijuana, and alcohol by students. Teachers reported the use of these substances was related to absences, tardiness, appearing at school smelling of alcohol, and appearing at school hung over. In addition, teachers expressed concern that these behaviors were appearing in younger children. For instance, third and fourth graders were described as using snuff and tobacco. Alcohol "abuse" was reported in eleven and twelve year olds.

In both villages there was concern about children and adolescents roaming the village at all hours of the night. The most common explanation for this behavior was that parents were drinking. A recurrent theme in discussions with city officials was the need for recreational facilities for teenagers and the need for more efficient measures to control their behavior. In one village a sense of fatalism and helplessness was noted when discussing child and adolescent behaviors. A subjective impression was that alcohol-use-related behavior was far more frequent. School officials and citizens had some rather unpleasant tales about sexual and aggressive acting out on the part of children and adolescents associate with alcohol. "The kids take over the town every night and nobody does anything about it." Both schools reported behavioral problems, acting out, and "disrespect" for teachers and those in authority. In one village this appeared to be a set of behaviors that was not tolerated and was in fairly good control. In the other village, as verified by direct observation, the lack of behavioral control appeared to be more frequent and more extreme, which often leads to physical violence and injury in the schools and in the village.

Reports from police and law officials in both villages had a theme which was repeated over and over and which might be summarized by the statement, "If it wasn't for alcohol, I wouldn't have a job." Patterns of consumption varied with the economy. During fishing season, drinking tended to decrease because people were busy. When the cash economy was more robust, people tended to drink distilled liquor. When the economy was down and cash was scarce, people drank home-brewed alcohol. A minority of families, in which parents and children all drank, constituted the majority of village problems. A prototypical "dangerous" drinker was a young male in his late teens or early 20s who "holds it all in for a long time, drinks, and goes wild." There were accounts of these situations and the dangers involved. "Don't believe that stuff about those little Eskimo guys. They're tougher than hell. Sometimes it takes five guys to get them under control and restrain them." The police regularly patrolled, especially in the winter, looking for intoxicated individuals who had fallen in the snow and ice. These individuals were placed in "protective custody." The pursuit of bootleggers and manufacturers of home brew was an ongoing police activity. Several police officers familiar with the situation in both villages stated that the "drinking problem" in terms of amount and frequency of drinking, public drunkenness, and alcohol-use-related offenses was worse in the more permissive village. In both villages there was concern expressed each year about drinking. "We used to worry about the high school kids. Now it seems as if high school is too late."

Health care in both villages was provided by a village health clinic, staffed by native health aides who varied in number from three to five. These aides, who were all women, were responsible for primary health care, tended to be highly respected, and were seen as valued members of the village. In all interviews, these women were tactful, circumspect, and guarded in their communication. On several occasions, always in an interview with a single aide and while strict confidentiality was maintained, insights were obtained into the stresses under which these women worked and the associated problems. The aides were all aware of alcohol problems in the community. However, villagers seldom went to the clinic seeking help for alcoholism. Rather, they saw associated problems like battered women from time-to-time and a variety of medical and psychological problems related to neglect by drinking parents.

PRESCHOOL PARENTS

Data were collected from 342 preschool Head Start parents over the project's five years. Parents with more than one child in the Head Start Program were included only once. When these data were examined, several things were apparent. An important consideration to keep in mind when looking at these data is that about two-thirds (64%) of respondents were female and over 9 of 10 were Alaska Natives (see Table 1). It should be noted that, although comparisons with United States data may not be as realistic for these native villages as they are for other

Table 1.

Selected Demographics of Head Start Parents (N = 342)

	%
Female	64
Race/ethnicity:	
Alaska Native	93
Education:	
Less than Grade 8	34
Completed Grade 8	3
High school	53
Some college	10
Employed	42
Religion:	
Catholic	69
Protestant	11
Other	5
Leisure time activities:	
Watch TV and videos	96
Play bingo	38
Play basketball	31
Snow machine racing	11
Attitudes and problems associated with substance use:	
Attitudes:	
Wrong to take drugs	86
Wrong to drink a lot	86
Wrong for someone to force you to drink	86
Wrong to take something	89
Wrong to lie	88
Ever encountered problems related to drinking	
Boating accidents	2
Snow machine accidents	11
Four wheeler accidents	6
Got arrested for drinking	14
Had money problems	16
Passed out	29
Memory loss	32
Parent self-reported alcohol and drug use	
Substance use in previous month:	
Any alcohol	38
Gotten drunk	15
Marijuana	19
Inhalants	0.2
Tobacco	56
Snuff	41

(*continued*)

Table 1. *Continued*

	%
Alcohol use in the previous year:	
Any alcohol	63
Gotten drunk	41
Weekend parties	31
At night with friends	32
At home	36
Away from village	25
At fish camp	7
Other drug use in the previous year:	
Marijuana	29
Inhalants	0.2
Tobacco	57
Snuff	45
Drug use ten times or more in previous year:	
Alcohol	14
Marijuana	11
Tobacco	28
Snuff	19

areas of the United States, comparisons are made to provide at least one frame-of-reference.

Over half (53%) of the Head Start parents involved in the study completed high school and 42% reported they were employed. Almost nine out of ten parents said they were religious, with 69% saying they were Catholic. Almost everyone (96%) reported they watched TV or videos. Other leisure time activities included playing bingo (38%) and playing basketball (31%).

There was a strong sense that using drugs and alcohol was wrong. Almost nine out of ten parents (86%) reported it was wrong to take drugs, to drink a lot, or for someone to force another person to drink. Stealing and lying were also reported as being wrong, at 89 and 88% respectively. There were a number of individual problems which were related to drinking. Specific problems reported by about one-third of the parents and related to their own drinking were memory loss (32%) and passing out (29%). Other drinking-related problems included money problems for 16% of parents and being arrested for their own drinking for 14% of parents. Alcohol and drug use were also reported to be dangerous. This included accidents on snow machines for 11%, four wheeler accidents for 6%, and boating accidents for 2% of these parents.

Alcohol use in the previous month, reported at 38%, was less than estimated for the 26–34 year olds in the National Household Survey at 63%, or about two-

thirds less use. Fifteen percent reported that they had gotten drunk in the previous month. Almost two-thirds (63%) reported that they had used alcohol in the previous year, with almost one-third reporting that they had used at weekend parties (31%), 32% at home with friends, 36% at home, 7% at fish camps, and one-fourth away from the village. Forty-one percent indicated that they had gotten drunk in the past year.

The level of smokeless tobacco use, reported as snuff use, in the past month was over 41%. When compared with the 4.4% estimated current users of smokeless tobacco in the 1995 National Household Survey for 26–34 year olds, this was almost 10 times more use by these Head Start parents. Tobacco use in the previous month was also more (56%) or at a level that was over one and one half times greater than the level of use (34.7%) estimated from the 1995 National Household Survey. The use of marijuana reported in the previous month at 19% was higher than estimates from the 1995 National Household Survey for 26–34 year olds at 6.7%—a level almost three times more than national estimates. The reported levels of other drug use, such as inhalants as 0.2%, was so small that comparisons with household data were not meaningful.

These data confirm an impression from key informants that there was more overall substance use by the preschool parent respondents than estimated in the 1995 National Household respondents except for alcohol. In other words, these data confirm the notion that the level of substance use was higher by villagers than self-reported use in other United States households. Most notably were the high levels of snuff use, marijuana use, and tobacco use.

DISCUSSION

It must be noted that there are limitations to the data presented in this article. The data were collected from a purposive sample of villagers and parents who do not represent all parents or adults in the two villages or other Alaskan native villages. However, using 1990 Census data, 342 (26%) of 1,316 villagers participated in the preschool survey. The villagers included in the key informant panel were purposively selected because they agreed to provide information and because of their status and role. In addition, the villages were purposively selected. However, there are similarities between the two villages and other villages in Alaska including their isolation, the economic conditions, the anecdotically reported number of issues related to alcohol and drug use, and the identified needs.

The findings suggest that, according to observations and the panel of key informants, along with modern technology and other changes has come movement away from traditions which bound many villagers to their culture. There was a consensus of concerns about the use of snuff, tobacco, inhalants, marijuana, and alcohol by students. Key informants indicated that the use of substances was observable for lower aged children with absences, tardiness, appearing at school smelling of alcohol, appearing at school hung over, and students accounts of their own behavior. Key informants described the use of alcohol and drugs as being related to a number of accidents and other "problem behaviors."

Findings from preschool parents indicated that the level of smokeless tobacco self-reported use in the previous month was over 41%. When compared with 4.4% estimated current users of smokeless tobacco in the 1995 National Household Survey for 26–34 year olds, use was almost *10 times greater* for these Head Start parents. The use of marijuana reported in the past month by preschool parents was higher at 19% when compared with 6.7% from the 1995 National Household Survey estimates for 26–34 year olds. This level was almost *three times greater* than national estimates. Tobacco use in the past month was reported at over 56% or at a level that was *over one and one-half times* the level of use at 34.7% estimated from the 1995 National Household Survey. Alcohol use in the past month, reported at 38%, *was lower than that estimated* for the 26–34 year olds from the 1995 National Household Survey at 63.0% or about two-thirds less use. In addition, the reported levels of other drug use *were so low* that comparisons with national household data are not meaningful.

These data suggest that the levels of drug use among preschool parents in these two very remote Alaska villages were at substantial levels. These data were complimented by key informant information which indicated that alcohol and drug use in these "dry" villages were associated with problem behaviors. In addition, drug and alcohol use and associated behaviors should be targeted with culturally specific prevention interventions. Developing targeted prevention interventions should be a policy priority.

There is a lack of consistent policy focused on prevention and interventions for Native Alaskans. There is a need for funding intervention programs and a need for staff training to implement prevention programs. In addition, there is a need to sensitize policymakers about the requirements of people who live in very rural areas. For example, very rural and rural populations need resources to develop tailored prevention interventions. Likewise, criteria should be developed to examine both process and outcome measures in order to implement successful prevention programs which are culturally relevant. Thus, policies should be developed for planning, implementing, and examining interventions. There is also a need for targeted and formative research to develop culturally bound prevention interventions in addition to examining the effectiveness of interventions. Clearly, an implication for policymakers is the need to sustain ongoing interventions in remote places.

In closing we would like to stress that there were thoughtful, responsible, and dedicated Native Alaskans in both villages who were keenly aware of the problems created by alcohol and drugs and who were committed to their resolution.

This commitment was evident in the indigenous native initiatives which have arisen to support sobriety for Alaska Natives.

ACKNOWLEDGMENTS

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F

THE IMPACT OF MARIJUANA ON PARENTS AND CHILDREN

I. **Marijuana is the primary substance abused in a significant number of homes generating reports of harm and CINA cases due to illegal drug abuse.**

- A 1998 national survey found that children whose parents abuse drugs or alcohol were almost three times (2.7) likelier to be physically or sexually assaulted and more than four times (4.2) likelier to be neglected than children of parents who are not substance abusers. *Children of Substance-Abusing Parents, (1999) citing, Sedlak, A.J., & Broadhurst, D.D. (1996). Third National Incidence Study of Child Abuse and Neglect: Final Report. U.S. Dept. of Health and Human Services, Administration for Children; and, National Center on Child Abuse and Neglect, (1998). Living Arrangements of Children Under 18 Years Old: 1960 to the Present; U.S. Advisory Board on Child Abuse and Neglect. (1993) Neighbors helping Neighbors.*
- 20.5% of the 915 social workers and family court professionals surveyed cited marijuana as the leading substance of abuse in child abuse or neglect cases involving illegal drugs.

Major drug bust rids Quinhagak of dope hub

by K.J. Lincoln

After a couple months of investigation and cooperation with villagers, Alaska State Troopers were successful in seizing a pound and a half of marijuana and $17,020 in cash from a residence in the village of Quinhagak, and closing down a central hub for marijuana.

"Each vacuum-sealed bag had 2 ounces of marijuana," said Western Alaska Alcohol and Narcotics Team Investigator Joe Hazelaar. "1 1/2 pounds of marijuana at $50 a gram equals a $28,000.00 street value. This amount is not uncommon in villages."

The success of the drug bust can be attributed to the citizens of Quinhagak who worked with the local village police, calling in tips and complaints. The overwhelming calls about the house were enough grounds to issue a search warrant.

"It was done in reference to the support we've gotten from the citizens and the Chief of police," said Trooper Sgt. Anthony April. "The tips from the local villagers led to the execution of the search warrant."

Community members had stepped forward and asked to help with the investigation, including going undercover and making drug purchases.

"They helped rid the village of a pretty prominent problem of the drug dealers," Hazelaar said.

Four adults have charges pending against them as a result of the bust, said Hazelaar.

"They were very uncooperative during the raid," he said. Their case is being forwarded to the District Attorney and it will be handled federally, instead of through the state.

The four adults were not the only ones in the house.

"There were three small children at the time of the search warrant," said Hazelaar. "An 18-month old baby was sleeping less than a foot away from a pound of marijuana."

The children, who have been taken into protective custody, had also been present during the transactions when the undercover informants purchased marijuana.

The house, which was also seized, will be donated back to the City of Quinhagak. "We're hoping the village will currently find a family that is need of a house," said Hazelaar. "I can't say thanks enough for the community involvement.

"If a community would just ban together and drive the dealers out - think about what that money could do for that community. The only one getting rich off the deal is the dealers," he added.

driving with a revoked license.

Wasilla / Drunken driving

At 1:40 a.m. Sunday, Alaska State Troopers **arrested** Alfred A. Shelde , age 44, of Wasilla on suspicion of drunken driving and leaving the scene of an accid nt. Troopers contacted Sh lden at his Glacier Drive home after receiving a report that he was drivin impaired in his 1990 Ford Tempo and, after a disturbance at a Serrano Drive residence sideswiped a 2000 Ford Ranger parked there. Shelden was held at the Mat-Su Pre-Trial Facility in lieu of $2,000 bail. Damage to the Ford Ranger was estimated at $200, and there was no damage to the Ford Tempo. No injuries were reported.

Wasilla / Drunken driving

At 3:47 a.m. Thursday, Alaska State Troopers stopped a vehicle for drifting over the centerline and speeding. The driver, Sovala Raylene Tapley, 44, of Wasilla was **arreste** on suspicion of felony drunken driving and driving with a revoked licen se. Tapley was held at the Mat-Su Pre-Trial Facility in lieu of $15,000 cash-only bail.

Wasilla / Drunken driving

At 4:59 a.m. Friday, Alaska State Troopers **arrested** Lofia T. Satini, 25, of Anchorage suspicion of drunken driving and driving without a valid license. Satini was stopped in a 1998 Chevrolet Malibu near the intersection of the Parks Highway and South Seward Meridian Road for erratic driving. He was held at the Mat-Su Pre-Trial Facility in lieu of $1,500 cash-only bail.

Wasilla / Drunken driving

At 12:45 a.m. Friday, Alaska State Troopers **arrested** Angela M. Moehring, 28, of Wasilla on suspicion of drunken driving. Moehring was stopped for erratic driving, drifti from the fog line to the centerline of the roadway. Moehring was held at the Mat-Su Pr Trial Facility until sober.

Houston / Drunken driving

At 12:37 a.m. Saturday, Alaska State Troopers stopped a vehicle at Jo sons Road and the Parks Highway in Houston for speeding. The driver, Neal Scott Bridgewater, 42, of Houston was **arrested** on suspicion of drunken driving and held at the Mat-Su Pre-Tria Facility in lieu of $2,500 bail.

Wasilla / Drunken driving

At 3:25 a.m. Sunday, Alaska State Troopers **arrested** Vaughn Nogle, 29, of Wasilla on suspicion of drunken driving. Nogle was stopped for failing to stop at a steady red light at Crusey Street and Bogard Road and for drifting from the fog line to the centerline. Nogle was held at the Mat-Su Pre-Trial Facility until sober.

Wasilla / Drunken driving

At 1:11 a.m. Friday, Alaska State Troopers **arrested** Giles Jackson, 26, of Wasilla on suspicion of drunken driving. Troopers stopped Jackson near the intersection of the Par Highway and Church Road for crossing the centerline. Jackson was held at the Mat-Su Pre-Trial Facility until he was released to a sober adult.

Wasilla / Growing **marijuana**

At 8 p m. Thursday, Alaska State Troopers **arrested** Jim A. Gardner, 47, of Wasilla for growing **marijuana** and reckless endangerment. Troopers contacted Gardner at his home near Beverly Lakes Road in Wasilla after receiving a tip about a person with an arrest warrant possibly located there. Troopers found Gardner had approximately 173

live **marijuana** plants at his home, where his young child lived with him. The Mat-Su Narcotics Team was called to the residence, eradicated the **marijuana** and seized the related equipment. Charges are being forwarded to the district attorney's office for review.

Wasilla / Domestic assault

At 12:42 a.m. Jan. 26, Alaska State Troopers responded to a domestic disturbance nea Twilight Drive and Horizon Drive in Wasilla. They **arrested** Richard M. Cassler, 40, and his ex-wife, Diane M. Juel, 43, on charges of assault on one another. Juel was taken to shelter for the night. Charges for each will be forwarded to the district attorney.

Wasilla / Stolen property

At approximately 8:24 p.m. Friday, Alaska State Troopers received a report of stolen property from a residence on Machen Drive in Wasilla. Joshua Morris, 26, of Wasilla reported a snowmachine motor stolen out of his 1999 Polaris 700 RMK. The estimated value of the stolen property is $2,000. Investigation is continuing.

Wasilla / Collision with moose

At 10:38 p.m. Saturday, Alaska State Troopers in Palmer responded to a motor-vehicle collision with a moose near the intersection of Wasilla Fishhook Road and Lake View Drive in Wasilla. The moose stepped into the lane and struck the driver's side of a 1997 Chevrolet pickup driven by Phillip A. Irrer, 41, of Wasilla. The moose died of its injuries Irrer was wearing his seat belt and was not injured. Total damage to the vehicle is estimated at $2,000. The moose was salvaged by a local charity.

Wasilla / Assault

At 11:34 p.m. Friday, Alaska State Troopers in Palmer **arrested** Joseph H. Bussard Jr., 63, of Wasilla on suspicion of assault and criminal mischief. Troopers responded to a home on Country Fair Drive, where Bussard was reported to have assaulted a family member and caused damage to the residence. Total damage was estimated at approximately $200. Bussard was **arrested** for fourth-degree assault and criminal mischief. He was held at the Mat-Su Pre-Trial Facility without bail. ${ILLUSTRATION:+

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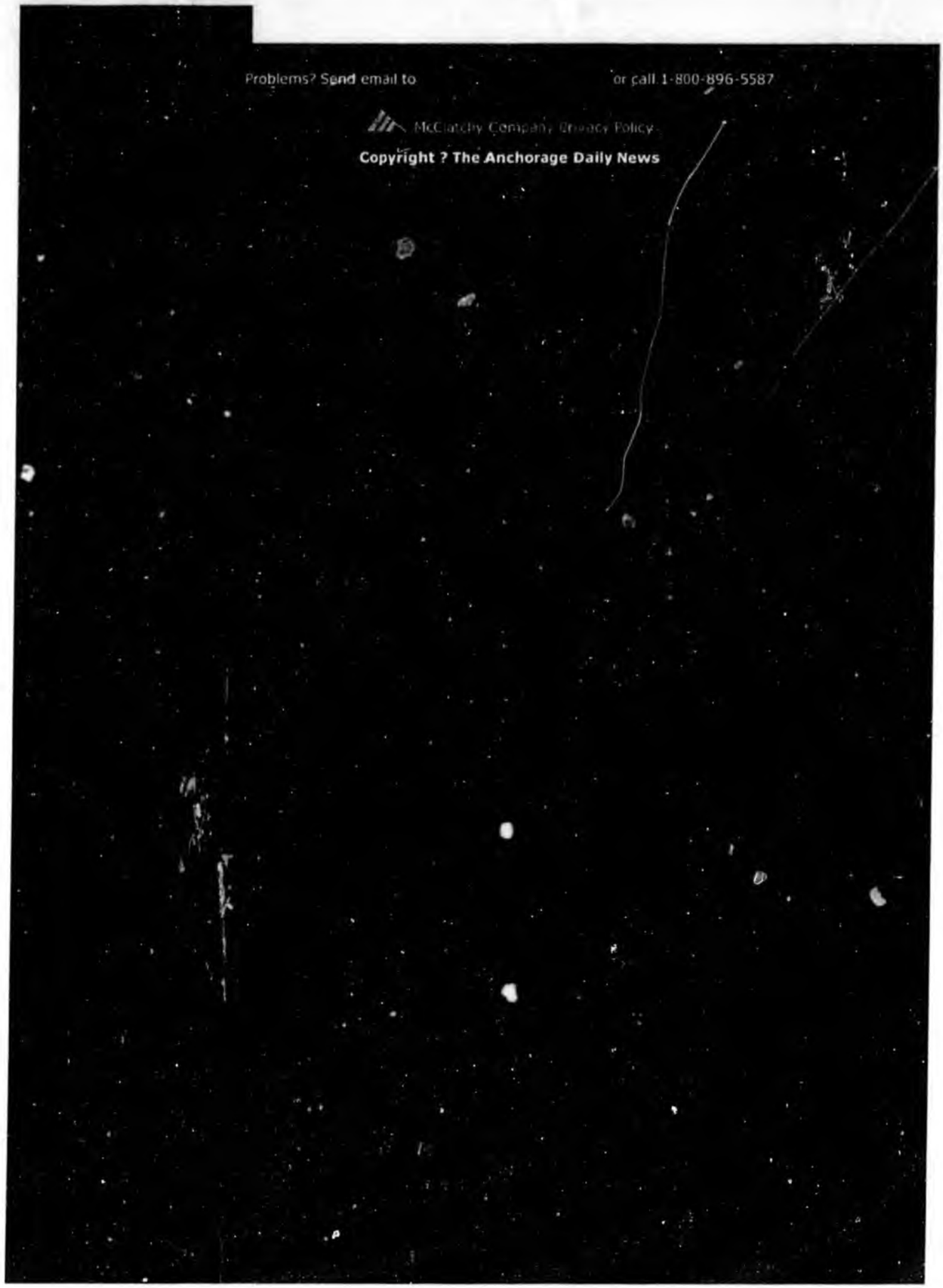
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Children of Substance-Abusing Parents

January 1999

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welfare of the nation's children. I remember discussing this project with Mrs. Helene Soref in Florida in 1996 and I regret that she did not live to see this product of her generosity and concern for children.
Jeanne Reid, M.P.A., a distinguished CASA senior research associate, was the principal investigator for this effort and she has done a typically brilliant and thoughtful job. Throughout the effort, she was most ably assisted by Peggy Macchetto, J.D. David Man, Ph.D., CASA's librarian, and library assistant Amy Milligan were a big help. Marcia Lee, M.P.P., my Special Assistant, edited the manuscript. Herbert Kleber, M.D., Executive Vice President and Medical Director, William Foster, Ph.D., Senior Vice President and Chief Operating Officer, Susan Foster, M.S.W., Vice President and Director of Policy Research and Analysis, Patrick Johnson, Ph.D., Deputy Director of Medical Research and Practice Policy, Lawrence Murray, M.S.W., Senior Program Associate, and I reviewed the report. Jane Carlson, as usual, handled the administrative chores with efficiency and good spirit.
The Advisory Board, a distinguished group of experts, were invaluable in guiding this effort and reviewed a draft of this report. But responsibility for the analysis and findings sits with CASA.

I. Introduction and Executive Summary

The number of children in America who are abused or neglected has more than doubled from
1.4 million in 1986 to about 3.0 million in 1997.[1] As child welfare officials have responded by focusing on investigating a flood of new cases, chronic child abuse and neglect has surged and the number of children dying while under the watch of the nation's child welfare system has risen. Without a concerted effort to assess and treat substance abuse, the tragic consequences for the nation's children will continue to accumulate.
This report is a comprehensive analysis of the deep and complex connection between substance abuse and child maltreatment.[2] It exposes how child welfare agencies and family court[3] systems struggle to handle the critical decision of child custody when a parent is a drug or alcohol abuser, and it recommends substantial changes in practice to safeguard our nation's children. The most significant findings of our two-year analysis are:

- Substance abuse and addiction severely compromise or destroy the ability of parents to provide a safe and nurturing home for a child.
- Substance abuse and addiction confound the child welfare system's ability to protect children.
- Timely and comprehensive treatment can work for substance-abusing parents, and such treatment is cost effective.

- Only a major overhaul of the child welfare system and dramatic changes in child welfare practice can make real progress against this formidable problem.

* In this report, "maltreatment" means abuse and/or neglect of a child. Abuse includes both physical and sexual abuse unless otherwise stated. Neglect includes abandonment, expulsion, delay or refusal of healthcare, inadequate supervision, inadequate nutrition (starvation), emotional neglect (such as witness to chronic/extreme spouse abuse) and other omissions of proper care.

† In this report, "family court" includes any court that hears cases involving child abuse and/or neglect. In some states or counties, these courts are referred to as juvenile courts or dependency courts.

"It's scary. It's scary to not have your mom there, to have to worry where you're gonna get your next meal and who's gonna change your diaper, who's gonna feed you and who's gonna put you to bed at night. Dad tried to stab himself when he was drinking and high on drugs. It was right in front of me. I was scared."[2]

-- Melissa, age 14

As part of this two-year analysis, CASA conducted a targeted, national survey of professionals who work in child welfare agencies or family courts to learn their perceptions of the extent of the substance abuse problem, how they decide who will care for the children in cases involving substance abuse and the changes that they believe would benefit the nation's children.* The key findings:

- Three of four (71.6 percent) cite substance abuse as one of the top three causes for the dramatic rise in child maltreatment since 1986, followed by better reporting of child maltreatment (35.4 percent) and poverty (31.8 percent).
- Most survey respondents (79.6 percent) report that substance abuse causes or contributes to at least half of all cases of child maltreatment; 39.7 percent say it is a factor in over 75 percent of the cases.
- Almost all survey respondents (81.6 percent) say that parents who abuse or neglect their children most commonly abuse a combination of alcohol and drugs; 7.7 percent cite alcohol alone.
- Overall, 89.3 percent of all respondents recognize alcohol as a leading substance of abuse among parents.
- 45.8 percent of all respondents say that cases of illegal drugs involve crack. One in five (20.5 percent) respondents say that cases of illegal drugs involve marijuana.
- Three of four survey respondents (75.7 percent) say that children of substance-abusing parents are likelier to enter foster care, and 73.0 percent say that children of substance- abusing parents stay longer in foster care than do other children.
- Almost half (42 percent) of all case workers say either they are not required to record the presence of substance abuse when investigating child maltreatment or do not know whether they are required to do so.
- 61.3 percent of respondents say that what treatment is "available" determines what treatment is "appropriate" for the parent.

- Only 5.8 percent of survey respondents say that there is no wait for parents who need residential substance abuse treatment. Only 26.0 percent say that there is no wait for outpatient treatment.
- Respondents overwhelmingly (85.8 percent) name lack of motivation as the number one barrier to getting parents into substance abuse treatment, followed by lack of residential treatment (53.0 percent), lack of insurance coverage for treatment (50.7 percent), lack of outpatient treatment (35.4 percent) and lack of child care (28.5 percent). It is not possible to determine from the survey how much the perceived lack of motivation is influenced by these other barriers.

* A copy of the questionnaire and a description of the survey methodology appear in Appendices A and B. A total of 3,486 surveys were distributed; 915 responses were recorded. The overall response rate is 26.4 percent.

In addition to the survey, CASA reviewed more than 800 technical articles, books and reports covering medical, social science, legal and substance abuse literature relevant to child maltreatment when parents are abusing alcohol and drugs. We interviewed numerous caseworkers, judges and other professionals. We conducted six case studies to identify promising innovations in the field to address substance abuse among parents who abuse or neglect their children and reviewed numerous other innovations.* Together, the CASA survey, literature review and case studies provide the foundation for the following key findings.

> *It's awful in the long run... When you grow up you have to deal with a lot more problems, 'cause when you're little you don't realize everything that's happening, and you try to understand and you don't. And then when you get older, it's so hard to think that your mom would do that to you. I mean she'll tell you that she loves you and that she'll help you in any way she can -- but she doesn't. She tries, but she can't; the drugs just take over. And, I don't know, it's just hard. It's really hard.*[3]
>
> -- Brandy, age 16

Substance abuse and addiction are the primary causes of the dramatic rise in child abuse and neglect and an immeasurable increase in the complexity of cases since the mid-1980s. In both CASA's survey and other research, child welfare and family court officials report that substance abuse--alcohol, crack cocaine and other drug use--is responsible for the dramatic rise in cases. Children whose parents abuse drugs and alcohol are almost three times (2.7) likelier to be abused and more than four times (4.2) likelier to be neglected than children of parents who are not substance abusers.[4] Substance abuse and addiction is almost guaranteed to lead to neglect of children.[5] Further fueling the number of cases, the rate of repeated abuse or neglect appears to be increasingly driven by alcohol and drug addiction.[6]

* A description of the case study methodology appears in Appendix C.

Crack cocaine was responsible for at least the initial spike in the caseload. While new crack use appears to have subsided nationally in the 1990s, the child welfare caseload has held steady. In some areas, child welfare officials report no decline in crack use by parents.[7] A judge in Washington, D.C. reported that, "The crack

ADDENDUM

SB 74 – Findings and Authority

(1). marijuana has been for many years and continues to be the most commonly used illegal controlled substance in the United States.

- Tab "C": *LEGALIZATION OF MARIJUANA: POTENTIAL IMPACT ON YOUTH, AMERICAN ACADEMY OF PEDIATRICS,* "Marijuana is the illicit substance most commonly abused by adolescents"

- Tab "D": *RESPIRATORY EFFECTS OF MARIJUANA AND TOBACCO USE IN A US SAMPLE, "Marijuana smoking remains the second most widely smoked substance in the US with conservative estimates indicating that more than 11 million people smoked marijuana during the last month and approximately 20% of these smoke almost daily."*

(2). marijuana has many adverse health and social effects, and there is evidence that it has addictive properties similar to heroin and other simile illegal controlled substances.

- Tab "C" (Behaviorial Health) and Tab "D" (Public Health)

- Tab "C" *LEGALIZATION OF MARIJUANA: POTENTIAL IMPACT ON YOUTH, AMERICAN ACADEMY OF PEDIATRICS, TECHNICAL REPORT, 2004* "**Scientists have demonstrated that the emotional stress caused by withdrawal from marijuana is linked to corticotropin-releasing factor, the same brain chemical that has been linked to anxiety and stress during opiate, alcohol, and cocaine withdrawal". Others report that tetrahydrocannabinol, the active ingredient in marijuana, stimulates release of dopamine in the mesolimbic area of the brain, the same neurochemical process that reinforces dependence on other addictive drugs."**

- Tab "C" *ALASKA STATE PLAN FOR DRUG ABUSE PREVENTION, FY 77 (57 marijuana treatment admissions in FY 75) compared to an average of about 420 a year now) SAMHSA Treatment admissions data set. On average in 2000, 2001, 2002, 2003 there were about 20 heroin admissions a year.*

(3). in addition to concerns about marijuana use generally, the legislature is particularly concerned with rates of use by young people and Alaska Natives which exceed national averages.

- Tab "E" *2003 ALASKA YOUTH RISK BEHAVIOR SURVEY RESULTS, (13.1% of Alaska students reporting use before age 13 vs. national figures of 9.9%); (Alaska native students 69.7% ever tried marijuana, 35.5% current users; All Alaska students 47.5% ever tried marijuana, 24% current users vs. 41% and 22.4% nationally); (In a survey of pre-school parents in two rural Alaska villages, rates of use were three times as high as the national average).*

- **Addendum.** *In another survey of rural Alaskans admitted to treatment facilities, 17.9% of male Alaska Natives were found to have a marijuana disorder; Average age of first use for American Indian / Alaska Native population group has slipped down to 14 years old. (vs. 16 for Alaska as a state)*

(4). early exposure of children to marijuana increases the likelihood of lifelong health and social problems, and makes it more likely that the person will go on to use more potent illegal controlled substances.

- Tabs "C" and "D"

- Tab "C", Table 5.1b, marijuana treatment admissions for youth aged 12-17 made up 63% of all treatment admissions in 2003.

- Tab "C" *INITIATION OF MARIJUANA USE: TRENDS, PATTERNS, AND IMPLICATIONS, 2002, Joe Gfroerer, SAMHSA, (Early initiation of marijuana use was associated with a greater risk of other drug use behaviors at age 26 or older, such as heroin use, cocaine use, etc., and with a greater risk of illicit drug dependence or abuse at age 26 or older) (6.3% percent of those initiating marijuana use at age 14 or younger were recent heavy users of other illicit drugs in comparison with the less than 1 percent of adults who had never used marijuana that reported heavy use of other illicit drugs).*

(5). a high percentage of adults arrested in this state for domestic violence test positive for marijuana at the time of arrest.

- Tab "A", *OFFICE OF NATIONAL DRUG CONTROL POLICY, ANCHORAGE, ALASKA, PROFILE OF DRUG INDICATORS, 69.2%*

(6). marijuana use by children is associated with an increased risk of attempting suicide.

- Tab "C", *ADOLESCENT DEPRESSION AND SUICIDE RISK, ASSOCIATION WITH SEX AND DRUG BEHAVIOR, (Youth engaging in risk behaviors such as marijuana use are at increased odds for depression, suicidal ideation, and suicide attempts)*

(7). marijuana consists of over four hundred different chemicals and can affect almost every organ and system in the body, including the lymph system, the heart, and the lungs; marijuana can disrupt memory, attention, judgment, and other cognitive functions and can impair motor coordination, time perception, and balance, escpecially in children.

- Tab "A", Tab "C", and Tab "D"

- *LEGALIZATION OF MARIJUANA: POTENTIAL IMPACT ON YOUTH, AMERICAN ACADEMY OF PEDIATRICS, TECHNICAL REPORT, 2004, "Some of the significant neuropharmocologic, cognitive, behavioral, and somatic consequences of acute and long-term marijuana use are well known and include negative effects on short-term memory, concentration, attention span, motivation, and problem solving, which clearly interfere with learning, adverse effects on coordination, judgment, reaction time, and tracking ability which contribute substantially to unintentional deaths and injuries among adolescents, and negative health effects with repeated use similar to effects seen with smoking tobacco.*

(8). marijuana smoke contains more carcinogenic hydrocarbons than tobacco smoke and a person who smokes several marijuana cigarettes a week may be taking in as many cancer causing chemicals as someone who smokes a full pack of cigarettes every day.

- Tab "D", and Addendum. *BRITISH LUNG FOUNDATION, A SMOKING GUN*

(9). potency of marijuana ...

- Tab "A" – Mississippi Monitoring Project Graphs and Charts

(10). treatment admissions ...

- Tab "C" – Treatment admissions data from SAMHSA.

(11). Alaska ranks in top 10 for indoor growing states ...

- Tab "A" – DEA Domestic Cannabis Eradication/Suppression Program Statistical Reports.

(12). A large percentage of persons arrested in this state, including adults and juveniles who commit violent offenses, have marijuana in their system at the time of arrest.

- Tab "A" and Tab "B"

(13). marijuana use by a parent has been, and will continue to be, a major contributing factor to children having easy access to and using marijuana.

- Tab "C" – State of Alaska Adolescent Health Survey, 1990 (Children in homes where parents used marijuana frequently were more likely than children in homes where parents did not use marijuana frequently to use themselves. (22.6% vs. 5%); Among youth perceiving parents would strongly disapprove of using marijuana only 5.4% had used marijuana in the past month vs. 28.7% in homes where the youth believed that their parents would only somewhat disapprove or neither approve or disapprove of their trying marijuana.

(14). criminal penalties for marijuana possession and education efforts are effective in reducing marijuana use and limiting its access by children.

- Addendum.

Reply Card
Safety City Brochure

Press Release
Proclamation
Key Messages
Strategy
Operation ABC

Success Stories
Rx for Prevention
Strides for Safety
Youth Fatalities

Materials Catalog
State Coordinators
Regional Offices

Down the Road
Don't Get Towed
Booster Seats
Kids Aren't Cargo
Fast Lane

Zero Tolerance
Alcohol Poisoning

Air Bag Safety
Occupant Protection
Primary Safety Belt
Patterns for Life
Road to Danger?

Bus Safety Points
Wise Cycling
Ped. Safety Points
Prevent Ped. Crashes

Expect a Train

Drug Impaired Driving

Did you know?

- If you are in the 5- to 24-year-old age group, you have a much greater chance of dying in a motor vehicle crash than dying from homicide, suicide, a fall, cancer, or heart disease.
- The Bureau of the Census estimates that there were more than 22 million young people ages 15 to 20 in the United States in 1996. The number of licensed drivers in this age group was estimated at just under 12 million. By the year 2005 the youth population is expected to have increased by almost 14 percent.
- There is a Presidential Initiative that establishes zero tolerance for drugs when possessed, used, or abused by youth.
- Alcohol, marijuana, cocaine, and inhalants are drugs commonly abused by youth.
- Research shows that marijuana is harmful to the brain, heart, lungs, and immune system. It limits learning, memory, perception, judgment, and complex motor skills like those needed to drive a vehicle.
- People under the influence of cocaine become easily confused and lose the ability to concentrate or to think clearly for any length of time.
- Inhalants can cause damage to the heart, kidneys, liver, brain, and other organs, depending on the types of inhalants used.
- Alcohol and other drugs create a serious highway safety problem among the general driving population. The National Highway Traffic Safety Administration (NHTSA) estimates that drugs are used by approximately 10 to 22 percent of drivers involved in crashes, often in combination with alcohol.
- In a 1990-91 NHTSA study of 1,882 fatally injured

drivers from 7 states, alcohol was found in 51.5 percent of the drivers, and other drugs were found in 17.8 percent of the drivers.

- Studies of drivers injured in crashes or cited for traffic violations also show that many of those drivers have used drugs. In an ongoing NHTSA study of non-fatally injured drivers in Rochester, New York, 12 percent of all drivers tested positive for drugs other than alcohol (43 of 360 cases), and 23.5 percent of drivers less than 21 years old tested positive for drugs other than alcohol (4 of 17 cases). Studies of drivers taken for medical treatment have shown positive drug rates ranging from below 10 percent to as high as 30 to 40 percent. Studies of drug incidence among drivers arrested for motor vehicle offenses have found drugs in 15 to 50 percent of drivers. The higher rates typically are more prevalent among drivers who have been arrested for impaired or reckless driving but who were not impaired by alcohol, as shown by low blood alcohol concentration (BAC) levels.

Self-reported information confirms that teenagers use marijuana in driving situations. PRIDE's 9th Annual Survey of Students, an annual self-administered questionnaire given to students in grades 6 through 12, sampled 129,560 students in 26 states during the 1995 96 school year. Twelfth grade students who reported that they smoke marijuana in a car equaled 20 percent; 16.3 percent drink beer in a car; 12.5 percent drink liquor in a car; and 9.5 percent drink wine coolers in a car. When all senior high school students were asked if and where they use marijuana, they reported: 23.9 percent at a friend's house, 15.9 percent in a car, 11.6 percent at home, 6.5 percent at school, and 19.5 percent in other places.

The evidence from nationally recognized surveys clearly and consistently indicates that drug use by youth is well below the peak levels attained in the late 1970's, but it has risen steadily in the 1990's.

Have you thought about this?

It is illegal in all states to drive a motor vehicle under the influence of alcohol, drugs other than alcohol, or a combination of alcohol and other drugs.

The Drug Evaluation and Classification (DEC) Program trains

law enforcement officers in advanced impaired driving detection techniques to remove drug impaired drivers from the highway.

The DEC process is a systematic, standardized, post-arrest procedure used to determine whether a suspect is impaired by one or more categories of drugs. It is a systematic process because it is based on a variety of observable signs and symptoms proven to be reliable indicators of drug impairment.

Officers who have completed the extensive DEC training program are certified as Drug Recognition Experts (DRE's). DRE's learn to observe a suspect's appearance, behavior, performance of psychological tests, eye movements in different lighting conditions, and vital signs to ascertain what category or categories of drugs are causing the impairment.

Thirty-two states using the DEC Program have officers trained to remove drug impaired drivers. Information about drug impaired driving cases and training are available for prosecutors and judges.

Following are some examples of DRE's effectiveness in removing young drivers who were impaired by drugs:

- In 1995, 8 percent of the evaluations conducted in New Mexico were on arrestees under age 21 (the state does not routinely test for marijuana).
- In a study of 500 DRE cases in Arizona, 10.4 percent of arrestees were under age 21.
- In 1996, Maine reported 27.6 percent of the DRE evaluations conducted were on subjects under age 21.
- In the first 5 months of 1996, New York State Police data indicate that 29.8 percent of DRE evaluations were under age 21.
- In the first 9 months of 1996, Oregon State Police reported that 14.6 percent of the evaluations were conducted on subjects under age 21.

Take action:

- Evaluate the effectiveness of your state laws that prevent youth from possessing and using alcohol and other drugs.

- Provide materials that convey practical information about drugs, the health risks of drug use, how drugs impede safe driving, and the driving sanctions for drug impaired driving and other drug law violations.
- Implement an intervention program for drug impaired drivers that incorporates assessment, drug education, counseling, and other treatment as needed.
- Contact your State Highway Safety Office or NHTSA to obtain additional information on drug impaired driving.

AN OPEN LETTER TO PARENTS:

HERE'S WHAT THE EXPERTS SAY ABOUT MARIJUANA AND TEENS.

■ "Marijuana is not a benign drug. Use impairs learning and judgment, and may lead to the development of mental health problems."
- *American Medical Association*

■ "Smoking marijuana can injure or destroy lung tissue. In fact, marijuana smoke contains 50 to 70 percent more of some cancer causing chemicals than does tobacco smoke."
- *American Lung Association*

■ "Teens who are high on marijuana are less able to make safe, smart decisions about sex - including saying no. Teens who have used marijuana are four times more likely to have been pregnant or gotten someone pregnant than teens who haven't."
- *National Campaign to Prevent Teen Pregnancy*

■ "Marijuana can impair perception and reaction time, putting young drivers, their passengers and others on the road in danger. Teens, the highest risk driving population, should avoid anything that might impair their ability to operate a vehicle safely."
- *American Automobile Association*

■ "Marijuana use may trigger panic attacks, paranoia, and even psychoses, especially if you are suffering from anxiety, depression or having thinking problems."
- *American Psychiatric Association*

■ "Marijuana can impair concentration and the ability to retain information during a teen's peak learning years."
- *National Education Association*

■ "Recent research has indicated that for some people there is a correlation between frequent marijuana use and aggressive or violent behavior. This should be a concern to parents, community leaders, and to all Americans."
- *The National Crime Prevention Council*

And, according to the National Institute on Drug Abuse, marijuana can be addictive. In fact, more teens are in treatment with a primary diagnosis of marijuana dependence than for all other illicit drugs combined.

Teens say their parents are the single most important influence when it comes to drugs. Know their friends. Ask them where they are going and when they will be home. Take time to listen. Talk to your teens about marijuana.

PARENTS.
THE ANTI-DRUG.

Substance Abuse and Mental Health Services Administration
www.samhsa.gov

An Agency of the U.S. Department of Health and Human Services

SAMHSA
News Release

FOR IMMEDIATE RELEASE
February 14, 2005

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WWW.SAMHSA.GOV

Utah Has Lowest Use of Illicit Drugs; Alaska the Highest SAMHSA Unveils State Substance Abuse Data from 2003 National Survey on Drug Use and Health

Utah has the lowest rate of past month use of illicit drugs in the nation, as well as the lowest rate for binge drinking, the Substance Abuse and Mental Health Services Administration (SAMHSA) revealed today. Alaska has the highest rate of illegal drug use, while North Dakota has the highest rate for binging on alcohol.

The data are from "State Estimates of Substance Use from the 2002-2003 National Surveys on Drug Use and Health". SAMHSA combined two years of data from the annual National Survey on Drug Use and Health to enhance the precision of estimates for the less populous states. The report estimates state rates of use of illegal drugs, binge drinking, serious mental illness and tobacco use.

"State-by-state data is a powerful tool for policymakers at the federal, state and local levels to identify needs and target prevention and treatment resources. While we as a nation are making overall progress in reducing illicit drug use among youth, it is clear from the findings that illicit drug, alcohol and tobacco use vary substantially among states and regions," SAMHSA Administrator Charles Curie said. "To help continue to build on the gains we have made, SAMHSA announced last year a total of $230 million over five years to implement its Strategic Prevention Framework in 19 States and two territories to advance community-based programs for substance abuse prevention, mental health promotion and mental illness prevention. More awards are expected this year."

Estimates of past month use of any illicit drug ranged from a low of 6.3 percent in Utah to a high of 12.0 percent in Alaska for all persons ages 12 and older. Other states with high past month use of any illicit drug include Colorado, Montana, Oregon, Nevada, New Mexico, New Hampshire, Rhode Island, Vermont and the District of Columbia.

Utah had the lowest rate in the nation for binge alcohol use in the past month among all persons ages 12 or older, 15.9 percent. Binge alcohol use is defined as drinking five or more drinks on the same occasion on at least one day in the 30 days prior to the survey. North Dakota had the highest rate, 31.4. Colorado, Montana, South Dakota, Nebraska, Minnesota, Iowa, Wisconsin, Massachusetts and Rhode Island also had high rates of binge drinking.

The report estimates that Tennessee has the lowest rate of past year dependence on or abuse of alcohol, 6.0 percent. The highest rate of alcohol dependence or abuse is 10.8 percent in

North Dakota. The District of Columbia had the highest rate of past year illicit drug dependence or abuse, 4.0 percent. This compares with Kansas and Iowa, which had the lowest rate of dependence or abuse, 2.5 percent.

New Mexico had the highest percentage of persons ages 12 or older needing treatment for an illicit drug use problem, but not receiving it, 3.5 percent. Montana, Nebraska, New Mexico, and South Dakota all ranked in the top fifth of states for all three age groups for needing but not receiving treatment for an alcohol problem.

For specific drugs, Tennessee had the lowest rate, 7.4 percent, for marijuana use among those ages 12 and older in the past year, while Alaska had the highest rate, 16.7 percent. This compares to the national rate of 10.8 percent for marijuana use in the past year. For current use – use in the past month—Utah had the lowest rate, 4.0 percent of the population ages 12 and older, while New Hampshire had the highest rate, 10.2 percent. The national current use rate for marijuana was 6.2 percent.

The highest rate of past year cocaine use among persons ages 12 or older was found in Colorado, 3.9 percent. The lowest rate was found in Idaho, 1.6 percent. Arizona and Colorado were the only two states that ranked in the top fifth for all three age groups, 12-17, 18 to 25 and 26 or older.

Kentucky had the highest rate of past month tobacco use among persons ages 12 or older, 39.8 percent. Utah had the lowest rate, 19.7 percent.

Rhode Island had the highest rate of serious mental illness among persons ages 18 or older, 11 percent, while Hawaii had the lowest rate in the nation at 7.2 percent.

The report is available on the web at www.oas.samhsa.gov

SAMHSA, is a public health agency within the Department of Health and Human Services. The agency is responsible for improving the accountability, capacity and effectiveness of the nation's substance abuse prevention, addictions, treatment and mental health service delivery system

AUTHOR: Jennifer M. Lincoln; Ron Perkins; Freddie Melton; George A. Conway
TITLE: Drowning in Alaskan Waters
SOURCE: Public Health Reports v111 p531-5 N/D '96

PUBLISHER ABSTRACT AB Objective. To enumerate drowning fatalities in Alaska in order to identify risk factors and areas for intervention. Methods. Information from death certificates, state troopers' reports, and medical examiner reports were abstracted and analyzed. Rates were calculated using 1990 census figures as denominator data. Results. There were 542 drowning fatalities in Alaska for the years 1988 to 1992. The 20-29 age group had the highest frequency and rate of drownings. The incidence rate for the state was 20 drownings per 100,000 population per year, almost 10 times higher than the overall U.S. rate of 2.11 per 100,000 per year. Incidence rates were highest among adolescent males (10-19), young adult males (20-29), Alaska Natives, and rural residents. Alaska Native males, ages 30-39 averaged 159 drownings per 100,000 per year, the highest drowning rates in the state. Conclusions. Drowning is a major public health concern in Alaska. People who fish commercially and young Native males are groups at nigh risk for drowning. Intervention efforts should be concentrated on these two populations.

Drowning is the second leading cause of injury death in Alaska.(FN1) In the United States as a whole, drowning ranks fourth among unintentional injury deaths after motor vehicle-related deaths, poisonings, and falls, based on data from the National Center for Health Statistics. Drowning is the second leading cause of injury death among children and young adults ages 1 to 24 years.(FN2)

Alaska has the highest drowning rate of any state. During the years 1984 to 1990, the United States had an age-adjusted drowning rate of 2.11 per 100,000 population per year, while Alaska experienced an age-adjusted rate of 11.03 per 100,000 per year, more than five times higher than the national rate.(FN2) A previous study of causes of death in Alaska for 1980–1989 found an average drowning rate of 22 per 100,000 per year.(FN1) For this same time period, drowning was the leading cause of injury death among Alaska Natives, with an age-adjusted drowning rate of 51.9 per 100,000 per year.(FN1) Additionally, for the years 1990 to 1992, drowning was the leading cause of occupational fatalities in Alaska, according to statistics maintained by the Alaska Field Station of the National Institute for Occupational Safety and Health.

Despite these high rates and the potential to learn about a serious national problem by studying the worst-case state, there has not been a comprehensive drowning study for the state of Alaska since 1979. In 1993, the Alaska Area Native Health Service of the Indian Health Service and the Alaska Field Station, Division of Safety Research, National Institute for Occupational Safety and Health, undertook a collaborative study to enumerate drowning fatalities in Alaska. The goal of the study was to identify potential risk factors and possible interventions.

Alaska encompasses 586,412 square miles, is twice the size of Texas, and has more coastline than the rest of the continental United States combined—6640 miles, including islands. However, the state ranks 47th among the 50 states in total road miles. Alaska has more than 3000 rivers and three million lakes, but only 13,485 miles of roads. Only five of the state's urban centers are connected by road.(FN3) Alaskans, especially in the outlying communities, use rivers and coastal waterways as highways both in the summer (by boat) and winter (as ice roads) for travel, commercial purposes, subsistence (including hunting, wood gathering, and berry picking), and recreation.

METHODS

Drowning fatalities were identified by reviewing death certificates for the state of Alaska for the years 1988 through 1992. Demographic data, cause of death (including

E-code when available), and circumstances surrounding the incident (including location, activity, use of safety equipment) were recorded from certificates that cited drowning, immersion injury, or hypothermia with immersion as a cause of death.

To validate the resultant drowning database, we compared it with a computer listing obtained from the Alaska Bureau of Vital Statistics. The listing was sorted according to the following International Classification of Diseases (ICD) External Cause Codes (E-codes):

E 830 accident to watercraft causing submersion [for example, injury resulting from vessel overturning, sinking, or burning]

E 832 other accidental submersion or drowning in water transport accidents

E 910 accidental drowning and submersion

E 954 suicide by submersion [drowning]

E 964 assault by submersion [drowning]

E 984 submersion [drowning], undetermined whether accidentally or purposely inflicted.

We also compared our drowning database for 1988–1992 with the Alaska Occupational Injury Surveillance System (AOISS) database that records occupational fatalities occurring in the state. AOISS collects information from a variety of agencies, including the United States Coast Guard, the state of Alaska's Department of Epidemiology, and the Bureau of Vital Statistics. AOISS includes data from 1990 on, so only the years 1990, 1991, and 1992 could be validated. Forty-four percent (108) of the occupational fatalities recorded in AOISS for the years 1990 to 1992 were drownings or presumptive drownings.

After the data were abstracted, the fatalities were classified by geographic location, whether the injury occurred while working, occupation of those injured at work, and activity at time of incident. Fatality rates were calculated by age group, racial categories, and gender. Denominators for the incidence rates were based on the 1990 Alaska population.(FN4) Medical examiners' and public safety officers' reports were used to assess use of personal flotation devices (PFDs) and toxicologic evidence of alcohol or drug consumption.

RESULTS

A total of 542 fatal drownings occurred in Alaskan waters from 1988 through 1992. Of these, 60% occurred during the months of May through September, while 221 (40%) occurred from October through April. The frequency of drownings varied by age and sex (see Figure 1), with the highest frequency and the highest rate in the 20-29 age group. This group accounted for 168 (31%) of the total drownings, equivalent to a rate of 35.5 drownings per 100,000 per year. The 30-39 age group also had 168 drownings (31% of the total), representing a rate of 28.6 drownings per 100,000 per year. During the five-year period, there were 497 male drowning victims (92%) and 45 females (8%). The greatest number of victims, 148 (27%) were fishing commercially when they drowned; 124 (23%) were using boats for nonrecreational purposes, and 38 (7%) deaths were attributed to falls from docks (Figure 2).

For the five-year period, we calculated the average annual drowning rate for the state as 20 per 100,000 population per year. Of the victims, 335 (62%) were white, 186 (34%) were Alaskan Native, and 21 (4%) were neither white nor Alaska Native. The drowning rate for Alaska Natives was 43 per 100,000 per year. The combined rate for all non-Natives was 15 per 100,000 per year.

Alaska Native males (78 per 100,000 per year) and females (8 per 100,000 per year) had fatal drowning rates almost three times those for non-Native males (27 per 100,000 per year) and non-Native females (2 per 100,000 per year) (Figure 3). Alaska

Native males ages 10 to 19 had a drowning rate of 74 per 100,000 per year, those ages 20 to 29 had a rate of 140 per 100,000 per year, and those in the 30 to 39 age group had a rate of 159 per 100,000 per year.

Of the drowning victims, 326 (60%) drowned in salt water and 199 (37%) drowned in fresh inland waters. The other 3% drowned in bathtubs and hot tubs. Thirty-eight percent of the drownings were work-related, 72% of these among commercial fishing industry workers.

Information on PFD use was available on fewer than 10% of the death certificates. Medical examiner and state trooper reports were requested for all of the drownings. These reports contained information on PFD use and on alcohol and drug involvement. Of the 542 total drownings detected by our surveillance, 349 drownings were not presumptive; a body was recovered and a medical examiner's report should have been filed. Of these, 186 medical examiner reports were located, with all of these victims having been tested for alcohol: 113 (61%) had detectable blood alcohol. In 94 (51%) of these people the level was above 100 milligrams per deciliter (mg/dl). Alcohol testing was completed on 54% of the Alaska Native victims and on 53% of the non-Native victims. Of the 100 Alaska Native decedents tested, 49 (49%) had detectable blood alcohol levels of more than 100 mg/dl for the 86 non-Natives tested, 41 (52%) had a blood alcohol level of more than 100 mg/dl. In addition, 162 victims were tested for illicit drugs: 18 (11%) victims had detectable cannaboids, one victim had detectable cocaine metabolites, one had detectable amphetamine metabolites, and another had detectable opiate and cannaboid metabolites. Thirteen (8%) victims had both detectable alcohol and one of the drug metabolites.

We divided the drowning incidents into census boroughs and calculated the drowning rate for each borough. The geographic region with the highest drowning rate was the Lake-peninsula Borough in Southwest Alaska that includes the villages of Illiamna, Nondalton, and Chignik. The drowning rate for this area was 160 per 100,000 per year. The Aleutians East Borough had a rate of 110 per 100,000 per year, and the Dillingham Borough and the Aleutians West Borough each had a rate of 90 per 100,000 per year.

In validating the drowning database with the AOISS database, we detected seven (1%) additional presumptive drownings that were unaccounted for in the death certificate database. We notified the Alaska Bureau of Vital Statistics of these missing certificates, and the missing cases were added to our drowning database for analysis.

DISCUSSION

The incidence of drowning is extremely high among Alaska Natives residing in rural areas and among Alaskan commercial fishing workers, likely reflecting the very high exposure to water hazards in these populations.

For the study period, the Alaskan drowning rate was approximately ten times the national incidence rate of 2.11 drownings per 100,000 population per year, and the Alaska Native population had a rate 20 times higher than the national rate.(FN1) The drowning rate of Alaska Native males was three times as high as the combined rate for non-Native males. The rate ratio of Alaska Native males (78.1 per 100,000 per year) to non-Native males (26.7 per 100,000 per year) was 2.9:1. Alaska Native males of all ages had very high rates: the rate of the 30-39 age group was 35 times higher than the national average, for the 20-29 group it was 66 times higher, and for the 10-19 group it was 75 times higher.

To combat drownings in rural native villages, the Alaska Area Native Health Service has developed programs in which flotation coats are sold at or below cost. There are currently seven active floatcoat sales programs located in hub communities across the

state. More than 3500 floatcoats were sold in the first three years (1991 to 1993) of the program. The Yukon/Kuskokwim Health Corporation in southwest Alaska has been the most active of the seven programs, accounting for more than 70% of the floatcoat sales. From October 1992 to September 1993, at least 16 people in this region attested that their floatcoats saved their lives.(FN5)

Blood alcohol concentration (BAC) studies in decedents must be regarded with some caution. Blood alcohol levels in corpses can be exaggerated by alcohol produced by the decomposition process. One study showed a difference of 18% in those testing positive for alcohol depending on length of time in the water 29% positive BACs among victims who had been submerged six hours or less and 47% positive BACs among victims who had been submerged up to 12 hours.(FN6) Whether parallel differences would be observed in arctic and subarctic conditions and cold waters is unknown because fermentation is a temperature-dependent process.

The problem of alcohol interacting with cold water hazards to cause drowning is by no means limited to Alaska. A review of 36 studies on drownings from 1947 to 1986 found that 21% to 47% of those who drowned had positive BACs.(FN7) There are several reasons to suspect alcohol as a contributing factor in drownings. Alcohol may hamper the ability to avoid dangerous circumstances. The warm sensation that alcohol creates may make some victims misjudge their heat loss, resulting in hypothermia. The risk for caloric labyrinthitis, an inner ear disturbance that disorients the swimmer, may be increased by intoxication.(FN6) Alcohol may also affect sober people since they may drown as a result of an intoxicated person's actions.

Commercial fishing contributes significantly to the national and regional economies. In 1989, the United States harvested one-fifth the world's total of fish. Alaska accounts for nearly 50% by volume and almost 40% by value of the total U.S. harvest. In the 1980s, Alaska's largest private employer was the fishing industry.(FN8)

U.S. Coast Guard casualty data show that the west coast of the United States accounted for the greatest share of total vessel losses and fatalities. Alaska ranked second in the nation in total vessel losses and fatalities.(FN8)

Strategies are currently being developed to reduce commercial fishing fatalities in Alaska by correcting instability problems, such as overloading, that cause vessels to sink or capsize and by using PFDs and "man overboard" alarms to prevent workers from drowning when falling overboard. It has been previously demonstrated that when fishers who drowned or were presumed to have drowned were compared with those who survived incidents in which at least one other fisher drowned, 63% of those wearing PFDs survived but only 12% of those not wearing PFDs survived.(FN9)

Nationally, the hazards of commercial fishing have also captured the attention of Congress, which enacted the Commercial Fishing Industry Vessel Safety Act (CFIVSA, P.L. 100-424) of 1988. These safety measures were implemented between 1990 and 1993. Two of the present authors analyzed U.S. Coast Guard statistics for Alaskan commercial fishing vessel casualties from 1991 to 1994.(FN10)

The number of vessel casualties (vessels lost) has remained relatively constant, as has the number of people on board (number at risk), while remarkable progress has been made in the case-fatality rate in these vessel casualties, which has dropped from 24% in 1991 to 2% in 1994. This impressive progress in reducing mortality has occurred primarily by keeping seamen who have evacuated capsized or sinking vessels afloat and warm (using immersion suits and life rafts) and being able to locate them readily, via emergency position indicating radio beacons (EPIRB's) all of which are required by the CFIVSA.(FN10)

Some possible sources of error and limitations of our data are worth noting. Out-of-state deaths of Alaskan residents were not included in this study. However, residents

of other states who drowned in Alaska, usually commercial fishing industry workers from out of state, were included. Since the denominators used to calculate rates were based on Alaskan 1990 census data, this inclusion could have resulted in artificially inflating drowning rates in the West Aleutian and East Aleutian districts, where most of these workers died. Death certificates reveal very little about circumstances surrounding the drownings.

Of the 542 people who died by drowning, 148 (27%) were commercially fishing at the time they drowned. Because most commercial fishing activities occur on salt water, more people drowned in salt water than in fresh water. Alaska Natives were most often using boats for transportation or subsistence or other non-recreational activities when they drowned. The National Institute for Occupational Safety and Health Alaska Field Station is focusing drowning prevention efforts on the commercial fishing industry—specifically on the acceptance and wearing of PFDs and the possible utility of man-overboard alarms. An ongoing surveillance system has been set up by the Alaska Field Station in collaboration with the Alaska Area Native Health Service and the Alaska Bureau of Vital Statistics to collect information on all drownings in Alaska regardless of occupational status. This database is linked to the AOISS database mentioned above.

Drowning continues to be a major public health problem in the United States and particularly in Alaska. In Alaska, further surveillance and detailed investigation of fatal and nonfatal immersion events via hospital records and medical examiners' and state troopers' reports are essential to increase information on risk factors such as alcohol and PFD usage. Studies focusing on specific geographic regions would permit more detailed analysis of the problem. Such information is critical for developing and targeting intervention efforts to reduce drownings.

Added material

Ms. Lincoln and Dr. Conway are with the Alaska Field Station, Division of Safety Research, National Institute for Occupational Safety and Health. Ms. Lincoln is an Occupational Safety and Health Specialist, and Dr. Conway is Chief of the Field Station. Mr. Perkins is Director of the Community Injury Prevention Program, Alaska Area Native Health Service. Mr. Melton, a student at East Central Oklahoma University, was a summer intern with the U.S. Public Health Service at the time of this study.

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John Tomaro and Al Zangri of the Alaska Bureau of Vital Statistics, Dr. Anne Lanier of the Indian Health Service, and Helen Peters and Anna Douglas of Arctic Investigations Program provided invaluable assistance.

Figure 1. Drownings by age and gender, Alaska, 1988–1992 (N=542)

Figure 2. Drownings by activity, Alaska, 1988–1992 (N=542)

Figure 3. Drowning rates for Alaska Natives and non-Natives by gender, Alaska, 1988–1992

FOOTNOTES

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WBN: 9630601055017

3. Trends in Marijuana Incidence

3.1 Introduction

Estimates of marijuana incidence, or the number of new marijuana users during a given year, provide an important measure of the Nation's marijuana use problem. They can suggest emerging patterns of use, give clues about the changes in the prevalence of use, identify at-risk subgroups for targeting prevention programs, and suggest substance abuse treatment needs for the Nation.

This chapter presents incidence estimates of marijuana use based on data from the 1999 and 2000 National Household Surveys on Drug Abuse (NHSDAs). These incidence estimates are based on the NHSDA questions on age at first use, year and month of first use for recent initiates, the respondent's date of birth, and the interview date. Using this information, along with editing and imputation when necessary, an exact year, month, and day of first use was determined for each substance used by each respondent. Because these data were collected on a retrospective basis, incidence estimates were always 1 year behind the data on current use. For age-specific incidence rates, the period of exposure was defined for each respondent and age group for the time that a respondent was in an age group during a calendar year.

The average age of new users in each year also was estimated. These rates are presented in this report as the number of new marijuana users per 1,000 potential new users because they indicate the rate of new use among persons who had not yet used the drug (i.e., potential new users). More precisely, the rates are actually the number of new users per 1,000 person-years of exposure. The numerator of each rate is the number of persons in the age group who first used the drug in the year. The denominator is the person time exposure measured in thousands of years. Each person's exposure time ends on the date of first use. For age-specific estimates, exposure is limited to the time during the year that the person was in that age group. Persons who first used the drug in a prior year had zero exposure to first use in the current year, and persons who still had never used the drug by the end of the current year had 1 full year of exposure to the risk.

Because these incidence estimates were based on retrospective reports, they were subject to several biases, as discussed in Chapter 2. It is possible that some of these biases, particularly telescoping and underreporting because of fear of disclosure, may affect estimates for the most recent years more significantly. However, further analysis is needed to understand the magnitude of these biases. In addition, the estimates in this report were based on the new CAI data, and the estimation methodology for these estimates was different from that used in NHSDAs prior to 1999 (i.e., based on paper-and-pencil interviewing [PAPI] methodology). The revised methodology had an impact on age-specific rates (Gfroerer et al., in press). Thus, comparisons with prior NHSDA estimates should not be made.

Estimated trends and incidence rates of marijuana use reported in this chapter were based on the combined sample of 1999 and 2000 CAI data. These estimates are presented by the overall sample, combined age groups and gender (e.g., 12 to 14 male, 12 to 14 female, 15 to 17 male, 15 to 17 female, 18 to 20 male, 18 to 20 female, 21 or older male, and 21 or older female), and race/ethnicity (e.g., white, black, Hispanic, Asian/Pacific Islander/Native Hawaiian, American Indian/Alaska Native, and persons reporting more than one race).

3.2 Trends in Marijuana Incidence

Table 3.1 summarizes the estimated number of new marijuana users, mean age of first use, and annual incidence rates from 1999 and 2000 NHSDA data. An estimated 2.0 million Americans aged 12 or older used marijuana for the first time in 1999, which was fewer than the estimated number of new users in 1998 (approximately 2.5 million Americans), but still above the 1989 and 1990 levels (1.4 million each year). Figure 3.1 shows that the rate of marijuana initiation increased during the late 1960s and early 1970s, with a peak in 1976 and 1977 (21.0 per 1,000 potential new users). After that period, the rate of new marijuana use decreased to 8.5 in 1990, followed by an increase to 16.8 in 1996, then a decrease to 13.6 in 1999. The mean age at first use was 19 years in the early 1970s and decreased to 17 years in the 1990s.

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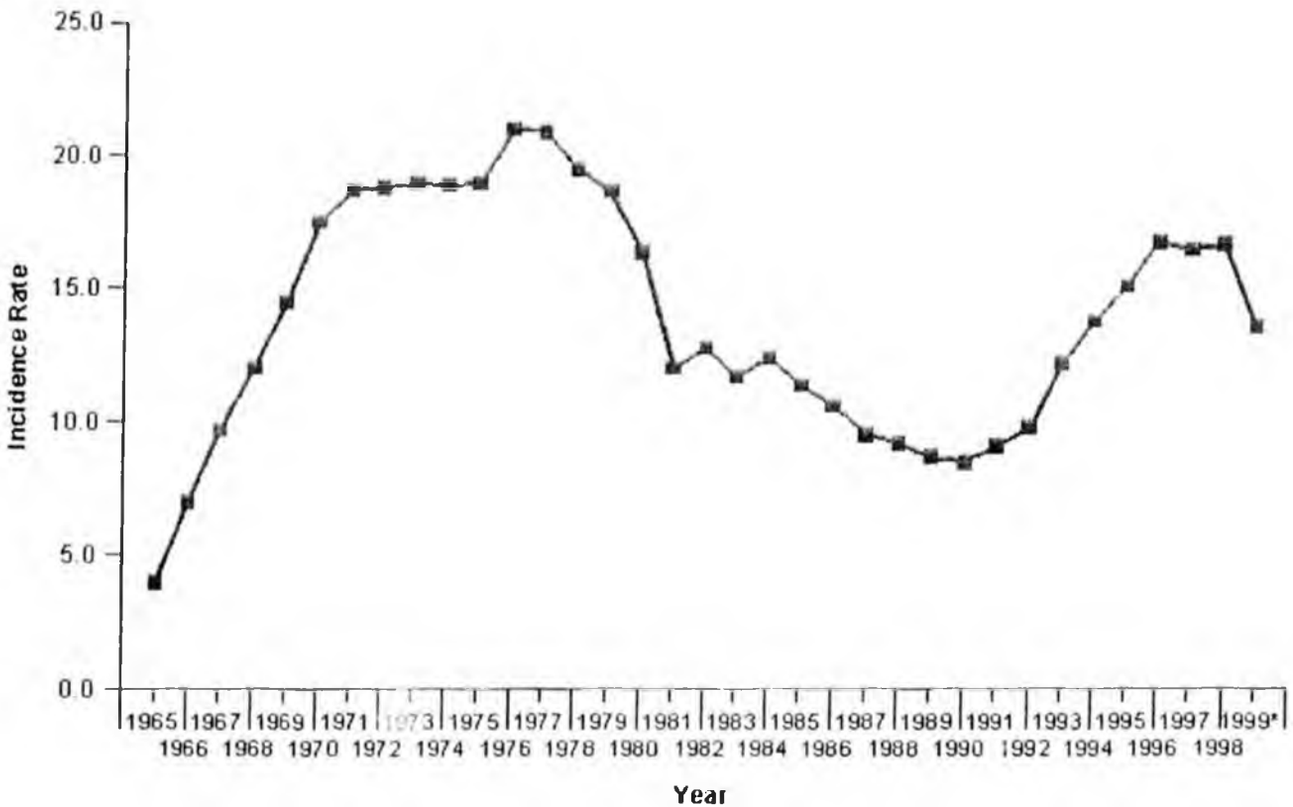
Figure 3.1 Marijuana Incidence Rates, by Year



Note: The numerator of each rate is the number of persons who first used marijuana in the year, while the denominator is the person-time exposure measured in thousands of years for persons aged 12 or older.

* Estimated using 2000 data only.

Source: SAMHSA, Office of Applied Studies, National Household Survey on Drug Abuse, 1999 and 2000.

3.3 Trends, by Age and Gender

Over the years, rates of marijuana incidence were generally higher among males than among females (Tables 3.2 and 3.3, Figure 3.2). Among males, the rate increased dramatically from 4.9 in 1965 to 22.9 in 1971. The highest peak was noted in 1976-1977 (close to 24). After the late 1970s, incidence rates for males declined to around 10 in the late 1980s, followed by a period of increase during the 1990s to 19.3 in 1997. For females, the incidence rate increased steadily from 3.3 in 1965 to 18.9 in 1976. Similar to the pattern of males, the rate was lower during the 1980s, followed by an increase during the early 1990s. The most recent peak for females was in 1996 (15.5). For both genders, the rate in 1999 (15.5 and 12.1, respectively, for males and females) was lower than the rate in 1996-1998.

The estimated mean age at first marijuana use generally has been slightly younger in males than in females. For males, the mean age at first marijuana use ranged from 18-19 years during late 1960s to 16-17 years in recent years. For females, the mean age at first marijuana use decreased from 20 years during late 1960s to around 17 years in recent years. The average age of new marijuana users in 1999 was 16.4 years for males and 17.6 years for females.

Detailed data on age- and gender-specific incidence rates are summarized in Table 3.4. The data indicate that trends of incidence rates peaked at different periods for youths and adults. Among youths aged 12 to 17, annual incidence rates reached peaks during the late 1970s and late 1990s, and the pattern was similar for both genders. Among adults, particularly males, a peak rate of initiation was reached during the late 1960s, with rates remaining high throughout the 1970s, before dropping significantly in the 1980s. In addition, among adults aged 21 or older, the data did not show a peak in new use during the late 1990s, while persons aged 18 to 20 did.

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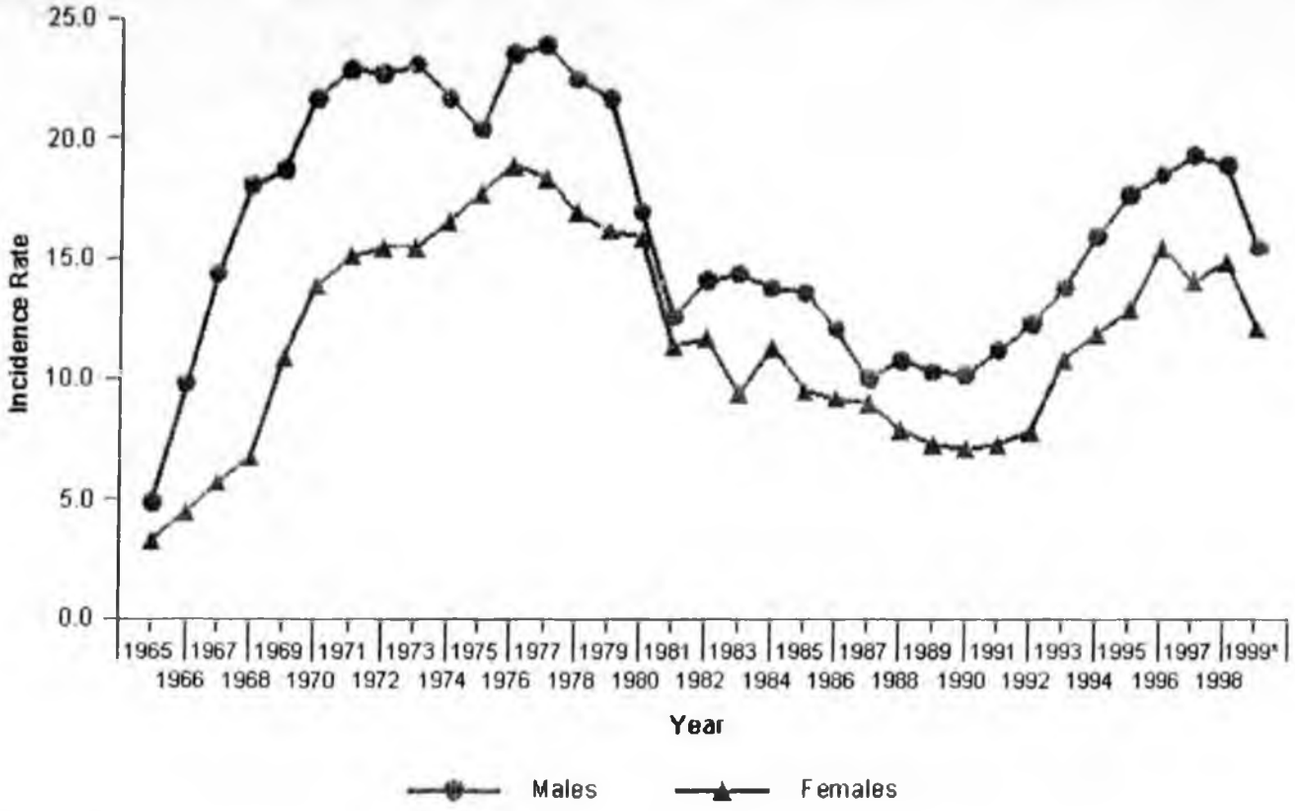
Figure 3.2 Marijuana Incidence Rates, by Gender and Year



Note: The numerator of each rate is the number of persons who first used marijuana in the year, while the denominator is the person-time exposure measured in thousands of years for persons aged 12 or older.

* Estimated using 2000 data only.

Source: SAMHSA, Office of Applied Studies, National Household Survey on Drug Abuse, 1999 and 2000.

3.4 Trends, by Race/Ethnicity

The trends of marijuana incidence also varied across racial/ethnic groups (Tables 3.5 to 3.7). In 1999, an estimated 1.4 million new marijuana users were white; there were 0.25 million black initiates, 0.25 million Hispanic initiates, 0.04 million Asian initiates (including other Pacific Islanders and Native Hawaiians), 0.03 million American Indian/Alaska Native initiates, and 0.03 million initiates who reported more than one race. Except for American Indians/Alaska Natives, the estimated numbers of new users were lower in 1999 than in 1998. In recent years, American Indians/Alaska Natives appeared to have a younger mean age of first marijuana use (14.1 years in 1999) than members of other racial/ethnic groups. In 1999, the mean age of marijuana initiation was 17.2 years for whites, about 16.4 years for blacks and Hispanics, 18.8 for Asians (including other Pacific Islanders and Native Hawaiians), and 15.8 years for persons reporting more than one race.

Among whites, the trend pattern was generally consistent with the overall trend seen in Table 3.1. Probably because of small samples, more variation was noted for non-Hispanic minority groups (American Indians/Alaska Natives, Asians/Pacific Islanders/Native Hawaiians, and persons reporting more than one race) and for years before 1990. Incidence rates between 1990 and 1999 for the racial/ethnic groupings are displayed in Figure 3.3.

Among blacks, the annual incidence rate (per 1,000 potential new users) increased from 8.0 in 1966 to 16.7 in 1968, reached a peak at about the same time as whites (19.4 in 1976), then remained high throughout the late 1970s. Following the low rates in the 1980s, rates among blacks rose again in the early 1990s, reached a peak in 1997 and 1998 (19.2 and 19.1, respectively), then dropped to 14.0 in 1999. Similar to the general pattern for whites and blacks, Hispanics' annual incidence rate rose during late 1970s and 1990s, with a peak in 1998 (17.8).

Asians (including other Pacific Islanders and Native Hawaiians) typically had lower annual incidence rates than the other racial/ethnic groups. However, the sample size did not allow for the generation of reliable estimates for trend data prior to 1985. Among recent initiates, rates of first marijuana use by racial/ethnic groups were generally lower in 1999 than in 1998, with the exception of American Indians/Alaska Natives. Estimates from Table 3.7 suggest a higher rate of new marijuana use in recent years among American Indians/Alaska Natives and among persons reporting more than one race. The annual incidence rate among American Indians/Alaska Natives was 21.2 (per 1,000) in 1995 and had risen over these years to a rate of 46.5 in 1999. Similar to the rates for American Indians/Alaska Natives, incidence rates among persons reporting more than one race were higher than among other racial/ethnic groups during the 1990s. Their incidence rate ranged from 26.2 to 35.4 between 1995 and 1999 compared with a rate below 20.0 among whites, blacks, Hispanics, and Asians/Pacific Islanders/Native Hawaiians.

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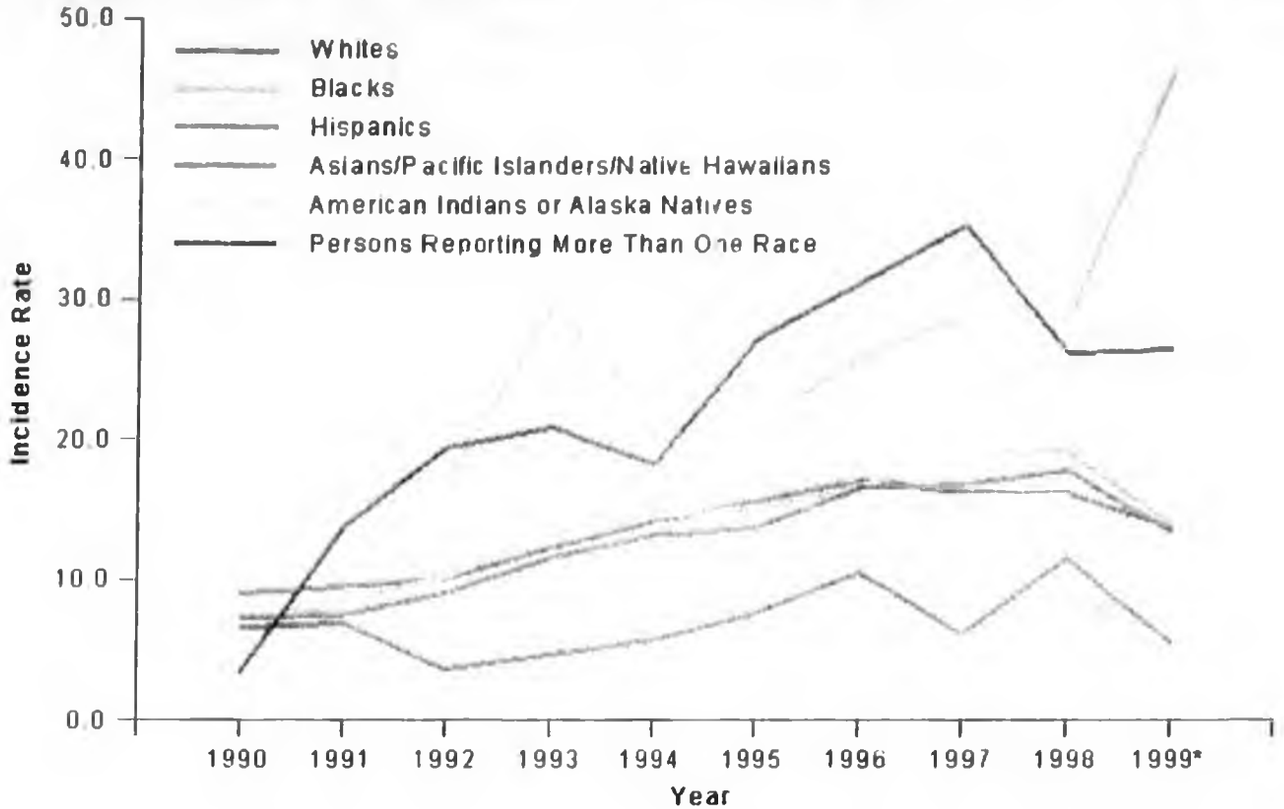
Figure 3.3 Marijuana Incidence Rates, by Race/Ethnicity and Year



Note: The numerator of each rate is the number of persons who first used marijuana in the year, while the denominator is the person-time exposure measured in thousands of years for persons aged 12 or older.

* Estimated using 2000 data only.

Source: SAMHSA, Office of Applied Studies, National Household Survey on Drug Abuse, 1999 and 2000.

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Table 3.1 Estimated Numbers (in Thousands) of Persons Who First Used Marijuana During the Years 1965 to 1999, Their Mean Age at First Use, and the Annual Incidence Rates of First Use (Per 1,000 Person-Years of Exposure), for All Ages

Year	Number of Initiates (1,000s)	Mean Age at First Use	Incidence Rates[1]

1965	553	20.4	4.0
1966	975	19.2	7.0
1967	1,385	19.5	9.7
1968	1,738	19.4	12.0
1969	2,123	19.0	14.5
1970	2,552	18.7	17.5
1971	2,789	18.7	18.7
1972	2,819	18.8	18.8
1973	2,854	18.6	19.0
1974	2,853	17.9	18.9
1975	2,874	18.3	19.0
1976	3,184	18.5	21.0
1977	3,163	18.3	20.9
1978	2,967	18.1	19.5
1979	2,859	18.1	18.7
1980	2,522	19.2	16.4
1981	1,867	17.9	12.0
1982	2,021	18.8	12.8
1983	1,865	18.2	11.7
1984	2,012	18.3	12.4
1985	1,865	18.1	11.4
1986	1,753	17.6	10.6
1987	1,588	17.6	9.5
1988	1,550	17.4	9.2
1989	1,447	17.7	8.7
1990	1,407	18.3	8.5
1991	1,485	18.0	9.1
1992	1,599	16.7	9.8
1993	1,954	17.2	12.2
1994	2,187	16.7	13.8
1995	2,357	16.5	15.1
1996	2,590	17.1	16.8
1997	2,494	17.0	16.5
1998	2,488	17.4	16.7
1999[2]	2,028	17.0	13.6

[1] The numerator of each rate is the number of persons who first used marijuana in the year, while the denominator is the person-time exposure measured in thousands of years for persons aged 12 or older.
[2] Estimated using 2000 data only.
Source: SAMHSA, Office of Applied Studies, National Household Survey on Drug Abuse, 1999 and 2000.

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Table 3.2 Estimated Age-Gender Numbers (In Thousands) of Persons Who First Used Marijuana During the Years 1965 to 1999

	Number of Initiates (1,000s)							
Year	**Males 12-14**	**Females 12-14**	**Males 15-17**	**Females 15-17**	**Males 18-20**	**Females 18-20**	**Males 21+**	**Females 21+**
1965	41	*	114	36	72	84	70	98
1966	64	*	159	86	271	129	142	102
1967	113	54	200	98	312	149	314	132
1968	98	38	248	109	552	195	293	184
1969	115	78	372	216	488	261	266	291
1970	197	187	435	328	496	279	333	303
1971	266	210	405	283	486	320	358	395
1972	264	148	496	453	414	308	385	326
1973	261	225	565	385	365	320	353	306
1974	245	271	584	468	329	301	253	307
1975	309	275	469	493	339	270	235	404
1976	213	208	665	603	414	317	303	420
1977	292	272	633	559	396	309	291	354
1978	263	221	691	542	317	341	230	296
1979	287	237	627	522	362	300	176	274
1980	184	165	486	531	215	297	249	312
1981	156	144	357	383	212	203	120	221
1982	189	132	385	391	254	215	154	258
1983	182	152	394	329	197	172	241	128
1984	237	176	382	385	209	207	160	2.5
1985	184	155	370	371	232	194	204	118
1986	155	134	361	382	212	183	159	118
1987	85	109	340	386	250	189	75	124

1988	132	80	348	327	210	164	112	136
1989	122	96	326	280	175	175	116	99
1990	130	94	309	240	197	135	103	148
1991	154	96	302	265	180	171	160	101
1992	185	159	347	258	222	173	104	82
1993	244	222	364	355	229	210	124	136
1994	276	261	450	394	242	234	123	121
1995	336	274	510	401	226	256	137	141
1996	350	294	523	523	235	268	138	202
1997	329	313	547	478	266	227	145	139
1998	334	313	519	467	236	250	154	175
1999[1]	291	255	446	399	151	175	124	159

* Low precision; no estimate reported.

[1] Estimated using 2000 data only.

Source: SAMHSA, Office of Applied Studies, National Household Survey on Drug Abuse, 1999 and 2000.

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Table 3.3 Estimated Numbers (in Thousands) of Persons Who First Used Marijuana During the Years 1965 to 1999, Their Mean Age at First Use, and the Annual Incidence Rates of First Use (Per 1,000 Person-Years of Exposure), by Gender

Year	Number of Initiates (1,000s)		Mean Age at First Use		Incidence Rates[1]	
	Males	Females	Males	Females	Males	Females
1965	315	239	18.1	23.4	4.9	3.3
1966	642	333	18.8	19.9	9.8	4.5
1967	952	433	19.1	20.4	14.4	5.7
1968	1,212	527	19.0	20.1	18.1	6.8
1969	1,264	859	18.6	19.5	18.7	10.9
1970	1,479	1,112	18.6	19.0	21.7	13.9
1971	1,570	1,218	18.4	19.0	22.9	15.1
1972	1,560	1,258	19.2	18.3	22.7	15.5
1973	1,587	1,267	18.6	18.6	23.1	15.5

1974	1,493	1,360	17.7	18.1	21.7	16.6
1975	1,405	1,469	17.7	18.9	20.4	17.8
1976	1,625	1,559	18.2	18.8	23.6	18.9
1977	1,647	1,517	18.0	18.5	23.9	18.4
1978	1,556	1,411	17.6	18.7	22.5	17.0
1979	1,507	1,352	17.5	18.7	21.7	16.2
1980	1,187	1,335	19.0	19.4	17.0	15.9
1981	896	971	17.2	18.6	12.6	11.4
1982	1,014	1,007	17.9	19.7	14.1	11.7
1983	1,049	815	18.9	17.4	14.4	9.4
1984	1,020	992	18.3	18.2	13.8	11.3
1985	1,021	844	18.2	17.9	13.6	9.5
1986	925	828	17.8	17.4	12.1	9.2
1987	773	815	17.3	17.9	10.0	9.0
1988	834	716	17.1	17.9	10.8	7.9
1989	787	660	17.5	17.8	10.3	7.3
1990	774	633	17.5	19.4	10.2	7.1
1991	837	648	18.1	17.8	11.2	7.3
1992	909	690	16.6	16.8	12.3	7.8
1993	1,009	945	16.8	17.6	13.8	10.8
1994	1,152	1,035	16.7	16.8	16.0	11.9
1995	1,254	1,103	16.4	16.7	17.7	12.9
1996	1,284	1,306	16.4	17.7	18.5	15.5
1997	1,318	1,176	17.0	16.9	19.3	14.1
1998	1,268	1,220	17.6	17.2	18.9	14.9
1999[2]	1,034	993	16.4	17.6	15.5	12.1

[1] The numerator of each rate is the number of persons who first used marijuana in the year, while the denominator is the person-time exposure measured in thousands of years.

[2] Estimated using 2000 data only.

Source: SAMHSA, Office of Applied Studies, National Household Survey on Drug Abuse, 1999 and 2000.

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Table 3.4 Estimated Annual Age-Gender Specific Incidence Rates of First Use (Per 1,000 Person-Years of Exposure) of Persons Who First Used Marijuana During the Years 1965 to 1999

Year	Age-Gender Specific Incidence Rates[1]							
	Males 12-14	Females 12-14	Males 15-17	Females 15-17	Males 18-20	Females 18-20	Males 21+	Females 21+
1965	7.2	*	21.5	5.9	18.2	16.0	3.0	3.4
1966	11.1	*	30.5	14.7	60.9	22.3	5.8	3.3
1967	19.7	8.8	37.7	17.2	68.0	24.0	12.4	4.1
1968	17.1	6.1	46.9	18.8	125.6	34.0	11.0	5.4
1969	19.1	11.9	71.2	37.4	121.7	49.1	9.6	8.2
1970	30.9	28.6	86.4	57.5	124.6	54.8	11.6	8.2
1971	41.3	32.3	83.0	48.9	125.5	64.1	12.2	10.3
1972	43.6	22.5	99.5	77.0	108.3	64.5	12.8	8.2
1973	43.9	33.5	110.6	68.0	98.2	68.3	11.4	7.5
1974	40.0	42.0	118.6	84.6	89.7	64.1	8.0	7.3
1975	48.3	44.4	99.4	88.5	93.2	58.2	7.2	9.4
1976	34.1	34.0	142.5	109.6	114.5	71.3	9.1	9.5
1977	49.9	44.5	131.6	108.3	117.5	72.6	8.5	7.8
1978	48.4	37.6	141.2	110.5	100.0	81.3	6.6	6.4
1979	57.0	41.6	133.2	106.3	114.3	73.7	4.9	5.8
1980	37.2	29.9	110.3	109.1	66.0	78.0	6.8	6.5
1981	30.9	26.2	82.9	79.7	60.3	54.4	3.2	4.5
1982	36.3	23.7	93.4	83.0	72.3	57.6	4.0	5.2
1983	34.5	26.9	96.2	69.6	58.4	44.9	6.2	2.5
1984	46.5	31.4	90.7	82.2	63.5	53.3	4.0	4.1
1985	38.1	28.8	85.8	79.2	73.7	50.5	5.0	2.2
1986	33.4	26.5	83.6	80.6	67.2	47.5	3.8	2.2
1987	18.5	22.0	80.8	81.6	76.0	50.0	1.8	2.2
1988	29.0	16.7	85.9	71.4	62.2	43.0	2.6	2.4
1989	26.3	19.6	82.9	64.3	51.7	45.3	2.6	1.7
1990	27.2	19.1	79.7	55.3	58.6	34.5	2.3	2.5
1991	31.5	18.6	77.3	62.2	56.5	44.3	3.5	1.7
1992	36.1	29.3	88.3	59.6	70.9	46.6	2.2	1.4
1993	45.6	39.6	90.5	82.5	75.2	57.4	2.6	2.2
1994	49.6	46.8	112.7	89.1	80.5	67.3	2.5	1.9
1995	61.2	49.9	126.8	90.3	76.9	74.6	2.8	2.2

1996	65.1	55.0	127.0	117.8	80.5	80.4	2.8	3.1
1997	60.2	59.2	130.5	110.3	94.0	67.7	2.8	2.1
1998	59.9	58.8	127.4	111.5	83.9	75.2	3.0	2.6
1999[2]	51.8	48.1	112.2	97.9	53.0	52.1	2.3	2.4

* Low precision; no estimate reported.

[1] The numerator of each rate is the number of persons who first used marijuana in the year, while the denominator is the person-time exposure measured in thousands of years.

[2] Estimated using 2000 data only.

Source: SAMHSA, Office of Applied Studies, National Household Survey on Drug Abuse, 1999 and 2000.

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Table 3.5 Estimated Numbers (in Thousands) of Persons Who First Used Marijuana During the Years 1965 to 1999, by Racial/Ethnic Subgroups

	Number of Initiates (1,000s)					
Year	**White**	**Black**	**Hispanic**	**Asian / Pacific Islander / Native Hawaiian**	**American Indian / Alaska Native**	**More Than One Race**
1965	427	*	*	*	*	*
1966	804	113	*	*	*	*
1967	1,180	128	49	*	*	*
1968	1,417	246	62	*	*	*
1969	1,834	175	63	*	*	*
1970	2,264	180	73	38	*	21
1971	2,313	228	177	*	14	*
1972	2,413	244	111	12	22	17
1973	2,442	260	91	*	*	*
1974	2,343	256	213	12	*	19
1975	2,377	296	171	12	*	*
1976	2,615	317	172	*	31	*
1977	2,608	277	163	74	*	28
1978	2,370	297	206	77	*	12
1979	2,388	275	127	*	8	23
1980	2,067	235	168	*	*	*

1981	1,518	195	120	*	6	*
1982	1,640	164	165	*	16	7
1983	1,459	149	187	39	11	*
1984	1,633	232	98	*	8	7
1985	1,437	179	165	65	7	12
1986	1,375	186	130	25	24	13
1987	1,242	140	134	52	10	12
1988	1,222	137	132	20	24	15
1989	1,074	137	183	21	*	16
1990	1,057	144	144	49	8	5
1991	1,092	164	146	50	14	20
1992	1,154	199	178	27	13	27
1993	1,388	256	225	34	23	28
1994	1,582	273	250	41	16	24
1995	1,711	282	259	54	16	35
1996	1,848	303	307	75	19	39
1997	1,733	345	308	44	20	43
1998	1,702	336	320	80	19	31
1999[1]	1,436	248	246	39	30	28

* Low precision; no estimate reported.
[1] Estimated using 2000 data only.
Source: SAMHSA, Office of Applied Studies, National Household Survey on Drug Abuse, 1999 and 2000.

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Table 3.6 Estimated Mean Ages at First Use of Persons Who First Used Marijuana During the Years 1965 to 1999, by Racial/Ethnic Subgroups

Year	Mean Age at First Use					
	White	Black	Hispanic	Asian / Pacific Islander / Native Hawaiian	American Indian / Alaska Native	More Than One Race
1965	21.3	*	*	*	*	*
1966	19.3	19.2	*	*	*	*
1967	19.7	18.5	22.0	*	*	*

1968	19.3	19.6	20.2	*	*	*
1969	19.0	19.0	18.6	*	*	*
1970	18.9	17.1	17.1	18.0	*	*
1971	18.8	18.4	17.9	*	*	*
1972	18.8	18.0	21.2	*	19.5	*
1973	18.7	18.4	18.0	*	*	*
1974	17.9	18.4	17.1	*	*	16.6
1975	18.5	17.3	18.1	*	*	*
1976	18.4	19.8	17.7	*	16.8	16.4
1977	18.4	18.0	18.1	17.7	16.6	*
1978	17.9	18.5	20.1	17.9	*	*
1979	18.2	17.7	16.7	*	14.5	15.2
1980	19.4	18.8	17.9	17.1	*	*
1981	18.0	18.6	15.9	*	*	*
1982	18.8	20.8	17.0	*	18.1	*
1983	18.2	18.2	18.8	18.5	16.2	14.0
1984	18.0	20.3	14.7	29.5	10.8	13.5
1985	18.2	17.6	17.4	17.1	14.8	19.1
1986	17.8	17.4	16.9	16.1	14.5	14.9
1987	17.7	16.6	17.3	19.2	19.6	18.3
1988	17.4	16.5	18.0	17.9	21.8	15.1
1989	17.9	17.2	17.0	17.3	16.5	15.5
1990	18.6	17.8	17.7	17.5	19.3	14.9
1991	18.3	17.5	16.0	17.7	22.2	16.5
1992	16.8	17.0	15.7	17.5	15.4	16.0
1993	17.1	17.9	16.7	18.1	22.7	14.4
1994	16.8	16.9	16.2	16.5	15.8	15.2
1995	16.5	16.8	16.0	18.3	15.1	14.9
1996	17.1	17.6	16.7	17.3	14.5	16.0
1997	17.0	17.7	16.0	16.6	15.8	15.9
1998	17.8	17.2	16.0	17.6	14.6	17.0
1999[1]	17.2	16.5	16.4	18.8	14.1	15.8

* Low precision; no estimate reported.

[1] Estimated using 2000 data only.

Source: SAMHSA, Office of Applied Studies, National Household Survey on Drug Abuse, 1999 and 2000.

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Table 3.7 Estimated Annual Incidence Rates of First Use (Per 1,000 Person-Years of Exposure) of Persons Who First Used Marijuana During the Years 1965 to 1999, by Racial/Ethnic Subgroups

Year	Racial/Ethnic Specific Incidence Rates[1]					
	White	Black	Hispanic	Asian / Pacific Islander / Native Hawaiian	American Indian / Alaska Native	More Than One Race
1965	4.0	*	*	*	*	*
1966	7.5	8.0	*	*	*	*
1967	10.8	8.9	4.1	*	*	*
1968	12.8	16.7	4.9	*	*	*
1969	16.4	11.7	4.9	*	*	*
1970	20.2	11.8	5.4	7.3	*	21.3
1971	20.6	14.7	12.7	*	20.0	*
1972	21.5	15.5	7.7	2.2	31.6	17.7
1973	21.8	16.3	6.2	*	*	*
1974	21.0	15.9	14.1	2.0	*	18.8
1975	21.3	18.2	11.1	2.0	*	*
1976	23.5	19.4	10.9	*	41.5	34.0
1977	23.5	16.8	10.1	11.7	*	27.0
1978	21.4	17.8	12.5	12.2	*	11.6
1979	21.6	16.3	7.5	*	10.3	21.3
1980	18.6	13.7	9.7	*	*	*
1981	13.5	11.1	6.8	*	*	*
1982	14.5	9.1	9.2	*	19.7	5.8
1983	12.8	8.1	10.1	5.7	14.1	*
1984	14.2	12.4	5.2	*	9.3	5.5
1985	12.4	9.4	8.6	9.1	8.0	9.2
1986	11.7	9.6	6.6	3.4	28.5	9.2
1987	10.5	7.1	6.7	7.0	11.4	8.2
1988	10.3	6.9	6.5	2.7	28.8	10.3
1989	9.2	6.9	9.1	2.9	*	10.9
1990	9.1	7.3	7.3	6.6	10.2	3.4

1991	9.5	8.4	7.4	6.9	16.9	13.9
1992	10.1	10.3	9.1	3.7	17.1	19.5
1993	12.3	13.4	11.6	4.7	29.3	20.9
1994	14.2	14.5	13.1	5.7	21.8	18.3
1995	15.6	15.2	13.7	7.6	21.2	27.1
1996	17.1	16.6	16.5	10.5	25.8	31.2
1997	16.3	19.2	16.8	6.2	28.8	35.4
1998	16.3	19.1	17.8	11.6	28.6	26.2
1999[2]	13.8	14.0	13.5	5.6	46.5	26.4

* Low precision; no estimate reported.

[1] The numerator of each rate is the number of persons who first used marijuana in the year, while the denominator is the person-time exposure measured in thousands of years.

[2] Estimated using 2000 data only.

Source: SAMHSA, Office of Applied Studies, National Household Survey on Drug Abuse, 1999 and 2000.

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The joint demand for cigarettes and marijuana: evidence from the National Household Surveys on Drug Abuse

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Abstract

Recent studies have shown that efforts to curb youths' alcohol use, such as increasing the price of alcohol or limiting youths' access, have succeeded but may have had the unintended consequence of increasing marijuana use. This possibility is troubling in light of the doubling of teen marijuana use from 1990 to 1997. What impact will recent increases in cigarette prices have on the demand for other substances, such as marijuana? To better understand how the demand for marijuana and tobacco responds to changes in the policies and prices that affect their use, we explore the National Household Survey on Drug Abuse (NHSDA) from 1990 to 1996. We find evidence that both higher fines for marijuana possession and increased probability of arrest decrease the probability that a young adult will use marijuana. We also find that higher cigarette taxes appear to decrease the intensity of marijuana use and may have a modest negative effect on the probability of use among males.

JEL classification: I1

Keywords: Marijuana; Cigarettes; Price; Complements; Elasticity; Demand

1. Introduction

Marijuana use among youths continues to rise despite community, state, and national efforts to educate and inform individuals of the harmful effects of drug use and abuse. For example, between 1990 and 1997, marijuana use among 12–17-year-old more than doubled,

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increasing from a prevalence of 4.4–9.7% (SAMHSA, 1998). The dramatic increase in marijuana use poses new challenges to decision makers developing policies to curb drug use among youths. During this same time period, current cigarette use has steadily increased among 8th, 10th, and 12th graders (MTF, 2000). Epidemiological studies indicate that licit drug use (e.g. tobacco and alcohol) may serve as a gateway to illicit drug use (Kandel, 1975; Kandel and Faust, 1975; Kandel and Yamaguchi, 1993; Duncan et al., 1998). If cigarette use is a gateway to marijuana use, recent policies directed at curbing current youth smoking may also lead to declines in marijuana use. Other studies have demonstrated interdependence between policies directed at curbing alcohol and marijuana use (DiNardo and Lemieux, 1992; Model, 1993; Chaloupka and Laixuthai, 1997; Pacula, 1998a,b).

All of these studies emphasize the importance of understanding the interdependence of widely used substances, such as alcohol, tobacco, and marijuana and suggest that policies affecting one substance may have unintended consequences on the others. Understanding these interdependencies is especially relevant in light of the US$ 0.45-per-pack cigarette price increase announced in November 1998 in response to the US$ 206 billion tobacco industry settlement with 46 states. Policy makers must understand whether proposals intended to reduce smoking among youths have unintended consequences among youths and the general population that may cause marijuana use and other substance use to rise.

The goal of this paper is to further explore the interdependencies between tobacco and marijuana using a rich database on drug use, the National Household Survey on Drug Abuse (NHSDA). The NHSDA is a nationally representative survey of the US noninstitutionalized population aged 12 and older. The detailed questions on substance use contained in the NHSDA allow us to better understand how marijuana use responds to changes in policies that affect the price and availability of marijuana and tobacco. We focus our analyses on youths aged 12–20. We chose this age group for several reasons. Recent trends show dramatic changes in marijuana use for youths aged 12–20 but not for adults aged 21–30. Also, many children first experiment with tobacco and marijuana in their teens.

The specific aim of this paper is to estimate the demand for marijuana and tobacco as a function of the policies and prices that affect their use. Often, empirical demand models of marijuana use are not a function of own prices because marijuana prices are not consistently available. The only time series data available for marijuana prices come from the Drug Enforcement Administration. Unfortunately, these data cover a limited number of cities throughout the US, and have very few price observations in each city in any 1 year, with only a few exceptions. In the absence of the price of marijuana, much of the literature (discussed below) includes policies that serve as a proxy for the price of marijuana. We follow this practice. We constructed a measure of the probability of being arrested for marijuana possession by dividing total annual marijuana possession arrests in a state by an estimate of the total number of marijuana users in the state (by age group). We also include state marijuana laws that specify fines and jail sentences for possession, rather than a simple indicator that marijuana use is decriminalized, because there has been nearly no change in marijuana decriminalization during the study period. Finally, we include the price of cigarettes to capture the possibility that tobacco is an economic complement or substitute with marijuana. We estimate comparable models for cigarette demand — both participation and demand conditional on use. Because of our concern that unobservable state-level

variables may bias the coefficients on the policies and price variables, all marijuana and tobacco models include state fixed effects.

The results of this paper will help guide the creation of comprehensive policies that curb the use of marijuana in two ways. First, we quantify the effects of policies aimed at curbing the use of marijuana, allowing policy makers to evaluate alternative policy options. For example, we provide estimates of the impact of police efforts to enforce marijuana possession laws and the impact of state-level marijuana possession fines. Second, we present results that clarify the cross-price effects between tobacco demand and marijuana use. With an understanding of this interdependency, policy makers can take into account how policy changes directed at one substance affect the demand for the other.

2. Previous studies

In this section, we discuss previous studies that have examined the interdependence of marijuana and tobacco use. There is an extensive literature on the relationship between cigarette and marijuana use, focusing primarily on tobacco use as a 'gateway' to other drug use, including marijuana. Cigarette smoking is considered a gateway drug by some because youths who start with tobacco and alcohol use are more likely to progress to marijuana and other drug use (Kandel, 1975; Kandel and Faust, 1975; Ellickson et al., 1992; Kandel and Yamaguchi, 1993; Duncan et al., 1998). The seminal work by Denise Kandel in 1975 involved tracking licit and illicit drug use by 7250 high school students in New York over a 2-year period. Kandel divides drug use into six categories — legal drugs, marijuana, pills, LSD, cocaine, and heroin — and finds that drug use tends to be cumulative. In other words, youths in any one category have used all 'lower-ranked' drugs. In subsequent work, Yamaguchi and Kandel (1984) find that current alcohol and cigarette use are both strong predictors of initiation of marijuana use. In more recent work, Duncan et al. (1998) find that cigarettes are a stronger predictor of future marijuana use than alcohol and that higher levels of cigarette use are predictive of greater future marijuana use.

From a physiological perspective, two studies suggest that marijuana may be a substitute for cigarettes among current users of both substances. Simmons and Tashkin (1995) obtained detailed marijuana and cigarette smoking histories from 467 adult regular smokers of marijuana and/or cigarettes and found that those who smoke both cigarettes and marijuana smoke significantly fewer cigarettes per day than those who do not smoke marijuana. However, marijuana use is not significantly different for smokers and nonsmokers of cigarettes. Of those who smoke both, 49% began smoking cigarettes first, while 33% smoked marijuana first. Similarly, a controlled experiment of current marijuana and cigarette users illustrates the interdependence of marijuana and cigarettes among current users. Kelly et al. (1990) find that active marijuana smoking (placebo versus active marijuana cigarettes were used) significantly decreased the number of daily cigarette smoking bouts, increased inter-bout intervals, and decreased inter-puff intervals. Although these studies illustrate the potential correlation between marijuana and tobacco, they are both based on relatively small samples of subjects.

Recent studies by economists have also explored the gateway effect and other relationships among licit and illicit drug use behaviors by examining how changes in prices and

policies can affect the use of the targeted substance as well as potentially related substances (DiNardo and Lemieux, 1992; Model, 1993; Thies and Register, 1993; Chaloupka and Laixuthai, 1997; Pacula, 1998a,b; Saffer and Chaloupka, 1998; Chaloupka et al., 1999). However, among these studies, only three have examined the relationship between marijuana and tobacco (Pacula, 1998a,b; Chaloupka et al., 1999). A limitation of all of these studies is that they lack data on the price of marijuana and hence must rely on proxies for the price of marijuana. The only readily available data on the price of marijuana come from Drug Enforcement Administration databases. These databases capture purchases made by undercover federal agents nationwide and police officers in Washington, DC. Because federal interdiction efforts focus primarily on cocaine, heroin, methamphetamines, and other illicit substances other than marijuana, there are relatively few price observations for marijuana in any 1 year in a given city, with the notable exception of Washington, DC. For example, between 1988 and 1997, there were an average of 44 price observations for DC, but only three observations on average in other states. For this reason, this and previous studies do not include the price of marijuana.

In the only published article on the relationship between marijuana and tobacco use, Pacula (1998a) analyzes the 1984 wave of the National Longitudinal Survey of Youth (NLSY) to estimate the joint demand for alcohol and marijuana using a sample of roughly 8000 individuals. Pacula estimates separate demand models for alcohol and marijuana demand and shows that increasing beer taxes decreases the prevalence and consumption of alcohol and decreases the prevalence of marijuana use. She also finds that respondents are more likely to use marijuana in states that have decriminalized marijuana and less likely to use marijuana in states with relatively high cigarette taxes. However, neither of these results is statistically significant.

In a continuation of this research, Pacula (1998b) analyzes two waves of the NLSY and estimates the effect of current and past cigarette prices on current marijuana use. She finds that the two substances are economic complements — higher current and past prices reduce the probability of current marijuana use.

Finally, in a recent working paper by Chaloupka et al. (1999), the authors examine the relationship between marijuana and tobacco use by 8th-, 10th-, and 12th-graders, using cross-sectional data from the 1992–1994 Monitoring the Future Surveys (MTF). They find that higher cigarette prices lead to a decrease in the probability and frequency of marijuana use. Surprisingly, the respective cross-price elasticities are −0.73 and −0.84, for a total elasticity of −1.57. This is larger than the own-price elasticities from their cigarette demand equations, which yielded a participation elasticity of −0.42 and a conditional demand elasticity of −0.71, for a total cigarette price elasticity of −1.13.

As noted, a complication of this literature is that there is no reliable price data for marijuana. Chaloupka et al. (1999) used several variables to proxy for the price of marijuana (e.g. state marijuana law fines and penalties and state decriminalization of marijuana) and found that youths are more likely to use marijuana and to use marijuana more frequently if they live in a state that has decriminalized the possession of small quantities of marijuana. Higher fines for marijuana possession were associated with reduced frequency of marijuana use but did not affect the probability of use. The authors did not include state-level fixed effects because there was not enough variation within states over the relatively short time frame of the data to identify price/policy effects.

In summary, the results of these studies provide some evidence that marijuana and tobacco are economic complements. However, it is difficult to draw strong conclusions from these studies for two reasons. First, all three studies that focus on marijuana and tobacco use rely on relatively few years of time-series cross-sectional data, which limits the variation in cigarette prices. Second, because of the limited number of cross-sections, none of these studies controlled for unobserved, state-specific characteristics. In the absence of state fixed effects, it is unclear whether the estimated effects reflect the preferences of individuals in the state or capture the effect of an exogenous policy change. For example, these studies rely on an indicator variable for states in which marijuana is decriminalized, without controlling for state fixed effects. It is not clear whether this indicator variable captures the effect of decriminalization on use or other state-specific characteristics that may be correlated with use, such as the willingness to accept alternative behaviors or lifestyles. The same may be true for cigarette prices, because they too may capture unobserved characteristics of the state. Failing to control for these unobserved characteristics may bias the estimate of the effects of all state policy and price variables.

The purpose of this paper is to examine the effects of cigarette taxes and nonprice marijuana policies on both marijuana and cigarette use. We are able to control for state effects using 7 years of pooled cross-sections and have a richer database of marijuana policies than have been used before. To proxy for the price of marijuana, we constructed an annual measure of the probability of being arrested for marijuana possession in each state. In addition, for selected years, we collected data on state fines and jail terms for violations of state marijuana laws to proxy for the price of marijuana. By including these state policies and state fixed effects, we are better able to distinguish the effects of state policies and prices from the effects of unobserved state characteristics. Finally, given the changes in cigarette tax policies across states and over time between 1990 and 1996, we are able to identify the effects of cigarette taxes on both the probability and frequency of marijuana use.

3. Data

In this study, we used data from the NHSDA. The NHSDA is a key national indicator of the nation's drug use behavior and problems. The National Institute on Drug Abuse (NIDA) sponsored the NHSDA from 1974 to 1992, and the Substance Abuse and Mental Health Services Administration (SAMHSA) has sponsored the surveys since 1992. The NHSDA is designed to provide data on the extent of drug use and abuse by the noninstitutionalized civilian population aged 12 and older in the US (SAMHSA, 1992, 1994).

We combined data from the 1990–1996 NHSDA to provide estimates of the own- and cross-price and policy effects on the demand for marijuana and tobacco. The NHSDA used identical survey questions in all 7 years for the prevalence of past-month use of marijuana and tobacco and the same five-stage area probability sample design. Sampling weights were computed based on the probability of selection at each stage, and these weights were used in all analyses.

Because of the sensitive nature of the survey topic, self-administered answer sheets were used for marijuana use questions to increase the confidentiality and anonymity of the respondents' answers. This format was designed to minimize underreporting of sub-

stance use, which is a potential limitation of self-reported surveys (Hoyt and Chaloupka, 1993). In a 1990 field test of various survey instruments, Turner et al. (1992) found that the self-administered format of the NHSDA decreases the underreporting of substance use compared to an interviewer-administered format. The NHSDA was revised in 1994 so that tobacco use questions were also reported using a self-administered questionnaire, resulting in some noncomparability of pre- and post-1994 estimates. In particular, youth tobacco use increased dramatically as a result of this change. For this reason, we include an additional indicator variable for the 1994–1996 surveys in the youth tobacco demand equations.

Although the NHSDA is the only survey that provides detailed and consistent data on drug use among members of the household population in the coterminous US, the NHSDA has a number of limitations. First, as mentioned above, the data are self-reports of drug use, so their value depends on respondents' truthfulness and memory. Although the self-administered format of the NHSDA decreases the underreporting of substance use in general, any given individual's propensity to report substance use may be affected by the degree of privacy during the interview. To examine the sensitivity of our results to the degree of privacy, we include the interviewer's report of the degree of privacy during the interview as a supplemental covariate in our demand equations. The interviewer indicates the degree of privacy on a scale from 1 (completely private) to 9 (constant presence of another). We included an indicator that represented no significant interruptions (value of 4 or less).

Second, a small proportion (roughly 1%) of the US population is excluded from the surveys. With the exception of 1991, the subpopulations excluded are those residing in non-institutional group quarters (e.g. military installations, college dormitories, group homes), those in institutional group quarters (e.g. prisons, nursing homes, treatment centers), and those with no permanent residence (e.g. the homeless and residents of single room in hotels). In 1991, the target population was extended to all 50 states and included residents of noninstitutional group quarters and civilians living on military bases. If the drug use of excluded groups differs from that of the household population, the NHSDA may provide slightly inaccurate estimates of drug use in the total population. This may be particularly true for the homeless and prison populations.

3.1. Analysis variables

The dependent variables used in our analyses include indicator variables for any past-month use of marijuana, any past-month use of cigarettes, the frequency of marijuana use in the past 30 days (1–30 days) conditional on use, and cigarettes per day conditional on use. The demographic controls used in our analyses are all self-reported measures from the NHSDA public use files. These controls consist of gender, age, number of people living in the household, number of children under age 12 in the household, marital status, race, family income, current school enrolment status, education, and size of the metropolitan statistical area (MSA) of residence. In addition to these self-reported variables, we also included two interviewer-reported variables: urban/rural status of the respondent's current residence and an indicator for the degree of privacy during the interview.

We merged state-level data on prices and policies that affect the use of marijuana and cigarettes with the NHSDA. These data include cigarette excise taxes (state + federal), marijuana possession arrest information for marijuana violations, and state fines and jail

terms for marijuana possession law violations. Unlike other studies, we do not include an indicator for states that have decriminalized marijuana possession because there is essentially no variation in this variable within states over time during 1990–1996. In addition, the concept of decriminalization is subsumed in our data on state marijuana possession fines.

Marijuana possession arrest data for youths and adults come from county-level Uniform Crime Reports for 1990–1996. Using these data and marijuana use data from the NHSDA, we created two measures of the probability of being arrested. The first measure is the state marijuana possession arrests for youth divided by the number of current marijuana users aged 12–20 in that state. This measure provides an estimate of the probability of being arrested for youth. The second measure is similar to the first but is calculated for all ages 12 and older, not just youth, by dividing the total marijuana possession arrests for all ages in a state by the number of marijuana users in that state. For both age groups, state-level measures of marijuana use were estimated by taking the weighted prevalence of current marijuana use state-by-state. We then multiplied this prevalence by the population in the respective age group from the NHSDA to estimate the total number of users in a state. The purpose of the first measure is to have a youth-specific measure of the probability of arrest. However, because the denominator, youth state marijuana use, may induce some negative correlation with the dependent variable in the marijuana demand equations, we also use the second measure for all ages to provide a lower and upper bound of the results.

Because the NHSDA was not designed during this time period to support state representative data, some states have small samples (therefore, state-level estimates will not be reported). The limited sample sizes should only increase the standard errors of our estimates and not bias our results of the effect of the probability of arrest on use. [1]

We also have state marijuana law data on fines for various quantities of marijuana possession for 1990–1996 that we collected from state legal code books. The marijuana possession laws specify the minimum and maximum monetary fines and jail terms for varying amounts of marijuana possession. In other words, states usually specify fines and penalties for an ounce of marijuana and then another set of penalties for some larger quantity. To characterize these penalties and document changes in the levels of fines within states over time, it is necessary to obtain the legislative histories of the state laws. This is a research-intensive process. We were able to successfully code all states with the exception of North Carolina, North Dakota, and Tennessee for 1990–1996 and New Hampshire, New York, Rhode Island, and Vermont for 1990–1993. Observations for these states and years were dropped from the analysis.

Characterizing state marijuana laws also poses some challenges not only because the penalties for possession of a given quantity vary from state to state, but also because there is not a standard schedule of quantities that trigger increased sanctions. In essence, the marijuana penalties in each state form a step function where, for example, between any positive quantity and 1 pound, some states may have three distinct penalty levels, while

[1] In previous specifications, we used total state marijuana arrests divided by total arrests as a proxy measure for the probability of being arrested for marijuana possession. The key concept behind this measure is that police have scarce resources that they can choose to devote to drug crimes or other crimes. This is consistent with measures used by Benson and Rasmussen (Benson and Rasmussen, 1991; Benson et al., 1992; Rasmussen and Benson, 1994). Overall, the results presented in this paper are consistent with this alternative measure.

others have only one. To capture these differences, we chose to estimate models with the minimum and maximum penalties for the first and second quantity categories (e.g. typically any positive quantity up to 1 ounce and then 1–4 ounces). In addition to these measures, we include a variable that indicates the height or change in the penalty of this first step and an indicator variable for states with only one level of penalties for all quantities. To reduce the potential for multicollinearity, we chose a final specification that includes the average of the minimum and maximum penalties for each quantity.

Data on cigarette excise taxes and prices come from the Tax Burden on tobacco, an annual report from the Tobacco Institute that contains state-level information on state and federal excise taxes and average state cigarette retail prices (Tobacco Institute, 1997). Summary statistics (mean and standard deviation) of both NHSDA survey data and state-level policy and price data are listed in Table 1.

Table 1
Descriptive statistics for ages 12–20, NHSDA 1990–1996

	$N = 50535$	
	Mean	Standard deviation
Age	15.99	2.57
Family size	4.27	1.71
Male	51.1%	50.0%
Divorced	0.4%	6.4%
Married	2.8%	16.5%
White	69.1%	46.2%
Black	14.5%	35.2%
Hispanic	12.1%	32.7%
Other race	4.2%	20.1%
Real family income	$37446.81	$32557.38
Enrolled in school	80.2%	39.9%
High school graduate	75.6%	42.9%
Some college education	9.2%	28.9%
College graduate	0.2%	4.3%
Some graduate school education	0.03%	1.8%
MSA > 1000000	42.2%	49.4%
MSA 250000–1000000	23.6%	42.5%
MSA < 250000	9.8%	29.7%
Rural resident	14.9%	35.6%
Interview with no significant interruptions	76.2%	42.6%
Real tax on cigarettes	$0.575	$0.159
Probability of arrest — youth	2.6%	2.5%
Probability of arrest — all ages	5.2%	4.3%
Average fine — lowest level of quantity possessed	$9186.30	$62604.24
Average fine — next level of quantity possessed	$2764.75	$10388.09
Difference between minimum quantity for first and second possession levels (in grams)	597.2	4347.0
Percent living in states with only one possession level	20.5%	40.4%
Cigarette use in the past month	20.2%	40.2%
Marijuana use in the past month	8.6%	28.0%
Number of cigarettes in past month (smokers)	9.508	9.222
Frequency of past month marijuana use	8.743	9.298

4. Methods

This section describes our study methodology using pooled independent cross-sections of the 1990–1996 NHSDAs. Because we are concerned with the contemporaneous effects of prices and policies on marijuana and tobacco use, we define current users of marijuana and cigarettes as those who have had any use in the past month.

In this paper, we focus on the decision to use marijuana and the frequency of marijuana use in the past month, defined as the number of days of any use. To address the impact of cigarette taxes and policies on marijuana use, we estimate the following demand specification for marijuana:

$$\text{prob}(M > 0) = \Phi(\beta_0 + \beta_1 + \beta_2 \text{Year} + \beta_3 \text{State} + \beta_4 P_{\text{MM}} + \beta_5 P_{\text{MC}}) \quad (1)$$

where M is current marijuana use (past 30 days), Φ the standard normal cumulative density function, and X a vector of the sociodemographic variables described above. P_{MM} represents the effect of the marijuana 'price' variable where price is measured by the probability of being arrested for marijuana possession, and P_{MC} is the price of cigarettes (using state excise taxes). We expect the sign of β_4 to be negative so that as the probability of getting arrested increases, individuals will be less likely to consume marijuana. If $\beta_5 < 0$, then high cigarette prices lead to a lower likelihood of smoking marijuana. If this is true, then marijuana and cigarettes are economic complements. We also estimate the demand for cigarettes by estimating Eq. (2) below, using similar notation:

$$\text{prob}(C > 0) = \Phi(\delta_0 + \delta_1 X + \delta_2 \text{Year} + \delta_3 \text{State} + \delta_4 P_{\text{CM}} + \delta_5 P_{\text{CC}}) \quad (2)$$

From Eqs. (1) and (2), we constructed demand elasticities for participation (any use in the past month) that indicate how sensitive demand is to prices and policies.[2] P_{CM} represents the cross effect for the probability of arrest in the cigarette demand equation, and P_{CC} represents the own-price effect for cigarettes. Although it is not a price elasticity, we calculated elasticities for the probability of arrest for marijuana because having a 'unitless' measure facilitates comparisons of the results across regressions. Comparable Eqs. to (1) and (2) for both the frequency of marijuana use and cigarettes smoked per day by current users are estimated using linear regression models.

The prevalence and intensity of marijuana and cigarette use may vary from state to state because of characteristics about the state not captured by the policy variables above. To account for this variation, we include state indicator variables or fixed effects. Analyses without state fixed effects may improperly attribute the effects of unobserved state characteristics to the policy variables. Therefore, in the absence of state fixed effects, the results inferred from state-level data on prices and policies may reflect a combination of both unobserved state characteristics and the effects of the price and policy variables. The advantage of including state effects in a pooled independent cross-sectional data set is that we con-

[2] We calculate participation elasticities as follows: the marginal effect for the jth variable is calculated as $\beta_j \phi(z)$, where $z = \Phi^{-1}(p)$ and p is the sample mean of the response variable (i.e. indicator variable for smoker), β_j the probit coefficient, Φ the standard normal probability density function, and Φ^{-1} the inverse of the standard normal cumulative density function.

trol for all unobserved state differences, including attitudes, preferences, and other state idiosyncratic characteristics that may affect demand.

Despite the advantages of including state effects, many previous studies have not included them in addition to state-level prices because of concerns over the amount of within-state variation in prices and policies over time. Without sufficient variation in the price/policy variables of interest within a state over time, it is not possible to identify both the state-specific effect and the price/policy variable. In response to this concern, researchers have often omitted state effects in favor of regional effects. While this is a reasonable approach given data limitations, results from these models should be interpreted carefully. When estimating the effects of state policies, regional effects models may simply reflect a correlation between tobacco/marijuana use and prevailing attitudes and behaviors within a state rather than the behavior changes that may result because of these policies. In this paper, we focus on the effect of cigarette excise taxes and marijuana law enforcement — policies that have experienced significant changes in the 1990s (e.g. the probability of arrest has almost tripled from 1.5 to nearly 4.5%). We chose not to examine the demand for alcohol in this paper because state beer taxes remained nearly constant in real terms over the study period. Because beer constitutes the majority of alcohol use, we determined that there was not sufficient variation in beer prices within states over time to identify own- and cross-price effects for alcohol.

To include the effects of national policies (e.g. changes in the national excise taxes on alcohol, increased national efforts to curb the supply of drugs entering the US) and other secular trends in our analyses, we included year indicator variables in the pooled independent cross-sectional data set. Although it is difficult to attribute changes in the national prevalence and intensity of marijuana and tobacco from year to year to specific policy changes, the inclusion of year indicators captures a combination of the effects of national policies and other nationwide secular trends. As noted above, we also include an indicator for the years 1994–1996 in the youth tobacco demand model to reflect the design change that occurred in 1994, causing the prevalence of tobacco use among youths to nearly double (SAMHSA, 1996).

5. Results

5.1. Base models

The results of our two-part models for marijuana and cigarettes are presented in Tables 2 and 3, respectively, with a focus on the key covariates of interest — state cigarette taxes and the probability of arrest for marijuana possession. The full models are presented in the Appendix A. State fixed effects models are presented in the top half of the tables. In both tables, specifications I and II differ only by the way in which we specify the probability of arrest variable. Specification I uses state aggregate measures of youth arrests and youth marijuana demand. Given that the denominator is aggregate youth use, this may bias the results to yield larger (more negative) effects. As a result, we also present specification II, which uses aggregate measures of both arrests and use for all ages. This specification is likely to bias the results toward zero. Hence, together the two specifications give upper and lower boundaries for the actual effect of the probability of arrest. Across both models, the

Table 2
Marijuana demand among 12–20-year-old[a]

	Specification I		Specification II	
	Participation (N = 49239)	Conditional demand (N = 3327)	Participation (N = 49499)	Conditional demand (N = 3327)
State effects				
Real tax on cigarettes	−0.008	−6.613	−0.0001	−0.0641
	(P = 0.635)	(P = 0.006)	(P = 0.38)	(P = 0.008)
	[−0.050]	[−0.436]	[−0.0979]	[−0.441]
Probability of arrest	−1.240	1.474	−0.4475	7.2838
	(P = 0.000)	(P = 0.912)	(P = 0.000)	(P = 0.304)
	[−0.3608]	[0.0044]	[−0.276]	[0.0417]
Pseudo R squared	0.113	0.1164	0.1087	0.1366
Regional effects				
Real tax on cigarettes	0.007	−2.187	−0.0001	−0.0222
	(P = 0.443)	(P = 0.076)	(P = 0.186)	(P = 0.068)
	[−0.0430]	[−0.1443]	[−0.0767]	[−0.153]
Probability of arrest	−0.921	−2.894	−0.3196	−2.5073
	(P = 0.000)	(P = 0.791)	(P = 0.000)	(P = 0.666)
	[−0.2681]	[−0.0086]	[−0.1971]	[−0.0144]
Pseudo R squared	0.1079	0.0989	0.1037	0.1084
No state or regional effects				
Real tax on cigarettes	0.011	−1.750	−0.0001	−0.0181
	(P = 0.104)	(P = 0.077)	(P = 0.129)	(P = 0.064)
	[−0.0741]	[−0.1155]	[−0.0717]	[−0.1248]
Probability of arrest	−0.890	−1.098	−0.3605	−3.8753
	(P = 0.000)	(P = 0.913)	(P = 0.000)	(P = 0.449)
	[−0.2591]	[−0.0032]	[−0.2224]	[−0.0222]
Pseudo R squared	0.1049	0.096	0.1021	0.1035

[a] Own- and cross-price/policy effects, NHSDA 1990–1996 marginal effect (P-value) [elasticity].

state fixed effect results suggest that marijuana and cigarettes are complements (the regional and no fixed effects models are discussed below). The cross-price effect for cigarettes in the marijuana participation and conditional demand models is negative, but statistically significant in only the conditional demand equation. Similarly, the probability of arrest, which can be thought of as a proxy for the price of marijuana in the absence of reliable price data, is negative and statistically significant in both parts of the two-part model for cigarettes for specification I (although small in magnitude, as one would expect).

The estimated cross-price elasticity of demand for cigarettes in specification I (II) of the marijuana equations is −0.05 (−0.10) and −0.44 (−0.44) in the participation and conditional demand models, respectively, assuming that cigarette taxes are fully passed on in the form of higher prices. The own-effect for the probability of arrest is −0.36 in specification I and somewhat smaller in absolute value in specification II, −0.28, as anticipated. In both conditional demand specifications, the probability of arrest is statistically insignificant. Therefore, a 10% increase in the probability that a marijuana user is arrested for possession decreases the probability of use by roughly 3%.

Table 3
Cigarette demand among 12–20-year-old[a]

	Specification I		Specification II	
	Participation ($N = 49253$)	Conditional demand ($N = 7678$)	Participation ($N = 49513$)	Conditional demand ($N = 7648$)
State effects				
Real tax on cigarettes	−0.032	0.832	−0.0005	0.013
	($P = 0.269$)	($P = 0.594$)	($P = 0.116$)	($P = 0.408$)
	[−0.0866]	[0.0519]	[−0.128]	[0.0768]
Probability of arrest	−0.582	−18.971	−0.4032	−1.7228
	($P = 0.000$)	($P = 0.001$)	($P = 0.000$)	($P = 0.622$)
	[−0.0712]	[−0.0530]	[−0.104]	[−0.0095]
Pseudo R squared	0.1389	0.2031	0.1391	0.2106
Regional effects				
Real tax on cigarettes	−0.036	−0.990	−0.0005	−0.0127
	($P = 0.013$)	($P = 0.205$)	($P = 0.001$)	($P = 0.101$)
	[−0.0986]	[−0.0617]	[−0.140]	[−0.0754]
Probability of arrest	−0.552	−19.298	−0.3234	−2.8578
	($P = 0.000$)	($P = 0.000$)	($P = 0.000$)	($P = 0.33$)
	[−0.0675]	[−0.0539]	[−0.0836]	[−0.0158]
Pseudo R squared	0.1361	0.1918	0.1361	0.1953
No state or regional effects				
Real tax on cigarettes	−0.051	−1.014	−0.00071	−0.0132
	($P = 0.000$)	($P = 0.105$)	($P = 0.000$)	($P = 0.035$)
	[−0.1398]	[−0.0632]	[−0.1862]	[−0.0783]
Probability of arrest	−0.532	−24.345	−0.2788	−4.4668
	($P = 0.000$)	($P = 0.000$)	($P = 0.000$)	($P = 0.098$)
	[−0.0650]	[−0.0680]	[−0.0721]	[−0.0248]
Pseudo R squared	0.1346	0.1893	0.1345	0.1906

[a] Own- and cross-price/policy effects, NHSDA 1990–1996 marginal effect (P-value) [elasticity]

With respect to cigarette demand, the own-price elasticities in both parts of the two-part model are imprecisely estimated (Table 3). Estimating cigarette demand for this age group is problematic during the 1990–1996 time period because the method to collect tobacco use among 12–17-year-old changed in 1994 from an interview format to a self-administered questionnaire (as was done for illicit drugs during the entire study period). Although we attempted to capture this effect with an indicator variable for the post-1993 period (and with price times the post-1993 indicator in another specification), we were not able to replicate standard price elasticities for youth. Based on recent estimates for this age group, one would expect total elasticities of demand from −0.4 to −0.6 (Evans and Huang, 1998; Farrelly and Bray, 1998; Tauras and Chaloupka, 1999).

The results from Table 3 yield a participation elasticity for cigarettes for specification I (II) of −0.09 (−0.13) in models with state fixed effects. The corresponding conditional demand models result in positive and statistically insignificant conditional elasticities. However, the probability of arrest in the cigarette demand equations is consistently negative, statistically significant, and small in magnitude across all state fixed effects specifications. This latter result confirms the pattern of complementarity found in Table 2.

Tables 2 and 3 also demonstrate the sensitivity of the estimates across various fixed effects models. Focusing first on the marijuana demand models, the effect of cigarette taxes on participation is statistically insignificant in all models. In specification I, the coefficient on taxes is negative in the state fixed effects models and becomes positive in the models with either regional or no fixed effects. In specification II, the result remains negative across the regional and no fixed effects specifications.

In contrast, the effect of cigarette taxes on conditional marijuana demand remains negative and statistically significant across all specifications, but the elasticity drops considerably as we move from the state to regional and no fixed effects models. This suggests that states with high levels of marijuana use have higher levels of cigarette taxation. The estimated effect for the probability of arrest remains relatively stable across all specifications.

In the cigarette demand models, the coefficient on taxes remains stable across all participation equations, while the standard error decreases from the state to regional to no fixed effects models, becoming statistically significant in the latter two models. However, in the conditional demand models, taxes remain imprecisely estimated in all specifications, with the exception of the no fixed effects model for specification II.

5.2. *Gender differences*

To further explore the effects of the probability of arrest and cigarette taxes on marijuana demand, we reestimate our models by gender (Table 4) using the probability of arrest defined for youth (specification I). These models reinforce the notion that marijuana and

Table 4
Demand for cigarettes and marijuana by gender[a]

	Marijuana		Cigarettes	
	Participation	Frequency	Participation	Frequency
Male				
Real tax on cigarettes	−0.040	−13.470	−0.070	2.441
	($P = 0.119$)	($P = 0.000$)	($P = 0.092$)	($P = 0.283$)
	[−0.223]	[−0.788]	[−0.185]	[0.144]
Probability of arrest	−1.367	7.799	−0.838	−14.314
	($P = 0.000$)	($P = 0.681$)	($P = 0.000$)	($P = 0.107$)
	[−0.337]	[0.020]	[−0.099]	[−0.038]
Number of observations	24319	1879	24326	4013
Adjusted R squared	0.1202	0.1048	0.1513	0.2245
Female				
Real tax on cigarettes	0.024	0.061	0.017	−1.095
	($P = 0.228$)	($P = 0.984$)	($P = 0.66$)	($P = 0.605$)
	[0.191]	[0.050]	[0.049]	[−0.073]
Probability of arrest	−1.076	−3.074	−0.381	−20.850
	($P = 0.000$)	($P = 0.867$)	($P = 0.005$)	($P = 0.003$)
	[−0.386]	[−0.011]	[−0.049]	[−0.062]
Number of observations	24900	1448	24920	3635
Adjusted R squared	0.1129	0.1349	0.139	0.1908

[a] Own- and cross-price/policy effects, NHSDA 1990–1996 marginal effect (P-value) [elasticity].

cigarettes are economic complements among males. For males, the effects of cigarette taxes on marijuana demand increase considerably relative to the results for the overall sample, while the effects for the probability of arrest remain stable. These results also show that the only result that remains robust for females is the deterrent effect of the probability of arrest on marijuana participation.

Turning to cigarette demand, the tax coefficient remains imprecisely estimated in all models with the exception of the participation model for males, where taxes are statistically significant at the 10% level and yield a reasonable price elasticity of roughly −0.2.

5.3. *Marijuana possession laws*

When deciding whether or not and how frequently to use marijuana, youths may also consider the penalties for marijuana possession in addition to the probability of arrest. As noted above, state marijuana laws generally take the form of a step function that is at the discretion of state legislators. To quantify the effect of these penalties on use, we reestimated our marijuana demand models including the average penalties (average of the minimum and maximum fines) for the first two steps in the penalty functions of states.[3]

Each step is characterized by the quantity interval (generally starting with any positive quantity up to 1 ounce and then from 1 to 4 ounces) and the penalty for possession of these amounts. Because a few states have one set of penalties for all possession violations, we also include an indicator variable for these states. Finally, because the height of this first step — or the difference in the penalty between the first and second quantity interval — varies from state to state, we also include the amount in grams required to trigger the second level of penalties. In theory, this variable is important because it captures the effect of more or less stringent penalty scales. One would expect, ceteris paribus, requiring greater quantities of marijuana to trigger a higher level of fine might encourage more and/or more frequent use.

Table 5 shows that higher penalties for possession are correlated with a lower probability of use in the past 30 days. Both the average fine for the lowest quantity level and next highest quantity level are negative and statistically significant. However, higher fines do not appear to affect the frequency of marijuana use among young adults. The amount required to trigger a higher penalty level (the difference between the first and second amounts) had no effect on the probability of use.

Therefore, both a higher probability of arrest and higher fines decrease the probability of use, but not the frequency of use. Consistent with the results for the probability of arrest, higher penalties discourage the probability of marijuana use in the past 30 days but do not discourage the frequency of use. In addition, the effect of higher cigarette taxes on frequency of marijuana use remains robust in this alternative specification.

We also estimated the effects of these penalty variables in cigarette demand and, once again, confirmed a pattern of complementarity. However, none of the effects were statistically significant (data not shown).

[3] We also estimated models including both the minimum and maximum fines, and although the results were qualitatively similar, the individual minimum and maximum variables were not precisely estimated, possibly due to a high degree of correlation among the penalties for the first two quantity categories. As a result, we chose to present only those models with average fines.

Table 5
Effects of marijuana possession fines on marijuana use, NHSDA 1990–1996

	Participation ($N = 44659$)	Frequency ($N = 3013$)
Minimum and maximum fines		
Real cigarette tax	0.0155	−9.2915
	($P = 0.365$)	($P = 0.000$)
Average fine — lowest amount	−0.00327	0.25
	($P = 0.062$)	($P = 0.298$)
Average fine — next highest amount	−6.07E−05	−0.00429
	($P = 0.042$)	($P = 0.286$)
Quantity difference between first and second amounts	0.000448	0.597
	($P = 0.902$)	($P = 0.239$)
Indicator for one penalty level	0.0081	−1.2559
	($P = 0.541$)	($P = 0.544$)
Pseudo R squared	0.1036	0.1362

6. Conclusion

Two clear policy implications emerge from the various models that we present in this paper. First, higher cigarette taxes decrease the intensity of marijuana use and may have a modest effect on the probability of use, especially among males. Overall, the total marijuana demand cross-price elasticity for cigarettes indicates that a 10% increase in cigarette prices would lead to a 5.4% decrease in total marijuana use (with a 95% confidence interval of 0–11%). We also found that these cross-price effects were driven by the males in the sample. For males, 10% increase in cigarette prices would lead to a 10% decrease in total marijuana demand (95% confidence interval of 3–19%). Therefore, although some have suggested that increases in cigarette prices may lead to an increase in marijuana use, the evidence presented in this paper suggests that these fears may be unfounded. All of the evidence in this paper supports that there is a complementary relationship between marijuana and cigarettes and that policies that are aimed at reducing cigarette use are likely to also reduce marijuana use. Second, both higher fines for marijuana possession and increased probability of arrest decrease the probability that a young adult will use marijuana, but these policies have little effect on the frequency of use.

Finally, in policy analyses of this sort, it is critical to recognize the importance of differences in the social and political environments across states and that these differences may be correlated with both public policies and aggregate behavior (e.g. cigarette excise taxes are extremely low, while smoking rates are high). As a result, we note the sensitivity of our results to whether or not state-specific indicator variables are included in the specifications to control for these cross-sectional differences. We conclude that specifications with these state-specific indicator variables yield the most reliable estimates. This approach ensures that the estimated policy effects are driven by correlations between changes in policies and behavior over time within states, rather than spurious cross-sectional correlations.

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Appendix A

The full models are presented in Table 6

Table 6
Basic participation model with own- and cross-price/policy effects for youths[a]

	Cigarettes ($N = 49253$)	Marijuana ($N = 49239$)
Real tax on cigarettes	−0.032	−0.008
	($P = 0.269$)	($P = 0.635$)
Probability of arrest-youth	−0.582	−1.240
	($P = 0.000$)	($P = 0.000$)
Age	0.171	0.120
	($P = 0.000$)	($P = 0.000$)
Age squared	−0.004	−0.003
	($P = 0.000$)	($P = 0.000$)
Family size	−0.011	−0.006
	($P = 0.000$)	($P = 0.000$)
Divorced	0.088	0.044
	($P = 0.001$)	($P = 0.003$)
Married	−0.026	−0.037
	($P = 0.004$)	($P = 0.000$)
Male	0.013	0.023
	($P = 0.000$)	($P = 0.000$)
African American	−0.124	−0.012
	($P = 0.000$)	($P = 0.000$)
Hispanic	−0.064	−0.017
	($P = 0.000$)	($P = 0.000$)
Other race	−0.056	−0.034
	($P = 0.000$)	($P = 0.000$)
Real family income	0.000	0.000
	($P = 0.000$)	($P = 0.000$)
Student	−0.113	−0.021
	($P = 0.000$)	($P = 0.000$)
High school dropout	0.080	0.024
	($P = 0.000$)	($P = 0.000$)
Some college	−0.045	0.002
	($P = 0.000$)	($P = 0.561$)
College graduate	−0.036	−0.026
	($P = 0.29$)	($P = 0.184$)
Some graduate/professional school	−0.120	
	($P = 0.064$)	

Table 6 (*Continued*)

	Cigarettes ($N = 49253$)	Marijuana ($N = 49239$)
MSA < 250000	0.011	−0.008
	($P = 0.176$)	($P = 0.072$)
MSA 250000–1000000	0.018	0.005
	($P = 0.012$)	($P = 0.245$)
MSA > 1000000	0.007	0.006
	($P = 0.316$)	($P = 0.126$)
Rural resident	−0.023	−0.024
	($P = 0.001$)	($P = 0.000$)
Interview with no significant interruptions	0.010	0.007
	($P = 0.019$)	($P = 0.004$)
Pseudo R squared	0.1389	0.113

[a] Also included but not shown: state and year effects, and a dummy variable for year >1994

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Table 15. Percentage of Alternative High School Students Who Used Selected Drugs by Sex, Race/Ethnicity, and Grade, 1998

Drug use behavior	Sex		Race/Ethnicity			Grade Level				All Groups
	Male	Female	White, non-Hispanic	Black, non-Hispanic	Hispanic	9th	10th	11th	12th	
Lifetime marijuana	88.0	82.1	89.4	77.7	84.0	81.0	85.3	86.0	86.8	85.4
Current marijuana[1]	58.2	46.7	56.7	47.2	50.6	51.2	52.9	55.7	51.2	53.0
Lifetime cocaine use[2]	38.6	33.0	43.8	5.7	46.4	32.7	36.4	37.8	36.5	36.1
Current cocaine use[1]	17.1	13.1	17.7	3.6	19.4	14.8	16.6	15.9	14.1	15.3
Lifetime crack or freebase use	23.5	19.4	26.2	3.5	26.8	20.9	22.9	24.2	18.9	21.6
Lifetime use of illegal steroids	9.8	7.4	10.5	6.6	6.9	12.0	9.6	6.9	7.6	8.7
Lifetime injected drug use	6.8	4.4	7.0	4.1	4.5	7.6	5.6	5.4	4.9	5.7
Episodic heavy drinking[3]	55.4	42.9	58.7	28.4	52.4	43.8	48.1	51.5	51.7	49.8
Current cigarette[1]	67.7	59.8	78.6	43.3	53.0	64.5	64.3	64.8	62.2	64.1

— Data not available.

[1]Used one or more times during the past 30 days.

[2]Ever tried any form of cocaine, including powder, crack, or freebase.

[3]Drank five or more drinks of alcohol on at least one occasion on one or more days during the past 30 days.

Source: "Youth Risk Behavior Surveillance—National Alternative High School Youth Risk Behavior Survey, United States, 1998," *Morbidity and Mortality Weekly Report* nters for Disease Control and Prevention, Public Health Service, Department of Health and Human Services.

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Table C.5 Average Age at First Marijuana Use Among Persons Reporting First Use of Marijuana at Age 25 or Younger in 1995 to 1997, by State: 1999

State	Average Age	95% C.I.	State	Average Age	95% C.I.
National	16.2	(16.1 -16.4)	Missouri	16.2	(15.3 -17.0)
Alabama	16.6	(15.6 -17.6)	Montana	15.1	(14.5 -15.7)
Alaska	16.0	(14.8 -17.2)	Nebraska	16.1	(15.0 -17.1)
Arizona	15.3	(14.4 -16.2)	Nevada	15.1	(14.3 -15.8)
Arkansas	15.9	(15.4 -16.4)	New Hampshire	16.5	(14.7 -18.2)
California	16.1	(15.8 -16.4)	New Jersey	16.9	(16.0 -17.7)
Colorado	15.9	(15.2 -16.6)	New Mexico	15.9	(15.1 -16.7)
Connecticut	16.8	(15.1 -18.6)	New York	16.7	(16.1 -17.3)
Delaware	16.2	(15.2 -17.1)	North Carolina	16.1	(15.6 -16.7)
District of Columbia	16.4	(15.0 -17.8)	North Dakota	16.9	(16.0 -17.7)
Florida	16.1	(15.6 -16.6)	Ohio	16.6	(16.2 -17.0)
Georgia	15.8	(15.1 -16.6)	Oklahoma	15.9	(14.9 -16.8)
Hawaii	16.5	(14.7 -18.4)	Oregon	16.0	(14.8 -17.2)
Idaho	16.7	(15.8 -17.6)	Pennsylvania	16.6	(16.2 -16.9)
Illinois	15.7	(15.4 -16.0)	Rhode Island	16.3	(15.1 -17.5)
Indiana	16.3	(15.7 -17.0)	South Carolina	16.0	(15.1 -16.8)
Iowa	16.9	(16.2 -17.7)	South Dakota	16.8	(15.5 -18.1)
Kansas	15.7	(15.0 -16.5)	Tennessee	16.9	(15.3 -18.4)
Kentucky	16.5	(15.8 -17.2)	Texas	16.1	(15.8 -16.5)
Louisiana	16.0	(15.2 -16.9)	Utah	15.6	(15.0 -16.2)
Maine	17.1	(15.5 -18.7)	Vermont	16.7	(15.1 -18.2)
Maryland	16.0	(14.9 -17.1)	Virginia	16.5	(15.4 -17.6)
Massachusetts	16.2	(15.2 -17.2)	Washington	15.8	(15.3 -16.3)
Michigan	16.6	(16.0 -17.2)	West Virginia	16.3	(15.5 -17.1)
Minnesota	15.6	(15.0 -16.2)	Wisconsin	16.6	(15.4 -17.7)
Mississippi	16.8	(16.1 -17.5)	Wyoming	15.9	(15.2 -16.6)

*Low precision; no estimate reported.

Source: SAMHSA, Office of Applied Studies, National Household Survey on Drug Abuse, 1999 CAI.

Mental Disorders of Eskimos Seen at a Community Mental Health Center in Western Alaska

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The charts of 343 Eskimos seen at a community mental health center in northwestern Alaska were reviewed, and data on demographic characteristics, *DSM-III-R* diagnoses, and history of suicide attempts were collected. Substance use disorders were the most common group of mental disorders. Substance use patterns differed substantially according to age and gender. Both children and adults had high rates of attempted suicide (66 percent and 67 percent). Rates of bipolar disorder and eating disorders were substantially lower than those seen in mental health clinics serving the general U.S. population. (*Psychiatric Services* 49:1485–1487, 1998).

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Rapid sociocultural changes in Native American communities are reflected in the nature and extent of mental health problems in these populations (1). Several community surveys have reported high rates of psychiatric disorders. Using struc-

Table 1

Psychiatric diagnoses of adult Eskimo patients evaluated at a community mental health center in Nome, Alaska[1]

Diagnosis	All patients (N=255)		Men (N=115)		Women (N=140)	
	N	%	N	%	N	%
Substance abuse or dependence[2]	189	74.1	98	85.2	91	65.0
Alcohol	129	50.6	57	49.6	72	51.4
Cannabis	33	12.9	20	17.4	13	9.3
Polysubstance[3]	26	10.2	20	17.4	6	4.3
Inhalant	1	.4	1	.9	0	–
Mood disorders[4]	117	45.9	35	30.4	82	58.6
Major depression, unipolar[5]	95	37.3	27	23.5	68	48.6
Dysthymia	15	5.9	6	5.2	9	6.4
Bipolar disorder	7	2.8	2	1.8	5	3.6
Psychotic disorders[6]	47	18.4	28	24.4	19	13.6
Schizophrenia[7]	29	11.4	21	18.3	8	5.7
Schizoaffective disorder	13	5.1	5	4.4	8	5.7
Other psychotic disorders	5	2.0	2	1.7	3	2.1
Personality disorders	32	12.6	13	11.3	19	13.6
Anxiety disorders	31	12.2	9	7.8	22	15.7
Panic disorder	16	6.3	4	3.5	12	8.6
Posttraumatic stress disorder	14	5.5	4	3.5	10	7.1
Generalized anxiety disorder	1	.4	1	.9	0	–
Adjustment disorder	25	9.8	12	10.4	13	9.3
Organic disorder	15	5.9	9	7.8	6	4.3
Dementia or delirium	11	4.3	6	5.2	5	3.6
Mental retardation	4	1.6	3	2.6	1	.7
Eating disorders	4	1.6	0	–	4	2.9
Other diagnoses[8]	5	2.0	1	.9	4	2.9

[1] All statistical test reports are for comparisons between men and women.
[2] $\chi^2=12.9$, df=1, p<.001
[3] $\chi^2=10.5$, df=1, p<.005
[4] $\chi^2=19.1$, df=1, p<.001
[5] $\chi^2=16$, df=1, p<.001
[6] $\chi^2=4.18$, df=1, p<.05
[7] $\chi^2=8.6$, df=1, p<.005
[8] Includes somatoform disorders, pedophilia, malingering, and multiple personality disorder

tured diagnostic interviews, Kinzie and associates (2) found that 69 percent of the adult population in an American Indian village had a definite or probable mental disorder, compared with 32 percent in the Epidemiologic Catchment Area study of the general U.S. population (3). Rates of addictive diseases and depression are especially high (2,4,5). For example, lifetime prevalence rates of alcohol dependence or abuse within selected American Indian communities range from 27 to 51 percent (2,6).

Most epidemiological surveys in Native American populations have used problem checklists or questionnaires to measure psychopathology (4,5). Some have used structured diagnostic interviews to classify American Indian subjects using a modern diagnostic system (2,6), but sample sizes have been small and such studies have not been performed in Eskimo populations.

During his clinical work at the regional community mental health center in Nome, Alaska, one of the authors (RJG) noted a low rate of bipolar disorder (manic-depressive illness) and eating disorders among Eskimo patients attending the clinic. This observation, along with the lack of studies measuring rates among Eskimos of psychopathology according to our current diagnostic classification system, prompted the study described in this paper. We report the rates of psychiatric disorders among Eskimos attending a community mental health center in Western Alaska and offer possible explanations for these findings.

Methods

The Eskimos in the Bering Straits region of Alaska are members of four distinct ethnic groups: Inuit, Inupiat, Yupik, and Siberian Yupik. Although the people retain much of their traditional values and life style, almost all are literate in English.

Any person in the region is eligible to receive services at the community mental health center (CMHC) in Nome. Many patients are referred by their local medical provider.

The study population includes all Eskimo patients evaluated by the staff psychiatrist (RG) at the CMHC between October 1990 and April 1993. Charts were reviewed retrospectively, and data on demographic characteristics, *DSM-III-R* diagnoses, and history of suicide attempts were collected. Between-group differences were analyzed using two-tailed chi square tests with Yates correction.

Results

Over the two years of the study, 343 Eskimo patients– 88 children and adolescents between the ages of six and 17 years and 255 adults age 18 and older– were evaluated. Among the children and adolescents there was a slight preponderance of females (N=49). The mean age of the children and adolescents was 14±2.3 years. The mean age of the adult patients was 37±15 years.

Most youths had problems with substance use disorders (N=49), but females most frequently used alcohol, and males surprisingly were more likely to have problems with inhalants. Eating disorders were infrequent (N=3).

Table 1 outlines the distribution of diagnoses among the adult patients. Substance use disorders were prevalent, especially among men. Whereas inhalant use was much less frequent among adults compared with children, alcohol and cannabis use were much more frequent.

Most surprising was the low frequency of bipolar disorder (manic-depressive illness) and eating disorders. One would expect that approximately equal numbers of patients would have bipolar disorder as would have schizophrenia in a mental health clinic (7), but less than 3 percent of

these Eskimo patients received a diagnosis of bipolar disorder.

Sixty-six percent of the children and 67 percent of the adults reported a previous suicide attempt. An interesting finding was that the two age groups differed in the gender distribution of the suicide attempters (χ^2= 11.6, df=1, p<.001), with females reporting higher rates among youths and adult men and women reporting approximately equal rates. This difference suggests that suicide may have different etiologies in different age groups.

Discussion and conclusions

Perhaps our most striking finding is the high prevalence of substance use disorders in both children and adults attending the mental health clinic. The substances of choice appeared to be alcohol, cannabis, and inhalants, and preference varied by age and by gender. Although striking, the finding was not unexpected, as high rates of substance use have been noted in surveys fairly consistently across Native American ethnic groups (8). Reasons for these consistent findings are unknown, but may include biological, psychological, and sociocultural factors (2,4).

Of concern was a 67 percent rate of reported suicide attempts. This rate compares with rates of 4 to 25 percent reported in other mental health clinics (7). Suicide rates vary widely among Native American tribes and subgroups (8). Acculturation and high rates of alcoholism have been the most common explanations given for Native American suicide (9), but a more recent study in this Eskimo population suggested that early parental loss and limited grieving mechanisms are important factors (10).

This study supported our prediction of low rates of eating disorders and bipolar disorder. In the general U.S. population, an outpatient mental health clinic might expect that approximately 8 percent of its adult patients would have bipolar disorder (7). In contrast, we found a rate of 3 percent in our clinic. To our knowledge, this is the first time that a low rate of bipolar disorder has been reported in a Native American population.

A low rate of eating disorders is easily explained by culturally based differences in attitudes towards body weight and appearance. It is more difficult to explain the low rate of bipolar disorder. One possibility is sampling bias– that is, the expected number of persons with bipolar disorder lived in the community, but they did not come to our clinic. We believe this explanation is unlikely given the disabling nature of the illness and the lack of alternative mental health resources in the region.

Another possible explanation is that our subgroup, or Native Americans as a whole, have low genetic loading for bipolar disorder or a different phenotypic expression of the illness. For example, high rates of cannabis use may have led to a psychotic diathesis of a bipolar predisposition, thereby causing a predominantly psychotic manifestation of bipolar illness. In support of this explanation, we found that cannabis use was highly correlated with assignment of a psychotic disorder (χ^2=23.6, df=1, p<.001). In addition, our clinical observation was that many of the patients that were diagnosed with schizophrenia appeared to respond to mood stabilizers.

The limitations of the study include its use of retrospective analysis and assignment of diagnoses based on the clinical evaluations of a single psychiatrist. This study highlights the need for similar studies in other Native American clinic populations, as well as systematic community surveys employing structured diagnostic interviews and a modern diagnostic classification system. ♦

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Marijuana impairs growth in mid-gestation fetuses

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Abstract

Marijuana (*Cannabis sativa*) is the most commonly used illicit drug by pregnant women, but information is limited about the effects of prenatal cannabis exposure on fetal development. The present study evaluated the influence of early maternal marijuana use on fetal growth. Women electing voluntary saline-induced abortions were recruited at a mid-gestational stage of pregnancy (weeks 17–22), and detailed drug use and medical histories were obtained. Toxicological assays (maternal urine and fetal meconium) were used in conjunction with the maternal report to assign groups. Subjects with documented cocaine and opiate use were excluded. Main developmental outcome variables were fetal weight, foot length, body length, and head circumference; ponderal index was also examined. Analyses were adjusted for maternal alcohol and cigarette use. Marijuana (n=44)- and nonmarijuana (n=95)-exposed fetuses had similar rates of growth with increased age. However, there was a 0.08-cm (95% CI −0.15 to −0.01) and 14.53-g (95% CI −28.21 to 0.86) significant reduction of foot length and body weight, respectively, for marijuana-exposed fetuses. Moreover, fetal foot length development was negatively correlated with the amount and frequency of marijuana use reported by the mothers. These findings provide evidence of a negative impact of prenatal marijuana exposure on the mid-gestational fetal growth even when adjusting for maternal use of other substances well known to impair fetal development.

Keywords: Fetal growth; Cannabis; Alcohol; Intrauterine growth; Nicotine

1. Introduction

Cannabis is the most commonly used illegal drug among young women of childbearing age in most western societies. For example, 13–23% of females aged 16–24 report marijuana use in the UK [4]. Approximately 4% of women in the USA report using illicit drugs (i.e., marijuana, cocaine, heroin, hallucinogens, inhalants, nonmedical psychotherapeutic) during pregnancy, with marijuana being the most commonly (75%) used drug among pregnant women [43]. Significant advances have been made in recent years as to the biology of the cannabis system, including identification of the cannabis receptors, their distribution in the brain and periphery, pharmacology, and signaling pathways [28,40]. Despite the growing interest in the biological actions of cannabis, there are still only few studies regarding the consequences of cannabis exposure, especially in relation to the development of the human fetus. Such information is essential when considering the current debates as to the potential legalization of marijuana in many western societies and the establishment of national policies related to marijuana's effects on health.

Prenatal effects of maternal drug use on fetal development are primarily assessed by measures of fetal growth.

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There is evidence in the literature that marijuana-exposed infants at birth have reduced weight [15,21,25,50] and/or head circumference [15,19], as well as decreased gestation length [6,20,21,25]. These findings are not, however, unequivocal since some studies have failed to document significant effects of in utero cannabis exposure on fetal development [17,39] or gestation length [32,48]. There has also been a report of increased birthweight in association with prenatal marijuana use, primarily associated with marijuana use during the third trimester [8]. Multiple reasons could account for the discrepant findings, such as the stringency of the control group, the accuracy of drug use, genetic and social differences of the populations investigated, and the developmental time period when growth parameters are evaluated. Another important consideration for the conflicting results in the literature may relate to confounding effects of maternal use of other drugs, such as cigarette and alcohol. Animal studies in which experimental conditions can be well controlled have documented reduced weight in association with prenatal cannabis exposure [1,3], thus substantiating the findings in humans of a negative impact of maternal marijuana use on fetal growth. The potential long-term prenatal effects of marijuana exposure have also been examined in longitudinal studies. Such investigations have documented specific abnormalities in cognitive (e.g., verbal skills, memory) and behavioral (impulsivity, inattention, social disturbances) functioning in offspring of women who used marijuana during pregnancy [14,18,22,41].

Despite increasing evidence of developmental impairment, as well as behavioral disturbances with in utero marijuana exposure, there is still a virtual lack of information as to the influence of early prenatal marijuana exposure on human fetal growth. Only few studies to date have investigated the prenatal effects of marijuana, and those have mainly evaluated newborns, which make it difficult to dissociate the influence of early versus late in utero drug exposure. Since women are more likely to discontinue their drug use during the early stages of pregnancy, evaluation of an early to mid-developmental time period is of particular importance. To assess developmental events prior to the third trimester, the current project examined standard measures of development in aborted fetuses. The study focused on the early to mid-gestation (weeks 17–22) developmental period since it is the latest stage during which normal specimens can be obtained from voluntary abortions. Thus, in comparison to most investigations that have examined the cumulative impact of cannabis exposure throughout the entire prenatal developmental period, the present study sought to identify the influence of early to mid-gestational marijuana exposure on fetal growth. We hypothesized that indices of fetal growth, particularly body weight, would be reduced in association with maternal marijuana use during early to mid-gestation pregnancy.

2. Methods

2.1. Sample collection

Pregnant women who had elected to carry out a voluntary saline-induced abortion at Kings County Hospital, Brooklyn, NY, between January 2000 and December 2002 were the focus group of the project. The study was approved by the Institutional Review Boards of Kings County Hospital Center and SUNY Downstate. Women were recruited for the study if they were estimated (based on ultrasound and/or maternal physical exam) to be at a mid-gestational stage (weeks 17–22) of pregnancy. The women provided written consent to participate in the study that entailed completion of a verbal questionnaire (requiring about 45 min to obtain demographic and drug use information) and urine analysis. Participants could withdraw at any time from the study. The questionnaires, maternal urines, and fetal samples were given coded identifiers, and no patient identifiers, such as the person's name, remained on any of the data sheets or drug screening results. Fetuses were included in the study if the postmortem interval did not exceed 24 h. The fetus was examined by the pathologist and/or study coordinator for routine physical measures, such as gender, birth weight (g), body length (supine length on a horizontal, flat surface; cm), foot length (cm), and occipital–frontal head circumference (cm). Meconium was also collected for subsequent toxicological analysis. An estimate of symmetrical fetal development was determined by ponderal index ([weight (g)/length $(cm)^3 \times 100$]).

2.2. Maternal demographic, drug use, and medical history assessment

Mothers were interviewed by a study coordinator using a standardized interview format established by Drs. Nancy Day and Gale Richardson (Department of Psychiatry and Epidemiology, University of Pittsburg, PA) [41]. The interview included information pertaining to maternal demographic status (e.g., race, age, educational level), maternal substance use (illicit and prescription drugs), and medical history. The substance use questions were structured to assess drug use patterns prior to pregnancy and during pregnancy. In addition to the amount and pattern of marijuana use, the interview included questions related to the use of cigarettes, beer, wine, liquor, cocaine, crack, amphetamines, heroin and other opiates, hallucinogens, and inhalants. The questions included information regarding the number of joints smoked per day (blunts were calculated to be equaled to three joints), number of cigarettes smoked per day, and number of standard drinks consumed per day. Standardization of the number of drinks for each type of alcohol (i.e., beer 12 oz, wine 5 oz, and liquor 1.5 oz) and calculation of the total amount of drug usage for each substance during prepregnancy

(the year prior to pregnancy) and the pregnancy were calculated according to established published protocols (see below).

2.3. Toxicological assessment

Maternal urine screening for illicit drug use was performed by EMIT® (Dade-Behring, Irvine, CA) with a cut-off of 50, 300, and 300 ng/ml for cannabinoid, cocaine, and opiate, respectively. Meconium toxicology was carried out at the Karolinska hospital to screen (immunoassay) for cannabis, cocaine, opiates, and amphetamine using CEDIA urine screening reagents (Microgenics, CA, USA; Hitachi 917; Roche Diagnostics, IN, USA). Immunoassay response greater than the limit of detection (approximate limits: cannabis 10 ng/g, opiate 75 ng/g, cocaine 15 ng/g, amphetamines 50 ng/g, benzodiazepines 40 ng/g, phencyclidine 1 ng/g) was taken as a positive indication, and a second analysis was carried out using gas chromatography–mass spectroscopy (SIM-GC-MS).

Subjects were included in the cannabis-exposed group based on positive toxicology (urine and/or meconium) and/or positive maternal self-report. The remaining subjects were assigned to the non-cannabis-exposed group.

2.4. Data analysis

The presence and extent of marijuana use was assessed using two approaches: a dichotomized variable, positive maternal report and/or positive toxicology, and as continuous variables, number of joints normally used and frequency (times/week) of maternal use. Maternal marijuana use was expressed as average daily joint (ADJ) to dissociate the contribution of the pattern of marijuana exposure on fetal development; only subjects who provided detailed drug use history were included in such analyses. Weekly drug use was converted to daily use based on the yearly pattern of use; for example, seven joints per week was converted as 7 joints/week×4 weeks/month)/(31 days/month)=0.89 joint/day. Marijuana users were divided into four groups: no use, light users (0>ADJ<0.4), moderate users (0.4≥ADJ<0.89), and heavy users (ADJ≥0.89) according to the characterization by Goldschmidt et al. and Richardson et al. [22,41]. An ADJ of 0.4 is approximately three joints/week. The influence of other drugs was also assessed as to maternal use (yes/no) and the amount of use. For alcohol use, 1 drink=12 oz. can beer, 4 oz. glass wine, 1.5 oz. shot of liquor, and average daily volume (ADV, drink/day) of 1 drink/day=0.5 oz. absolute alcohol [41].

Four fetal outcome measures (body weight, body length, foot length, and head circumference) were assessed. Outliers, as assessed by residual plots, Cooks Distance Influence, and normality plots, were excluded from analysis to minimize the influence of a few cases on the results. An examination of the normal residual distribution was carried out for each dependent variable; no transformation of the data was carried out since the residuals were normally distributed. Univariate nonparametric analyses were carried out to obtain an overall estimate of the general characteristics of the groups. Univariate analyses do not consider the influence of other variables, thus, such analyses were not used when assessing specific significant effects of prenatal drug exposure. General linear models were conducted with confounding variables (e.g., gestation age, fetal gender, maternal age, maternal education, and married status) for the initial model testing. Cannabis exposure was always included in the model since this was the primary question of interest. Backward selection regression was carried out sequentially deleting the variables that had the weakest effect on the equation. Except for maternal alcohol and cigarette use, only variables with a $p<0.10$ correlation with the dependent variable were included in the final statistical analysis. Linear modeling was also performed to assess the amount and frequency of marijuana use on the developmental outcome variables. Data related to women who reported no marijuana use but whose toxicology revealed positive cannabis exposure were excluded from all analyses that evaluated the pattern and frequency of drug use. Statistical analyses were carried out using JMP (5.1) software package (SAS Institute, Cary, NC, USA). Statistical significance was set as $p<0.05$ and trends considered for $p<0.10$.

3. Results

3.1. Maternal characteristics of the marijuana-exposed and nonexposed groups

There was an approximately 30% refusal rate for participation in the study by pregnant women who fulfilled the project criteria. A total of 139 subjects gave informed consent, completed the questionnaire, and were included in the study (demographics in Table 1). In this cohort, 31.7% had evidence, from either toxicology and/or maternal report, of marijuana use during pregnancy. Of the women in the cannabis-use group who admitted marijuana intake, 81.8% reported using marijuana at a rate of 1.39±0.4 ADJ before pregnancy, a pattern that decreased to 0.85±0.2 during pregnancy. There were no significant demographic differences between the groups in regard to race (approximately 80% Black), marital status (predominantly unmarried), or maternal age (Table 1). To minimize the potential bias of fetal growth deficits associated with young mothers, fetuses from 15-year-old and younger (four cases) subjects were excluded from analyses regarding drug effects on fetal growth. The noncannabis group was slightly more educated (11.9 vs. 11.3 years; $p=0.0264$). The groups also differed in regard to the use of cigarettes and alcohol. Women in the cannabis-use group had an approximately fourfold higher rate of cigarette smoking and twofold higher amount of alcohol intake during

Table 1
Maternal characteristics of marijuana users (documented marijuana use before and/or during pregnancy) and nonusers as determined by positive toxicology and/or positive maternal self-report

Variables	Nonusers	Users	*p*-value
N	95	44	
Maternal age (years)	23.4±0.7	22.4±0.6	0.8380
Maternal education (years)	11.9±0.2	11.3±0.2	0.0192
Race/ethnicity			0.0753
White	5	0	
Black	80 (84.2%)	35 (79.5%)	
Hispanic	9	9	
Married status	7 (7.4%)	4 (9.1%)	0.4295
Cigarette use before pregnancy	28 (29%)	31 (70.5%)	
Average amount/day	2.1±0.4	5.9±0.9	<0.0001
Cigarette use during pregnancy	17 (18%)	17 (39%)	
Average amount/day	1.2±0.3	4.9±0.2	<0.0001
Nonsmoker	83	27	
≤5 cigarettes/day	11	1	
5 to 10 cigarettes/day	5	10	
≥10 cigarettes/day	2	6	
Alcohol use before pregnancy	28 (29%)	27 (70%)	
Average daily volume (drink/day)	0.30±0.1	0.45±0.1	0.0005
Alcohol use during pregnancy	22 (23%)	24 (54%)	
Average daily volume (drink/day)	0.22±0.09	0.42±0.1	<0.0001
None	73	20	
Light	13	11	
Moderate	4	8	
Heavy	5	5	
Use of other illicit drugs* during pregnancy	6	0	

The values represent mean±SE; percentage of some variables in parentheses.
p-Values for nominal and ordinal variables are based on Chi-squared tests, and continuous variables are based on nonparametric univariate analyses. ADV—average drinks/day; light—ADV ≤0.4 drink/day; moderate—0.4>ADV<1 drink/day; heavy—ADV>1 drink/day. *Cocaine and opiate.

pregnancy (Table 1). Both groups reduced their cigarette use during pregnancy with a greater decrease reported by the noncannabis group (44% vs. 17%). The use of alcohol decreased for 27% during pregnancy in the noncannabis group but only 5% in the cannabis users. Overall, few women reported moderate-to-heavy cigarette smoking (5.8% of the cannabis group) or heavy alcohol use (7.2% of the cannabis group) as characterized as >10 cigarettes/day and ≥1 drink/day, respectively. Many women (45.3% in the control group; 50% in the cannabis group) reported morning sickness or heartburn during the first trimester of pregnancy that purportedly affected their eating pattern and lead to weight loss. There was no statistical difference (p=0.550) between the cannabis and control groups in relation to the number of subjects reporting weight loss during pregnancy as a consequence of morning sickness or heartburn.

3.2. Toxicological evidence

Toxicological evidence was not found to match the maternal self-report in all cases. Of the cannabis-exposed group, eight (18.2%) had a positive toxicology although the mothers failed to report marijuana use during pregnancy (Table 2). In addition, 10 subjects (23% of the group) had negative toxicological evidence for cannabis exposure, but the mothers reported marijuana use during pregnancy (predominantly light; 0.37±0.15 ADJ). Women who were identified as heavy users were more likely to have toxicological evidence of recent marijuana use (50%) as compared to women who were identified as light users (16.7%). Women who reported heavy marijuana use also smoked approximately twice as many cigarettes both before and during pregnancy than women reporting light marijuana use. Heavy marijuana users reported having approximately double alcohol consumption before pregnancy but reported similar alcohol intake during pregnancy as the light marijuana users. None of the women in the marijuana-use cohort had toxicological or self-report evidence of either cocaine or opiate use. There were six cocaine/opiate cases (two subjects using both drugs) users in the noncannabis group. Due to the sample size of the cocaine and heroin subjects, the influence of these drugs could not be evaluated in the statistical analyses, and these subjects were excluded from all analyses regarding marijuana effects on fetal growth.

3.3. Fetal characteristics

The overall characteristics of the fetuses in the cannabis-exposed and nonexposed groups are presented in Table 3. The average gestational age at the time of the voluntary abortion was similar between the nonexposed (19.8±0.2 weeks) and cannabis-exposed (20.0±0.3 weeks) groups. There was also no significant difference in the gender of the fetuses, 53.6% and 59.1% males in the nonexposed and cannabis-exposed groups, respectively. There was a very strong correlation (Spearman ρ=0.898 to 0.958) between the primary growth outcome measurements. Head circumference was the least correlated with the other developmental

Table 2
Prevalence of cannabis use reported for the "cannabis users" group

Cannabis users	Before pregnancy	During pregnancy
Frequency of cannabis use (time/day)	0.43±0.1	0.35±0.1
No. reporting nonuse	8	8*
No. reporting light use	17	13
No. reporting moderate use	4	7
No. reporting heavy use	15	10
ADJ	1.39±0.4	0.85±0.2

* Negative maternal report but positive cannabis toxicology. ADJ—average number of joints/day: light use—0>ADJ<0.4; moderate use—0.4≥ADJ< 0.89; heavy use—ADJ≥0.89.

Table 3
General overall comparison of the fetuses in the cannabis and noncannabis groups

Variables	Noncannabis	Cannabis
Gestation age (weeks)	19.8±0.2	20.0±0.3
Fetal gender (male/female)	51/44	26/18
Fetal weight (grams)	274.5±11.7	272.3±18.7
Fetal foot length (cm)	3.07±0.1	3.0±0.1
Fetal body length (cm)	23.1±0.4	23.03±0.5
Fetal head circumference (cm)	16.14±0.2	15.78±0.5
Ponderal index	2.14±0.04	2.09±0.05

The values are expressed as mean ± SE.

measures, but the correlation was nevertheless strong (Spearman ρ approximately 0.90). There was, however, a very weak correlation between the fetal growth measures and the secondary outcome variable, ponderal index. The correlations with ponderal index ranged from 0.0382 (non-significant) for body length to 0.2990 (p=0.008) for head circumference. Statistical analyses revealed that gestation age had the greatest impact on all outcome measures of fetal growth (approximately 59–73% prediction); thus, this variable was always included in the general linear models. All developmental measures increased with increasing gestational age though lower growth was evident in the cannabis-exposed group (Table 4); body weight: cannabis exposed, R^2=0.756; nonexposed, R^2=0.747; body length: cannabis exposed, R^2=0.693; nonexposed, R^2=0.729; foot length: cannabis exposed, R^2=0.694; nonexposed, R^2=0.720; head circumference: cannabis exposed, R^2=0.610; nonexposed, R^2=0.722. The estimated growth pattern over the developmental period examined is consistent with published [2,11,47] fetal growth rates of approximately 64 g, 0.32 cm, 1.79 cm, 1.31 cm increase of fetal weight, foot length, body length, and head circumference, respectively, for the 17–22 weeks age range. There was only a weak association between ponderal index and gestational age: cannabis exposed, R^2=0.233; nonexposed, R^2=0.0259.

Other than gestation age and drug exposure (see below), no other variable obtained from the maternal report, such as initial weight loss as a consequence of morning sickness or heartburn, illness, injury, or radiation (X-ray) during pregnancy or family history of medical problems (e.g., mental retardation or birth defects), was associated with the measurements of fetal growth.

3.3.1. Cannabis exposure on fetal growth

Cigarette smoking and alcohol intake were always included as confounding variables in the final statistical models due to the greater abundance of these substances in women in the cannabis-use group and the known influence of these substances on fetal development [9,26].

Cannabis-exposed fetuses were lighter in weight with an estimated 14.53 g difference as compared to the non-cannabis fetuses (p=0.037; Table 4). Of the other substances, only maternal alcohol use contributed significantly to fetal weight growth (estimated 13 g reduction; Table 4). Maternal marijuana use before pregnancy was also examined in an attempt to ascertain the potential cumulative effects of very early drug exposure on fetal development. Only a trend for reduced fetal weight was observed when the cumulative pre- and pregnancy marijuana history was evaluated for cannabis (p=0.093) and alcohol (p=0.056) exposure (Table 5). Examination of the pattern of marijuana intake during pregnancy revealed a trend (p=0.085) for increased amounts of maternal marijuana use during pregnancy to be associated with reduced fetal body weight. No significance was observed in regard to the frequency of marijuana use (Table 6).

Foot length growth was also significantly influenced (0.08 cm reduction) by maternal marijuana use, as well as by alcohol and cigarette exposure during pregnancy (Table 4). The cumulative pre- and pregnancy exposure period was similarly associated with a significant negative impact of

Table 4
Estimates and 95% confidence intervals (CIs) of the effect of maternal cannabis use (positive toxicology and/or maternal report) during pregnancy on parameters of fetal development adjusting for maternal cigarette and alcohol use (yes/no)

	R^2	Estimate	CI lower	CI upper	p-value
Weight	0.764				
Gestation age		64.33	57.53	71.13	<0.0001
M. cannabis use		−14.53	−28.21	0.86	0.0374
M. cigarette use		−7.94	−21.34	5.45	0.2425
M. alcohol use		−13.33	−24.97	−1.69	0.0252
Foot length	0.761				
Gestation age		0.32	0.29	0.36	<0.0001
M. cannabis use		−0.08	−0.15	−0.01	0.0227
M. cigarette use		−0.09	0.02	0.16	0.0168
M. alcohol use		−0.07	−0.13	0.01	0.0214
Body length	0.671				
Gestation age		1.79	1.56	2.02	<0.0001
M. cannabis use		−0.05	−0.41	0.52	0.8245
M. cigarette use		−0.08	−0.53	0.37	0.7266
M. alcohol use		−0.44	−0.84	0.04	0.0299
Head circumference	0.722				
Gestation age		1.31	1.15	1.47	<0.0001
M. cannabis use		−0.07	−0.42	0.28	0.6927
M. cigarette use		−0.03	−0.36	0.30	0.8664
M. alcohol use		−0.22	−0.49	0.05	0.1072
Ponderal index	0.079				
Gestation age		0.04	0.01	0.06	<0.0001
M. cannabis use		−0.03	−0.09	0.02	0.2501
M. cigarette use		−0.03	−0.03	0.08	0.3114
M. alcohol use		−0.00	−0.05	0.05	0.9539

Reference group=nonusers.
N=85 for the noncannabis group; N=38 for the cannabis group.
M.=Maternal.

Table 5
Estimates and 95% confidence intervals (CIs) of the effect of combined maternal marijuana use (yes/no) reported before and during pregnancy on parameters of fetal development

	R^2	Estimate	CI lower	CI upper	p-value
Weight					
	0.757				
Gestation age		64.74	57.83	71.64	<0.0001
M. cannabis use		−10.41	−22.59	1.77	0.0931
M. cigarette use		−1.54	−13.46	10.38	0.7982
M. alcohol use		−10.65	−21.58	0.29	0.0562
Foot length					
	0.736				
Gestation age		0.33	0.29	0.36	<0.0001
M. cannabis use		−0.08	−0.14	−0.01	0.0181
M. cigarette use		−0.02	−0.04	0.08	0.5061
M. alcohol use		−0.07	−0.13	0.01	0.0204
Body length					
	0.696				
Gestation age		1.82	1.59	2.04	<0.0001
M. cannabis use		−0.22	−0.61	0.18	0.2773
M. cigarette use		−0.11	−0.49	0.28	0.5868
M. alcohol use		−0.29	−0.65	0.06	0.1053
Head circumference					
	0.682				
Gestation age		1.20	1.04	1.35	<0.0001
M. cannabis use		−0.16	−0.45	0.14	0.2973
M. cigarette use		−0.00	−0.29	0.30	0.9661
M. alcohol use		−0.31	−0.58	0.04	0.0251
Ponderal index					
	0.076				
Gestation age		0.04	0.014	0.07	<0.0032
M. cannabis use		−0.03	−0.07	0.02	0.3092
M. cigarette use		−0.00	−0.05	0.05	0.9025
M. alcohol use		−0.01	−0.05	0.04	0.8107

Reference group=nonusers.
N=84 for the noncannabis group; N=44 for the cannabis group.
M.=Maternal.

maternal marijuana use on foot length (0.08 cm; p=0.018; Table 5) and alcohol use (0.07 cm; p=0.020). There was a significant negative association with the amount and frequency of maternal marijuana use during pregnancy and the fetal foot length measures (Table 6). Fetal subjects exposed to moderate maternal marijuana use/day (0.40≥ADJ<0.89) during pregnancy had significantly (p=0.036) reduced foot growth with a trend (p=0.082) observed for subjects with heavy marijuana exposure (ADJ>0.0819; Table 6).

Maternal cannabis use during pregnancy or during the cumulative pre- and during pregnancy period failed to show a significant association with body length development (Tables 4 and 5). Consistently, there was no significant contribution of the pattern of marijuana use reported during pregnancy on body length (Table 6). However, maternal alcohol use during pregnancy was associated with a significant reduction of fetal body length (0.44 cm; p=0.029; Table 4).

Head circumference was not significantly associated with maternal marijuana, cigarette, or alcohol use during pregnancy (Table 4). However, the cumulative maternal alcohol use reported before and during pregnancy revealed a significant effect of alcohol exposure on head circumference measures in this sample (p=0.025; Table 5). There were no significant effects evident for the amount or frequency of marijuana use on head circumference (Table 6).

Ponderal index was not significantly associated with maternal use of marijuana, cigarette, or alcohol either during pregnancy or when considering the cumulative prepregnancy period (Tables 4–6).

Table 6
Fetal development in regard to the amount (no. of joints normally used) and frequency (times/week) of maternal marijuana use reported during pregnancy after adjusting for gestation age, as well as the reported amount of maternal alcohol and cigarette use*

	Estimate	CI lower	CI upper	p-value
Weight				
Amount	−9.34	−21.05	1.38	0.0850
Frequency	−34.98	−80.32	10.36	0.1290
0>ADJ<0.40	−15.09	−53.71	23.52	0.4399
0.4≥ADJ<0.89	−54.19	−103.59	−4.78	0.0319
ADJ≥0.89	−22.17	−65.90	21.54	0.3167
Foot length				
Amount	−0.08	−0.14	−0.02	0.0071
Frequency	−0.27	−0.50	−0.03	0.0257
0>ADJ<0.40	−0.10	−0.30	−0.10	0.3270
0.4≥ADJ<0.89	−0.28	−0.54	−0.02	0.0362
ADJ≥0.89	−0.20	−0.43	0.03	0.0819
Body length				
Amount	−0.18	−0.55	0.19	0.3465
Frequency	−0.47	−1.92	0.99	0.5273
0>ADJ<0.40	−0.09	−1.29	−1.29	0.8766
0.4≥ADJ<0.89	−1.13	−2.73	−0.46	0.1618
ADJ≥0.89	−0.15	−1.56	1.27	0.8386
Head circum.				
Amount	−0.11	−0.42	0.21	0.5146
Frequency	−0.14	−1.34	1.06	0.8137
0>ADJ<0.40	−0.14	−1.03	0.75	0.7574
0.4≥ADJ<0.89	−0.33	−1.58	0.90	0.5904
ADJ≥0.89	−0.02	−1.19	1.16	0.9741
Ponderal index				
Amount	0.00	−0.05	0.05	0.9713
Frequency	−0.12	−0.30	0.06	0.1911
0>ADJ<0.40	−0.05	−0.11	0.20	0.5450
0.4≥ADJ<0.89	−0.10	−0.32	0.11	0.3357
ADJ≥0.89	−0.06	−0.25	0.12	0.5052

The pattern of marijuana use is also presented in regard to the categorized groups for the average number of joints/day (ADJ) as compared to the reference nonuser group (ADJ=0).
N=85 for the nonuser group; N=30 for the group reporting marijuana use during pregnancy (N=13, 7, and 10 for light, moderate, and heavy use, respectively).
* Subjects reporting nonuse but had positive cannabis toxicology were excluded.

4. Discussion

Consistent with previous evaluations of the trend of drug use in the innercity community currently investigated [35], pregnant women in this population had a high rate of marijuana use (31.6%) with a lower incidence of cocaine (4%) and opiate (2.2%) intake. The high use of marijuana in many communities [4,43] is disturbing in light of the current findings revealing an adverse influence of early prenatal cannabis exposure on various indices of fetal growth. Despite the strong correlations apparent between the four primary developmental measures, body weight and foot length were the variables that that were significantly associated with maternal marijuana use in the mid-gestation fetuses.

The present data extend previous observations of a harmful influence of maternal marijuana use on fetal growth evaluated in newborns by documenting that the negative impact of marijuana exposure is already apparent by mid-gestational fetal development. A number of investigations have provided evidence that the pattern of marijuana exposure is an important variable in regard to fetal growth. Newborn infants with frequent and regular marijuana exposure throughout pregnancy have significant reductions in birth weight as compared to those with infrequent exposure to the drug [15]. Fried et al. [20] also reported reductions of fetal growth in subjects with >5 joints/week. In addition, increasing frequency of marijuana use was found to be directly associated with increasing decrements in birth weights in one cohort of women; the findings were not, however, replicated in a second cohort in that investigation [30]. The current study provides evidence which substantiates that the pattern, particularly the amount, of maternal marijuana use is linked with a greater reduction of fetal growth, primarily for foot length in this population. Although one would predict that heavy maternal marijuana use would be most associated with the greatest impairment of fetal growth, significance was only primarily evident for those with moderate, regular marijuana exposure of approximately three to six joints/week. It is impossible, however, to exclude the impact of heavy marijuana exposure given the small sample size in our population.

As compared to body weight and foot length, there was no significant effect of maternal marijuana use on fetal body length and head circumference in the present study. Positive relationships between utero marijuana exposure and head circumference [17,39] or body length [50] have been documented in newborns. Thus, these growth parameters may be more sensitive to marijuana exposure during later stages of pregnancy. The greater sensitivity currently observed for foot growth with early prenatal marijuana (and cigarette) exposure could be related to the special feature of fetal blood flow which makes the lower limbs particularly sensitive to hypoxia [31]. It is well established that intrauterine hypoxia is induced by cigarette and marijuana exposure which could therefore account for the greater impact of these substances on fetal foot length growth. Although ponderal index is widely used as an indicator of fetal growth, this variable was only weakly correlated to the other fetal growth measures and to gestational age in the early developmental period studied. The lack of significant effect observed for the ponderal index is not unexpected since variables of direct growth measures, such as body weight, have been shown to be a better predictor of in utero growth retardation than ponderal index [23], and ponderal index, which reflects symmetrical growth, is more sensitive to disturbances in late pregnancy [42]. Moreover, no alterations in ponderal index have previously been observed in association with prenatal marijuana exposure [16,19].

Consistent with findings from other investigations, women in the current marijuana group were more likely to smoke cigarettes and drink alcohol during pregnancy [10,20,48]. Of these substances, alcohol use had the most significant adverse impact on all primary growth measures perhaps due to fewer women reducing their alcohol intake as compared to cigarette smoking during pregnancy. Although both nonusers and marijuana users tended to decrease their cigarette smoking approximately twofold during pregnancy, the same was not apparent for alcohol use. Alcohol intake during pregnancy was reported in 54% and 23% of the marijuana and nonuser groups, respectively. Moreover, the number of subjects with moderate and heavy cigarette use was quite low which also could account for the weak contribution observed for maternal cigarette smoking on fetal development in this population. The lack of significant effect of cigarette on fetal growth parameters, except for foot length, is most likely due to the findings that cigarette smoking during early pregnancy has a weaker impact on fetal growth as compared to cigarette smoking in the later stages of pregnancy [33,38,45]. Nevertheless, the fact that significant marijuana-related effects were revealed when adjusted for both maternal cigarette and alcohol use emphasize an important contribution of marijuana exposure during the first half of pregnancy on fetal growth.

Consideration of the cumulative prepregnancy history of marijuana use revealed similar but weaker influence on all growth measures compared to drug exposure limited to pregnancy. It would thus appear that drug exposure during the very early stages of pregnancy, where maternal drug use patterns frequently mimic the prepregnancy period, had minimal contribution to the developmental effects currently observed. A limitation of any study of this kind is the reliance on the self-report of drug use. It is generally acknowledged that self-report of illicit drug use is more biased than the self-report of legal substances, such as alcohol and cigarettes. Underreporting of drug use is particularly evident during pregnancy [13,29]. The fact that women in the present study were already in the process of a voluntary abortion at the time of recruitment for the study might lend itself to more accurate drug reporting. In line

with this speculation, 23% of women admitted marijuana use during pregnancy although the drug toxicology was negative. However, we also determined that approximately 18% of the women in this study denied marijuana use during pregnancy but had a positive toxicology. It is quite likely that the number of subjects with early light marijuana use could be misjudged if there is a long time span between the mother's last marijuana use and the time of testing. Such limitations make it likely that there is an underestimation of the influence of marijuana in the present study since there may be marijuana users in the nonuser group. Moreover, light and chronic marijuana users would be expected to metabolize cannabinoids at different rates [34] which could also confound the interpretation of the urine analyses.

Other considerations should be noted about the current study. It included only women who were in the process of a voluntary saline-induced abortion, were within the mid-gestation stage of pregnancy, provided a detailed report of their drug use and medical history, and had a fetal expulsion time ≤24 h (required for subsequent neurochemical/molecular analyses being carried out on the fetal brain specimens). As such, the sample size in this study was small and limited the statistical power. Another limitation of the present investigation is the lack of direct information regarding maternal nutrition [36,49] and body weight measurement [12] which can impact fetal growth. Furthermore, fetal growth is also influenced by maternal weight gain during pregnancy [37,44], but this could not be assessed in the current study because maternal contact only occurred at a single time period. Nevertheless, information obtained from maternal interviews revealed that a similar percentage (between 45% and 50%) of women in the marijuana user and nonuser groups had morning sickness and/or heartburn that negatively affected their eating habit and weight gain during the first trimester of pregnancy. Moreover, there was no significant correlation between the reported early maternal weight loss and the fetal growth measures. The fact that the statistical analyses covaried for maternal nicotine and alcohol use, which are often associated with poor nutrition [7,24], would also appear to discount general deficits in maternal nutrition as a major factor for the fetal growth impairments documented in the marijuana-exposed group.

The consequences of the long-term impact of prenatal marijuana effects on fetal development on health and behavior are still being evaluated. Follow-up studies of children exposed to marijuana during pregnancy have found inconsistent long-lasting impairments in growth parameters beyond infancy [5,19]. However, longitudinal studies have generally documented significant associations of in utero marijuana exposure with impairments of cognitive development and behavioral disturbances, such as inattention, hyperactivity, and impulsivity [18,22,41]. Thus, early exposure to marijuana that appears to affect fetal growth could potentially have an impact on brain development. Several studies have documented an association between small birth weight and impaired neurobehavioral function (e.g., see Ref. [27]). Our recent studies have revealed that mid-gestation fetuses exposed to marijuana have discrete molecular alterations in brain regions that are important for emotional function and behavior [46].

Overall, the current investigation provides data suggestive of detrimental effects of early maternal marijuana intake on the mid-gestation fetus. The results also emphasize that the pattern of maternal marijuana use is of importance to fetal foot length and body weight growth. Thus, in addition to alcohol and cigarettes, information should be given to women about the potentially harmful effects on fetal development of smoking even marijuana during early pregnancy.

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Effects of prenatal cigarette and marijuana exposure on drug use among offspring

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Abstract

The present study investigated whether maternal cigarette smoking and marijuana use during pregnancy were associated with an increased risk of initiation and daily/regular use of such substances among one hundred fifty-two 16- to 21-year-old adolescent offspring. The participants were from a low risk, predominately middle-class sample participating in an ongoing, longitudinal study. Findings indicated that offspring whose mothers reported smoking cigarettes during their pregnancy were more than twice as likely to have initiated cigarette smoking during adolescence than offspring of mothers who reported no smoking while pregnant. Offspring of mothers who reported using marijuana during pregnancy were at increased risk for both subsequent initiation of cigarette smoking (OR=2.58) and marijuana use (OR=2.76), as well as daily cigarette smoking (OR=2.36), as compared to offspring of whose mothers did not report using marijuana while pregnant. There was also evidence indicating that dose–response relationships existed between prenatal exposure to marijuana and offspring's use of cigarettes and marijuana. These associations were found to be more pronounced for males than females, and remained after consideration of potential confounds. Such results suggest that maternal cigarette smoking and marijuana use during pregnancy are risk factors for later smoking and marijuana use among adolescent offspring, and add to the weight of evidence that can be used in support of programs aimed at drug use prevention and cessation among women during pregnancy.

Keywords: Cigarettes; Marijuana; Prenatal; Adolescent; Initiation and regular use of drugs; Gender differences

1. Introduction

Cigarettes and marijuana are two of the most commonly used non-medicinal drugs that are taken during pregnancy [13,34]. Results from several epidemiological studies indicate that maternal cigarette smoking during pregnancy might induce a predisposition in offspring to initiate cigarette smoking later in life [9,25,30]. In a retrospective study of two separate cohorts, the authors reported approximately a 4-fold increased risk of tobacco use and persistence in tobacco use among female (but not male) offspring who were exposed to tobacco prenatally; this association was found to be independent of mothers' postnatal smoking and the child's age [30]. In another report, it was found that maternal cigarette smoking during pregnancy was significantly associated with higher levels of child behaviour problems and that these behaviour problems increased the likelihood of smoking among daughters between the ages of 9 and 17 [25]. Results from a prospective study of lower class 10-year-old children also suggest that maternal cigarette smoking during pregnancy heightens the risk for tobacco experimentation [9]. Children exposed to tobacco at the level of at least one-half pack of cigarettes per day during gestation had a 5.5-fold increased risk for early tobacco experimentation, after controlling for prenatal exposure to other substances and their mothers' current smoking habits. The only factor that produced a greater risk of early experimentation was exposure to smoking within the child's peer group [9]. These above studies suggest a positive association between maternal cigarette smoking during pregnancy and risk of subsequent smoking initiation among offspring that is independent of the mother's postnatal smoking.

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Recent results from a 30-year prospective study indicate that maternal cigarette smoking during pregnancy is also a risk factor for subsequent nicotine dependence among offspring [4]. In this report, offspring whose mothers reported smoking a pack or more of cigarettes per day while pregnant were significantly more likely to meet the *Diagnostic and Statistical Manual of Mental Disorders—Third Edition* [3] criteria for lifetime tobacco dependence than offspring of mothers reporting no maternal smoking during pregnancy. This association remained significant after adjustments for offspring's gender and age, and maternal socio-economic status (SES) and age at pregnancy. In contrast to the finding pertaining to lifetime tobacco dependence, this prospective study reported similar odds of ever smoking and becoming a regular smoker (defined as smoking daily for 30 days or more at some point during one's lifetime) for offspring of maternal smokers and non-smokers [4]. This latter observation is inconsistent with previous reports from other investigators (e.g., Refs. [9,25,30]). It is of interest to note that data on offspring's postnatal exposure to cigarette smoke was not collected or considered in this study [4].

While the mechanisms underlying the association between maternal cigarette smoking during pregnancy and subsequent smoking among offspring remain to be determined, a physiological explanation is plausible. Nicotine and other substances in cigarette smoke cross the placental barrier. The nicotine that passes from the mother to the fetus stimulates nicotinic receptors, which are reported to be present in the fetal brain as early as the first trimester [26]. Since nicotine stimulates the actions of cholinergic neurons and enhances activity in dopaminergic systems involved in addictive behaviour [11], it has been suggested that nicotine and other substances released by maternal smoking may affect the fetus, perhaps through the nicotine input into the mesolimbic dopaminergic reward system, so as to predispose the brain in a critical period of its development to the subsequent addictive influence of nicotine consumed later in life [7,10,30, 31,33,36]. These effects, which may occur even at low nicotine doses and in the absence of notable fetal abnormalities [35], may result in a greater liability to nicotine dependence than in those offspring who have not been prenatally exposed to cigarette smoke [4].

Although several studies have examined the effects of prenatal marijuana exposure on birth outcomes [39], growth measures [8,20], and cognitive and attentional deficits [15,18,19,24], none have assessed the effects of such exposure on subsequent marijuana or cigarette use in offspring. Since nicotine and marijuana both activate the mesolimbic dopaminergic pathway [11,22,41], maternal marijuana use during pregnancy may heighten the risk for the initiation and daily use of cigarettes among adolescent offspring. In a similar vein, an association between prenatal exposure to cigarette smoke and subsequent marijuana use among offspring is also plausible. One study [4] has investigated this hypothesis, but found no evidence of such an association. Given the slight overrepresentation of lower income levels in this study's cohort, however, it is unclear whether this result should be interpreted as possibly representative of only other lower-class samples or if it can be generalized to those that are middle-class.

The objectives of the current study were to determine whether maternal cigarette smoking and marijuana use during pregnancy increased adolescent offspring's risk for: (a) initiating cigarette smoking and marijuana use; and (b) developing patterns of daily cigarette smoking and regular marijuana use. The possibility that dose–response relationships exist between prenatal exposure to cigarettes and marijuana and offspring's use of these substances was also assessed. This article reports findings from the Ottawa Prenatal Prospective Study (OPPS), an ongoing longitudinal investigation that was initiated in 1978, which has examined the neurobehavioural and developmental effects of prenatal exposure to cigarettes and marijuana in a low-risk cohort assessed from birth through adolescence.

2. Methods

2.1. Ottawa prenatal prospective study cohort

The OPPS is designed to explore the effects on offspring of maternal soft drug use during pregnancy in a predominately low-risk, White, middle-class sample. Participants in the OPPS have previously been the focus of a number of inquiries, with cigarettes and marijuana being the primary drugs of interest in recent reports. A total of 698 pregnant women initially volunteered to participate in the OPPS after learning of the study through their doctors, or through notices posted in the waiting rooms of the prenatal clinics in four of the largest hospitals in the Ottawa region. The study was described as an investigation of the influence of prenatal lifestyle habits on the developing fetus [17]. In order to obtain the necessary information, interviews were conducted, usually in the mother-to-be's home, during each trimester remaining in the pregnancy at the time of entrance into the study. The same interviewer was used throughout the entire pregnancy and this, combined with the repetition of interviews, appeared to enhance the rapport between the participant and the interviewer, while also providing an opportunity to assess the consistency of the self-report data [17]. Data were collected on a number of variables including the amounts and patterns of maternal drug use, maternal age, parents' level of education, and the family's SES. For cigarette use, a nicotine score was derived by multiplying the daily average of the number of cigarettes smoked by the nicotine content of the brand specified. Marijuana use was recorded in terms of the number of joints smoked per week. Measurement of alcohol consumption included beer, wine, and liquor use: both the quantity and the pattern of

consumption were recorded and converted to ounces of absolute alcohol (AA) per day.

Of the 698 pregnant women who were interviewed, a cohort of 190 children was selected for follow-up studies beyond birth. Included in this cohort were children of women who reported any use of marijuana during pregnancy, children of women who drank alcohol beyond a daily average of 0.85 ounces AA, and children whose mothers smoked an average of at least 16 mg of nicotine (equivalent to one package of cigarettes of average strength) per day during pregnancy. In addition to these 140 youth, children of 50 women who were non-users of marijuana, who abstained or drank little alcohol, and who were non-smokers were randomly selected to also be included in follow-up studies for comparison purposes.

Of these 190 participants who were initially selected for follow-up studies, 152 adolescents ranging in age from 16 to 21 years inclusive were available to participate in the present study. Of the remaining 38 not tested, most involved families had moved out of the Ottawa area. In addition, two families withdrew from the study and a few adolescents were unavailable for testing. No differential loss of participants with respect to drug variables occurred. The final sample of 152 adolescents consisted of 85 males and 67 females, with five 16-year olds, seventy-seven 17-year olds, forty-two 18-year olds, nineteen 19-year olds, seven 20-year olds, and two 21-year olds.

2.2. Instruments and procedure

As part of an overall neuropsychological assessment, an extensive battery of tests was administered to the participants by a trained female assessor who was blind with respect to maternal drug history. Informed consent was obtained from all of the participants, and all testing was conducted in controlled conditions in the laboratory at Carleton University, Ottawa, Canada. Included in the battery was a *Drug History Questionnaire* (DHQ). This questionnaire was developed for use in this research and was adapted from that used in the Monitoring the Future Study (MTF), a longitudinal survey focusing on the lifestyles, attitudes, and preferences of American youth [28]. The DHQ was intended to serve as a measure of participants' history of use, as well as their current use of a number of both licit and illicit substances including cigarettes and marijuana. Variables of interest in the current study from the DHQ include adolescents' initiation and daily (in the case of cigarettes)/regular (in the case of marijuana) use of cigarettes and marijuana, the average number of cigarettes smoked per day, and the mean number of joints smoked per week.

Cigarette smoking initiation referred to adolescents' ever use of cigarettes (beyond just trying out one or two) and it was dichotomously coded (i.e., never smoked cigarettes vs. have smoked cigarettes). Daily cigarette smoking was defined as smoking cigarettes at least once per day and was similarly coded as a binary variable (i.e., not smoking cigarettes at least once per day vs. smoking cigarettes at least once per day). The initiation of marijuana use was defined as the ever use of this substance and was coded as a dichotomy (i.e., never tried marijuana vs. have tried marijuana). Regular marijuana use, however, was defined as using this substance at least once per week, and was similarly coded as a binary variable (i.e., not using marijuana at least once per week vs. using marijuana at least once per week).

A urine sample was obtained from the participants during the neuropsychological assessment, and was immediately frozen until later analyzed by immunoassay for the presence of cotinine (a major degradation product of nicotine metabolism), cannabinoids, cocaine, opiates, and amphetamines. This allowed for a direct, objective validation of the self-report measures of recent drug use. Each urine specimen was analyzed under blind conditions according to the manufacturer's instructions using sensitivity measures that distinguished concentrations from zero with at least 95% confidence. For all assays, the dilution of urine was corrected for by creatinine adjustment.

2.3. Statistical procedures

2.3.1. Group categorization

For analytic purposes, maternal cigarette smoking (average use across pregnancy) was categorized into two groups: non-smoking and smoking (>0 cigarettes/day). Similarly, maternal average marijuana use across pregnancy was also categorized into two groups: no use and use (>0 joints/week). In the case of cigarettes, the control group was comprised of non-smokers. For marijuana, the control group included mothers reporting no use of marijuana during their pregnancies. Prenatal drug exposure was dichotomized in order to increase the sample size of individual cells, which allowed for a satisfactory subject to variable ratio and a reasonable amount of statistical power for the logistic regression analyses [40]. Using two categories for the two prenatal drug exposure variables, a sample of 152 allowed for the detection of a medium effect size (f=.025) with approximately 87% power [6].

2.3.2. Confounding variables

Because this study is a quasi-experimental design, random assignment to groups was not possible. As a result, there was a risk that observed differences would represent only the pre-existing differences in history and background. A number of variables, therefore, were examined as potential confounds prior to conducting any statistical analyses, as has been done in previous publications involving the OPPS (e.g., Refs. [16,21]). Variables that were examined included family income during pregnancy, average level of parental education, postnatal passive cigarette and marijuana smoke exposure, parity, gender of

the offspring, maternal use of alcohol and caffeine during pregnancy, and the offspring's age at time of testing. Mother's age at the time of the child's birth was also considered since women who smoke cigarettes during pregnancy tend to be younger than non-smokers [12].

Using one-way analyses of variance, each of the potentially confounding variables were tested for an association with prenatal cigarette smoke and marijuana exposure, respectively, using an alpha level of .10. Variables that were found to significantly relate to either drug at an alpha level of .10 or less were then further examined for an association with each of the outcome variables. Those variables that were found to be significantly related to the outcome variable of interest at an alpha level of .05 or less were subsequently included as covariates in the analysis [27]. Hence, the covariates differed from one analysis to another depending on which potential confounds met the aforementioned criteria. Maternal alcohol use during pregnancy and the maternal use of the drug that was not considered to be of primary interest (i.e., in the case of cigarettes, use of marijuana) were statistically controlled in all analyses.

2.3.3. Analysis

A series of logistic regression analyses for analysis of covariance [38] were performed in order to assess the contribution of prenatal exposure to cigarettes and marijuana on adolescents' initiation and daily/regular use of these substances, while controlling for any potential confounding variables. Separate logistic regression models were conducted for the initiation of cigarette smoking and marijuana use, respectively, as well as for the daily/regular use of these two substances. Each of these models was then recalculated separately for male and female offspring in order to examine possible gender differences. All logistic regression models included two binary predictor variables: one representing maternal cigarette smoking during pregnancy and the other representing maternal marijuana use during pregnancy. An alpha level of .05 was used to test the significance of the omnibus tests for each of the logistic regression models. The significance of each predictor variable was then tested using the Wald test [40] with an alpha level of .05. For the gender-specific analyses, these procedures were followed separately among samples of male and female offspring.

Multiple regression was also utilized to examine the predictive relation of the amount of prenatal exposure to cigarettes (mg nicotine/day) and marijuana (joints/week) to offspring's average use of cigarettes (per day) and marijuana (joints/week). Separate regression models were conducted for offspring's use of cigarettes and marijuana, and each of these models were then recalculated by gender in order to test for possible sex differences. In all of these analyses, maternal cigarette smoking and marijuana use during pregnancy, as well as offspring's use of these substances, were treated as continuous variables.

Assumptions regarding independence of errors, absence of multicollinearity and outliers, normality, linearity, homogeneity of regression slopes (and regression planes and hyperplanes in the case of two or three covariates, respectively), adequacy of expected frequencies, and linearity in the logit were satisfied for all statistical analyses. Maternal cigarette smoking and marijuana use, as well as subjects' use of cigarettes (in terms of amount of nicotine consumed per day), marijuana, and alcohol were all log transformed prior to statistical analyses to reduce positive skewness. Maternal alcohol use was normalized using an inverse transformation, while passive exposure to nicotine at assessment was normalized using a square root transformation [40].

3. Results

The Pearson correlation between the number of cigarettes reported being smoked on average per day and the amount of metabolite detected in the urine was found to be .73 ($p<0.0001$). A Pearson correlation of .71 ($p<0.0001$) was obtained for the concordance between the number of joints reported being smoked on average per week and the amount of metabolite detected in the urine. These high concordance rates validated using self-reported drug use in the statistical analysis as well as lending credence to the self-report information provided on the DHQ that could not be tested by the pharmacological analysis of the urine.

Drug usage and demographic characteristics of the sample across levels of maternal cigarette smoking and marijuana use during pregnancy are presented in Table 1. Annual family income, parity, and mother's age at time of birth are similar to those of women who gave birth in the Ottawa region at the time that participants in the OPPS sample were recruited for the study [14]. More than half (52.6%; n=80) of the adolescents in the OPPS reported having initiated cigarette smoking at some point in their lifetime, with the mean age of initiation being 13.99 years (SD=1.75). No significant gender differences were found with respect to the initiation of cigarette smoking, $\chi^2(1, N=152)=.32$, $p=0.57$. Of those 80 youth who reported initiating cigarette smoking, 87.5% (n=70) reported daily smoking at some point in their lifetime, with such use first occurring at the mean age of 14.72 years (SD=1.61). There was also no significant gender difference found with respect to daily cigarette smoking among the adolescents in the OPPS, $\chi^2(1, N=152)=.08$, $p=0.78$.

In terms of marijuana use, the majority (73.7%; n=112) of youth reported having initiated the use of this substance at some point in their lifetime, with the average age of initiation being 14.64 years (SD=1.57). No significant gender difference was found with respect to the initiation of marijuana use, $\chi^2(1, N=152)=.02$, $p=0.89$. Of those 112 youth in the OPPS who reported initiating the use of marijuana, only 27.6% (n=31) reported having used

Table 1
Drug usage and demographic characteristics of prenatal drug exposure groups

	Cigarettes (mg nicotine/day)		Marijuana (joints/week)	
	Not exposed (0)	Exposed (>0)	Not exposed (0)	Exposed (>0)
Sample size	65	87	103	49
Family characteristics				
Annual income (×CAN$1000)[a]	35.93	28.50**	36.33	21.90****
Mother's age[a]	29.66	26.85****	29.54	24.92****
Average parent education[a,b]	3.02	2.29****	2.82	2.15****
Parity	2.02	1.78	2.03	1.57**
Prenatal substance exposure				
Nicotine (mg/day)	.00	1.01****	.55	.64
Marijuana (joints/week)	.21	.30	.00	.80****
Alcohol (oz AA/day)	.86	.87	87	.86
Postnatal substance exposure				
Passive exposure to nicotine until age 15 (no. of years exposed as a proportion of age)[a]	.25	.66****	.42	.58
Passive exposure to nicotine at assessment (no. of hours exposed both in and out of home)	2.36	3.64***	2.74	3.83**
Passive exposure to marijuana at assessment[d]	1.23	1.21	1.05	1.57**
Offspring characteristics				
Sex, % female	42.00	46.00	44.00	45.00
Age at assessment (years)	18.01	18.07	18.04	18.06
Age of cigarette smoking initiation (years)	14.19	13.89	14 02	13.94
Cigarettes smoked/day	2.39	3.92	2.50	4.89**
Nicotine (mg/day)[e]	.31	.48	.33	.57*
Age of marijuana use initiation (years)	14.68	14.61	14.77	14.42
Joints smoked/week	.23	.24	.14	.42****

Note. Statistical tests were one-way between-subjects analyses of variance.

[a] Values are based on figures obtained at birth of offspring.

[b] Education coded as: 1=did not finish high school; 2=graduated high school; 3=graduated college or university; 4=post-graduate degree.

[c] Data for only 80 subjects on this variable.

[d] Coding for passive exposure to marijuana: 1=more than one month ago; 2=between 1 week and 4 weeks ago; 3=between 2 and 6 days ago; 4=yesterday; 5=today.

[e] Calculated by multiplying the number of cigarettes smoked per day by the nicotine content of the brand specified.

* p=0.05.

** p=0.01.

*** p=0.001.

**** p=0.0001.

marijuana on a regular basis at some point, with such use first occurring at the mean age of 15.30 years (SD=1.67). No significant gender difference was found with respect to using marijuana on a regular basis, $\chi^2(1, N=152)=1.17$, p=0.28.

3.1. Correlates of cigarette smoking behaviour

Offspring of mothers who reported smoking cigarettes while pregnant were more than twice as likely to have initiated smoking later in adolescence, compared to offspring of non-smokers (referent group) after adjusting for maternal marijuana and alcohol use during pregnancy, maternal age at time of pregnancy, and family income (Table 2). Results also revealed that offspring who were prenatally exposed to marijuana had almost three times the odds of initiating cigarette smoking during adolescence compared to offspring whose mothers reported no use of marijuana while pregnant. In terms of gender differences, male offspring of mothers who reported smoking cigarettes while pregnant were more than three times as likely to have initiated smoking during adolescence compared to offspring of non-smokers (Table 3). The association between maternal marijuana use during pregnancy and male offspring's initiation of cigarette smoking was found to be even more pronounced, with offspring exposed in utero to marijuana being almost five times as likely to have initiated cigarette smoking. The associations between

Table 2
Associations between prenatal exposure to cigarettes and marijuana and offspring's cigarette smoking initiation and daily cigarette smoking

Offspring Cigarette Smoking Behaviour (N=152)	N	B	SE	OR (95% CI)[a]
Cigarette smoking initiation[b]				
Prenatal cigarette exposure				
Not exposed	65			1.00
Exposed	87	.77*	.36	2.16 (1.06, 4.39)
Prenatal marijuana exposure				
Not exposed	103			1.00
Exposed	49	.95*	.43	2.58 (1.11, 6.00)
Daily cigarette smoking[c]				
Prenatal cigarette exposure				
Not exposed	65			1.00
Exposed	87	.34	.40	1.41 (.65, 3.06)
Prenatal marijuana exposure				
Not exposed	103			1.00
Exposed	49	.86*	.44	2.36 (1.00, 5.57)

Note. B=unstandardized regression coefficient; SE=standard error; OR=odds ratio; CI=confidence interval.

[a] The reference category for all odds ratios is offspring who were not prenatally exposed to the drug of interest.

[b] Based on a logistic regression model including maternal alcohol use during pregnancy, maternal age at time of pregnancy, and family income as covariates.

[c] Based on a logistic regression model including maternal alcohol use during pregnancy, maternal age at time of pregnancy, family income, and average parental education as covariates.

* $p \leq 0.05$.

prenatal exposure to cigarettes and marijuana and smoking initiation were found to be generally less pronounced for female offspring (Table 3).

With respect to the correlates of daily cigarette smoking, the results showed that offspring of mothers who reported using marijuana during pregnancy were more than twice as likely to smoke cigarettes at least once per day during adolescence compared to offspring whose mothers did not report using marijuana while pregnant, after controlling for maternal marijuana and alcohol use during pregnancy, maternal age at time of pregnancy, family income, and average parental education (Table 2). No significant association was observed between prenatal exposure to cigarettes and later daily cigarette smoking (Table 2), and similar results were yielded from the sex-specific analyses (Table 3). However, the results did show that male offspring of mothers who reported using marijuana while pregnant had more than three times the odds of smoking cigarettes at least once per day as an adolescent compared to offspring of non-users (Table 3). No significant association was observed between in utero exposure to marijuana and daily cigarette smoking among female offspring.

When prenatal exposure to cigarettes (mg nicotine/day) and marijuana (joints/week), and offspring's use of cigarettes (per day) were treated as continuous variables, regression analyses revealed a significant positive association between mother's use of marijuana during pregnancy and the average number of cigarettes smoked per day by offspring (r=.23, p<0.01), controlling for maternal alcohol and cigarette use during pregnancy, family income, and mother's age at time of pregnancy (Table 4). Although prenatal exposure to cigarettes was also positively related to offspring's average number of cigarettes smoked per day, this result only approached statistical significance (r=.15,

Table 3
Gender-specific associations between prenatal exposure to cigarettes and marijuana and offspring's initiation and daily cigarette smoking

Offspring Cigarette Smoking Behaviour (N=152)	Males				Females			
	N	B	SE	OR (95% CI)[a]	N	B	SE	OR (95% CI)[a]
Cigarette smoking initiation[b]								
Prenatal cigarette exposure								
Not exposed	38			1.00	27		.59	1.00
Exposed	47	1.19*	.51	3.28 (1.20, 8.95)	40	.33		1.39 (.44, 4.44)
Prenatal marijuana exposure								
Not exposed	58			1.00	45			1.00
Exposed	27	1.48*	.62	4.37 (1.31, 14.64)	22	.41	.65	1.51 (.43, 5.38)
Daily cigarette smoking[c]								
Prenatal cigarette exposure								
Not exposed	38			1.00	27			1.00
Exposed	47	.77	.55	2.17 (.75, 6.31)	40	−.10	.67	.90 (.24, 3.37)
Prenatal marijuana exposure								
Not exposed	58			1.00	45			1.00
Exposed	27	1.27*	.62	3.56 (1.06, 11.97)	22	.44	.69	1.55 (.40, 5.95)

Note. B=unstandardized regression coefficient; SE=standard error; OR=odds ratio; CI=confidence interval.

[a] The reference category for all odds ratios is offspring who were not prenatally exposed to the drug of interest.

[b] Based on a logistic regression model including maternal alcohol use during pregnancy, maternal age at time of pregnancy, and family income as covariates.

[c] Based on a logistic regression model including maternal alcohol use during pregnancy, maternal age at time of pregnancy, family income, and average parental education as covariates.

* $p \leq 0.05$.

Table 4
Multiple regression analyses predicting offspring's average use of cigarettes and marijuana joints from prenatal exposure to cigarettes and marijuana

Offspring Substance Use (N=152)	B	SE	β	(95% CI)
Cigarettes/day[a]				
Prenatal cigarette exposure[b]	1.39	.73	.16	(.06, 2.83)
Prenatal marijuana exposure[c]	2.85*	1.00	.25	(.86, 4.83)
Joints/week[d]				
Prenatal cigarette exposure[b]	−.08	.06	−.12	(−.20, .03)
Prenatal marijuana exposure[c]	.30**	.07	.34	(.15, .44)

Note. B=unstandardized regression coefficient; SE=standard error; β=standardized regression coefficient; CI=confidence interval.

[a] Based on a regression model including maternal alcohol use during pregnancy, family income, and mother's age at time of pregnancy as covariates.

[b] Expressed in terms of mg nicotine/day.

[c] Expressed in terms of joints/week.

[d] Based on a regression model including maternal alcohol use during pregnancy, family income, mother's age at time of pregnancy, and average parental education as covariates.

* $p \leq .01$.

** $p \leq 0.0001$.

p=0.06; Table 4). When gender differences were examined, the results indicated that prenatal exposure to both cigarettes (r=.25, p<0.05) and marijuana (r=.24, p<0.05) were significantly associated with increases in the number of cigarettes smoked per day by male offspring, after controlling for potentially confounding variables (Table 5). No significant associations were observed, however, between prenatal drug exposure and the number of cigarettes smoked per day by female offspring (Table 5).

No significant interactive effects of prenatal cigarette and marijuana exposure were noted in any of the above analyses.

3.2. Correlates of marijuana use behaviour

In terms of offspring's marijuana use, findings indicated that offspring of mothers who reported using marijuana while pregnant were almost three times as likely to have initiated the use of marijuana during adolescence compared to offspring of non-users, and this was found to be independent of maternal cigarette and alcohol use during pregnancy (Table 6). However, no significant association was observed between prenatal exposure to cigarettes and offspring's initiation of marijuana use. When gender differences were examined, the results indicated a significant relationship between maternal use of marijuana during pregnancy and the subsequent initiation of marijuana use during adolescence among males. Specifically, male offspring of mothers who reported using marijuana while pregnant had nearly four times the odds of initiating marijuana use compared to offspring whose mothers did not report using marijuana during pregnancy (Table 7). In contrast, no significant associations were observed between prenatal drug exposure and marijuana use initiation among female offspring. Moreover, there was no evidence of a significant association between offspring's regular use of marijuana during adolescence and prenatal exposure to either cigarettes or marijuana for either gender (Table 7).

When prenatal exposure to cigarettes and marijuana and offspring's use of marijuana were treated as continuous variables, results from a multiple regression analysis indicated a significant positive association between maternal use of marijuana during pregnancy and offspring's average number of joints smoked per week (r=.29, p<0.0001), independent of mother's use of cigarettes and alcohol during pregnancy, family income, mother's age at time of pregnancy, and average parental education (Table 4). No significant association was noted between prenatal exposure to cigarettes and the average number of joints smoked per week by offspring (Table 4). Results from the

Table 5
Gender-specific multiple regression analyses predicting offspring's average use of cigarettes and marijuana joints from prenatal exposure to cigarettes and marijuana

Offspring substance use (N=152)	Males (n=85)				Females (n=67)			
	B	SE	β	(95% CI)	B	SE	β	(95% CI)
Cigarettes/day[a]								
Prenatal cigarette exposure[b]	2.30*	.93	.26	(.44, 4.15)	1.05	1.27	.12	(.27, 2.63)
Prenatal marijuana exposure[c]	2.82*	1.22	.26	(.40, 5.24)	2.66	1.76	.21	(.59, 7.56)
Joints/week[d]								
Prenatal cigarette exposure[b]	−.01	.09	−.01	(−.18, .16)	−.16	.08	−.31	(−.32, −.01)
Prenatal marijuana exposure[c]	.38**	.10	.42	(.18, .58)	.13	.11	.18	(−.08, .35)

Note. B=unstandardized regression coefficient; SE=standard error; β=standardized regression coefficient; CI=confidence interval.

[a] Based on a regression model including maternal alcohol use during pregnancy, family income, and mother's age at time of pregnancy as covariates.

[b] Expressed in terms of mg nicotine/day.

[c] Expressed in terms of joints/week.

[d] Based on a regression model including maternal alcohol use during pregnancy, family income, mother's age at time of pregnancy, and average parental education as covariates.

* $p \leq 0.05$.

** $p \leq 0.0001$.

Table 6
Associations between prenatal exposure to cigarettes and marijuana and offspring's initiation and regular use of marijuana

Offspring Marijuana Use Behaviour (N=152)	N	B	SE	OR (95% CI)[a]
Marijuana use initiation[b]				
Prenatal cigarette exposure				
Not exposed	65			1.00
Exposed	87	.13	.38	1.14 (.53, 2.41)
Prenatal marijuana exposure				
Not exposed	103			1.00
Exposed	49	1.02*	.46	2.76 (1.11, 6.86)
Regular marijuana use[b]				
Prenatal cigarette exposure				
Not exposed	65			1.00
Exposed	87	.25	.42	1.29 (.57, 2.93)
Prenatal marijuana exposure				
Not exposed	103			1.00
Exposed	49	−.23	.45	.79 (.33, 1.90)

Note. B=unstandardized regression coefficient; SE=standard error; OR=odds ratio; CI=confidence interval.

[a] The reference category for all odds ratios is offspring who were not prenatally exposed to the drug of interest.

[b] Based on a logistic regression model including maternal alcohol use during pregnancy as a covariate.

* $p \leq 0.05$.

gender-specific analyses demonstrated that prenatal exposure to marijuana was significantly associated with increases in the number of joints smoked per week by male offspring (r=.36, p<0.0001), after controlling for potentially confounding variables (Table 5). There was no significant evidence, however, indicating that a similar relationship existed among female offspring (Table 5). Findings also failed to suggest that maternal use of cigarettes during pregnancy was significantly related with offspring's average number of joints smoked per week for either males or females (Table 5).

No significant interactive effects of prenatal cigarette and marijuana exposure were noted in any of the above analyses.

4. Discussion

The results in this report continue the presentation of findings arising from the OPPS—a long-term prospective study of the effects of in utero exposure to cigarettes and marijuana. The current investigation was undertaken to examine the effects of maternal cigarette smoking and marijuana use during pregnancy on subsequent initiation and daily/regular use of these two substances among 16- to 21-year-old offspring. Findings indicated that approximately 53% of offspring reported initiating cigarette smoking, which is consistent with results from various prevalence studies in Canada and the United States [2,5,28]. In contrast, about 46% of the OPPS sample reported daily cigarette smoking, which is considerably higher than rates reported by the MTF Study [28] (i.e., 24%) and the Youth Risk Behavior Surveillance (YRBS) Study [5] (i.e., 16%). The 74% rate of marijuana use initiation in the present work was also substantially higher than corresponding rates reported by other investigators (i.e., 45% in the MTF Study [28] and 40% in the YRBS [5]). Finally, about 20% of offspring in the present study reported regular use of marijuana. Although this rate appears to be similar to that reported by the MTF Study [28] and the YRBS [5], it should be

Table 7
Gender-specific associations between prenatal exposure to cigarettes and marijuana and offspring's initiation and regular use of marijuana

Offspring Marijuana Use Behaviour (N=152)	Males				Females			
	N	B	SE	OR (95% CI)[a]	N	B	SE	OR (95% CI)[a]
Marijuana use initiation[b]								
Prenatal cigarette exposure								
Not exposed	38			1.00	27			1.00
Exposed	47	.40	.51	1.49 (.54, 4.06)	40	−.18	.59	.84 (.27, 2.63)
Prenatal marijuana exposure								
Not exposed	58			1.00	45			1.00
Exposed	27	1.30*	.68	3.67 (.97, 13.88)	22	.75	.65	2.11 (.59, 7.56)
Regular marijuana use[b]								
Prenatal cigarette exposure								
Not exposed	38			1.00	27			1.00
Exposed	47	.27	.53	1.31 (.47, 3.69)	40	.36	.72	1.43 (.35, 5.81)
Prenatal marijuana exposure								
Not exposed	58			1.00	45			1.00
Exposed	27	−.14	.56	.87 (.29, 2.61)	22	−.36	.75	.70 (.16, 3.01)

Note. B=unstandardized regression coefficient; SE=standard error; OR=odds ratio; CI=confidence interval.

[a] The reference category for all odds ratios is offspring who were not prenatally exposed to the drug of interest.

[b] Based on a logistic regression model including maternal alcohol use during pregnancy as a covariate.

* $p \leq 0.05$.

noted that the definition of regular marijuana use in the current investigation (i.e., at least once per week) is more conservative than that of the MTF Study (i.e., use in the past 30 days) and the YRBS Study (i.e., use at least once during the past 30 days). Thus, the rate of regular marijuana use, like daily cigarette smoking, is actually higher in the current work compared to both of these national prevalence studies [5,28].

A number of unique findings were observed in the current study. Most notably was the evidence of a positive association between maternal marijuana use during pregnancy and risk of subsequent marijuana use initiation among adolescent offspring. Although no significant association was observed in relation to offspring's regular use of marijuana, this finding should be interpreted with some caution as this observation was based on only 31 offspring reporting regular use of marijuana. When the drug use variables were treated as continuous variables, there appeared to be a dose–response relationship between the number of joints smoked per week by the mother while pregnant, and those later consumed by her offspring. Interestingly, the impact of prenatal marijuana exposure on offspring's marijuana use was found to be stronger for male than female offspring. The present work is also the first to suggest that the impact of maternal marijuana use during pregnancy is not specific to subsequent marijuana use. That is, the results revealed a positive association between prenatal exposure to marijuana and offspring's risk of both cigarette smoking initiation and daily smoking during adolescence, with the impact of such exposure also being more pronounced among male offspring. A dose–response relationship was also noted between mother's use of marijuana during pregnancy and the number of cigarettes smoked per day by offspring.

The present findings are also consistent with earlier investigations (e.g., Refs. [9,25,30]) reporting a positive association between maternal cigarette use during pregnancy and risk of subsequent cigarette smoking initiation among adolescent offspring. However, there was no significant evidence in the current work suggesting that prenatal exposure to cigarette smoke increases offspring's risk of daily smoking during adolescence, and this result is congruent with findings pertaining to regular cigarette smoking from other researchers [4]. Although Kandel and colleagues [30] reported that maternal cigarette smoking during pregnancy increased female offspring's odds of persisting in cigarette smoking, their definition of persistent smoking (i.e., smoking in last three months) differed from that used for daily smoking in the present study (i.e., smoking at least once per day), which was adapted from the MTF Study [28]. Results from the present investigation also indicate that the impact of maternal cigarette smoking during pregnancy on offspring's smoking initiation is stronger for males than females. While this result is in accordance with the findings concerning the impact of prenatal marijuana exposure, it is inconsistent with the results of other investigators [30] who have reported a greater maternal effect of cigarette smoking for females. It is unclear why this discrepancy has occurred, but it may possibly be the result of differences between the OPPS sample and the cohorts of youth studied by Kandel et al. [30]. While the OPPS sample is predominately White and middle-class, Kandel et al. studied a cohort of youth that is representative of adolescents in New York State public high schools during 1971–72, and another cohort that is representative of youth born from 1957 through 1963 in the coterminous United States.

Consistent with the results of other investigators [4], the current work did not find evidence supporting an association between maternal cigarette smoking during pregnancy and risk of later marijuana use among offspring. Such findings suggest that the impact of prenatal cigarette smoke exposure is specific to subsequent cigarette smoking and that any fetal perturbances associated with maternal smoking during pregnancy do not affect adolescent marijuana use. This observed specificity is also in accordance with other studies suggesting a pathophysiological pathway between prenatal exposure to cigarettes and smoking initiation (e.g., Refs. [29,30]), and suggests that the pathophysiological pathways for marijuana use are different from those for cigarette smoking [4]. Interestingly, these findings regarding the specificity of cigarettes are the opposite of what was observed with respect to marijuana, with the current study indicating that maternal marijuana use during pregnancy is associated with subsequent marijuana and cigarette use among adolescent offspring.

The present findings indicate that fetal exposure to cigarettes and marijuana may have a significant impact on the initiation of cigarette smoking and marijuana use in adolescent offspring, and a number of mechanisms may contribute to this relationship. In utero cigarette exposure may cause physiological changes resulting in increases in nicotine receptors that may increase susceptibility to later cigarette use [7,10,31,33,36]. Such exposure to cigarettes and marijuana may also predispose the brain via the mesolimbic dopaminergic reward system to the subsequent addictive influence of nicotine consumed later in life [30]. Interestingly, results from a recent animal study [1] indicate that maternal cigarette smoking during pregnancy alters offspring's subsequent response to nicotine in adolescence, suggesting that biological mechanisms underlie the association between prenatal cigarette smoke exposure and adolescent smoking in offspring. As data indicates that the cannabinoid receptors are present in the placenta [37] and the fetal and neonatal brain [23], it is possible that prenatal exposure to marijuana also sensitizes the brain to the subsequent influence of marijuana consumed later in life. The transmission of a genetic predisposition for drug use, or other conditions such as depression or anxiety that are associated with smoking and

marijuana use [9,29], is yet another potential explanation for the observed association between maternal cigarette and marijuana use during pregnancy and offspring's subsequent use of these two substances.

In interpreting and generalizing the present findings, several caveats must be considered. The relatively small sample size, particularly for the gender-specific analyses, may lead to instability in the coefficients. The current work was also unable to statistically control for the effect of postnatal tobacco exposure, as there was an excess of missing data on this variable. In addition, this study did not collect data on parent's current use of cigarettes or other substances. Finally, since the OPPS is comprised of a predominately White, middle-class, low-risk sample, the findings from the current work may not be generalizable to other ethnic groups or other samples of youth that are not similarly low-risk.

In summary, the present findings indicate differential effects of maternal cigarette smoking and marijuana use during pregnancy on risk of subsequent substance use among adolescent offspring. While prenatal exposure to cigarettes appears to be linked with offspring's cigarette smoking initiation, the data suggest that in utero exposure to marijuana is associated with cigarette smoking and marijuana use initiation, as well as daily cigarette smoking in offspring. There also appears to be dose–response relationships between prenatal exposure to marijuana and offspring's use of cigarettes and marijuana. In contrast to reports from national prevalence studies [5,28], the current investigation yielded substantially higher rates of daily cigarette smoking and the initiation and regular use of marijuana among adolescent offspring of maternal drug users. Therefore, from a public health perspective, a reduction in rates of cigarette smoking and marijuana use may not only yield direct health benefits for the substance users themselves, but it may also have unanticipated benefits for their offspring including reduced risk of subsequent cigarette smoking and marijuana use later in life which may in effect influence the use of other illicit substances [32].

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PRICE AND ENFORCEMENT EFFECTS ON COCAINE AND MARIJUANA DEMAND

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This article estimates equations for past year cocaine and marijuana use among adult and juvenile respondents of the 1990–97 National Household Surveys on Drug Abuse. Unlike most previous studies, we control for the monetary price of marijuana, probabilities of arrest for marijuana and cocaine possession, and state fixed effects. Results indicate that cocaine prices are inversely related to adult cocaine and marijuana demand but are unrelated to juvenile drug demand, marijuana price effects are always statistically insignificant, estimated price effects are inflated when state effects are omitted, and increases in each arrest probability diminish both types of drug use. (*JEL* K42, I18, D12)

I. INTRODUCTION

The responsiveness of cocaine and marijuana demand to changes in their prices is a key determinant of the effectiveness of illegal drug enforcement policy. By harassing sellers and seizing drugs, enforcement attempts to reduce the consumption of illegal drugs by restricting their supply and thereby raising their prices. Even if enforcement is able to increase drug prices, its success in reducing illegal drug use depends on the elasticity of drug demand with respect to drug prices. Reciprocally, unless this elasticity is close to zero, legalization of cocaine and marijuana would likely increase their consumption substantially by drastically reducing their prices.

A complementary goal of enforcing cocaine and marijuana possession violations is to reduce their demand at prevailing prices. This occurs through both incarceration of drug users who will no longer be able to purchase drugs and deterrence of drug consumption by potential users. Price and enforcement effects may be dissimilar if consumers respond differently to changes in their budget constraints than to changes in expected punishment. In particular, the relative magnitudes of the responses in drug demand to changes in possession arrest probabilities and prices is an important determinant of how enforcement resources can most efficiently be allocated between buyers and sellers. But in spite of this policy relevance, there is little direct evidence on the relationship between

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ABBREVIATIONS

DEA: Drug Enforcement Administration
FBI: Federal Bureau of Investigation
MSA: Metropolitan Statistical Area
MTF: Monitoring the Future
NHSDA: National Household Surveys on Drug Abuse
STRIDE: System to Retrieve Information from Drug Evidence

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arrest probabilities for cocaine and marijuana possession and demand for these drugs.

Meanwhile, the relationship between the consumption of cocaine and marijuana is both theoretically and empirically uncertain. In theory, cocaine and marijuana act as substitutes in the production of intoxication but also can provide complementary intoxicating effects. Empirically, this relationship determines whether policies designed to reduce demand for one drug have effects on the other that reinforce or counteract the impacts of policies designed specifically for that other drug. For instance, marijuana possession arrests more than doubled nationally between 1990 and 1997, both in number and as a fraction of total arrests. This might have reinforced any effect of cocaine possession enforcement on cocaine use if the two drugs are complements but had an unintended counteractive effect if they are substitutes.

This study provides evidence on the impacts of cocaine and marijuana prices and possession violation enforcement on the demand for these drugs. We analyze data on past year cocaine and marijuana use among 12- to 39-year-old respondents to the annual 1990–97 National Household Surveys on Drug Abuse (NHSDA). Along with various individual characteristics, the set of explanatory variables includes regional prices of cocaine and marijuana, state-level measures of the probability of arrest for cocaine and marijuana possession, and fixed effects for states and years. Our goals are to estimate the size of the response in the demand for cocaine and marijuana to changes in their prices, to do the same with respect to changes in possession violation enforcement intensity, and to examine whether unmeasured state characteristics can potentially bias estimated price and enforcement effects.

The analysis is novel in several ways. Most important, it is the first study of cocaine demand to control for state fixed effects in nationally representative data. Previous studies impute cocaine prices at the state level and use both cross-state and temporal variation in prices to identify price effects. But it is possible that a substantial component of cross-state price variation is explained by unobservable, time-invariant state-level factors that also explain cross-state variation in illegal drug use. For instance, states with more permissive attitudes regarding drug use are likely to have both lower cocaine prices and higher drug prevalence rates than antidrug states. Cocaine price elasticities estimated from analyses that ignore these fixed state effects might overstate the impact of an exogenous price change on the change in drug use within an average state, which is the true elasticity of interest.

The inclusion of state fixed effects necessitates constructing our cocaine prices differently than previous studies. Motivated by evidence from Rhodes et al. (1994) and Caulkins (1995) that region and population size are the crucial geographic determinants of cocaine prices, we calculate cocaine prices that vary by census division and metropolitan area size. This allows for the temporal price variation necessary to simultaneously identify cocaine price effects and fixed state effects. In addition, our analysis is the first to examine the effect of marijuana prices on cocaine demand and to explicitly estimate the effect of cocaine possession arrest rates on cocaine and marijuana demand and of marijuana possession arrest rates on cocaine demand.

The article proceeds as follows. The next section reviews the relevant literature. Section III discusses the NHSDA data as well as separate data on cocaine and marijuana prices and possession arrests with which we merge the NHSDA data. Section IV presents our empirical methodology. Section V reports and examines the estimation results, and section VI summarizes our conclusions.

II. PREVIOUS STUDIES

Several recent studies estimate elasticities of cocaine and marijuana demand with respect to the price of cocaine. Typically the dependent variables in these studies are binary indicators of whether or not the respective drug is used, so that estimated price elasticities are with respect to participation in drug use rather than actual drug consumption.[1]

1. Some of the reviewed studies also estimate equations for the number of times cocaine or marijuana is used by users and then calculate a price elasticity of consumption frequency by adding the elasticities of participation and frequency conditional on participation. Although it is possible that prices and arrest rates have differential effects on these two decisions, we confine

The first published analysis of the price elasticity of cocaine demand is by DiNardo (1993) using state cross-sections aggregated from the 1977–87 Monitoring the Future (MTF) surveys. DiNardo (1993) finds that past month cocaine participation by high school seniors is not related to the price of cocaine, and that neither cocaine demand nor price are related to Drug Enforcement Administration (DEA) cocaine seizures.

Caulkins (1996) indirectly estimates cocaine participation price elasticities from estimates of the price elasticity of the percent arrestees testing positive for cocaine. Invoking conservative assumptions about the fractions of drug users testing positive and of arrests attributable to drug use, drug spending, and other causes, his estimated elasticities range between −1.48 and −2.08.

Two 1999 studies by Saffer and Chaloupka (1999a, 1999b) estimate past year participation equations for cocaine and marijuana in pooled data from 1988, 1990, and 1991 NHSDA respondents age 12 and older. Averaging across five specifications, Saffer and Chaloupka (1999a) estimate a cocaine price elasticity of −0.40 and a positive relationship between marijuana use and living in a state where marijuana is decriminalized. Estimated cross-price and cross-decriminalization effects indicate complementarity between cocaine and marijuana. Saffer and Chaloupka (1999b) divide the same sample into seven demographic groups and estimate past year participation elasticities for each. The estimated cocaine price elasticity is insignificant for blacks and Asians, −1.83 for Native Americans, and between −0.5 and −0.8 for white males, Hispanics, women, and youth. Marijuana decriminalization is positively related to marijuana participation for all groups except Native Americans. However, cross-price and cross-decriminalization relationships are each insignificant for six groups, with each indicating complementarity for the remaining group. A major limitation of these studies is that they do not control for fixed state or regional effects.

Chaloupka et al. (1999) estimate equations for past year cocaine and marijuana participation by high school seniors in the 1982 and 1989 MTF surveys. The estimated cocaine price elasticity is −0.88 in the combined sample but only −0.24 in the 1989 sample. The impact of cocaine possession fines is also negative in 1989. Similarly, decriminalization increases marijuana use and increases in marijuana possession fines decrease marijuana use. Fines for sales do not impact the use of either drug.

Finally, Grossman and Chaloupka (1998) use a rational addiction framework, in which current consumption depends on both past and future consumption, to estimate price elasticities of past year cocaine participation among 18- to 27-year-olds in the 1976–85 MTF panels and associated follow-ups. In a model with person-specific fixed effects, estimated short- and long-run price elasticities are −0.42 and −0.54, respectively. The analogous model without these fixed effects yields short- and long-run elasticities of −0.72 and −1.40. Marijuana decriminalization increases cocaine use, again implying that cocaine and marijuana are complements.

Because of deficient marijuana price data, only two previous studies have estimated the elasticity of marijuana demand with respect to its price.[2] Nisbet and Vakil (1972) surveyed UCLA students regarding quantities of marijuana purchased at current prices and after various hypothetical price changes. Their estimated price elasticities ranged from −0.40 to −1.51. The only study to use actual price data is Pacula et al. (2001) in 1985–96 MTF data on high school seniors. Controlling for state effects, their estimated past year participation elasticity is −0.33 when time effects are omitted but only −0.06 when time is entered quadratically.

our analysis to drug participation for various reasons related to data quality. First, the only frequency measures available in the NHSDA are the number of days in the past month, which is a continuous variable but does not match the time frame of our participation variable, and frequency of use in the past year, which is a categorical variable with intervals ranging from "1–2 days in the past year" to "3–6 days per week." Second, frequency measures are more likely to be affected by recall error than the binary participation decision. Third, because few respondents report using illegal drugs, particularly cocaine, the sample sizes for analyses of frequency conditional on participation are small.

2. Our review of marijuana decriminalization effects covers only those studies that analyze cocaine demand. Pacula et al. (2001) summarize the extensive literature examining the effect of decriminalization on marijuana demand, which has yielded mixed results. We cannot empirically identify decriminalization effects because we control for state-fixed effects and no state has changed its decriminalization policy in the past decade.

The only study besides DiNardo (1993) to directly examine the effect of drug enforcement on drug consumption is Farrelly et al. (2001). Controlling for state fixed effects in 1990–96 NHSDA panels, they find that increases in the probability of arrest for marijuana possession decrease the probability that 12–20-year-olds will use marijuana. Meanwhile, using annual data on 29 large U.S. cities from 1981–95 and controlling for fixed city and year effects, DeSimone (2001) estimates a positive relationship between the price of cocaine and the number of cocaine purchases per capita by undercover drug enforcement agents. Further results indicating a negative relationship between crime rates and cocaine prices suggest that cocaine consumption is price-elastic.

In sum, cocaine consumption appears to respond to cocaine price changes, but the range of elasticity estimates is wide, and all except those from the Grossman and Chaloupka (1998) models that include individual fixed effects come from models that fail to control for geographic fixed effects.[3] Few studies have examined the relationship between drug demand and either marijuana prices or intensity of drug possession law enforcement.

III. DATA

This study analyzes pooled 1990–97 cross-sections from the NHSDA, administered annually to a nationally representative sample of the U.S. household population aged 12 and higher.[4] We restrict our sample to respondents aged 39 and younger, because the overwhelming majority of illegal drug use occurs in this age group,[5] and conduct separate analyses for those aged 12–17 and 18–39 because of the different treatments of these two age groups by the legal system. In that spirit we henceforth refer to the former group as juveniles and the latter as adults.

Dependent Variables

We specify two dependent variables, one corresponding to cocaine use and the other to marijuana use. Both are binary indicators of past year participation in drug consumption.[6]

Cocaine Price

A measure of the average cocaine price per pure gram faced by the respondent is appended to the NHSDA data.[7] Cocaine price data are collected by undercover drug agents, mostly from the DEA, and recorded by the DEA in their System to Retrieve Information from Drug Evidence (STRIDE). These prices are expected to be relatively accurate because an unreasonable price offer by an agent would invoke suspicion by the seller and thus endanger the agent. Transaction sizes must be standardized because, as Caulkins and Padman (1993) and Rhodes et al. (1994) show, sizable quantity discounts exist for cocaine.

We impute cocaine prices from STRIDE data using the ordinary least squares regression

$$\log Price = b_0 + b_1(\log Predicted\ Purity + \log Weight) + b_2 Area + b_3 Year + b_4 Area \times Year + w,$$

where purity represents the weight of actual cocaine in the purchase divided by the total weight, *Predicted Purity* is the predicted value from a regression of purity on the other

3. As long as respondents do not move, geographic fixed effects drop out of an individual fixed effects model because they are time-invariant.

4. The NHSDA excludes individuals with no permanent residence and who reside in group quarters, categories that include the homeless and residents of homeless shelters, prisons, and college dormitories. Although drug use among NHSDA respondents is thus likely to be disproportionately low relative to the U.S. population, the excluded group represents only about 1% of U.S. residents.

5. For instance, in 1997, the fraction of respondents reporting past year cocaine (marijuana) use is 2.2% (15.8%) among 12–17-year-olds, 3.6% (17.1%) among 18–39-year-olds, and 0.7% (3.2%) among 40+-year-olds. The specific choice of age 39 as the cutoff corresponds to the 5-year age groupings reported by SAMHSA (1997).

6. NHSDA interviews are conducted throughout the year, so that the time interval implied by "past year" varies from almost entirely the previous calendar year for January interviews to almost entirely the current calendar year for December interviews. Because the price variables represent the current calendar year and the consumption time frame extends to the previous calendar year, the time intervals for the price and consumption variables do not strictly match. This is done for simplicity, imitates the practice of many previous studies, and should not affect the results much because current and past year prices are highly correlated.

7. All nominally valued variables are converted to 1990 dollar terms using the Consumer Price Index for all urban consumers.

explanatory variables, *Weight* is the total gram weight of the purchase, *Area* is a vector of indicators corresponding to 28 geographic areas in the United States that we assume have distinct cocaine prices, *Year* is a vector of year indicators, and *Area* × *Year* represents a complete set of interactions between the *Area* and *Year* vectors. For a particular area and year our predicted cocaine price is $\exp(b_0 + b_2 + b_3 + b_4)$, which represents the median price of one gram of 100% pure cocaine in the area and year with corresponding indicators set equal to one in the *Area* and *Year* vectors. We follow Caulkins (1994) in excluding outliers before estimating equation (1).[8]

Our methodology assumes that prices vary by census region or division and metropolitan statistical area (MSA) size. Appendix Table A-1 lists the census regions and divisions and the states encompassed by each. MSAs containing more than 1 million people are grouped together within each census division. This creates eight distinct areas, because the East South Central division contains no MSAs of this size. Similarly, MSAs containing between 500,000 and 1 million people are grouped together within each division, creating nine additional areas. Because there are fewer STRIDE observations from less populated areas, we divide the South census region into the South Atlantic and South Central divisions, which partitions the United States into three census regions and two census divisions. Within each of these five regions, grouping together MSAs containing between 250,000 and 500,000 people and MSAs/rural areas containing fewer than 250,000 people creates 10 additional price areas. Finally, the District of Columbia is considered a separate area because abundant STRIDE data are collected there. In each year, therefore, there are 28 different predicted prices corresponding to 28 geographic areas.[9] Each NHSDA respondent is assigned the cocaine price for their area of residence among these 28.

This methodology differs in two important ways from that used by previous researchers. The first is that previous methodologies impute city-level prices by including city rather than area indicators in equation (1) and then calculate a state-level price as the population-weighted average of prices from each city represented in STRIDE from each state. This ignores evidence from Rhodes et al. (1994) and Caulkins (1995) that prices increase as the distance from points of entry into the United States increases, because of lateral transaction costs, and as market size decreases, because of economies of scale associated with distribution. For example, therefore, the price of cocaine in Greenville, North Carolina, is likely to be closer to the price in Charlottesville, Virginia, which is in a different state but the same census division and population category, than that in Charlotte, North Carolina, which is in the same state but has a much larger population.

The second departure of our method is that previous methods have not included an interaction vector analogous to our *Area* × *Year* interaction vector. This is because data are insufficient to identify a complete set of

8. STRIDE contains prices for 35,674 cocaine purchases made during 1990–97. We begin by eliminating the 780 observations with purity less than or equal to .001% or greater than 100%, because these values represent either data errors or purchases containing trivial amounts of the actual drug. Then we estimate an initial price standardized by total weight as the predicted price from a regression of log *Price* on log *Weight* and *Year*. For each year, we throw out observations with standardized prices that are less than one-eighth of or greater than eight times the mean price for that year. We then recompute the mean for each year and throw out observations with standardized prices that are less than one-fourth of or greater than four times the mean price for that year. Finally we calculate an alternative price per pure gram from observed values of price, weight, and purity and eliminate observations with a price per pure gram of greater than $3,000. Overall these latter three steps eliminate only an additional 546, or 1.6%, of the remaining STRIDE observations. Estimated price effects are slightly less precise but otherwise quite similar to those reported here when these latter 546 STRIDE observations are not eliminated.

9. Not surprisingly, the number of STRIDE observations in each price region varies greatly across both population size and census division. Washington, DC, has the largest sample size, averaging 746 observations annually during the analysis period. Average annual sample sizes range from 102 to 435 for the remaining 8 areas formed from populations greater than 1 million, from 30 to 215 for MSAs with between 500,000 and 1 million people, from 23 to 94 for MSAs with between 250,000 and 500,000 people, and from 17 to 130 for areas with less than 250,000 people. The lower ends correspond to the West North Central division for the two larger population sizes and to the Northeast for the two smaller population sizes, whereas the higher ends correspond to the South Atlantic for all population categories. The sample size is less than 10 in only three cases, all in the Northeast for the smaller population categories, with a minimum of four. In the aggregate, the temporal variation is reasonably small, with the average number of STRIDE observations per area ranging from 106 in 1993 to 196 in 1991.

interaction terms when prices are estimated for individual cities rather than broader areas. An advantage of our methodology is that it allows for geographic variation in intertemporal price changes, making detection of price effects in drug demand equations possible even when state fixed effects are included.

For more direct comparison with estimates from previous studies, we also obtain results with a state-level cocaine price measure. The regression used to construct this variable is equation (1) with *Area* representing a vector of state indicators, rather than of the 28 price regions described, and b_4 set to zero. Models estimated with the state-level cocaine price measure exclude state fixed effects, which are no longer identified.

Marijuana Price

A measure of the price of marijuana faced by the respondent is also appended to the NHSDA data. Because DEA agents concentrate on cocaine and heroin trafficking, STRIDE contains insufficient marijuana price information with which to construct regional price estimates. We instead follow Pacula et al. (2001) by constructing a marijuana price estimate from prices listed in the *Illegal Drug Price/Purity Report*, a publication of the DEA Intelligence Division. This report contains quarterly estimates of the minimum and maximum marijuana price in 19 cities for both pound and ounce purchases of two different types of marijuana, commercial-grade and sinsemilla-grade.

Our price variable is the average price per gram of a pound purchase of commercial grade marijuana. We choose the pound-level commercial series because it is by far the most complete of the four series.[10] For each city, a quarterly price is obtained by taking the midpoint of the reported price range for each quarter, and an annual price is obtained by averaging all quarterly prices that are reported for that year.[11]

Our NHSDA data indicate the state of residence of each respondent but nothing more specific regarding location of residence. Of the 19 cities for which marijuana prices are constructed, 14 are the only city reporting a price in that state. Each of these states is assigned the price of its reporting city. Annual prices for the two cities in Texas and the three cities in California are averaged in each year to form annual prices for those states. Each remaining state of residence in the NHSDA, which sampled all states except Vermont and Wyoming during 1990–97, is assigned the price from the closest of these 16 states that is in the same census division as the state. Thus the United States is divided into 16 regions, each of which is assigned a different marijuana price series. Appendix Table A1 lists these 16 regions according to the cities that contribute prices and the states that are assigned the price from each region.

Cocaine and Marijuana Enforcement

Variables representing the probability of arrest for cocaine and marijuana possession violations in the state of residence of the respondent are also appended to the NHSDA data.[12] For each drug, we proxy for the annual possession arrest probability with a variable equaling the number of possession arrests in the state divided by the number of drug users in the state that year. Drug possession arrest information comes from the Uniform Crime Reporting system of the Federal Bureau of

10. Prices of commercial grade marijuana are likely more relevant than those of the more potent sinsemilla variety given evidence from National Narcotics Intelligence Consumers Committee (1998) that commercial marijuana dominates the U.S. market. In contrast, because purchases of a pound likely represent wholesale purchases by low-level dealers whereas purchases of an ounce likely represent retail purchases by a typical user, in principle ounce-level prices are more appropriate for the analysis than pound-level prices. Results from Pacula et al. (2001) indicate that multiplying the estimated marijuana price regression coefficients by 0.5 yields a rough estimate of the response of drug demand to retail price changes. This is because $\partial d/\partial r = (\partial d/\partial w)(\partial w/\partial r)$—where d is drug use, r is the retail price, and w is the wholesale price—the estimated marijuana demand regression coefficient is $\partial d/\partial w$, and their estimated $\partial w/\partial r$ from a regression of the wholesale price on the retail price is 0.5.

11. This typically represents all four quarters because pound-level commercial-grade prices are rarely missing. Also, we cannot control for potency because only one national potency average is reported for each year.

12. A concern regarding the price and enforcement variables is that they measure local prices and enforcement levels faced by respondents with error. If these measurement errors are random, estimated price and enforcement effects are biased toward zero. The extent to which measurement error plagues the estimates, however, is mitigated by fact that NHSDA responses, price observations, and arrests all disproportionately occur in large population centers.

Investigation (FBI).[13] Because there are no published estimates of the number of drug users by state, we construct the denominator by multiplying the unweighted percentage of state respondents who use the drug by the 1 July Census estimate of the state population.[14] The logic behind these arrest rate variables is that the probability of apprehending a given criminal falls as the level of police resources devoted to enforcing the corresponding crime falls, and, as Ehrlich (1973) argues, the number of criminals rises.

However, because the denominator of the arrest rate variable is by construction positively correlated with the dependent variable, the effect of the arrest rate for a drug on the demand for that drug is likely to be overestimated in magnitude for two reasons. First, the variable is statistically endogenous. In particular, reverse causality may result in a reduction in the arrest probability from an increase in the number of users. Second, errors in measurement of the number of users are negatively correlated with errors in measurement of the arrest rate. Overestimates of the number of users, as expected in states with lower than average true drug use rates, generate underestimates of arrest rates, with the opposite occurring in states with higher than average true drug use rates. If the actual elasticity of the number of drug users with respect to arrest rates is less than one in absolute value, measurement error reduces observed arrest rate differences across states by a greater proportion than observed drug use rate differences, making smaller changes in arrest rates appear to induce larger changes in drug use.[15]

To reduce the extent of the endogeneity and measurement error problems, each arrest rate variable is constructed using all ages in both the numerator and denominator rather than separately for each age group.[16] Furthermore, we also obtain results using alternative arrest probability variables that instead specify total type I arrests in the state, which are also reported by the FBI, as the denominator.[17] Previous studies such as Benson and Rasmussen (1991) use this variable to measure enforcement of drug crimes relative to nondrug crimes. The advantage of this variable is that it is neither statistically endogenous by construction nor affected by errors in measurement of the number of drug users. The disadvantage is that it is a less direct proxy for the arrest probability, because the denominator is not a measure of drug consumption activity. For example, if the number of cocaine arrests and users increase by identical proportions while the number of type I arrests does not change, this arrest rate measure increases even though the percentage of cocaine users arrested, a much closer proxy for the probability of arrest for cocaine possession, does not.

Other Explanatory Variables

We control for a variety of additional explanatory variables. Other continuous measures include age and age squared, family size, and real family income. The remaining variables are indicators for males, blacks, Hispanics, other races, marriage, divorce, enrollment in school, four levels of educational attainment (high school graduate, some college, college graduate, some graduate school), the interview not being interrupted,[18] whether the interview interruption variable is missing, three MSA population categories (population greater than 1 million, between 500,000 and 1 million, and between 250,000 and 500,000), and rural residence. Age squared and indicators for divorce, college completion, and graduate

13. The cocaine arrest variable numerator represents total arrests for possession of cocaine and opium derivatives, because the FBI does not separately report cocaine and opium-related arrests.

14. This denominator is multiplied by the percentage of the state population covered by local agencies from which the FBI obtains arrest data, which is 100% for later years but around 90% on average for earlier years. We also considered an alternative denominator calculated as the sample-weighted sum of respondents in each state using the drug. Although this measure yields similar results, it is potentially problematic because the NHSDA sample weights are not designed to represent individual states.

15. We thank an anonymous referee for pointing out this measurement error issue, a mathematical derivation of which is available from the authors.

16. Farrelly et al. (2001) constructs this variable for marijuana and estimates similar effects on marijuana use by 12–20-year-olds regardless of whether the variable is calculated only for 12–20-year-olds or encompasses all ages.

17. Type I crimes are the major nondrug crimes: murder, rape, aggravated assault, robbery, burglary, larceny, and motor vehicle theft.

18. The degree of privacy during the interview is coded on a scale from 1 (completely private) to 9 (constant presence of another). Our indicator of no interruptions represents values of 4 or less for this privacy variable.

school attendance are not included in the juvenile regressions.

Sample Characteristics

Table 1 lists separate summary statistics for adults (18–39-year-olds) and juveniles (12–17-year-olds). Marijuana use is considerably more prevalent than cocaine use for both age groups, and use of each is higher among adults than juveniles. The average cocaine price over the period is about $120 per pure gram, which is substantially higher than the average marijuana price of $2.65 per gram.[19] The percentage of users arrested for cocaine possession is about four times the percentage arrested for marijuana possession. However, the arrests per type I arrest measures show that possession arrests occur slightly more frequently for marijuana than for cocaine.

IV. EMPIRICAL METHODOLOGY

Because the dependent variables are binary indicators, the cocaine and marijuana participation equations are estimated with probit regressions. The full model is

$$(2)\quad D_i = b_0 + b_1 P_i^C + b_2 P_i^M + b_3 A_i^C + b_4 A_i^M + b_5 X_i + S_i + Y_i + e_i,$$

where for respondent i, D_i is a binary indicator of past year cocaine or marijuana use; P_i^C and P_i^M are real prices of cocaine and marijuana, respectively; A_i^C and A_i^M are probabilities of arrest for possession of cocaine and marijuana, respectively; X_i is a vector of other relevant socioeconomic variables; S_i is a vector of binary variables representing each state indicating whether or not the respondent lived in the particular state; Y_i is a vector of binary variables for each year from 1990 to 1997 indicating whether or not the respondent was interviewed in the particular year; and e_i is a random error term. All regressions are weighted using the NHSDA sampling weights.

For both cocaine and marijuana use, six variants of equation (2) are estimated separately for both adults and juveniles. The first regression excludes the arrest variables. The second includes only the own-arrest variable, the third includes only the cross-arrest variable, and the fourth includes both arrest variables, which is the complete equation (2) model. Comparing these specifications might reveal the impact of any collinearity between price and arrest variables and between the individual arrest measures. The fifth is identical to the fourth except that it substitutes census division effects for state effects; the sixth entirely excludes fixed geographic effects.

A major departure from the previous literature, other than Farrelly et al. (2001) and Pacula et al. (2001), is the inclusion of state fixed effects. Cocaine prices vary at the regional level, whereas marijuana prices and arrest probabilities vary at the state level. Unobservable state-level factors, such as public willingness to accept alternative behaviors or the political environment, may thus simultaneously affect both illegal drug consumption and the price and arrest variables. The inclusion of state fixed effects controls for variation in unobservable state-level characteristics, eliminating bias-inducing spurious correlation between illegal drug use and the price and arrest variables. Put differently, controlling for state effects reduces the likelihood that differences in cocaine and marijuana use across states resulting from unobserved variation in attitudes and preferences are incorrectly attributed to variation in drug prices and arrest rates.

V. RESULTS

We first report results for cocaine and marijuana use by adults and then proceed to the analogous models for juveniles. Regression sample sizes are 92,784 for adults, 42,464 for juvenile cocaine use, and 43,147 for juvenile marijuana use.[20]

Cocaine Use by Adults

Column (1) of Table 2 shows that when the two arrest variables are excluded from

19. A crack vial contains roughly 0.1 pure gram of cocaine; a line of powder cocaine has about 0.02 pure grams. A marijuana joint typically contains about 0.4 grams of marijuana.

20. In each cell of each table, the first row indicates the change in probability of drug use resulting from a unit change in the explanatory variable, the second row indicates the standard error of the first row estimate (in parentheses), and the third row indicates the elasticity computed from the weighted sample means (in brackets). All regressions include the additional explanatory variables listed in Tables 1 and A2.

TABLE 1
Descriptive Statistics

Variable	Age 18–39 (n = 92,784)	Age 12–17 (n = 43,147)
Cocaine use past year	.044	.015
	(.205)	(.122)
Marijuana use past year	.157	.118
	(.364)	(.322)
Cocaine price per pure gram	118.88	119.54
	(35.12)	(34.98)
Marijuana price per gram	2.653	2.658
	(.789)	(.793)
Cocaine arrests per user	.041	.040
	(.035)	(.035)
Marijuana arrests per user	.011	.011
	(.007)	(.007)
Cocaine arrests per type I arrest	.120	.115
	(.078)	(.077)
Marijuana arrests per type I arrest	.136	.139
	(.073)	(.073)
Interview without interruptions	.822	.712
	(.382)	(.453)
Interview without interruptions—missing	.016	.022
	(.126)	(.148)
Age	29.05	14.49
	(6.28)	(1.68)
Male	.491	.512
	(.500)	(.500)
Black	.122	.143
	(.327)	(.351)
Hispanic	.112	.122
	(.315)	(.328)
Other race	.043	.044
	(.204)	(.205)
Married	.522	.003
	(.500)	(.056)
Divorced	.092	
	(.289)	
Family size	3.50	4.47
	(1.62)	(1.56)
Enrolled in school	.200	.927
	(.400)	(.260)
High school graduate	.351	.013
	(.477)	(.112)
Some college education	.262	.001
	(.440)	(.031)
College graduate	.146	
	(.353)	
Some graduate school education	.075	
	(.263)	
Family income (1,000s)	34.24	30.78
	(23.54)	(24.90)
MSA population > 1 million	.463	.417
	(.499)	(.493)
MSA population between 500,000 & 1 million	.230	.237
	(.421)	(.425)
MSA population between 250,000 & 500,000	.089	.097
	(.284)	(.296)
Rural	.131	.166
	(.338)	(.372)

Notes: Standard deviations are in parentheses. The sample size for past year cocaine use is 42,464. Statistics are weighted using NHSDA sample weights.

TABLE 2
Probit Estimates for Past Year Cocaine Use by 18–39-Year-Olds

Variable	(1)	(2)	(3)	(4)	(5)	(6)
Cocaine price (×1,000)	−.152**	−.132**	−.149**	−.132**	−.113*	−.234***
	(.062)	(.057)	(.061)	(.057)	(.059)	(.061)
	[−.410]	[−.356]	[−.402]	[−.357]	[−.304]	[−.631]
Marijuana price (×100)	.172	−.064	.080	−.074	−.349*	−.335**
	(.232)	(.232)	(.231)	(.231)	(.211)	(.144)
	[.104]	[−.038]	[.048]	[−.044]	[−.210]	[−.202]
Cocaine arrests per user		−.453***		−.430***	−.200***	−.131***
		(.067)		(.071)	(.047)	(.036)
		[−.425]		[−.403]	[−.187]	[−.123]
Marijuana arrests per user			−1.084***	−.252	−.168	−.529***
			(.277)	(.296)	(.232)	(.187)
			[−.266]	[−.062]	[−.041]	[−.130]
Log likelihood	−15,401	−15,326	−15,383	−15,325	−15,447	−15,505
Geographic fixed effects	State	State	State	State	Division	None

Notes: In each cell, the first row indicates the marginal effect on the probability of cocaine use, the second row indicates the standard error (in parentheses), and the third row indicates the implied elasticity (in brackets). The sample size is 92,784. All equations include the variables listed in Appendix Table A2 along with year indicators. Regressions are weighted using NHSDA sample weights.
*, **, and *** indicate significance at the 90%, 95%, and 99% levels, respectively.

the equation, adult cocaine demand is significantly negatively related to the cocaine price with an elasticity of −0.41 but is unrelated to the marijuana price.[21] The next three columns reveal that these results are unchanged from adding the arrest variables except for a slight decrease in the cocaine price elasticity when the cocaine arrest rate is included. The cocaine arrest rate has a highly significant elasticity of around −0.4 regardless of whether the marijuana arrest rate is also included. However, the negative effect of the marijuana arrest rate falls by 75% and becomes insignificant when the cocaine arrest rate is also included. This provides weak evidence of complementarity between the two drugs and suggests some collinearity between the arrest rate variables. However, the fact that the arrest rate standard errors inflated only slightly in column (4) indicates that multicollinearity is not too severe. As expected, the elasticity of the cocaine arrest rate is larger than that of the marijuana arrest rate, even without controlling for the former. These patterns are repeated in Tables 3 and 4 and to some extent in Table 5.

21. In all regressions, price coefficients are unchanged when only one of the two price variables is included.

The estimates are from models that control for state fixed effects. When division effects replace state effects in column (5), the marijuana price elasticity increases by a factor of 5 and becomes significant, but the cocaine arrest rate elasticity halves. Omitting geographic fixed effects entirely doubles the cocaine price elasticity and triples the marijuana arrest rate elasticity while further decreasing the cocaine arrest rate elasticity. This pattern is also repeated in Tables 3–5.[22]

Marijuana Use by Adults

Table 3 shows that the cocaine price has a significant negative effect on adult marijuana

22. Throughout Tables 2–5, replacing state effects with division effects has little impact on cocaine price coefficients but large and significant effects on marijuana price coefficients. A possible explanation is that marijuana prices are not measured precisely enough for identification of coefficients in state fixed effects models because they vary primarily across groups of states within census divisions, and in contrast cocaine prices vary both across census divisions and within divisions by metropolitan area size. One might therefore argue that geographic fixed effects are more appropriately specified at the division than the state level. We prefer the more conservative interpretation that state effects models offer for the source of cross-state price variation and argue that differences in arrest rate coefficients between state and division effects models show the importance of controlling for state effects.

TABLE 3
Probit Estimates for Past Year Marijuana Use by 18–39-Year-Olds

Variable	(1)	(2)	(3)	(4)	(5)	(6)
Marijuana price (×100)	.107 (.594) [.018]	−.387 (.536) [−.065]	−.082 (.610) [−.014]	−.412 (.543) [−.070]	−1.699*** (.490) [−.287]	−1.437*** (.335) [−.243]
Cocaine price (×1,000)	−.284** (.136) [−.215]	−.252** (.125) [−.191]	−.264** (.135) [−.199]	−.248** (.125) [−.188]	−.305** (.132) [−.230]	−.314*** (.113) [−.238]
Marijuana arrests per user		−5.871*** (.839) [−.404]		−5.630*** (.853) [−.388]	−4.006*** (.666) [−.276]	−3.969*** (.494) [−.273]
Cocaine arrests per user			−.457*** (.164) [−.120]	−.110 (.125) [−.029]	−.007 (.107) [−.002]	.044 (.085) [.011]
Log likelihood	−36,935	−36,802	−36,907	−36,800	−36,953	−36,987
Geographic fixed effects	State	State	State	State	Division	None

Notes: In each cell, the first row indicates the marginal effect on the probability of marijuana use, the second row indicates the standard error (in parentheses), and the third row indicates the implied elasticity (in brackets). The sample size is 92,784. All equations include the variables listed in Appendix Table A2 along with year indicators. Regressions are weighted using NHSDA sample weights.
*, **, and *** indicate significance at the 90%, 95%, and 99% levels, respectively.

TABLE 4
Probit Estimates for Past Year Cocaine Use by 12–17-Year-Olds

Variable	(1)	(2)	(3)	(4)	(5)	(6)
Cocaine price (×1,000)	.005 (.040) [.040]	.012 (.036) [.096]	.006 (.039) [.046]	.013 (.036) [.099]	.020 (.038) [.158]	−.010 (.036) [−.078]
Marijuana price (×100)	−.058 (.136) [−.102]	−.152 (.134) [−.266]	−.074 (.136) [−.129]	−.152 (.133) [−.267]	−.303** (.140) [−.530]	−.268*** (.082) [−.470]
Cocaine arrests per user		−.165*** (.036) [−.437]		−.180*** (.041) [−.475]	−.101*** (.024) [−.268]	−.069*** (.017) [−.183]
Marijuana arrests per user			−.259* (.146) [−.188]	.117 (.160) [.085]	−.061 (.115) [−.045]	−.199* (.106) [−.145]
Log likelihood	−2,915	−2,895	−2,912	−2,894	−2,942	−2,951
Geographic fixed effects	State	State	State	State	Division	None

Notes: In each cell, the first row indicates the marginal effect on the probability of cocaine use, the second row indicates the standard error (in parentheses), and the third row indicates the implied elasticity (in brackets). The sample size is 42,464. All equations include the variables listed in Appendix Table A2 along with year indicators. Regressions are weighted using NHSDA sample weights.
*, **, and *** indicate significance at the 90%, 95%, and 99% levels, respectively.

TABLE 5
Probit Estimates for Past Year Marijuana Use by 12–17-Year-Olds

Variable	(1)	(2)	(3)	(4)	(5)	(6)
Marijuana price (×100)	−.007	−.264	−.293	−.389	−1.295**	−.747**
	(.588)	(.582)	(.598)	(.593)	(.519)	(.357)
	[−.002]	[−.060]	[−.066]	[−.088]	[−.292]	[−.169]
Cocaine price (×1,000)	.013	.023	.044	.043	−.011	−.198*
	(.130)	(.126)	(.129)	(.126)	(.121)	(.115)
	[.013]	[.024]	[.045]	[.043]	[−.011]	[−.201]
Marijuana arrests per user		−3.066***		−2.171***	−1.214**	−2.289***
		(.660)		(.659)	(.510)	(.394)
		[−.287]		[−.204]	[−.114]	[−.215]
Cocaine arrests per user			−.573***	−.40[illegible]**	−.352***	−.205**
			(.156)	(.15[illegible])	(.110)	(.094)
			[−.195]	[−.137]	[−.120]	[−.070]
Log likelihood	−13,795	−13,767	−13,767	−13,755	−13,832	−13,875
Geographic fixed effects	State	State	State	State	Division	None

Notes: In each cell, the first row indicates the marginal effect on the probability of marijuana use, the second row indicates the standard error (in parentheses), and the third row indicates the implied elasticity (in brackets). The sample size is 43,147. All equations include the variables listed in Appendix Table A2 along with year indicators. Regressions are weighted using NHSDA sample weights.

*, **, and *** indicate significance at the 90%, 95%, and 99% levels, respectively.

demand with a magnitude about half as large as its effect on cocaine demand. However, adult marijuana demand is not related to its own price. The marijuana arrest rate has a strong negative effect regardless of whether the cocaine arrest rate is included, but the cocaine arrest rate effect indicates complementarity only when the marijuana arrest rate is omitted. Removal of state effects again has a large impact. The cocaine price elasticity increases by one-quarter, and the marijuana price elasticity rises by a factor of four and becomes highly significant.

It thus appears that drug demand is higher in states with lower drug prices, but states with lower drug prices have other unobservable characteristics leading to higher drug demand. These unobservable factors are the predominant reason for the negative correlation between marijuana prices and drug use. In contrast, arrest rates for possession of drugs, particularly cocaine, might be higher in states where drug use is greater, whereas additional drug enforcement reduces use within states over time. In other words, state fixed effects control to some extent for the endogenous enforcement response to drug use that is apparent from estimates relying on variation across states at a given time.

Cocaine Use by Juveniles

Table 4 reveals that the main difference between juvenile and adult cocaine demand is that the former is not responsive to cocaine price changes. The effects of the marijuana price and drug arrest rate variables are similar for juveniles and adults. Removal of state effects again inflates the marijuana price elasticity and allows it to attain significance.

Marijuana Use by Juveniles

Table 5 indicates that juvenile marijuana demand is similar to juvenile cocaine demand in that neither price affects demand. The difference from earlier results is that both arrest rates significantly impact juvenile marijuana demand even when both are simultaneously included in the equation, providing more convincing evidence of complementarity between the two drugs. The effect of the marijuana arrest rate is comparable with that found by Farrelly et al. (2001). The impact of removing state and then division effects is consistent with previous results.

Various potential explanations exist for the insignificant effect of the cocaine price on juvenile drug demand despite its significant negative effect on adult drug demand.

TABLE 6
Probit Estimates with State-level Cocaine Price Measure

Variable	Cocaine use (1)	(2)	(3)	Marijuana use (4)	(5)	(6)
18–39-year-olds						
Original cocaine price measure (×1,000)	−.228*** (.061) [−.615]		−.156** (.062) [−.421]	−.309*** (.114) [−.234]		−.315** (.124) [−.239]
State-level cocaine price measure (×1,000)		−.218*** (.055) [−.701]	−.167*** (.058) [−.537]		−.084 (.104) [−.075]	.015 (.112) [.013]
12–17-year-olds						
Original cocaine price measure (×1,000)	−.011 (.037) [−.089]		.013 (.038) [.101]	−.175 (.116) [−.179]		−.135 (.118) [−.138]
State-level cocaine price measure (×1,000)		−.061** (.027) [−.569]	−.065** (.031) [−.605]		−.140 (.111) [−.169]	−.099 (.115) [−.120]

Notes: In each cell, the first row indicates the marginal effect on the probability of cocaine or marijuana use, the second row indicates the standard error (in parentheses), and the third row indicates the implied elasticity (in brackets). The sample size is 92,136 for the top part, 42,179 for cocaine use the bottom half, and 42,794 for marijuana use in the bottom half. These are slightly smaller than in the earlier tables because state-level prices cannot be imputed for several of the least-populous states. All equations include the variables listed in Appendix Table A2 and year indicators but exclude geographic fixed effects. Regressions are weighted using NHSDA sample weights.
*, **, and *** indicate significance at the 90%, 95%, and 99% levels, respectively.

First, some juveniles might use their parents' money to purchase cocaine. Second, if as Koch (2000) argues sellers find it profitable to give the drug away to young initiators in an attempt to hook them and charge them higher prices when they become addicts, or if kids share cocaine with their friends, some juvenile users might not pay the market price for cocaine. Third, sample statistics in Table 1 showing that prevalence for adults relative to juveniles is three times as high for cocaine but only one-third larger for marijuana suggests that a substantial proportion of cocaine initiation occurs after age 17. As Kandel and Yamaguchi (1993) report, tobacco is generally initiated before marijuana, which is initiated before cocaine. This could explain why evidence, as reviewed in Chaloupka and Wechsler (1997), generally shows that the cigarette own-price elasticity is higher for teens than adults, and we find the reverse for cocaine.

State-Level Cocaine Price Measure

To evaluate more directly the extent to which our cocaine price construction methodology accounts for the difference between our results and those of previous studies, Table 6 presents results of models in which the state-level cocaine price measure described earlier is used in place of our preferred cocaine price measure. For each age group and drug type, we estimate three regressions specified identically to column (6) of Tables 2–5: one with our price measure, one with the state-level price measure, and one that includes both price measures.[23] These models exclude geographic fixed effects because state effects are not identified when the state-level price measure is included. For cocaine, the state-level price has a similar effect on adult use and a stronger negative effect on juvenile use than does our price measure. But in both cases, when the state-level variable is included, the effects of our price variable are nearly identical to those with state effects included, as indicated in column (4) of Tables 2 and 4. This suggests that state fixed effects are effectively embedded into the state-level price

23. The coefficients of the models including only our original price variable are slightly different than those shown in column (6) of Tables 2–5 because the Table 6 regression samples exclude respondents from a few low-population states for which insufficient data exist to construct state-level prices and are thus slightly smaller.

series, so that at least some of the estimated state-level price coefficients represent fixed state effects rather than the true impacts of price changes. Indeed, the R^2 from a regression of the cocaine price on a set of state indicators is 0.30 for our price measure but 0.61 for the state-level measure. Meanwhile, for marijuana, our price measure has a stronger effect on adult use and a very similar effect on juvenile use.

Alternative Arrest Measure

Table 7 shows results for the alternative arrest rate variable that uses total type I arrests as the denominator. The cocaine arrest rate has a consistent significant negative effect on both cocaine and marijuana demand for both adults and juveniles regardless of whether the marijuana arrest rate is also controlled for, with own-arrest elasticities slightly larger than cross-arrest elasticities. In contrast, the impact of the marijuana arrest rate is consistently insignificant. These results reinforce the conclusion that cocaine possession enforcement reduces demand for both drugs and that marijuana possession enforcement does not affect cocaine demand. They also suggest that the earlier results showing a negative effect of marijuana arrests on marijuana demand could to some extent be a product of endogeneity of the arrest rate variable.

The limitation of the alternative arrest rate variable is that it is not as close a proxy for the probability of arrest for drug possession as the version specifying the number of users in the denominator. Thus the theoretical link between the alternative arrest variable and drug demand is weaker. For instance, if drug arrests and type I arrests both increase by the same percentage because of an increase in resources devoted to law enforcement while the number of drug users holds constant, the corresponding increase in drug arrest probability is reflected by our original arrest rate variable but not by the type I arrest rate measure. This is a potential alternative explanation for the weaker effects of the own-arrest rate for marijuana. Furthermore, because possession of cocaine is considered more serious than that of marijuana, it is possible that enforcement agencies divert resources from type I arrests to cocaine but not marijuana arrests, making standardization by type I arrests more relevant for cocaine than

TABLE 7
Probit Estimates of Alternative Drug Arrest Measure

	Cocaine use			Marijuana use		
Variable	(1)	(2)	(3)	(4)	(5)	(6)
18–39-year-olds						
Cocaine arrests per type I arrest	−.126**		−.154**		−.490***	−.445***
	(.061)		(.072)		(.169)	(.170)
	[−.344]		[−.420]		[−.374]	[−.340]
Marijuana arrests per type I arrest		−.003	.039	−.181		−.061
		(.033)	(.039)	(.115)		(.114)
		[−.010]	[.123]	[−.157]		[−.053]
12–17 year-olds						
Cocaine arrests per type I arrest	−.069**		−.074**		−.331**	−.358**
	(.032)		(.036)		(.130)	(.152)
	[−.524]		[−.560]		[−.323]	[−.349]
Marijuana arrests per type I arrest		−.016	.005	−.057		.034
		(.018)	(.021)	(.079)		(.093)
		[−.148]	[.050]	[−.067]		[.040]

Notes: In each cell, the first row indicates the marginal effect on the probability of cocaine or marijuana use, the second row indicates the standard error (in parentheses), and the third row indicates the implied elasticity (in brackets). The sample size is 92,784 for the top, 42,464 for cocaine use in the lower half, and 43,147 for marijuana use in the lower half. All equations include the variables listed in Appendix Table A2 along with state and year indicators. Regressions are weighted using NHSDA sample weights.

*, **, and *** indicate significance at the 90%, 95%, and 99% levels, respectively.

marijuana. In any event, the combined results for the two arrest variable specifications represent strong evidence that cocaine arrests are negatively related to both cocaine and marijuana demand.

Other Determinants

Appendix Table A2 contains estimates for the full set of explanatory variables in the complete equation (2) models reported in column (4) of Tables 2–5. For adults, drug demand falls as education, family size, and family income rise and is lower for females, nonwhites, married respondents, students, and rural residents. As age increases, cocaine demand increases at a declining rate until age 27 and then decreases, whereas marijuana demand falls. Among juveniles, drug demand increases with age, decreases with family income, and is lower for nonwhite non-Hispanic respondents and students. Interview interruptions and MSA size have no consistent effect on drug demand.

VI. CONCLUSION

This article estimates the effect of cocaine and marijuana prices and probabilities of arrest for cocaine and marijuana possession on past year participation in cocaine and marijuana use, controlling for various socioeconomic variables as well as state fixed effects. The results indicate that adult cocaine and marijuana demand are each sensitive to the price of cocaine but not to that of marijuana, and juvenile drug demand is not price sensitive at all. Meanwhile, for both cocaine and marijuana, increases in the probability of arrest for possession of the drug reduce the probability that the drug is used. Estimated cross-arrest effects, particularly those of cocaine arrests on marijuana demand, suggest complementarity between the two drugs.

Three important conclusions emerge. First, caution is advised when interpreting results of similar analyses that do not control for geographic fixed effects. Although cocaine demand is indeed responsive to cocaine price changes, as such analyses have shown, the magnitude of price responsiveness is overestimated when state fixed effects are excluded. Moreover, marijuana prices appear to affect both cocaine and marijuana demand for both adults and juveniles when state fixed effects are omitted. This suggests that state variation in drug use rates is partially explained by unobserved state characteristics that are also correlated with drug prices. Second, enforcement of drug possession violations reduces drug demand separately from any effects of enforcement on drug prices. Third, both price and arrest probability results provide evidence that cocaine and marijuana are complements.

Data limitations restrict our analysis to pooled cross-sections rather than longitudinal observations. This might be one reason that our estimated price and policy effects fail to account for the substantial increase in past year marijuana and cocaine prevalence among high school students during our period of analysis, as indicated by MTF survey responses summarized in Johnston et al. (2001). Past year participation rates among high school seniors increased from nadirs of 3.1% for cocaine and 21.9% for marijuana in 1992 to 5.5% for cocaine and 38.5% for marijuana in 1997. Yet possession arrests rates, which are significantly negatively related to use of both drugs by juveniles, almost doubled in per user terms during 1992–97, from .033 to .060 for cocaine and from .009 to .018 for marijuana. Changes in arrest rates during 1992–97 predict percentage point decreases of 0.4 in cocaine participation and 3.0 in marijuana participation among juveniles during this time, rather than increases in each.[24] Clearly, factors other than prices and arrests are important in determining changes in drug use across cohorts.[25] Potential demand shifters that have been suggested include a decrease in the perceived risk of using drugs, as indicated in Johnston et al. (2001), the introduction of the Internet as a forum for

24. Prices per gram declined slightly during this time, from $119 to $101 for cocaine and from $2.91 to $2.65 for marijuana. But prices are not significantly related to juvenile use; regardless, the predicted participation changes are unchanged when price effects are taken into account. In addition, because some high school seniors are age 18 or older, it is technically inappropriate to use our juvenile regressions to predict behavior for an entire cohort of high school seniors. However, similar prevalence rate increases are apparent for 8th- and 10th-graders surveyed by MTF.

25. Indeed, year coefficients from the juvenile regressions indicate that, controlling for all other explanatory variables, cocaine participation increased by 1.2 percentage points from 1992 to 1997 and marijuana participation increased by 13.3 percentage points during the same period.

drug information dissemination, an increasing glamorization of drugs in popular culture, and decreased parental supervision because of the increased divorce rate and proportion of single-parent families.

An additional data limitation is the imprecision of our local drug prices and possession arrest probability measures. Still, our improvements over past methods strengthen the reliability of our results and their associated policy implications. In particular, the added temporal variation provided by our methodology for estimating regional cocaine prices allows for the detection of price effects even when controlling for fixed state effects, which is difficult when state-level prices are used. Our methodological changes reveal that increases in marijuana and cocaine prices do not decrease drug demand as much as many previous studies have estimated. But these changes also establish that even though unobserved time-invariant differences across states account for some of the negative cross-sectional correlation between drug use and its cost, in terms of monetary prices and expected punishment, drug enforcement policy that increases prices and arrest rates still has the potential to reduce drug use.

APPENDIX TABLE A1
Census Divisions and Marijuana Price Regions

Census region	Census division	States
Northeast	New England	Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island
	Middle Atlantic	New Jersey, New York, Pennsylvania
North Central	East North Central	Illinois, Indiana, Michigan, Ohio, Wisconsin
	West North Central	Iowa, Kansas, Minnesota, Missouri, Nebraska, North Dakota, South Dakota
South	South Atlantic	Delaware, DC, Florida, Georgia, Maryland, North Carolina, South Carolina, Virginia, West Virginia
	East South Central	Alabama, Kentucky, Mississippi, Tennessee
	West South Central	Arkansas, Louisiana, Oklahoma, Texas
West	Mountain	Arizona, Colorado, Idaho, Montana, Nevada, New Mexico, Utah
	Pacific	Alaska, California, Hawaii, Oregon, Washington

City or state in which marijuana price is reported	States assigned marijuana price from this city/state
Atlanta	Georgia, North Carolina, South Carolina
Boston	Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island
California (Los Angeles, San Diego, San Francisco)	California, Hawaii
Chicago	Illinois, Indiana, Wisconsin
Denver	Colorado, Idaho, Montana, Nevada, Utah
Detroit	Michigan, Ohio
Miami	Florida
New Orleans	Alabama, Arkansas, Kentucky, Louisiana, Mississippi, Tennessee
New York City	New York
Newark	New Jersey
Philadelphia	Pennsylvania
Phoenix	Arizona, New Mexico
Seattle	Alaska, Oregon, Washington
St. Louis	Iowa, Kansas, Minnesota, Missouri, Nebraska, North Dakota, South Dakota
Texas (Dallas, Houston)	Oklahoma, Texas
Washington, DC	Delaware, DC, Maryland, Virginia, West Virginia

APPENDIX TABLE A2
Probit Estimates for Past Year Cocaine and Marijuana Use: Full Models from Column (4), Tables 2–5

Variable	Cocaine ages 18–39	Marijuana ages 18–39	Cocaine ages 12–17	Marijuana ages 12–17
Cocaine price (×1,000)	−.132**	−.248**	.013	.043
	(.057)	(.125)	(.036)	(.126)
Marijuana price (×100)	−.074	−.412	−.152	−.389
	(.231)	(.543)	(.153)	(.593)
Cocaine arrests per user	−.430***	−.110	−.180***	−.403***
	(.071)	(.125)	(.041)	(.150)
Marijuana arrests per user	−.252	−5.630***	.117	−2.171***
	(.296)	(.853)	(.160)	(.659)
Interview w/o interruptions	−.000	.002	−.000	.025***
	(.002)	(.005)	(.001)	(.005)
Interview w/o interruptions—missing	−.008	.000	−.005**	.022
	(.005)	(.014)	(.001)	(.017)
Age	.006***	−.008**	.004***	.043***
	(.001)	(.004)	(.000)	(.001)
Age squared (×100)	−.010***	.006		
	(.002)	(.006)		
Male	.023***	.067***	−.001	.012***
	(.002)	(.004)	(.001)	(.004)
Black	−.004*	−.027***	−.005***	−.011*
	(.002)	(.005)	(.001)	(.005)
Hispanic	−.013***	−.081***	.003	−.006
	(.002)	(.005)	(.002)	(.006)
Other race	−.014***	−.078***	−.003*	−.039***
	(.004)	(.007)	(.002)	(.009)
Married	−.031***	−.091***	−.002	.029
	(.003)	(.005)	(.006)	(.041)
Divorced	.004*	.006		
	(.003)	(.007)		
Family size	−.001**	−.010***	−.001***	−.008***
	(.001)	(.001)	(.000)	(.001)
Enrolled in school	−.015***	−.023***	−.017***	−.038***
	(.002)	(.005)	(.004)	(.009)
High school graduate	−.014***	−.037***	−.004	−.028**
	(.002)	(.005)	(.002)	(.011)
Some college education	−.017***	−.043***	.121***	.087
	(.002)	(.005)	(.087)	(.114)
College graduate	−.026***	−.075***		
	(.002)	(.006)		
Some graduate education	−.028***	−.069***		
	(.002)	(.008)		
Family income (×10,000)	−.002***	−.004***	−.001***	−.004***
	(.000)	(.001)	(.000)	(.001)
MSA pop. > 1 million	−.001	.014	−.002	.016*
	(.004)	(.009)	(.002)	(.010)
MSA pop. between 500,000 & 1 million	.001	.016*	.001	.027***
	(.004)	(.010)	(.002)	(.010)
MSA pop. between 250,000 & 500,000	.005	.010	−.001	.017
	(.005)	(.011)	(.002)	(.013)
Rural	−.010***	−.030***	−.002	−.024***
	(.003)	(.008)	(.002)	(.007)
Sample size	92,784	92,784	42,464	43,147
Log likelihood	−15,325	−36,800	−2,894	−13,755

Notes: In each cell, the first row indicates the marginal effect on the probability of cocaine or marijuana use and the second row indicates the standard error (in parentheses). All equations include state and year indicators. Regressions are weighted using NHSDA sample weights.

*, **, and *** indicate significance at the 90%, 95%, and 99% levels, respectively.

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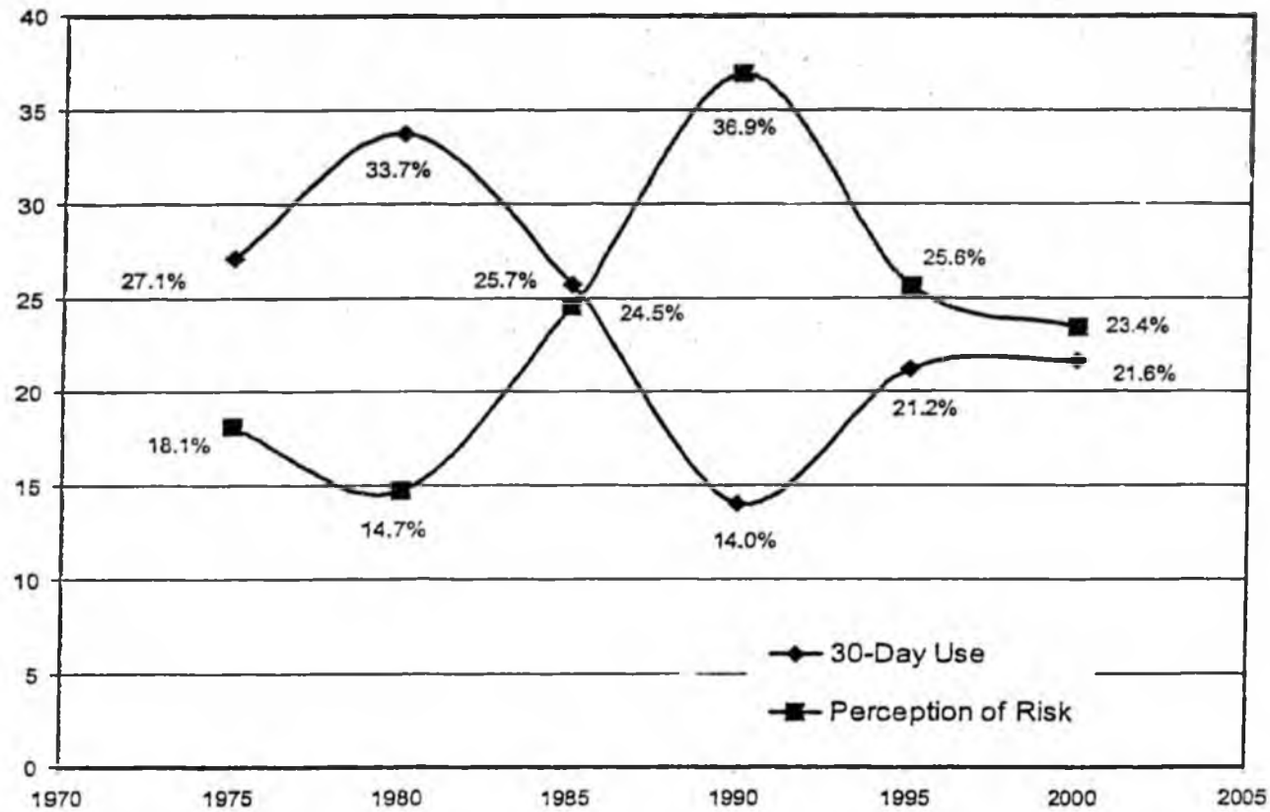
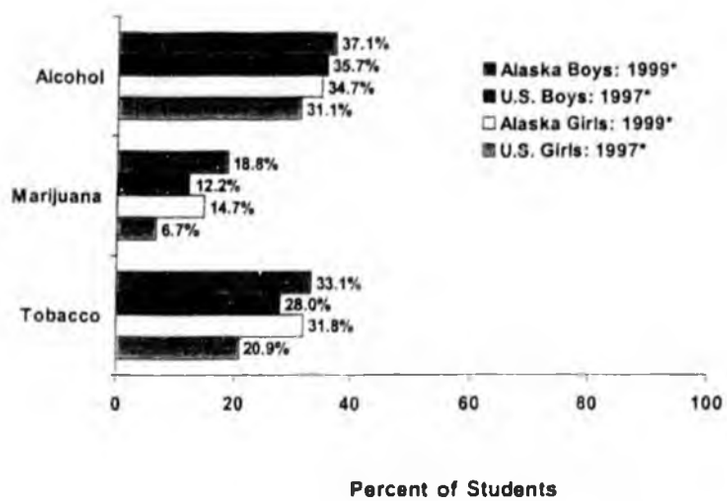
Marijuana Use and Perceived Risk

Data from Monitoring the Future Survey, Dec. 2001
www.monitoringthefuture.org



Use of Alcohol, Marijuana, or Tobacco Before the Age of 13 Years

Almost 40% of Alaska high school boys report having had a first drink of alcohol before age 13 years. Also by age 13 years, 18.8% of boys and 14.7% of girls report having tried marijuana for the first time, accounting for about a quarter of those who have ever used marijuana. Percentages of age at first use are higher for Alaska boys and girls than U.S. boys and girls in use of alcohol, tobacco, and marijuana.



*Use of alcohol, marijuana, or tobacco before the age of 13 years.

Year 2000 Objectives:

- ***Increase by at least 1 year the average age of first use of cigarettes, alcohol, and marijuana by adolescents aged 12-17.***

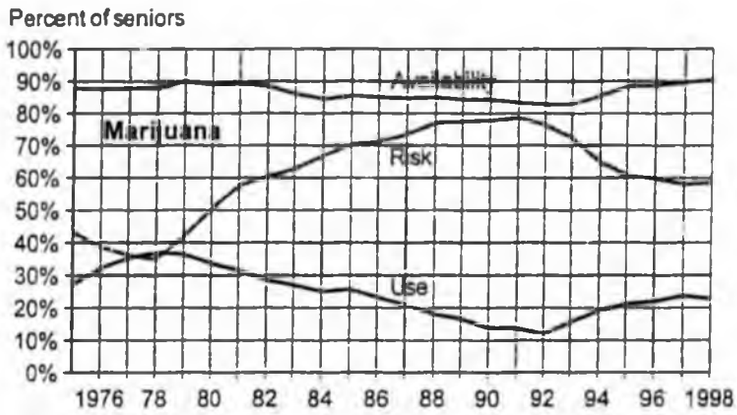
Change in students' use of marijuana and alcohol is tied to their perception of possible harm from use

The annual Monitoring the Future Study, in addition to collecting information about students' use of illicit drugs, alcohol, and tobacco, also collects data on students' perceptions regarding the availability of these substances and the risk of harm from using them.

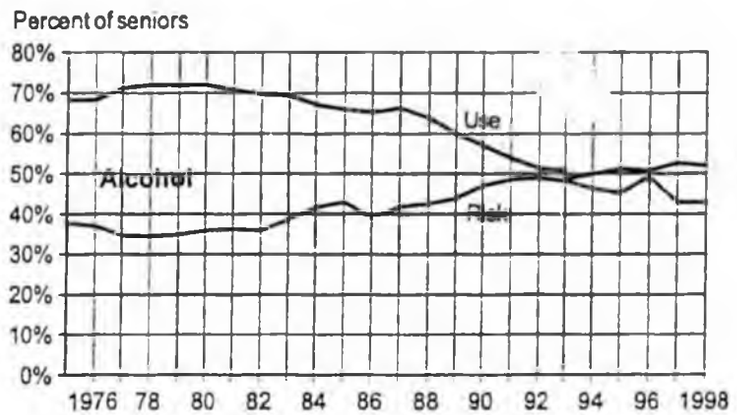
Between 1975 and 1998, the proportion of high school seniors reporting use of marijuana in the 30 days prior to the survey fluctuated, peaking in 1978 and then declining consistently through 1992. Since then, reported use has increased, but the 1998 rate was still far below the peak level of 1978. When the perceived risk of "great harm" from either regular or occasional use of marijuana increased, use declined; when perceived risk declined, use increased. The perception that obtaining marijuana was "fairly easy" or "very easy" remained relatively constant between 1975 and 1998.

Students' reported use of alcohol also shifted from 1975 to 1998. After 1978, alcohol use declined through 1993. Alcohol use fluctuated within a limited range thereafter, but the 1998 rate was far lower than the 1978 rate. As with marijuana, when the perceived risk of "great harm" from either weekend "binge" drinking or daily drinking increased, use declined; when perceived risk declined, use increased.

Over the past 20 years, while availability remained constant, changes in marijuana and alcohol use reflected changes in perceived harm



Availability: Percent saying fairly easy or very easy to get.
Risk: Percent saying great risk of harm in regular use.
Use: Percent using once or more in the past 30 days.



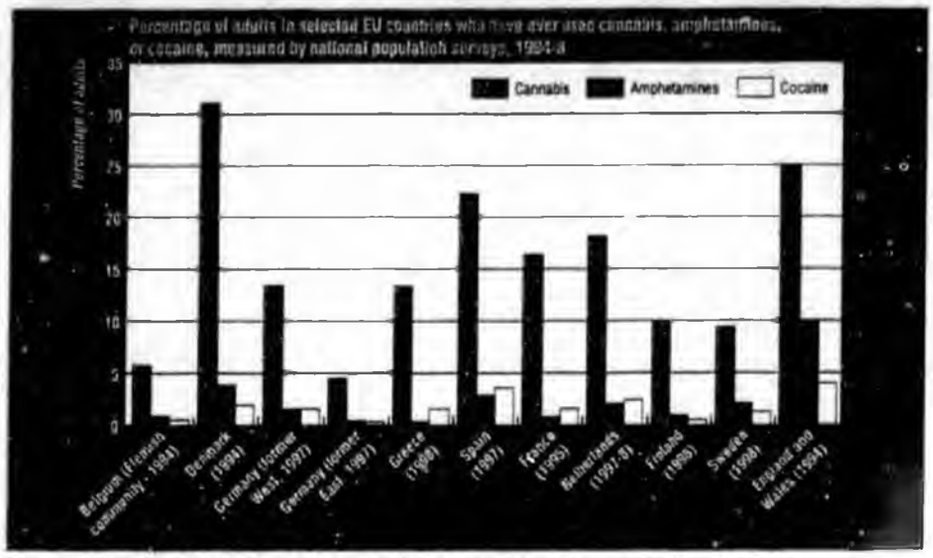
Risk: Percent saying great risk of harm in having five or more drinks once or twice each weekend.
Use: Percent using once or more in the past 30 days.

Note: The survey question on alcohol use was revised in 1993 to indicate that a "drink" meant "more than a few sips." In 1993, half the sample responded to the original question. In 1994 through 1998, all respondents were asked the revised question.

Source: Authors' adaptation of Johnston, O'Malley, and Bachman's *Drug use by American young people begins to turn downward.*

EU centre calls for policies to help female drug users

Rory Watson *Brussels*



The Danes top the table for cannabis use, with the former East Germany trailing the field

Patterns of drug misuse in the European Union are changing, with a chronically ageing population among heroin addicts and a wider use of cocaine, cannabis, and combinations of amphetamines, ecstasy, and medicines.

The picture is contained in the annual report of the European Union's European Monitoring Centre for Drugs and Drug Addiction in Lisbon. It estimates that the number of drug addicts has remained stable at around 1.5 million, but within that figure lie different trends.

The numbers of people starting treatment for heroin are decreasing and users tend to be older with serious social and psychiatric problems. In contrast, new admissions for cocaine or cannabis use are rising, especially among the young.

Among schoolchildren, experience of cannabis ranges from 5-7% in Portugal and Sweden to 30-40% in the Republic of Ireland, the Netherlands, and the United Kingdom.

The centre makes a plea for more tailor-made responses to take account of female drug users who fear they may lose their children if they enrol for treatment. It also highlights the need for policies addressed at women who finance their habit through the sex industry. Although 12 EU countries have specific programmes in this area, Belgium, Finland, and Sweden do not.

The report draws attention to the drug prevention schemes in Austria, Germany, and Sweden directed at very young women and schoolgirls to prevent them from picking up the habit from older boyfriends.

Given that at least 45 million people in the European Union have tried cannabis at least once and that around 15 million have done so in the past year, it is not surprising that policymakers are targeting the phenomenon.

But the European monitoring centre's director, Georges Estievenart, criticised a zero tolerance approach. "No one really sees this as a crime to be repressed with an iron fist," he said. □

Marijuana has potential for misuse

Abi Berger *BMJ*

Marijuana has the potential for misuse, according to a study from the United States. New evidence that monkeys self administer the active component of marijuana has been shown by Dr Steven Goldberg and his team at the National Institutes of Health in Baltimore (*Nature Neurosci...* 2000;3:1073-4).

One of the criteria used to help decide if a drug has the potential for misuse is whether animals will work to obtain it. This is known as self administration. Virtually all psychoactive drugs misused by humans, including nicotine, have been shown to be self administered by animals, but up to now a positive self administration test has been elusive whenever THC (delta-9-tetrahydrocannabinol), the active part of marijuana, has been tested. This has led to some people concluding that marijuana is less likely to lead to drug misuse than other illegal substances.

Dr Goldberg, a pharmacologist at the National Institute of Drug Abuse, has shown now that monkeys can be trained to self administer THC. In this study the team used a low-but clinically relevant-dose of THC administered intravenously in a clear solution. This solution rapidly distributed THC to the brain. Previous attempts to show self administration, using much higher doses of THC held in a suspension, failed. One reason for this may be that, although higher doses were used, the suspension resulted in less brain penetration.

In this study the monkeys had previously been trained to self administer cocaine by pressing a lever 10 times. When saline was substituted for cocaine, self administration stopped. When THC replaced the saline, the monkeys quickly started to press the lever again. The monkeys gave themselves about 30 injections during an hour long session, which equates roughly with the dose received by a person smoking a marijuana joint.

The team went on to confirm that giving the monkeys a second drug that directly blocks cannabinoid receptors in the brain could prevent self administration. This suggests that THC antagonists may be useful in combating marijuana addiction in humans. Dr Goldberg's team will next be trying their approach in "naive" monkeys (animals that have not previously been exposed to other psychoactive drugs) to see if this alters the animals' behaviour.

Dr Goldberg's team concludes from its observations that THC "has as much potential for abuse as other drugs of abuse, such as cocaine and heroin." □

Reactions to the cannabis study

Martin Jarvis, professor of health psychology at University College London said that to suggest that the potential for misusing marijuana is as great as with drugs such as cocaine and heroin is probably overstating the case. He said that misuse is "a judgment best made by looking at patterns of actual human use." He continued: "We shouldn't assume that unreasonable behaviour in society follows from the observation of brain reward behaviour in animals alone".

Ian Stolerman, professor of behavioural pharmacology at the Institute of Psychiatry in London, agreed: "This is an important study because for the first time it provides a method for studying directly the intake of THC by a laboratory animal and thus models a key behavioural feature of addictive states generally. It will lead to studies of how and where THC works in the brain to generate drug abuse. It does show that THC shares properties with other drugs of abuse, but whether it is really as potentially abusive as cocaine and heroin is not so clear."

ceased or reduced smoking before surgery compared with less than 10% of those in the control group.[11] The intervention group was much less likely to experience postoperative complications, especially wound healing and cardiovascular complications, and to need secondary surgery. A Cochrane review found that intensive behavioural interventions with patients admitted to hospital were associated with higher quit rates when linked to follow up contact for at least a month.[12]

Given this evidence, it is arguable that resources expended on smoking rooms might be better used to fund a concerted effort to implement a smoking ban and to expand smoking cessation activities. Hopefully other hospitals facing a similar situation will act differently in the future.

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Comparing cannabis with tobacco

Smoking cannabis, like smoking tobacco, can be a major public health hazard

Britain now has 13 million tobacco smokers. This number has been steadily decreasing due to public awareness of the harm caused by tobacco smoking. At the same time the number of cannabis smokers is increasing. Between 1999 and 2001, the number of 14-15 year olds who had tried cannabis rose from 19% to 29% in boys and 18% to 25% in girls, and a Home Office document estimates that 3.2 million people in Britain smoke cannabis.[1 2] However, the harmful effects of smoking cannabis are widely known and have recently been highlighted.[3 4] Although the active ingredients of the cannabis plant differ from those of the tobacco plant, each produces about 4000 chemicals when smoked and these are largely identical. Although cannabis cigarettes are smoked less frequently than nicotine cigarettes, their mode of inhalation is very different. Compared with smoking tobacco, smoking cannabis entails a two thirds larger puff volume, a one third larger inhaled volume, a fourfold longer time holding the breath, and a fivefold increase in concentrations of carboxyhaemoglobin.[5] The products of combustion from cannabis are thus retained to a much higher degree. How is this likely to translate into adverse effects on health?

We already know that regular use of cannabis is associated with an increased incidence of mental illnesses, most notably schizophrenia and depression,[6] but it is also worth examining its potential to cause other illnesses, especially those of the heart and respiratory system.

At present, there is an understandable dearth of epidemiological evidence of cardiopulmonary harm from cannabis, because its use is a relatively new phenomenon and its potency is changing. The amount of the main active constituent, tetrahydrocannabinol (THC), in cannabis has increased from about 0.5% 20 years ago to nearer 5% at present in Britain, whereas "Nederweed" (the variety smoked in the Netherlands) has an average of 10-11% tetrahydrocannabinol. At the same time little study has been undertaken of any concomitant change in the content of tar. Case-control studies are difficult to perform since cannabis cigarettes do not come in standard sizes, which makes dose-response relations difficult to establish. Furthermore, most users of cannabis also smoke tobacco, which makes it difficult to dissect out individual risks. As with tobacco, there will be a latent period between the onset of smoking and the development of lung damage, cardiovascular disease, or malignant change.

Tobacco smoking is responsible for 120 000 excess deaths each year in Britain, 46 000 from cancers, 34 000 from chronic respiratory disorders, and 40 000 from diseases of the heart and circulation. However, there are indications that smoked cannabis may cause similar effects to smoking tobacco, with many of them appearing at a younger age. Smoking cannabis causes chronic bronchitis, emphysema, and other lung disorders, which were recently summarised in a review released by the British Lung Foundation.[7] A striking feature of cannabis smoking is that it is associated with

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bullous lung disease in young people.[5] Inflammatory lung changes, chronic cough, and chest infections are similar to those in cigarette smokers, but may also be commoner in younger people.[5,6] Premalignant changes have been shown in the pulmonary epithelium, and there are reports of lung, tongue, and other cancers in cannabis smokers.

Tetrahydrocannabinol has cardiovascular effects, and sudden deaths have been attributed to smoking cannabis.[7,8] Myocardial infarction is 4.2 times more likely to occur within an hour of smoking cannabis.[11] However, despite these alarming facts, there is no evidence at present on whether smoking cannabis contributes to the progression of coronary artery disease, as smoking cigarettes does. More studies of the cardiovascular and pulmonary effects of cannabis are essential.

It may be argued that the extrapolation from small numbers of individual studies to potential large scale effects amounts to scaremongering. For example, one could calculate that if cigarettes cause an annual excess of 120 000 deaths among 13 million smokers, the corresponding figure for deaths among 3.2 million cannabis smokers would be 30 000, assuming equality of effect. Even if the number of deaths attributable to cannabis turned out to be a fraction of that figure, smoking cannabis would still be a major public health hazard. However, when the likely mental health burden is added to the potential for morbidity and premature death from cardiopulmonary disease, these signals cannot be ignored. A recent comment said that prevention and cessation are the two principal strategies in the battle against tobacco.[12] At present, there is no battle against cannabis and no clear public health message.

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People missing as a result of armed conflict

Standards and guidelines are needed for all, including health professionals

Mass graves from past or present conflicts, massacres in the Balkans, disappearances—South American style—and the missing in action are politically sensitive. One reason is that they usually entail violations of international humanitarian law (the wartime rules that protect people who are not in combat or no longer in combat) or human rights law. International criminal tribunals to try individuals believed to be responsible for the violations attract equal attention. Why these events and the reactions to them by the international community are of direct concern to health professionals is not immediately obvious, although it has been widely recognised that they have an important part to play in upholding such laws.[1,2] However, the specific roles, responsibilities, and expertise of the profession either in ascertaining the fate of the missing or in helping affected families have not been as widely recognised.

The story of people unaccounted for as a result of armed conflict or internal violence is told differently according to the narrator's discipline. Each discipline has its own work and objectives. Lawyers uphold international law and attempt to prosecute the perpetrators of violations; forensic specialists identify remains, contribute to the reconstruction of events surrounding the death, and establish the cause of death. Psychologists address the kind of mental torture associated with uncertainty of the whereabouts of a family member. Military bodies emphasise the importance of measures such as the wearing of identification tags and registering deaths of their personnel. Red Cross workers respond to families' requests to trace a missing person and to visit and register prisoners of war. This is an incomplete list, and each discipline has worked largely in its own sphere. Furthermore in a given situation there are different actors each employing, manipulating, or even hindering the work of the different disciplines. These actors may be the governments, military bodies, international organisations including the United Nations, and non-governmental organisations. Clearly it is time for standards and guidelines on best practice for all professionals.

The International Committee of the Red Cross has been forced into undertaking an initiative, "The Missing," which has taken the form of a series of expert workshops and studies and a review of its own practice over time and by continent. The outcome has revealed ambiguity about the legal and ethical basis of any action involving forensic specialists, the lack of best practice guidelines to guide these specialists, the difficulty of accommodating local customs and culture in an investigation, and recognition of an inconsistency of the International Committee of the Red Cross's own practice with regard to missing people. At centre stage, however,

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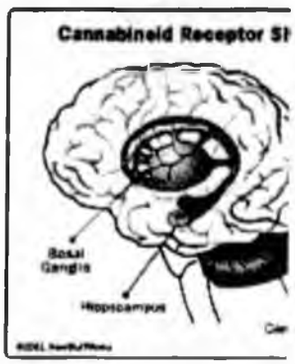
Drug Related News and Announcements

Marijuana may affect blood flow in brain

Study suggests users of drug have narrowed arteries



Reuters: February 7, 2005

WASHINGTON - Marijuana users have faster blood flow in their brains, even after a month of not smoking, U.S. researchers reported Monday.

The findings suggest they have narrowed arteries, similar to patients with high blood pressure and dementia, and could help explain reports that heavy marijuana users have trouble on memory tests, said the researchers at the National Institute on Drug Abuse in Baltimore.

Ronald Herning and Jean Lud Cadet tested 54 marijuana users, who smoked anywhere between two and 350 joints a w and 18 non-smokers.

They used Doppler sonograms to measure blood flow in volunteers' brains at the beginning of the study and a month lat everyone agreed to abstain from marijuana for the four weeks.

The smokers had faster blood flow, both at the start and after a month of abstinence, Herning and Cadet reported in the Neurology.

The smokers also had a higher pulsatility index score, or PI, which measures the amount of resistance to blood flow. Th researchers believe the higher PI is caused by narrower blood vessels.

"The marijuana users had PI values that were somewhat higher than those of people with chronic high blood pressure a diabetes," Herning said in a statement.

"However, their values were lower than those of people with dementia. This suggests that marijuana use leads to abnorr in the small blood vessels in the brain."

They found that blood flow improved in people who smoked up to 70 marijuana cigarettes a week -- people they defined moderate users -- after a month of avoiding cannabis.

Heavy users, who smoked up to 350 joints a week, saw no change in blood flow even after a month, the researchers sai

Researchers at Montreal's McGill University have reported that chronic consumers of cannabis lose molecules called CE receptors in the brain's arteries.

This reduces blood flow to the brain, causing attention deficits, memory loss, and impaired learning ability.

state convention. The Governor may declare to honor an anniversary of the association in conjunction with the convention.

- Another exception may be made when a national organization is holding a national meeting in Tennessee (e.g. NAACP National Conference). The Governor may declare "NAACP Week in Tennessee" in honor of the state and national organization in conjunction with its convention.

- Proclamations are **not** issued in honor of people, living or dead unless required by Tennessee Code Annotated (TCA).

- Requests will be accepted no more than 6 months in advance and will not be issued more than 3 months in advance of the event.

- A 14 business day notice is required to provide proclamations. If notice is given the Governor's office reserves the right to decline.

- Because of cost involved in writing and printing proclamations, a maximum of 5 originals of issued proclamations will be sent per year per constituent.

- Any draft language provided may be edited or rewritten at the discretion of the Governor's office.

- All proclamation requests must be in writing and can be submitted online via webform or via mail or fax and sent to:

Cara Wilson
State Capitol
Nashville, TN 37243
615-532-4562 phone
615-532-9712 fax

Governor's Office
Tennessee State Capitol
Nashville, TN 37243-0001
615.741.2001

National Institutes of Health
National Institute on Drug Abuse

FOR IMMEDIATE RELEASE
October 15, 2000

CONTACT:
Beverly Jackson
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(301) 443-6245

NIDA Researchers Find That Animals Exposed to Marijuana's Active Component Will Self-Administer the Drug

Scientists at the National Institute on Drug Abuse have demonstrated that laboratory animals will self- administer marijuana's psychoactive component, delta-9-tetrahydrocannabinol, in doses equivalent to those used by humans who smoke the drug. Self-administration of drugs by animals, long considered a model of human drug-seeking behavior, is characteristic of virtually all addictive and abused drugs.

"This study is simple and its findings are clear," says NIDA Director Dr. Alan I. Leshner. "Animals will work to get THC. This emphasizes further the similarity between marijuana and other abusable, addicting substances. Both animals and humans will work to acquire access to marijuana in the same way that both animals and humans change their behavior to get other drugs of abuse, like cocaine and heroin."

Dr. Steven Goldberg and colleagues at NIDA's Intramural Research Program in Baltimore, Maryland, report in the current issue of "Nature Neuroscience" that squirrel monkeys will self-administer intravenous injections of THC.

"This is the first study in which it has been possible to show that monkeys or other research animals will self- administer THC. There are many factors which may explain this behavior, including the fact that in our study we used doses of THC that are directly comparable to doses in marijuana smoke inhaled by humans," Dr. Goldberg says.

Before the study began, the scientists first established self-administration behavior in squirrel monkeys that received repeated intravenous injections of cocaine after pressing a lever 10 times for each injection. At the start of the study, the researchers replaced cocaine with saline solution and the animals' self-administration stopped. When saline was replaced with THC in a solution that would rapidly pass from blood to the brain, the animals resumed self-administration, rapidly pressing the lever to obtain on average 30

injections of THC during each of a series of 1- hour sessions. Treatment with a compound that prevented THC from binding to cannabinoid receptors on brain cells almost completely eliminated self-administration of THC, but had no effect in another group of monkeys self-administering cocaine under identical conditions, according to Dr. Goldberg.

"The drug-seeking behavior in these animals was comparable in intensity to that maintained by cocaine under identical conditions, and was obtained from a range of doses comparable to those self-administered by humans smoking a single marijuana cigarette," Dr. Goldberg says. "This finding suggests that marijuana has as much potential for abuse as other drugs of abuse, such as cocaine and heroin."

NOTE TO REPORTERS: The full text of the brief communication about this study is available in "Nature Neuroscience 2000", volume 3, pgs 1073-74 or at www.neurosci.nature.com.

The National Institute on Drug Abuse is a component of the National Institutes of Health, U.S. Department of Health and Human Services. NIDA supports more than 85 percent of the world's research on the health aspects of drug abuse and addiction. The Institute carries out a large variety of programs to ensure the rapid dissemination of research information and its implementation in policy and practice. Fact sheets on the health effects of drugs of abuse and other topics can be ordered free of charge in English and Spanish from NIDA Infofax at 1-888-NIH-NIDA (644-6432) or 1- 888-TTY-NIDA (889-6432) for the deaf. These fact sheets and further information on NIDA research and other activities can be found on the NIDA home page at www.drugabuse.gov.

1988	132	80	348	327	210	164	112	136
1989	122	96	326	280	175	175	116	99
1990	130	94	309	240	197	135	103	148
1991	154	96	302	265	180	171	160	101
1992	185	159	347	258	222	173	104	82
1993	244	222	364	355	229	210	124	136
1994	276	261	450	394	242	234	123	121
1995	336	274	510	401	226	256	137	141
1996	350	294	523	523	235	268	138	202
1997	329	313	547	478	266	227	145	139
1998	334	313	519	467	236	250	154	175
1999[1]	291	255	446	399	151	175	124	159

* Low precision; no estimate reported.

[1] Estimated using 2000 data only.

Source: SAMHSA, Office of Applied Studies, National Household Survey on Drug Abuse, 1999 and 2000.

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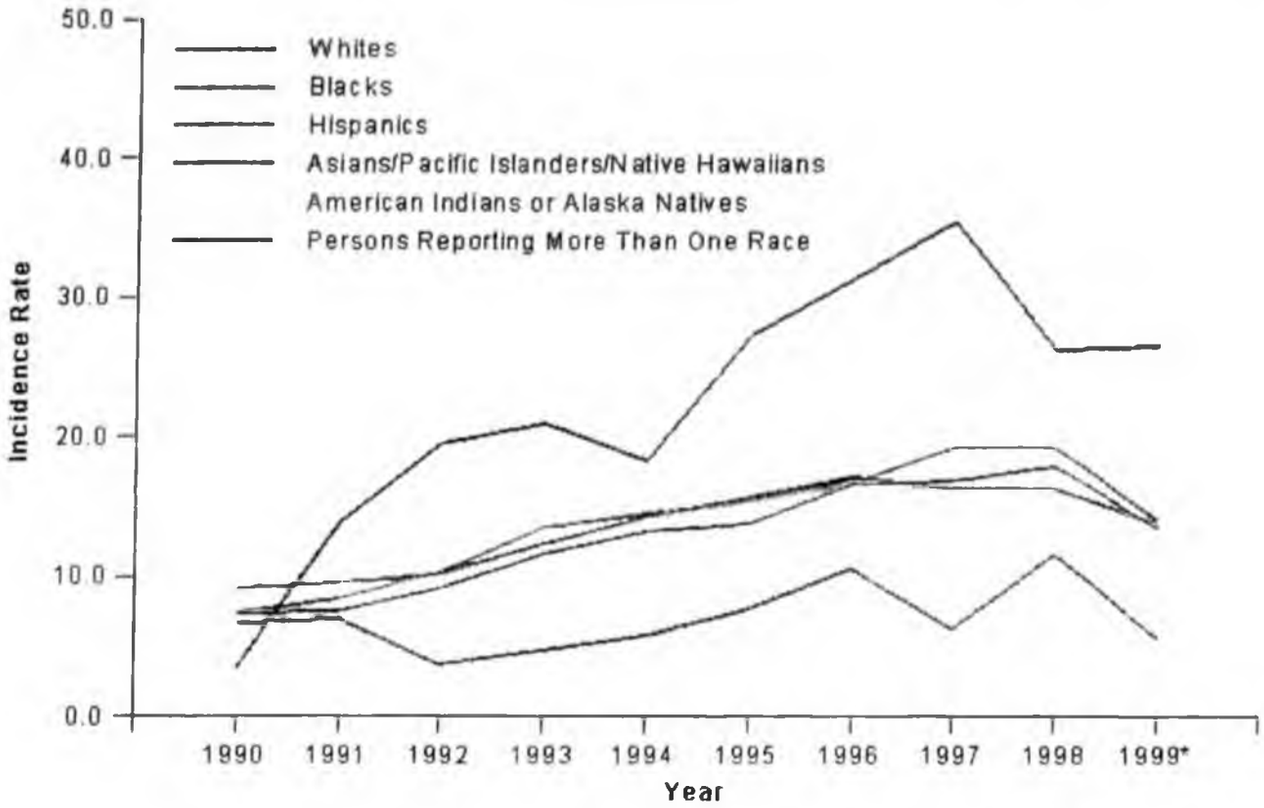
Table 3.3 Estimated Numbers (in Thousands) of Persons Who First Used Marijuana During the Years 1965 to 1999, Their Mean Age at First Use, and the Annual Incidence Rates of First Use (Per 1,000 Person-Years of Exposure), by Gender

Year	Number of Initiates (1,000s)		Mean Age at First Use		Incidence Rates[1]	
	Males	Females	Males	Females	Males	Females
1965	315	239	18.1	23.4	4.9	3.3
1966	642	333	18.8	19.9	9.8	4.5
1967	952	433	19.1	20.4	14.4	5.7
1968	1,212	527	19.0	20.1	18.1	6.8
1969	1,264	859	18.6	19.5	18.7	10.9
1970	1,479	1,112	18.6	19.0	21.7	13.9
1971	1,570	1,218	18.4	19.0	22.9	15.1
1972	1,560	1,258	19.2	18.3	22.7	15.5
1973	1,587	1,267	18.6	18.6	23.1	15.5



Note: The numerator of each rate is the number of persons who first used marijuana in the year, while the denominator is the person-time exposure measured in thousands of years for persons aged 12 or older.

* Estimated using 2000 data only.

Source: SAMHSA, Office of Applied Studies, National Household Survey on Drug Abuse, 1999 and 2000.

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Table 3.1 Estimated Numbers (in Thousands) of Persons Who First Used Marijuana During the Years 1965 to 1999, Their Mean Age at First Use, and the Annual Incidence Rates of First Use (Per 1,000 Person-Years of Exposure), for All Ages

Year	Number of Initiates (1,000s)	Mean Age at First Use	Incidence Rates[1]

1974	1,493	1,360	17.7	18.1	21.7	16.6
1975	1,405	1,469	17.7	18.9	20.4	17.8
1976	1,625	1,559	18.2	18.8	23.6	18.9
1977	1,647	1,517	18.0	18.5	23.9	18.4
1978	1,556	1,411	17.6	18.7	22.5	17.0
1979	1,507	1,352	17.5	18.7	21.7	16.2
1980	1,187	1,335	19.0	19.4	17.0	15.9
1981	896	971	17.2	18.6	12.6	11.4
1982	1,014	1,007	17.9	19.7	14.1	11.7
1983	1,049	815	18.9	17.4	14.4	9.4
1984	1,020	992	18.3	18.2	13.8	11.3
1985	1,021	844	18.2	17.9	13.6	9.5
1986	925	828	17.8	17.4	12.1	9.2
1987	773	815	17.3	17.9	10.0	9.0
1988	834	716	17.1	17.9	10.8	7.9
1989	787	660	17.5	17.8	10.3	7.3
1990	774	633	17.5	19.4	10.2	7.1
1991	837	648	18.1	17.8	11.2	7.3
1992	909	690	16.5	16.8	12.3	7.8
1993	1,009	945	16.8	17.6	13.8	10.8
1994	1,152	1,035	16.7	16.8	16.0	11.9
1995	1,254	1,103	16.4	16.7	17.7	12.9
1996	1,284	1,306	16.4	17.7	18.5	15.5
1997	1,318	1,176	17.0	16.9	19.3	14.1
1998	1,268	1,220	17.6	17.2	18.9	14.9
1999[2]	1,034	993	16.4	17.6	15.5	12.1

[1] The numerator of each rate is the number of persons who first used marijuana in the year, while the denominator is the person-time exposure measured in thousands of years.

[2] Estimated using 2000 data only.

Source: SAMHSA, Office of Applied Studies, National Household Survey on Drug Abuse, 1999 and 2000.

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1965	553	20.4	4.0
1966	975	19.2	7.0
1967	1,385	19.5	9.7
1968	1,738	19.4	12.0
1969	2,123	19.0	14.5
1970	2,592	18.7	17.5
1971	2,789	18.7	18.7
1972	2,819	18.8	18.8
1973	2,854	18.6	19.0
1974	2,853	18.9	18.9
1975	2,874	18.3	19.0
1976	3,184	18.5	21.0
1977	3,163	18.3	20.9
1978	2,967	18.1	19.5
1979	2,859	18.1	18.7
1980	2,522	19.2	16.4
1981	1,867	17.9	12.0
1982	2,021	18.8	12.8
1983	1,865	18.2	11.7
1984	2,012	18.3	12.4
1985	1,865	18.1	11.4
1986	1,753	17.6	10.6
1987	1,588	17.6	9.5
1988	1,550	17.4	9.2
1989	1,447	17.7	8.7
1990	1,407	18.3	8.5
1991	1,485	18.0	9.1
1992	1,599	16.7	9.8
1993	1,954	17.2	12.2
1994	2,187	16.7	13.8
1995	2,357	16.5	15.1
1996	2,590	17.1	16.8
1997	2,494	17.0	16.5
1998	2,488	17.4	16.7
1999[2]	2,028	17.0	13.6