The Medicinal Use of Marijuana
Medical Grand Rounds
University of Texas Southwestern Medical Center
April 1, 1999

Philip Keiser MD
Assistant Professor of Medicine

Disclaimer
Dr. Keiser does not have a significant relationship with growers, producers, or distributors of marijuana or any marijuana products.

Introduction

Marijuana has been widely used for hundreds of years as an intoxicant or an herbal remedy. Marijuana has been used worldwide as a medicine by millions of people. The first written account of marijuana use was published in China in the Fifth century BC. The plant has been used at various times in history as a treatment for tetanus, convulsive disorders, migraine, neuralgia, dysmenorrhea, postpartum psychoses, senile insomnia, depression, gonorrhea, and dependence on opium and chloral hydrate However, by 1941 marijuana was considered to have no therapeutic value. Since that time, possession and sale of marijuana remains illegal. Marijuana is been classified as a schedule I drug by the Drug Enforcement Agency, meaning that it has high abuse potential and no therapeutic value. Interest in the therapeutic potential of marijuana was revived in the early 1970s, when it was widely used as part of the counter. Several cancer patients discovered that smoking marijuana relieved chemotherapy induced nausea and vomiting. These anecdotal accounts led to the development of THC, one of the active ingredients of marijuana, as an anti-nausea and appetite stimulant for cancer and AIDS patients. At the same time efforts to legalize the use of marijuana for medicinal use began. Numerous groups reported anecdotal stories of the curative properties of marijuana. In addition to nausea and decreased appetite, marijuana was reported able to ameliorate the symptoms of glaucoma, multiple sclerosis, headache, dysentery, menstrual cramps, pain, and depression. These efforts, often supported by major medical journals, culminated in the approval of several propositions in several states that would legalize the possession of marijuana for medical purposes. The Drug Enforcement Agency strongly disagreed with the passage of the state statues. Citing supremacy of federal law, General Barry McCaffrey threatened to prosecute physicians who prescribed marijuana for their patients. Despite this stance, there has been growing support for the use of medicinal marijuana and currently 8 states either have or are considering legalization of this substance for medical use. Regardless of the popular support for the legalization of marijuana, several important questions must be answered before physicians should prescribe marijuana to their patients.

1. What actually constitutes a medicine?

2. Is marijuana effective in the treatment of diseases?

3. Is marijuana safe?

Epidemiology of Marijuana use

Marijuana has been tried by many European young adults and by most young adults in the USA and Australia. From 1962 to 1982, the use of marijuana increased 30-fold. It was estimated that more than a quarter of the American population has used it by the early eighties. Concurrent with the increase was a decrease in the age at which persons first used marijuana. In 1982, many marijuana users reported that they first used this agent in junior high school. The incidence of marijuana use decreased throughout the eighties but dramatically increased in the 1990s. By 1993, the proportion of participants in a Center for Disease Control survey who reported marijuana use was similar to those who reported marijuana use in 1983. Nearly one third (32.8%) of high school students nationwide had used marijuana during their lifetime. In 1995, this number had increased to 42.4% and by 1998 this percentage had increase to 47.1% . The proportion of students who reported active marijuana use also increased. In 1993 17.7% of students reported using marijuana within the past 30 days; in 1995 this percentage had increased to 25% and increased further to 26.5% in 1998. In each of these surveys, males are more likely to use marijuana than females. Studies of usage by race are inconsistent, with whites using marijuana more frequently that blacks in some surveys but not in others. Breakdown of marijuana use by race and sex, however, consistently demonstrates that African American females are least likely to use marijuana. Most marijuana use is intermittent. Most marijuana users stop in their smoking in their mid to late 20s, and very few engage in daily cannabis use over a period of years. In the USA and Australia, about 10 % of those who ever use cannabis become daily users, and another 20-30% use the drug weekly." Daily cannabis users are more likely to be white, male, to be less well educated, to use alcohol and tobacco regularly, and to use amphetamines, hallucinogens, psychostimulants, sedatives, and opioids. Because of uncertainties about

THC content, heavy cannabis use is generally defined as daily or near daily use for the purposes of studies of the effects of marijuana.

Pharmacology of Marijuana

Marijuana is obtained from the flowering tops of the female plant of *Cannabis sativa.* The active ingredient of marijuana is delta-9-tetrahydrocannabinol (THC). There are 480 other substances in marijuana including 66 other cannabinoid compounds. Little, if any, is known about the action of these other constituents of marijuana. The THC content is highest in the flowering tops, declining in the leaves, lower leaves, stems, and seeds of the plant. Marijuana is prepared from the dried flowering tops and leaves and has a THC content 0.5-5.0%. Hashish, on the other hand, is made dried cannabis resin and compressed flowers and has a THC content of 2-20%. Hashish oil may contain between 15% and 50% THC. The average THC content of marijuana probably increased over the past several decades. This increase is because of increased demand for more potent marijuana that was met by better methods of growing high-THC-content. For example, the Sinsemilla and Netherwood varieties can have a THC content of up to 20%.

Marijuana can is usually smoked in a rolled in paper call a "joint" or in a water pipe. Tobacco may or other objects are sometimes added to assist burning. Users usually inhale deeply and hold their breath to maximize absorption of THC by the lungs. Marijuana and hashish may also be eaten, but smoking is the easiest way to achieve the desired psychoactive effects. After inhalation, THC reaches the bloodstream rapidly. The bioavailability of THC ranges from 5% to 24%. Intoxication occurs within 6 to 121 minutes. Maximum effects occurring 15 to 30 minutes after the first puff; effects persist for 2 to 4 hours. As little as 2-3 puffs produces a "high" in occasional users, but regular users may smoke five or more joints a day. Users learn to modulate the effects by changing the depth and length of inhalation. Because THC is lipid soluble, it remains distributed in fat cells long after the psychoactive effects have worn off. THC has a half-life reported to be as long as hours. The lungs and liver convert THC to an active metabolite, 1 1-hydroxy-THC. The liver converts this compound to inactive metabolites, which are excreted by the kidneys. Orally administered, however, THC is slowly and erratically absorbed, giving blood levels that increase only gradually over four to six hours after administration. The total time THC or its metabolites may remain in the body is unknown. but studies show that THC does not accumulate in the blood, brain or testes.

Oral THC was developed as an alternative to smoking marijuana. It is available in a capsule known as dronabinol and is marketed under the trade name Marinol. The drug is erratically absorbed from the gastrointestinal tract. It is highly protein bound and fat-soluble and thus is distributed to many body organs. The drug is rapidly metabolized in the liver to several metabolites, of which several may be active. The drug is eliminated in the feces and in the urine. The half-life of the drug is 19 hours. It is approve by the Food and Drug Administration for the treatment of chemotherapy related nausea and for AIDS associated wasting. The recommended dosage for nausea is 5 mg/M^2 while the dosage for AIDS wasting is 2.5 mg twice daily. Most studies examining the effectiveness of THC have used dronabinol.

The National Institute of Drug abuse has developed standardized marijuana cigarettes in order to better study the effects of marijuana in humans. The cigarettes were blended to produce a final THC content of 1.0 to 1.5% and each cigarette weighed about 900 grams. Thus a standard dose of marijuana could be determined for each cigarette smoked. Since 1992, these cigarettes are no longer available through the NIDA.

In 1988 a cannabinoid receptor was identified in the central nervous system. Shortly thereafter, a natural internal ligand, arachidonoylethanolamide, commonly called anandamide (after the Sanskrit word *ananda* for "internal bliss") was identified. Anandamide is much less potent and has a shorter durtation than THC. Additional work revealed a peripheral receptor and five additional endogenous ligands. The central and peripheral receptors are termed CB1 and CB2 respectively. The CB1 receptors are found in regions of the brain involved in cognition, memory reward, pain perception, and motor coordination but are sparse in the

brainstem, which governs the cardiovascular and respiratory systems. CB1 receptors are also sparsely distributed throughout the spinal cord. In animal studies, anandamide binds easily to CB1 receptors, but with a 30-fold less affinity to peripheral receptors. CB2 receptors have been found in the testes and in the spleen. Cannabinoid receptors have also been identified in a wide variety of species ranging from humans to sea urchins. The biologic purpose of this system in humans and lower animals is unknown. CB1 receptors are believed to alter neuronal function by inhibition of adenylyl cyclase through the G protein system.

Marijuana has marked effects on the frontal lobe and other higher centers of the brain. Its effects are highly variable and modified by the individuals prior experience and expectations. The acute effects are dose dependent and peak 30 to 60 minutes after smoking. The major effects include euphoria, joviality, relaxation, and alterations of cognition, as well as alteration in sensory, and motor functions. When used in a social setting it may produce infectious laughter and talkativeness. Loss of short-term memory is significant effect of marijuana intoxication. As a consequence, time passes slowly for the intoxicated user. There is enhancement of sensory sensations including touch, hearing and taste. Depersonalization, a sensation of viewing oneself from outside the body, occurs. Attention, motor skills, reaction time, and skilled activities are impaired while a person is intoxicated. This particularly effects the ability to perform sequential mental tasks. Panic attacks and a perception or fear of permanent insanity are occasional effects. Reddened eyes accompany the marijuana high. Smoking or ingestion of marijuana increases heart rate by 20-50% within a few minutes to a quarter of an hour; this effect lasts for up to three hours. Blood pressure is increased while the person is sitting, and decreased while standing. The cardiovascular effects are negligible in healthy young users because tolerance develops to them. Drowsiness occurs after the euphoric effects.

Potential Therapeutic Uses of Marijuana

The therapeutic claims for marijuana are quite broad, spanning the spectrum from nausea to mental illness. Table 1 lists some of the conditions for which marijuana reportedly has a therapeutic benefit.

Table 1. Illness for which marijuana is claimed to be effective

AIDS related stress and depression	Epilepsy
AIDS Wasting	Glaucoma
Alcohol and Narcotic Withdrawal	Insomnia
Anorexia Nervosa	Migraine headaches
Asthma	Nausea
Back Spasms	Pain
Bacterial Infections	Paraplegia and Quadriplegia
Corns, Fistulas, Fibrosis	Spasticity and Paralysis from Multiple Sclerosis
Depression	Skin diseases (pruritis)
Emphysema	Smog related illnesses

Review of the medical literature, however, reveals few controlled studies of the efficacy of marijuana in the treatment of diseases. There is information suggesting a role of marijuana or of oral THC, the active ingredient of marijuana, in the treatment of chemotherapy induced nausea, as appetite stimulants, as a therapy for glaucoma, as a pain reliever, and as a treatment for the spasticity associated with multiple sclerosis. The studies demonstrating a positive effect in these illness are summarized in table 2.

Table 2. Illness for which there is credible medical evidence that marijuana has beneficial effects

Entity	Evidence
Chemotherapy related nausea	Case Reports from Marijuana Users Placebo Controlled Trials of THC Comparative trial of THC and standard anti-emetics Combinations of THC/anti-emetics vs anti-emetics alone THC versus smoked marijuana
AIDS Wasting	Case Reports from Marijuana Users Placebo Controlled Trial of THC
Pain	Case Reports from Marijuana Users Comparative Trial of THC and Codeine
Glaucoma	Decreased intra-ocular pressure with oral or topical THC
Multiple Sclerosis	Case Reports from Marijuana Users Placebo Controlled Trial of THC

Nausea

Most research on the effectiveness of marijuana has involved the use of oral THC (dronabinol). Marijuana or THC can be effective in the treatment of chemotherapy induced nausea that is refractory to other therapy. In one of the few studies that actually used smoked marijuana to treat nausea caused by cancer chemotherapy, Vinciguerra and colleagues found that smoked marijuana controlled nausea in patients in whom other conventional forms of antiemetic therapy had failed. Persons who responded to smoked marijuana tended to have previously used marijuana. This study was uncontrolled, and patients themselves evaluated the results. Smokers were required to inhale deeply and hold the smoke for 10 seconds. Twenty-five percent of the patients refused to smoke the marijuana. More than 20% of the patients dropped out of the smoking group before the end of the study, and 22% of the remaining patients reported no benefit from smoking marijuana. Kluin- Neleman and colleagues found that oral THC to be superior to placebo in the treatment of nausea. In this study, the toxicity of THC was so pronounced that over half of the subjects stated that they preferred nausea to THC. In some subjects, the plasma THC levels were as high as 300 ng/ml, levels consistent with those achieved by recreational marijuana smokers. Orr and colleagues studied patients who were refractory to other antiemetic regimens and found that THC was superior to prochlorperazine, which was superior to placebo. In another study of patients with refractory nausea, nausea completely or partially resolved in 72% of patients. The selection of refractory patients, however, introduces bias against the regimens that do not include THC.

Studies of THC in the treatment of non-refractory nausea also show a benefit to this agent. Ekert and colleagues found that oral THC was more effective than oral metoclopramide and prochlorperazine. They also found that drowsiness was more common with THC than with either metoclopramide or prochlorperazine. In a randomized, double-blind study comparing pure THC with smoked marijuana, Levitt and colleagues found that pure THC was more effective for nausea than smoked marijuana in 35% of patients. Forty-five percent of patients voiced no preference between the two. Lane and associates compared dronabinol plus prochlorperazine with single antiemetic agents. The combination regimen seemed to slightly mitigate the toxic effects of THC. However, 23% of the 60 patients withdrew from the

study because of adverse effects (which were psychotropic effects in all but 1 patient who withdrew). Gralla and associates found that intravenous metoclopramide provided more protection than did THC.

The effectiveness of THC was usually correlated to the blood levels of the drug. Chang and colleagues that plasma THC levels of at least 10 ng/mL were necessary to prevent nausea. If nausea occurred after the initial treatment, patients were assigned to smoked THC or placebo. Both THC and prochlorperazine were found to be more effective than placebo. In a study by Frytak and colleagues peak levels of THC ranged from 2.7 to 6.3 ng/mL levels below those required to prevent nausea.

There was also a high incidence of side effects in each of these studies. Sallan and colleagues reported adverse events in 81% of subjects, including hallucinosis, distortion of reality, and mental depression. Frytak reported that 32% reported toxicity even though they had low levels of blood THC. In addition, these studies were complicated because of their high drop out rates. In a study by Ungerleider et. al. 75 of 214 subjects dropped out because of uncertainty of their treatment assignments. Only one study compared intravenous anti-emetics with oral THC.

In summary, oral THC has been effective in treating nausea associated with cancer chemotherapy if patients are pretreated and doses are then repeated every 3 to 6 hours for approximately 24 hours. Efficacy is often associated with a sensation of intoxication. The studies included a wide and heterogeneous representation of tumors and chemotherapy regimens and there was no pattern of THC efficacy for any one type of tumor or chemotherapy. None of the studies compared THC or marijuana with the serotoxin antagonists ondansetron or granisetron.

Appetite Stimulants

Marijuana has been proposed as a therapy for weight loss associated with cancer or with HIV infection. The rationale for marijuana use is that it stimulates appetite resulting in increased caloric intake and weight gain. Mattes and colleagues compared the effects of oral and rectal suppository preparations of THC on appetite stimulation and calorie intake with those of smoked marijuana in healthy persons. All participants in this double blind, placebo-controlled study were experienced marijuana users; thus, the drug acceptance rate was relatively high. Smoked marijuana was no more effective than suppository THC in stimulating appetite, as measured by calorie intake. Rectal suppositories and oral THC were given at a dosage of 2.5 mg twice daily. Patients assigned to smoked marijuana had to inhale for 3 seconds and hold the smoke deeply in their lungs for 12 seconds; this process was continued until the cigarette was smoked to a stub. The plasma THC levels peaked more quickly with the inhaled THC but also decreased more quickly; in contrast, the levels achieved with suppository THC were more sustained.

There is limited data that marijuana increases appetite and weight gain in cancer and HIV infected patients. In an open labeled, prospective, uncontrolled study, low doses of THC improved appetite in patients with terminal cancer. Twenty-two percent of patients withdrew from the trial because of typical cannabinoid toxicity. Studies of have demonstrated a benefit of THC in AIDS patients. In a double blind, placebo-controlled, parallel group study 2.5 mg of oral THC twice daily effectively stimulated appetite in patients with AIDS. The investigators did not evaluate muscle mass or total body fat but did find that in patients who received oral THC, weight was maintained or increased slightly.

Glaucoma

THC can reduce intra-ocular pressure in laboratory animals and humans who have glaucoma. Cannabinol, nabilone, THC, and delta-8-tetrahydrocannabinol have been found to decrease intra-ocular pressure, whereas cannabidiol had no effect. They appear to act only against a primary symptom of the disease rather than against the underlying disease process. Intra-ocular pressure is reduced only if patients stay under the effects of THC almost continuously. Merritt and colleagues concluded that such side effects as hypotension, tachycardia, palpitations, and altered mental status precluded the use of these drugs in the general population with glaucoma.

Pain

There are limited controlled studies of the analgesic effects of marijuana. A study using rats found analgesic activity for cannabinoids in neuropathic pain. In a study comparing THC with codeine in 34 cancer patients, 10 mg of THC was roughly equivalent to 60 mg of codeine. This dose was well tolerated, with sedative but not psychic effects. Twenty milligrams of 20 of THC was more efficacious than codeine but, as with other dose ranging studies of THC, there were more side effects including causing depersonalization and other effects associated with the marijuana high.

Multiple Sclerosis

Anecdotal report and a case report have suggested that THC has benefits for patients with the spasticity of multiple sclerosis. Excruciating facial pain from up to 50 attacks per day of trigeminal neuralgia is experienced by 25 to 30% of patients with multiple sclerosis. Morphine can be an effective therapy for this condition but anecdotal reports suggest that marijuana gives prompt relief. A double blind, randomized, placebo controlled study of the effect of smoking marijuana in patients with multiple sclerosis showed an anti-spasticity and anti-tremor and anti-ataxia action. However, posture and balance were negatively affected by the treatment and were actually worse than at baseline. These findings are consistent with the deterioration of mental, motor, and postural functions associated with marijuana smoking in normal volunteers.

Hazards of Marijuana

The toxic or negative effects of exposure to marijuana depend on the route of delivery, the duration of exposure, the patient's age and immunologic status. Short- or long-term use often affects the central nervous system. Both smoked and oral THC have been associated with distortion of reality, euphoria, dysphoria, and changes in coordination and concentration. Some investigators have found more serious toxic effects, including hallucinosis, depersonalization, and paranoia.

Short Term Toxicities

Concentration, motor coordination, memorization, memory retrieval, and the ability to sort unimportant information are all adversely affected by the use of marijuana. These impairments are larger and more

Table 3. Acute Toxicities of Marijuana

Decreased Concentration
Impaired Motor Coordination
Decreased Short Term Memory
Impaired Driving Ability
Hallucinations
Dysphoria
Tachycardia/hypotension

persistent for difficult tasks that depend on sustained attention. The severity of these effects is not as grossly debilitating as those that are found with chronic heavy alcohol use. The ability to drive an automobile or fly an airplane is impaired with short-term marijuana use. The effects of recreational doses of cannabis on driving performance in laboratory simulators and standardized driving courses have been reported by some researchers as being similar to the effects when blood alcohol concentrations are between 0.07% and 0.10%. Marijuana use is frequently associated with vehicular trauma. Epidemiological studies of road-traffic accidents are equivocal because most drivers who have cannabinoids in their blood also have high blood alcohol concentrations. The separate effects of alcohol and cannabis on psychomotor impairment and driving performance are additive in laboratory tasks, however, so the main effect of cannabis use on driving may be in amplifying the impairments caused by alcohol.

Serious dysphoria and even hallucinosis have been reported with brief use of marijuana. Large doses of THC produce confusion, amnesia, delusions, hallucinations, anxiety, and agitation. Such reactions are rare, occurring after unusually heavy cannabis use; in most cases they remit rapidly after abstinence from cannabis.

Long Term Toxicities

Cognitive Effects

The chronic effects on the frontal lobe after prolonged use of marijuana are uncertain. There is some preliminary, but disputed, evidence that slightly diminished ability to concentrate may linger for months in chronic users after they stop using the drug. The reported effects are very subtle and of unknown duration. In one study, former users of cannabis were compared with current users and with controls. The three groups were closely matched for sex, age, years of education, I.Q., frequency of alcohol use, and frequency and duration of cannabis use. The former users (28 subjects) had smoked cannabis for an average of 3.8 years or 10.9 days per month, and had abstained for a mean of 2 years (range 3 months to 6 years). In an experiment to measure selective auditory attention, the three groups were given headphones to listen to a series of tone pips of varying duration, pitch, and location. They were required to press a button to identify a pre-described tone. Former users made a significantly lower percentage of correct selections than nonusers, but about the same number of correct selections as the current users. In another study, a group of heavy users who smoked at least 22 of the past 30 days were compared with a group of "occasional users" who used the drug a maximum of 9 out of the past 30 days. Both groups were abstinent for a minimum of 19 hours and then given a neuropsychologic test battery to measure verbal IQ, attention and memory. Heavy users showed greater impairment of attentional/executive functions than light users, particularly in learning of word lists and card sorting. The longer cannabis has been used, the more pronounced the cognitive impairment." Early studies that suggested gross structural brain damage with heavy use have not been supported by better controlled studies with better methods. These impairments are subtle, so it remains unclear how important they are for everyday functioning, and whether they are reversed after an extended period of abstinence.

Amodivational Syndrome

There is a cross-sectional association between heavy marijuana use in as a teenager and the risk of leaving high school education and of experiencing job instability in young adulthood. In longitudinal studies, however, the strength of this association is reduced when adjustments are made for the fact that heavy marijuana users have poorer high-school performance compared with their peers. There is some evidence that heavy use has adverse effects on family formation, mental health, and involvement in drug-related crime. As in the case of high school performance, the associations in cross-sectional studies are more modest in longitudinal studies after statistical adjustments for other pre-existing characteristics that independently predict these adverse outcomes.

Dependence syndrome

There is evidence that a cannabis dependence syndrome in heavy users of marijuana. Animals develop tolerance to the effects of repeated doses of THC. Tolerance to marijuana does develop, but its degree varies considerably among individuals. Heavy smokers of cannabis also develop tolerance to its subjective and cardiovascular effects. Dependence also develops but only after heavy daily use. Heavy users report withdrawal symptoms on the abrupt cessation of cannabis use. One study reports that approximately 16% of users report restlessness, sleep disturbance, decreased appetite upon marijuana withdrawal. Placing these symptoms in perspective, marijuana withdrawal appears to be mild compared to opiates or benzodiazepines. Heavy chronic users report problems in controlling their use and continue to use the drug despite experiencing adverse personal consequences. Marijuana addiction is not as common as other forms of addiction. About one in ten of those who ever use cannabis become dependent on it at some time during their 4 or 5 years of heaviest use compared to 15% addiction rate for alcohol, a 23% rate for opioids and a 32% rate for nicotine.

Table 4. Long Term Effects of Marijuana Use

	Long Term Effect	Association
Psychiatric Effects		
	Long Term Decrease in Concentration	Moderate
	Amodivation Syndrome	Moderate
	Dependence Syndrome	Strong
	Schizophrenia	Weak
	Other Addictions	Weak
Physiologic Effects		
	Lung Disease	Strong
	Cardiac Disease	Weak
	Immunosuppression	Weak
	Infections	Moderate
	Premature Death	Moderate
	Decreased Cognition in Offspring	Moderate

Marijuana and Addiction

Long-term and repetitive use of THC derivatives, especially by young persons, poses the problem of addiction. In the United States, marijuana use is consistently associated with subsequent use of harder drugs such as cocaine and heroin. This is most likely to occur because adolescents who are likely to use marijuana also have a propensity to use other illicit drugs. Once they begin using marijuana, they have social interaction with drug-using peers and greater access to illicit-drug markets, making them more likely to use other illicit drugs. The less compelling hypothesis is that cannabis use directly increases the use of other drugs. The best evidence that marijuana use does not predispose to other drug use is the fact that marijuana is less likely to be the entree drug in European countries.

Schizophrenia

There is an association between schizophrenia and chronic marijuana use. A cohort study of over 45000 Swedish conscripts were asked to report their frequency of cannabis use and followed for 15 years in the national register of psychiatric care, which records all psychiatric inpatient admissions in Sweden. Draftees who had used marijuana more than 50 times before induction into the military had an increased incidence of schizophrenia compared to non-users (relative risk = 6.0, 95% confidence interval 4.0-8.9). Those with moderate marijuana use, 11 to 50 times prior to induction, had less of risk of schizophrenia. (relative risk = 3.0, 95% Cl 1.6-5.5). A more recent study compared 63 individuals never exposed to marijuana with three groups: 37 current, 61 recent, and 50 past users. The three user groups had statistically significant higher mean scores on a personality scale measuring for schizotypy and psychoticism. Despite these associations, these studies are confounded by the fact many schizophrenic patients self medicate with alcohol and other illegal drugs.

Lung Disease

Smoking marijuana exposes patients to 50% higher levels of the procarcinogen benz-a-pyrene than does smoking tobacco. Marijuana smoking results in carboxyhemoglobin levels that are five times higher and tar levels that are three times higher than those produced by tobacco smoking. Long-term exposure to smoked marijuana is associated with many adverse effects, including impaired lung function, reduced

specific conductance and increased airway resistance, heightened alveolar cellular response. In vitro studies have demonstrated DNA damage to human alveolar macrophages and suppression of anti-herpes activity by alveolar macrophages. Long-term marijuana smokers also use health care resources at an increased rate because of respiratory problems. These findings suggest that long term marijuana use would cause lung cancer and COPD. Despite these findings there are no long term studies associating marijuana use with these lung diseases.

Cardiac Disease

Marijuana causes tachycardia, orthostatic hypotension and peripheral vasodilatation and decreased platelet aggregation. THC increased heart rate with concomitant local vasodilatation causes the reddened conjunctivae associated with marijuana use. Prolonged exposure causes hypotension and bradycardia. Despite these effects, there have been myocardial infarctions or arrhythnias reported with marijuana use. This may be because most marijuana users are young and are at low risk for cardiac disease.

Carcinogenesis

Marijuana smoke is mutagenic *in vivo* and *in vitro*. It may also be carcinogenic. Three studies have shown an increased risk of nonlymphoblastic leukemia, rhabdomyosarcoma, and astrocytoma in children whose mothers reported using marijuana during their pregnancies. None of these was a planned study of the association. In these studies marijuana use was one of many potential confounders included in statistical analyses of the relation between the exposure of interest and childhood cancer.

Immunologic suppression and risks of infections

THC impairs cell-mediated and humoral immunity rats, decreasing their resistance to infection. Non-cannabinoids in marijuana smoke impair the actions of alveolar macrophages. The relevance of these findings to human health is uncertain because the doses of THC used in animal studies have been very high, and tolerance may develop to the effects on immunity in human beings. A few studies that have pointed to the adverse effects of cannabis on human immunity have not been replicated. There is no conclusive evidence that consumption of cannabinoids impairs human immune function, as measured by numbers of T lymphocytes, B-lymphocytes, or macrophages, or immunoglobulin concentrations. Despite initial case reports, there is no reliable evidence that smoking marijuana increases the viral load in AIDS patients. Many patients with AIDS commonly smoke marijuana to relieve the nausea caused by antiretroviral drugs and for weight gain. Two prospective studies of HIV positive homosexual men have shown that cannabis use is not associated with an increased risk of progression to AIDS.

Numerous pathogenic bacteria including Klebsiella, Enterobacter, group D Streptococcus, and Bacillus species have been cultured from marijuana, and infections with salmonella and fungi have been associated with marijuana use. AIDS patients are especially susceptible to pulmonary aspergillosis and other pathogenic contaminants that may be in marijuana. Smoking drugs does increase the risk of *Pneumocystis carinii* and bacterial pneumonias in HIV-positive patients. Despite these reports, there have not been wide spread epidemics of pulmonary infections associated with marijuana use.

Marijuana and Pregnancy

Smoking marijuana may cause birth defects. Chronic administration of high doses of THC to animals lowers testosterone secretion, impairs sperm production, motility, and viability, and disrupts the ovulatory cycle. Cannabis administration during pregnancy reduces birth-weight in animals. Low birth weight has been reported in children of mothers who smoke marijuana. These studies are confounded by the fact that low birth weight commonly occurs in children of mothers who smoke cigarettes. There is also an increased prevalence of nonlymphocytic leukemia in children of mothers who smoked marijuana while pregnant, suggesting a causal relationship. Children born to mothers who smoked marijuana very subtle impairments of executive function or individual's ability to plan ahead, anticipate and suppress behaviors that are, incompatible with a current goal. For example, three year olds have lower scores on intellegence tests than three year olds whose mothers did not smoke marijuana. At age four, there are increased problems with

behavior, language, sustained memory, and sustained attention. These problems are persistent at age 6and are significantly more pronounced at about age nine.

Premature mortality

There have been two prospective epidemiological studies of mortality among marijuana users. A Swedish study of mortality during 15 years among male military conscripts showed an increased risk of premature death among men who had smoked marijuana 50 or more times by age 18. Violent and accidental death was the main contributor to this excess. The association between mortality and marijuana use disappeared after multivariate statistical adjustment for alcohol and other drug use. Sydney and colleagues reported a 10-year study of mortality in marijuana users aged between 15 and 49 years among 65 171 members of the Kaiser Permanente Medical Care Program. The sample consisted of 38% who had never used marijuana, 20% who had used fewer than six times, 20% who were former users, and 22% who were current users. Regular marijuana use had a small association with premature mortality (RR 1-33), which was wholly explained by increased deaths from AIDS in men. This may have been because marijuana use was a marker for male homosexual behavior in this cohort.

Physicians and Marijuana Use

Several surveys have examined oncologists' choices of therapy for the nausea caused by chemotherapy. Doblin and Kleiman surveyed 2430 oncologists (response rate, 43%) and found that 44% of the respondents had recommended illegal marijuana to at least one patient having chemotherapy. These oncologists said smoking the drug was more effective and at least as safe as oral THC. The results of this survey have been widely misquoted. For example, Grinspoon and Bakalar incorrectly stated in a major medical journal that "44% of oncologists," rather than 44% of oncologists responding to the survey, had recommended marijuana to their patients. Schwartz and Beveridge surveyed oncologists practicing in the Washington, DC area to determine their preferences for the treatment of nausea caused by chemotherapy. Oral THC or smoked marijuana ranked ninth of nine choices for mild nausea and sixth out of nine for severe nausea. Approximately 25% of the respondents who treated their patients with marijuana reported that the patients had adverse side effects. Another survey of 1500 clinical adult oncologists conducted in 1994 found that serotonin receptor antagonists were the treatment of choice for chemotherapy associated nausea. This study had a 75% response rate. Eighty eight percent of physicians 88% of respondents had never marijuana to a patient and only 1% estimated that they had recommended marijuana more than five times a year.

Legal Barriers

Use of marijuana was legal in the United States until 1938. Possession and selling of the substance remains a felony under federal statues and in most of the states. With increase in illegal usage of marijuana in the 1960s the drug was classified as schedule I in 1970, signifying that the drug was considered to have no therapeutic value and was highly addictive and dangerous. Currently, this list includes heroin, PCP and LSD as well as marijuana. In 1972 a California group petitioned the Drug Enforcement Agency to reclassify marijuana. The group requested that marijuana be reclassified as schedule II. This would allow for limited therapeutic use of the substance. In 1988, the DEA asked administrative law judge Francis Young asked by the Drug Enforcement Administration to comment on the merits of rescheduling marijuana. Young suggested that marijuana be rescheduled for nausea associated with cancer chemotherapy. He also concluded that there was insufficient evidence to warrant the use of marijuana for glaucoma or pain. Young rejected as ``specious" the argument that medicinal use of marijuana would encourage recreational use. ``Marijuana can be harmful. But the same is true of dozens of drugs or substances," he said. ``It is essential for this agency, and its administrator, calmly and dispassionately to review the evidence of record, correctly to apply the law, and act accordingly."

The administrator of the Drug Enforcement Administration rejected Young's opinion and stated that Young had relied mostly on anecdotal information and ignored the prevailing scientific. The rescheduling petition was then appealed to the U.S. Court of Appeals for the District of Columbia. In rejecting the petition to reschedule marijuana, the Court determined that only rigorous scientific proof can satisfy the

requirement of "currently accepted medical use," which is necessary for a substance to be considered a medicine. All potential medicines are submitted to this standard. Specifically, the court ruled that the marijuana did not meet the definition of a drug because it was not a pure substance with a standard delivery system and that there was insufficient scientific evidence to demonstrate conclusively that marijuana was effective in the treatment of any specific illness.

In 1993 Congressman Dan Hamburg of the United States House of Representatives requested that the National Institutes of Health review the reported therapeutic benefits of marijuana make recommendations regarding its medicinal usage. The report delivered to Congress in July 1994 stated that " ... studies supporting these claims are lacking despite anecdotal claims that smoked marijuana is beneficial. Scientists at the National Institutes of Health indicate that after carefully examining the existing preclinical and human data, there is no evidence to suggest that smoked marijuana might be superior to currently available therapies for glaucoma, weight loss associated with AIDS, nausea and vomiting associated with cancer chemotherapy, muscle spasticity associated with multiple sclerosis, or intractable pain".

Table 5. Status of Medicinal Marijuana Laws

Laws in effect	Doctor Approval?	Amount patient can posses	ID card required?	Status of law
Alaska	Yes	1 oz. and 6 plants, 3 flowering	Yes, costs $25	Took effect March 4
Arizona	Yes	Unspecified limits	No	Took effect after 1996 vote; reaffirmed in 1998
California	Yes	Unspecified limits	No	Took effect after 1996 vote; implementation under way
Oregon	Yes	Up to 3 oz. With 7 plants, 3 flowering	Yes	Took effect Dec. 3
Washington	Yes	60-day supply	No	Took effect Dec. 3
Laws pending or proposed				
Colorado	Yes	2 oz. And 6 plants, 3 flowering	Yes	Voters approved Nov. 3 but vote invalid for lack of petition signatures; new vote expected in 2000
District of Columbia	Yes	"Sufficient quantity " to treat illness	No	Congress blocked Nov. 3 vote count; now in court
Maine	Yes	1.25 oz. And 6 plants, 3 flowering	No	On ballot Nov. 2 1999
Nevada	Yes	Legislature to decide	Yes	Constitutional amendment must pass twice; approved in 1998, newt vote in 2000

Despite these seemingly definitive legal and scientific pronouncements regarding the medicinal usage of marijuana, there has been a strong and effective grass roots effort to legalize the medicinal use of marijuana. In November 1996, ballot initiatives in California and Arizona allowed physicians to either recommend or prescribe crude marijuana. These initiatives placed no limitations on age or on the disorders for which crude marijuana could be used. The response from the federal government was swift and harsh. General Barry McCaffrey, Director of the White House Office of National Drug Control Policy threatened

to prosecute physicians for prescribing or helping patients obtain marijuana. In addition, the implementation of these laws has met resistance. State courts overturned Arizona's law five months after the referendum. The Attorney General of California, Dan Lungren, blocked implementation of the proposition 215. Public outcry against this position was so strong that the Department of Health and Human Services advised that "physicians could discuss medical marijuana with patients but could not recommend it." In November 1998, voters in six states (Alaska, Arizona, Colorado, Nevada, Oregon, and Washington) passed ballot initiatives in support of medical marijuana.

The Colorado vote was invalid, however, because a state court ruled that there had not been enough valid signatures to place the initiative on the ballot. Initiatives to legalize medical marijuana are being put on the ballot in Maine this November and in Nevada and perhaps in Colorado in 2000. They are under consideration in another four states: Florida, Massachusetts, Michigan and Ohio. In California, the republican attorney general was replaced by the Democrat Bill Lockyer, who announced that he favors the law and will work to lift all legal obstacles. Each of these laws is problematic as possession and distribution of marijuana remains illegal. The paradox of these statues is that patients who wish to legally use marijuana for medicinal purposes must at some point, obtain the drug from someone who is illegally distributing the marijuana. The laws explicitly permit patients with specific chronic or terminal diseases to smoke marijuana as long as they have a doctor's recommendation. The U.S. Justice Department continues to prosecute marijuana law violators, including some medical users, at a record pace. So far, the government has not prosecuted any doctors who recommend marijuana to patients

The Institute of Medicine Report

In January 1997, the White House Office of National Drug Control Policy (ONDCP) asked the Institute of Medicine to conduct a review of the scientific evidence to assess the potential health benefits and risks of marijuana and its constituent cannabinoids. That review began in August 1997. A report was issued in March 1999. Information for this study was gathered through scientific workshops, site visits to cannabis buyers' clubs and HIV/AIDS clinics, analysis of the relevant scientific literature, and extensive consultation with biomedical and social scientists. After extensive review, the Institute of Medicine appointed a panel of nine experts to advise the study team on technical issues.

This panel concluded that " for patients, such as those with AIDS or undergoing chemotherapy, who suffer simultaneously from severe pain, nausea, and appetite loss, cannabinoid drugs might offer broad spectrum relief not found in any other single medication." They also concluded that marijuana is not a completely benign substance. Marijuana smoke delivers harmful substances, including most of those found in tobacco smoke. Because marijuana is a plant, its contain a mixture of biologically-active compounds thus will have variable pharmacological effects. Thus the authors conclude that future of cannabinoid drugs lies in the development of chemically defined drugs that act on the cannabinoid systems. Based on their extensive review, the panel made the following recommendations.

Recommendation 1:

Research should continue into the physiological effects of synthetic and plant-derived cannabinoids and the natural function of cannabinoids found in the body. Because different cannabinoids appear to have different effects, cannabinoid research should include, but not be restricted to, effects attributable to THC alone.

Recommendation 2:

Clinical trials of cannabinoid drugs for symptom management should be conducted with the goal of developing rapid-onset, reliable, and safe delivery systems.

Recommendation 3: Psychological effects of cannabinoids such as anxiety reduction and sedation, which can influence medical benefits, should be evaluated in clinical trials.

Recommendation 4: Studies to define the individual health risks of smoking marijuana should be conducted, particularly among populations in which marijuana use is prevalent.

Recommendation 5: Clinical trials of marijuana use for medical purposes should be conducted under the following limited circumstances: trials should involve only short-term marijuana use (less than six months); be conducted in patients with conditions for which there is reasonable expectation of efficacy; be approved by institutional review boards; and collect data about efficacy. The goal of clinical trials of smoked marijuana would not be to develop marijuana as a licensed drug, but rather as a first step towards the possible development of nonsmoked, rapid-onset cannabinoid delivery systems.

Recommendation 6: Short-term use of smoked marijuana (less than six months) for patients with debilitating symptoms (such as intractable pain or vomiting) must meet the following conditions:

1. failure of all approved medications to provide relief has been documented;
2. the symptoms can reasonably be expected to be relieved by rapid-onset cannabinoid drugs;
3. such treatment is administered under medical supervision in a manner that allows for assessment of treatment effectiveness;
4. and involves an oversight strategy comparable to an institutional review board process that could provide guidance within 24 hours of a submission by a physician to provide marijuana to a patient for a specified use.

CONCLUSIONS

Marijuana has a beneficial effect in a variety of conditions, particularly in the treatment of intractable nausea vomiting associated with cancer chemotherapy. Marijuana also may be beneficial in the treatment of AIDS associated wasting and in pain control. There is reason to believe that smoked marijuana may be more efficacious than oral THC for these conditions because it achieves higher serum levels of THC more rapidly than dronabinol. Despite these benefits, marijuana cannot be considered a drug. There are no standardized preparations of marijuana and levels of the active ingredients vary greatly in crops of marijuana. In addition, there are many other components of marijuana smoke that are uncharacterized and their pharmacologic action remains unknown. Smoking marijuana is not safe by any definition. Marijuana smoke contains all of the components of tobacco smoke and delivers higher concentrations of these components to the lungs. Although there is little evidence that marijuana causes lung cancer other diseases, this lack of data is because there has been little effort to examine the relationship to between marijuana smoking and lung cancer. The limited data that marijuana is helpful for asthma must be weighed against extensive data that smoking is harmful to people with asthma and other lung diseases. Marijuana can also be contaminated with bacteria and fungi and has been associated with dangerous lung infections. The recommendation by the Institute of Medicine that alternative deliverey systems of the active form of marijuana be developed is reasonable. However, their recommendation that marijuana be provided until such time that these systems are available seems unrealistic, given the legal barriers and risks of marijuana use.

REFERENCES

1. Abel EL. Effects of prenatal exposure to cannabinoids. In: Pinkert TM, ed. Current research on the consequences of maternal drug abuse. NIDA Research Monograph no 59. Washington: Department of Health and Human Services, 1985.
2. Adams IB, Martin BR. Cannabis: pharmacology and toxicology in animals and humans. *Addiction. 1*996;91(11):1585-614.
3. Agurell S, Halldin M, Jan-Erik L, et al. Pharmacokinetics and metabolism of delta- 1 -tetrahyd roca nnabinol and other cannabinoids with emphasis on man. Pharmacol *Rev. 1*986;38(l):21-43.
4. Alexander PC, et al. Effect of marihuana on intraocular and blood *pressure in* glaucoma. Ophthalmology. 1980;87(3):222-8.and its consequences. In: Kalant H, Corrigal W, Hall W, Smart R, eds.
5. Andreasson S, Allebeck P, Engstrom A, Rydberg U. Cannabis and schizophrenia: a longitudinal study of Swedish conscripts. Lancet 1987; ii: 1483-86.
6. Andreasson S, Allebeck P. Cannabis and mortality among young men: a longitudinal study of Swedish conscripts. Scand,7 Social Med 1990; 18: 9-15.
7. Andreasson S, Engstrom A, Allebeck P, et al. Cannabis and schizophrenia. *Lancet 1*987;2:1483-5.
8. Anthony JC, Warner LA, Kessler RC. Comparative epidemiology of dependence on tobacco, alcohol, controlled substances and inhabitants: basic findings from the National Comorbidity Study. Clin Exp Psychopharmacol 1994; 2: 244-68.
9. Bachman JG, Wadsworth KN, O'Mally PM, et al. Smoking, drinking and drug use in voung adulthood. Malwah, New Jersey: Lawrence Erlbaum Associates, 1997.
10. Barbers RG, Gong H Jr, Tashkin DIP, Oishi J, Wallace JIM. Differential examination of bronchoalveolar lavage cells in tobacco cigarette and marijuana smokers. Am Rev Respir Dis. 1987 135:1271-5.
11. Beal JE, Olson R, Laubenstein L, Morales JO, Bellman P, Yangco 6, et al. Dronabinol as a treatment for anorexia associated with weight loss in patients with AIDS. J Pain Symptom Manage. 1995;lOi89-97.
12. Bell R, Wechsler H, Johnston LD. Correlates of college student marijuana use: results of a US national survey. *Addiction. 1*997;92(5):571-81.
13. Benowitz NL, Jones RT. Cardiovascular effects of prolonged delta-9tetra hydroca n nabincil ingestion. Clin Pharmacol Ther. 1975;18:287-97.
14. Bloch E. Effects of marijuana and cannabinoids on reproduction, endocrine function, development and chromosomes. In: Fehr KO, Kalant H, eds. Cannabis and health hazards. Toronto: Addiction Research Foundation, 1983.
15. Block RI, Wittenborn JR. Marijuana effects on the speed of memory re-trieval in the letter-matching task. Int J Addict. 1986;21:281-5.
16. Bloom JW, Kaltenbom WT, Paoletti P, et al. Respiratory effects of non-tobacco cigarettes. BMJ 1987; 295: 1516-18.
17. Bonner R. Marijuana rescheduling petitions. Federal Register. 1992:10499-508. Alliance or Cannabis Therapeutics v. DEA. U.S. Court of Appeals for the District of Columbia. 92-1168. Petition for the review of controlled substance. February 1994.
18. Brookoff D, Campbell EA, Shaw LM. The unclerreporting of cocainerelated trauma: drug abuse warning network reports vs. hospital toxicology tests. Am J Public Health. 1993;83:369-71.
19. Cabral GA, Vasquez R. delta-9-tetrahydrocannabinol suppresses macrophage extrinsic antiherpesvirus activity. Proc Soc Exp Biol Med. 1992;199: 255-8.
20. Cabral GA, Vasquez R. delta-9-Tetrahydrocannabinol suppresses macrophage extrinsic anti-herpesvirus activity. In: Nahas GG, Latour C, eds. Cannabis: Physiopathology, Epidemiology, Detection. Boca Raton, FL: CRC Pr; 1993: 137-53.
21. Caiaffa W, Vlahof D, Graham NMH, et al. Drug smoking, *pneumocystis* carinii pneumonia, and immunosuppression increase risk of bacterial pneumonia in human immunodeficiency virus-serocositive injection drug users. Am J *Respir Crit Care Med.* 1994;150:1493--8.
22. Caplan GA, Brigham BA. Marijuana smoking and carcinoma of the tongue. Is there an association? Cancer 1989; 66: 1005-06.
23. Chait LD, Piern J. Effects of smoked marijuana on human performance: a critical review. In: Murphy A, Bartke J, eds. Marijuana/cannabinoids: neurobiology and neurophysiology. Boca Raton: CRC, 1992.
24. Chang AE, Shiling DJ, Stillman RC, Goldberg NH, Seipp CA, Barofsky 1, et. al. Delta-9-tetahydrocannabinol as an antiemetic in cancer patients receiving high-dose methotrexate. A prospective, randomized evaluation. Ann Intern Med. 1979,91:819-24.

25. Chesher G. Cannabis and road safety: an outline of research studies to examine the effects of cannabis on driving skills and actual driving performance. In: Road Safety Committee, Parliament of Victoria. The effects of drugs (other than alcohol) on road safety. Melbourne: Road Safety Committee, Parliament ofVictoria, 1995: 67-96.
26. Chopra GS, Smith JW. Psychotic reactions following cannabis use in East Indians. Arch Gen Psychiatry 1974; 30: 24-27.
27. Coates RA, Farewell VT, Raboud J, et al. Cofactors of progression to acquired immunodeficiency syndrome in a cohort of male sexual contacts of men with human immunodeficiency virus disease. Am I Epidemiol 1990; 132: 717-22.
28. Committee on Drug Abuse of the Council on Psychiatric Services. Position statement on psychoactive substance use and dependence: update on marijuana and cocaine. Am J Psychiatry. 1987;144:698-702.
29. Compton DR, Dewey WL, Martin BR. Cannabis dependence and tolerance production. Adv Alcohol Subst Abuse. 1990;9:129-47.
30. Consroe P, Musty R, Rein J, et al. The perceived effects of smoked cannabis on patients with multiple sclerosis. Eur *NeurolL* 1997;38:44-5.
31. Dahl RE, Scher MS, Williamson DE, Robles N, Day N. A longitudinal study of prenatal marijuana use. Effects on sleep and arousal at age 3 years. Arch Pediatr Adolesc Med. 1995;149:145-50.
32. Day NL, Richardson GA, Goldschmidt L. Robles N, Taylor PM, Stoffer DS, et al. Effect of prenatal marijuana exposure on the cognitive development of offspring at age three. Neurotoxicol Teratol. 1994; 16:169-75.
33. De Fonseca FR, Carrera MRA, Navarro M, et al. Activation of corticotropin-releasing factor in the limbic system during cannabinoid withdrawal. Science. 1997;276:2050-4.
34. Denning W, Follansbee E, Scolaro M, et. al. Pulmonary aspergillosis in the acquired immunodeficiency syndrome. N *Engl J Med.* 1991;324:654-62.
35. Der G, Gupta S, Murray RM. Is schizophrenia disappearing? Lancet 1990;335:513-16.
36. Devane WA, Dysarz FAI, Johnson MR, et al. Determination and characterization of a cannabinoid receptor in rat brain. Mol Pharmacol. 1988;34:60r-13.
37. Devane WA, Hanus L, Breurer A, et al. Isolation and structure of a brain constitutent that binds to the cannabinoid receptor. *Science.* 1992;258:1946-9.
38. Doblin RE, Kleiman MA. Marijuana as antiemetic medicine: a survey of oncologists' experiences and attitudes. J Clin Oncol. 1991;9:1314-9.
39. Ekert H, Waters KID, Jurk IH, Mobilia J, Loughnan P. Amelioration of cancer chemotherapy-induced nausea and vomiting by delta-9-tetrahydrocannabinol. Med J Aust. 1979;2:657-9.
40. Elsohly MA, Harland E, Murphy Jr- Wirth P, Waller CW. Cannabinoids in glaucoma: a primary screening procedure. J Clin Pharmacol. 1981,21:472S-SS.
41. Elsohly MA, Harland EC, Benigni DA, Waller CW. Cannabinoids in glaucoma II: the effect of different cannabinoids on intraocuiar pressure of the rabbit, Curr Eye Res. 1984;3:841-50.
42. Fergusson D, Horwood J. Early onset cannabis use and psychosocial adjustment in young adults. Addiction 1997; 92: 279-96.
43. Fleisher M, Winawer SJ, Zauber AG. Aspergillosis and marijuana [Letter], Ann Intern Med. 1991; 115:578-9.
44. Fletcher JM, Page JB, Francis DJ, et al. Cognitive conrelates of longterm cannabis use in Costa Rican men. Arch Gen Psychiatry 1996; 53: 1051-57.
45. Fligiel SE, Venkat H, Gong H Jr, T~shkln DIP. Bronchial pathology in chronic marijuana smokers: a light and electron microscopic study. J Psychoactive Drugs. 1988,20:33-42.
46. Fligiel SEG, Rodi MD, Kleerup EC, et al. Tracheobronchial histopathology in habitual smokers of cocaine, marijuana and/or tobacco. Chest 1997; 112: 319-26.
47. Fried PA, Watkinson B, Willan A. Marijuana use during pregnancy and decreased length of gestation. Am i Obstet Gynecol. 1984; 150:23-7.
48. Fried PA. Marijuana use by pregnant women: neurobehavioral effects inneonates. Drug Alcohol Depend. 1980;6:415-24.
49. Fried PA. Prenatal exposure to tobacco and marijuana: effects during pregnancy, infancy and early childhood. Clin Obstet Gynecol 1993; 36: 319-36.
50. Fried PA. The Ottawa Prenatal Prospective Study (OPPS): methodological issues and findings-it's easy to throw the baby out with the bath water. Life Sci. 1995;56:2159-68.
51. Fried PA. The Ottawa Prenatal Prospective Study (OPPS): methodological issues and findings-it's easy to throw the baby out with the bath water. *Life Sci.* 1995;56:2159-68.
52. Friedman H, Shivers SC, Klein TW. Drugs of Abuse and the Immune System. In: Dean JH, Luster M1, eds. Immunotoxicology *and Immunopharmacology, New* York: Raven Press; 1994.

53. Frytak S, Mcertel CG, O'Fallon JR, Rubin J, Creagan ET, O'Connell MJ, et al. Delta-9-tetrahydrocannabinol as an antiemetic for patients receiving cancer chemotherapy. A comparison with prochlorperazine and a placebo. Ann Intern Med. 1979;91:825-30.
54. Gardner EL. Cannabinoid Interaction with Brain Reward Systems-The Neurobiological Basis of Cannabinoid Abuse. In: Murphy L, Bartke A, eds. *MarijuanalCannabinoids Neurobiology and Neurophysiology.* Boca Raton, Fla: CRC Press; 1992:275-335.
55. Gerard CM, Mollereau C, Vassart G, et al. Molecular cloning of a human cannabinoid receptor which is also expressed in testis. Biochemistry. 1991;279:129-34.
56. Gerostamoulos J, Drummer OH. Incidence of psychoactive cannabinoids in drivers killed in motor vehicle accidents. J Forensic Sci. 1993;38:649-56.
57. Gjercle H, Kinn G. Impairment in drivers due to cannabis in combination with other drugs. Forensic Sci Int. 1991;50:57-60.
58. Goodman L, Gilman A. The *Pharmacological Basis of* Therapeutics. New York: Macmillan; 1941.
59. Gralla RJ, Tyson LB, Clark RA, Bordin LA, Kelsen DP, Kalman LB. Antiemetic trials with high dose metoclopramide: superiority over THC, and preservation of efficacy in subsequent chemotherapy courses [Abstract]. Proceedings of the American Society of Clinical Cincology. 1982;1:58.
60. Greenberg HS, Werness AS, Pugh JE, Andrus RD, Anderson DJ, Domino MD. Short-term effects of smoking marijuana on balance in patients with multiple sclerosis and normal volunteers. Clin Pharmacol Ther. 1994;55:324-8.
61. Grinspoon L, Bakalar JB. Marihuana as medicine. A plea for reconsideration. JAMA. 1995;273:1875-6.
62. Grinspoon L, Bakalar JB. *Marihuana: The* Forbidden Medicine. New Haven: Yale University Press, 1997.
63. Gross G, Roussaki A, Ikenberg H, Drees N. Genital warts do not respond to systemic recombinant interferon alfa-2a treatment during cannabis consumption. Dermatologica. 1991 ' 181203-7~
64. Grufferman S, Schwartz AG, Ruymarm FB, Mauer HM. Parent's u e of cocaine and marijuana and increased risk of rhabdomyosarcoma in their children. Cancer, Causes & Control 1993; 4: 217-24.
65. Hall W, Solowij N, Lemon J. The health and psychological consequences of cannabis use. National Drug Strategy Monograph Series no 25. Canberra: Australian Government Publishing Service, 1994.
66. Herkenham M. Localization of Cannabinoid Receptors in Brain and Periphery. In: Pertwee R, ed. *Cannabinoid* Receptors. 1st ed. San
67. Hesketh PJ, Beck TM, Uhlenhcpp M, et al. Adjusting the dose of intravenous ondansetron plus dexamethasone to the emetogenic potential ofthe chemotherapy *regimen. J* Clin Onco/. 1995;13(8):2117-22.
68. Hindrik WJ, O'Hanlon JF. Marijuana and actual driving performance. Washington, DC: U.S. Department of Transportation. 1993. Report no. DOT HS 808078.
69. Hingson R, Alpert A Day N, Dooling E, Kayne H, Morelock S, et al. Effects of maternal drinking and marijuana use on fetal growth and development. Pediatrics. 1982;70:539-46.
70. Hoffman D, Brunneman DK, God GB, Wynder EL. On the carcinogenicity of marijuana smoke. Recent Advances in Phytochemistry. 1975;9:63-81.
71. Hollister LE. Marijuana and immunity. I Psychoactive Drugs 1992; 24: 159-64.
72. Institute of Medicine. *Marijuana and Health. Washington,* DC: National Academy Press: 1982.
73. Jessor R, Chase JA, Donovan JE. Psychosocial correlates of marijuana use and problem drinking In a national sample of adolescents. *Am J Public Health.* 1980;70(6):604-13.
74. Johnston L, O'Malley P, Bachman *J. Monitoring the :7Liture Study.* University of Michigan; 1996.
75. Jurgensen K. Anti-drug focus keeps marijuana from the ill. USA Today. 18 July 1995:14A.
76. Kandel DB, Davies M. Progression to regular marijuana involvement: phenomenology and risk factors for near daily use. In: Glantz M,
77. Kaplan HB, Martin SS, Johnson RJ, Robbins CA. Escalation of marijuana use: application of a general theory of deviant behavior. J Health Soc Behav. 1986;27:44-61.
78. Kaslow RA, Blackwelder WC, Ostrow DG, et al. No evidence for a role of alcohol or other psychoactive drugs in accelerating immunodeficiency in HIV-1 -positive individuals: a report from the Multicentre AIDS Cohort Study. JAA1A 1989; 261: 3424-29.
79. Kiplinger GF, Manno JE, Rodda BE, Forney RB. Dose-response analysis of the effects of tetrahydrocannabincil in man. Clin Pharmacol Ther. 1971;12: 650-7.
80. Kirby JM, Maull KI, Fain W. Comparability of alcohol and drug use in injured drivers. South Med J. 1992;85:800-2.
81. Kline J, Stein Z, Hutzler J. Cigarettes, alcohol and marijuana: varying associations with birthweight. Int J Epidemiol. 1987;16:44-51.

82. Kluin-Neleman JC, Neleman FA, Meuwissen OJ, Maes RA. delta-9-tetra hydrocannabinol (THQ as an antiemetic in patients treated with cancer chemotherapy: a double-blind cross-over trial against placebo. Vet Hum Toxicol. 1979 ' 21:338-40.
83. Kuitjen RR, Bunin GR, Nass CC, Meadows AT. Parental occupation
84. Lane M, Vogel CL, Ferguson J, Krasnow S, Sailers JL, Hamm J, et al. Dronabinol and prochlorperazine in combination for treatment of cancer chemotherapy-induced nausea and vomiting. J Pain Symptom Manage. 1991;6: 352-9.
85. Leirer VO, Yesavage JA, Morrow DG. Marijuana carry-over effects on psychomotor performance: a chronicle of research. in: Nahas GG, Latour C, eds. Cannabis: Physicipathology, Epidemiology, Detection. Boca Raton, FL: CRC Pr; 1993:47-60.
86. Lemberger L, Weiss J, Watanabe A, et al. Delta-9-tetrahydrocannabino]: temporal correlation of the psychological *effects and* blood levels aftervarious routes of administration. *NEngl.J Med. 1*972;286:685-8.
87. Leon-Carrion J. Mental performance in long-term heavy cannabis use: a preliminary report. Psychol Rep. 1990;67:947-52.
88. Leuchtenberger C. Effects of marihuana (cannabis) smoke on cellular biochemistry of in vitro test systems. In: Fehr KO, Kalant H, eds. Cannabis and health hazards. Toronto: Addiction Research Foundation, 1983.
89. Levitt M, Faiman C, Hawks R, Wilson A. Randomized double blind comparison of delta-9-tetrahydrocannabinol and marijuana as chemotherapy antiemetics [Abstract). Proceedings of the Annual Meeting of the American Society of Clinical Oncology, Toronto, 6-8 May 1984. 1984 3:91.
90. Linn S, Schoenbaurn SC, Monson FIR, et al. The association of marijuana use with outcome of pregnancy. *Am* J *Public Health* 1983;73:1161-4.
91. Linszen DH, Dingemans PM, Lenior ME. Cannabis abuse and the course and outcome of schizophrenia. Schizophrenia Bull 1990; 16: 87-372.
92. Lucas VS Jr, Laszlo J. delta-9-Tetrahydrocannabinol for refractory vomiting induced by cancer chemotherapy. JAMA. 1980;243:1241-3.
93. Martin BR. Cellular effects of cannabinoids. Pharmacol *Rev.* 1986;38:45-74.
94. Martin BR. The THC receptor and its antagonists. In: Na as GG, Bu s TF, eds. Drug Abuse in the Decade of the Brain. Amsterdam: IOS Pr; 199 :13944.
95. Marzuk PM, Tardiff K, Leon AC, Sitajic M, Morgan EB, Mann JJ. Prevalence of recent cocaine use among motor vehicle fatalities in New York City. JAMA. 1990;263:250-6.
96. Mathers DC, Gh~dse AH. Cannabis and psychotic illness. Br J Psychiatry. 1992;161:648-53.
97. Mattes RD, Engelman K, Shaw LM, Elsohly MA. Cannabinoids and appetite stimulation. Pharmacol Biochem Behav 1994,49:187-95.
98. McLaughlin MA, Chiou GC. A synopsis of recent developments in antiglau-coma drugs. J Ocul Pharmacol. 1985,1:101-21.
99. Mechoulam R, Feigenbaum JJ. Towards cannabinod drugs. In: Ellis GP, West GB, eds Progress in Medicinal Chemistry. v 24. Oxford, UK: Elsevier; 1987.
100. Meinck HM, Schonle PW, Conrad B. Effect of cannabinoids on spasticity and ataxia in multiple sclerosis. J *Neurol. 1*989;236(2):120-2.
101. Merritt JC, Crawford WJ, Alexander PC, Anduze AL, Gelbart SS. Effect of marijuana on intraocular and blood pressure in glaucoma. Ophthalmology. 1980;87:222-8.
102. Miller NS, Gold MS, Pottash AC. A 12-step treatment approach for marijuana (cannabis) dependence. J Subst Abuse Treat. 1989;6:241-50.
103. Munro S, Thomas KL, Abu-Shaar M. Molecular characterization of a peripheral receptor for cannabinoids. Nature. 1993;365:61-4.
104. Munson AE, Fehr KO. Immunological effects of cannabis. In: Fehr KO, Kalant H, eds. Cannabis and health hazards. Toronto: Addiction Research Foundation, 1983.
105. Murison G, Chubb CB, Maeda S, Gemmell MA, Huberman E. Cannabinods induce incomplete maturation of cultured human leukemia cells. Proc Natl Acad Sci. U S A. 1987;84:5414-8.
106. Murray JB. Marijuana's effects on human cognitive functions, psychomotor functions, and personality. J Gen Psychol. 1986 113:23-55.
107. Musty RE, Kaback L. Relationships between motivation and depression in chronic marijuana users. *Life Sci.* 1995;56(23/24):2151--8.
108. Nahas CG. Historical outlook of the psychopathology of cannabis. In: Nahas GG, Latour C, eds. Cannabis: Physiopathology, Epidemiology, Detection. Boca Raton, FL: CRC Pr 1993:95-9.
109. National Institute of Drug Abuse. Preliminary Estimates from the 1994 National Household Survey, Advance Report No. 10. in: Marijuana use and mortality. Am J Public *Health. 8*7:585--90

110. National Institute on Drug Abuse. *Marijuana: Facts* for Teens. 1995; U.S. Dept. of Health and Human *Services.* NIH Publication no. 95-4037.
111. Nelson K, Walsh D, Deeter P, Sheehan F. A phase 11 study of delta-9tetrahydrocannabinol for appetite stimulation in cancer-associated anorexa. J Palliat Care. 1994;10:14-8.
112. Newcombe T, Bender P. Consequences of adolescent drug use: impact on the lives of young adults. Newbury Park, California: Sage Publications, 1988.
113. Noyes RJ, Brunk FS, Avery DH, et al. The analgesic properties of delta9-tetrahydrocannabinol and codeine. Clin Pharmacol Ther. 1975;18(l):84-9.
114. OhIsson A, Lindgren JE, Wahlen A, et al. Plasma delta-9-tetrahydrocannabinol concentrations and clinical effects after oral and intravenous administration and smoking. Clin Pharmacol *Ther.* 1980;28:409-16.
115. Onaivi ES, Chakrabarti A, Chaudhuri G. Cannabinoid *Receptor Genes. Prog Neurobiol.* 1996;48:275-305.
116. Orr LE, McKernan JF, Bloome B. Antemetic effect of tetrahydrocannabinol. Compared with placebo and prochlorperazine in chemotherapy-associated nausea and emesis. Arch Intern Med. 1980 ' 140:1431-3.
117. Pertwee RG. Pharmacological, Physiological and Clinical Implications of the Discovery of Cannabinoid Receptors: An Overview. In: Jenner P, ed. *Cannabinoid Receptors.* 1st ed. San Diego: Academic Press. 1995:263.
118. Polen MR. Health care use by frequent marijuana smokers who do not smoke tobacco. *West* J *Med.* 1993;158:596-601.
119. Pope FIG, Yurgelun-Todd D. The residual congitive effects of heavy marijuana use. JAA1A 1996; 275: 521-27.
120. Pope HG Jr, Yurgelun-Todd D. The residual cognitive effects of heavy marijuana use in college students. JAMA. 1996;275:521-7.
121. Poster DS, Penta JS, Bruno S, Macdonald JS. delta 9-tetrahydrocannabi-nol in clinical oncology. JAMA. 1981;245:2047-5
122. Richardson GA, Day NL, McGauhey PJ. The impact of prenatal marijuana and cocaine use on the infant and child. Clin Obstet Gynecol 1993;36:302-18.
123. Robison LI, Buckley JD, Daigle AE, et al. Maternal drug use and the risk of childhood nonlympholastic leukemia among offspring: an epiderniologic investigation implicating marijuana. Cancer 1989; 63: 1904-11.
124. Robison LL, Buckley JD, Daigle AE, Wells R, Benjamin D, Arthur DC. Maternal drug use and risk of childhood non-lymphoblastic leukemia among offspring. An epidemiologic investigation implicating marijuana (a report from the Childrens Cancer Study Group). Cancer. 1989;63:1904-11.
125. Ross SA, Elsohly MA. Constituents of Cannabis Sativa L. XXVIII. A review of the natural constituents: 1980-1994. 1 Pharm Sci. 1995;4: 1 -10.
126. Sallan SE, Cronin C, Zelen M, Zinberg NE. Antiemetics in patients receivtng chemotherapy for cancer: a randomized comparison of delta-9-tetrahy-
127. Sallan SE, Zinberg NE, Frei E 3d. Antiemetic effect of delta -9-tetrahydro-cannabinol in patients receiving cancer chemotherapy. N Engl J Med. 1975; 293:795-7
128. Schwartz RH, Beveridge RA. Marijuana as an antiernetic drug: how useful is it today? Opinions from clinical oncologists. J Addict Dis. 1994;13:53-65.
129. Schwartz RH, Voth EA, Sheridan MJ. Marijuana to prevent nausea and vomiting in cancer patients: a survey of clinical oncologists. South *MedJ. 1*997;90(2):167-72.
130. Schwartz RH. Gruienewald PJ, Klitzner M, iedio P. Short-term memory impairment in cannabis-dependent adolescents. Am J Dis Child. 1989;143: 1214-9.
131. Schwartz RH. Marijuana: an overview. Pediatr Clin North Am. 1987;34:305-17.
132. Sciderstrom CA, Tritillis AL, Shankar BS, Clark WE, Cowley A. Marijuana and alcohol use among 1023 trauma patients. In: Nahas GG, Latour C, eds. Cannabis: Physiopathology, Epidemiology, Detection. Boca Raton, FL: CRC Pr; 1993:79-91.
133. Sherman MP, Aeberhard EE, Wong VZ, Simmons MS, Roth MD, Tashkin DIP. Effects of smoking marijuana, tobacco or cocaine alone or in combination on DNA damage in human alveolar macrophages. Life Sci. 1995;56: 2201-7.
134. Sherrill DI_ Krzyzanowski JW, Bloom JW, Lebowitz MD. Respiratory effects of non-tobacco cigarettes: a longitudinal study in general population. Int Y Epidentiol 199 1; 20: 132-37.
135. Sidney S, Beck JE, Tekawa IE, et al. Marijuana use and mortality. Am J Public Health 1997; 87: 585-90.
136. Smiley A. Marijuana: on road and driving simulator studies. In: Kalant H, Corrigal W, Hall W, Smart R, eds. The health effects of cannabis. Toronto: Addiction Research Foundation, 1998.
137. Solomons K, Neppe VM, Kuyl JIM. Toxic cannabis psychosis is a validentity. S Afr Med J. 1990;78:476-81.
138. Solowij N. Cannabis and cognitive ftinctioning. Cambridge: Cambridge University Press, 1998.

139. Solowij N. Do cognitive impairments recover following cessation of cannabis use? Life Sci. 1995,5:2119-26.
140. Solowiji N, Michie PT, Fox AM. Differential impairments of selective attention due to frequency and duration of cannabis use. Biol Psychiatry. 1995;37: 731-9.
141. Specter SC, Klein TW, Newton C, Mondragon M, Widen R, Friedman H. Marijuana effects on immunity: suppression of human natural killer cell activity by delta-9-tetrahydrocannabinol. Int J Immuncipharmacol. 198618:741-5.
142. Sriclar KS, Raub WA, Weatherby NL, et al. Possible role of marijuana smoking as a carcinogen in the development of lung cancer at an early age. _7 Psychoactive Drugs 1994; 26: 285-88.
143. Stapleton S. Medical pot: feds say talk is OK, just don't recommena it. *American Medical News.* 1997;40:1,8 1.
144. Stephens RS, Roffman RA, Simpson EE. Adult marijuana users seeking treatment. Y Consult Clin Psychol 1993; 61: 1110-04.
145. study. Ani J Obstet G - vnecol 1995; 172: 19-27.
146. Tanda G, Pontieri FE, Chiara GD. Cannabinoid and heroin activation of mesolimbic dopamine transmission by a common mu-1 opioid receptor mechanism. *Science.* 1997;276:2048-50.
147. Tashkin DIP, Calvarese BM, Simmons MS, Shapiro BJ. Respiratory status of seventy-four habitual marijuana smokers. Chest. 1980,78:699-706.
148. Tashkin DIP, Coulson AH, Clark VA, Simmons M, Bourque LIB, Duann S, et al. Respiratory symptoms and lung function in habitual heavy smokers of marijuana alone, smokers of marijuana and tobacco, smokers of tobacco alone, and nonsmokers. Am Rev Respir Dis. 1987;135:209-16.
149. Tashkin DIP, Shapiro BJ, Lee YE, Harper CE. Subacute effects of heavy marijuana smoking on pulmonary function in healthy men. N Engl J Med. 1976 ' 294:125-9~
150. Tashkin DP, Fligiel S, Wu TC, et al. Effects of habitual use of marijuana and/or cocaine on the lung. In: Chiang CN, Hawks RI, eds. Research findings on smoking of abused substances. National Institute on Drug Abuse Research Monograph 99. Rockville, Maryland: National Institute on Drug Abuse, 1990.
151. Tashkin DP, Simmons M, Clark V. Effect of habitual smoking of marijuana alone and with tobacco on nonspecific airways hyperreactivity. J Psychoactive Drugs. 1988;20:21-5.
152. Tashkin DP, Simmons MS, Sherrill DL, Coulson AH. Heavy habitual marijuana smoking does not cause an accelerated decline in FEV1 with age. Am Y Respir Critical Care Med 1997; 155: 141-48.
153. Taylor DN, Wachsmuth lK, Shangkuan YH, Schmidt EV, Barrett TJ. Schrader JS, et al. Salmonellos(s associated with marijuana: a multistate outbreak traced by plasmid fingerprinting. N Engl J Med. 1982;306:1249-54,
154. Turner WM, Tsuang MT. Impact of substance abuse on the course and outcome of schizophrenia. Schizophrenia Bull 1990; 16: 87-95.
155. Ungerleider JT, Andrysiak T, Tashkin DIP, Gale RP. Contamination of marijuana cigarettes with pathogenic bacteria-possible source of infection in cancer patients. Cancer Treat Rep, 1982,66:589-90.
156. Ungerleider JT, Andrysialk T, Fairbanks L Goodnight J, Sarnia G, Jamison K. Cannabis and cancer chemotherapy: a comparison of oral delta-9tetrahydrocannabinol and prochlorperazine. Cancer. 1982,50:636-45.
157. Varma VK, Malhotra AK, Dang R, Das K, Nehra R. Cannabis and cognitive functions: a prospective study. Drug Alcohol Depend. 1988;21:147-52.
158. Vincent BJ, McQuiston DJ, Einhorn LH, et al. Review of cannabinoids and their antiernetic effectiveness. Drugs. 1983;25(Suppl. 1):53-62.
159. Vinciguerra V, Moore T, Brennan E. Inhalation marijuana as an antiemetic for cancer chemotherapy. N Y State J Med. 1988,88:525-7.
160. Vinciguerra V, Moore.T, Brennan E. Inhalation marijuana as an antiernetic for cancer chemotherapy. New York State Journal *of Medicine. 1*988;88:525-7.
161. Voth EA, Brookoff D. Book review of Marijuana: The Forbidden Medicine. Ann Intern Med. 1994;120:348.
162. Wall ME, Sadler BM, Brine D, et al. Metabolism, disposition, and kinetics of delta-9-tetrahydrocannabinol in men and women. *Clin* Pharmacol *and Ther.* 1983;34:352-63.
163. Weisbeck GA, Schuckit MA, Kalmijn JA, et al. An evaluation of the history of marijuana withdrawal syndrome in a large population. Addiction 1996; 91: 1469-78.
164. Wiesbeck GA, Schuckit MA, Kalmijn JA, et al. An evaluation of the history of a marijuana withdrawal syndrome in a large population. Addiction. 1996;91(10):1469-78.
165. Williams JH, Wellman NA, Rawlins JNP. Cannabis use correlates with schizotypy in healthy people. *Addiction.* 1996;91(6):869-77.
166. Wu TC, Tashkin DIP, Djahed B, Rose JE. Pulmonary hazards of smoking marijuana as compared with tobacco. N Engl J Med. 1988;318:347-51,

167. Wu TC, Tashkin DP, Djahed B, et al. Pulmonary hazards of smoking marihuana as compared with tobacco. *NEnglJMed. 1*988;318:347-51.
168. Yamaguchi K, Kandel DB. Patterns of drug use from adolescence to adulthood: II-sequences of progression. Am Y Public Health 1984; 74: 668-72.
169. Yesavage JA, Leirer VO, Denarl M, Hollister LE. Carry-over effects of marijuana intoxication on aircraft pilot performance: a preliminary report. Am J Psychiatry. 1985;142:1325-9.
170. Young FIL Opinion and recommended ruling, marijuana rescheduling petition. U.S. Department of Justice, Drug Enforcement Administration. Docket 86-22. September 1988.
171. Zeltser R, Seitzer Z, Eisen A, et al. Suppression of neuropathic pain behavior in rats by a non-psychotropic synthetic cannabinoid with NIVIDA receptor-blocking *properties. Pain.* 1991;47(l):95-103.
172. Zimmerman S. Zimmerman AM. Genetic effects of marijuana. Int J Addict. 1990-91;25:19-31

Zuckerman 6, Frank DA, Hingson R, Ami H, Levenson SM, Kayne H, et. al. Effects of maternal marijuana and cocaine use on fetal growth. N Engl J Med. 1989;320:762-8.