SB

74

TESTIMONY AGAINST (FILE 1)

Alaska Civil Liberties Union

An Affiliate of the American Civil Liberties Union
P. O. Box 201844, Anchorage, AK 99520-1844
Phone: (907) 258-0044 Fax: (907) 258-0288 Email: akclu@akclu.org

Documents Submitted by William R. Satterbert, Jr., Esq., in Support of Response of David S. Noy to State's Petition for Hearing Dated 1/22/04, State v. Noy, Supreme Court No. S-11297

Submitted to Senate Health, Education and Social Services Committee
Friday, April 1, 2005

SB 74 – *An Act making findings relating to marijuana use and possession…*

A. Earleywine, Mitch, Understanding Marijuana: A New Look at the Scientific Evidence (New York: Oxford University Press, 2002), "Cannabis Pharmacology", Chapter 6.

B. Senate of Canada: Special Committee on Illegal Drugs. 37th Parliament, 1st Session. Cannabis: Our Position for a Canadian Public Policy, Summary Report (September, 2002)

C. Senate of Canada: Special Committee on Illegal Drugs. 37th Parliament, 1st Session. Cannabis: Our Position for a Canadian Public Policy, "Cannabis: From Plant to Joint", Chapter 5 (September, 2002).

D. Earleywine, Mitch, Understanding Marijuana: A New Look at the Scientific Evidence (New York: Oxford University Press, 2002), References (listing approximately 600 reference sources)

E. Pacula, R. and Kilmer, B., "Marijuana and Crime: Is There a Connection Beyond Prohibition?", National Bureau of Economic Research (October 2003).

F. Fals-Stewart, W. et al., "Intimate Partner Violence and Substance Use: A Longitudinal Day-to-Day Examination", 28 Addictive Behaviors (2003).

G. Putnins, A., "Substance Use and the Prediction of Young Offender Recidivism", 22 Drug and Alcohol Review (June 2003).

H. Earleywine, Mitch, Understanding Marijuana: A New Look at the Scientific Evidence (New York: Oxford University Press, 2002), "Stepping Stones, Gateways, and the Prevention of Drug Problems", Chapter 3.

I. Sidney, S. et al., "Marijuana Use and Cancer Incidence, California, United States", 8 Cancer Causes and Control (May 1997).

J. Bredt, B. et al., "Short-Term Effects of Cannabinoids of Immune Phenotype and Function in HIV-1-Infected Patients", 42 Journal of Clinical Pharmacology (2002).

K. Grant, I. et al., "Non-Acute (Residual) Neurocognitive Effects of Cannabis Use: A Meta-Analytic Study", 9 Journal of the International Neuropsychological Society (December 2002).

L. Jones, S. et al., "Cannibinoid Receptor Systems Therapeutic Targets for Tumour Intervention", 7 Expert Opinion (2003).

M. Iversen, L., "Cannabis and the Brain", 126 Brain (2003).

N. DSM-IV criteria for substance abuse and substance dependence.

O. "Trends in Initiation of Substance Use", National Survey on Drug Use and Health, Chapter 6 (2002).

P. "Discussion", National Survey on Drug Use and Health, Chapter 10 (2002).

Q. Drug and Alcohol Information Services Information System (March 29, 2002).

R. Morral, A. et al., "Reassessing the Marijuana Gateway Effect", 97 Addiction (2002).

S. Senate of Canada: Special Committee on Illegal Drugs. 37th Parliament, 1st Session. Cannabis: Our Position for a Canadian Public Policy, "Stepping Stone to Other Drugs?" Chapter 6 (September, 2002).

T. Earleywine, Mitch, Understanding Marijuana: A New Look at the Scientific Evidence (New York: Oxford University Press, 2002), "Social Problems", Chapter 9.

A

6
Cannabis Pharmacology

Understanding marijuana's impact on biological systems requires a description of its active components. This chapter begins by identifying the mind-altering molecules in marijuana, the substances that contain these chemicals, and their respective potencies. It continues with a discussion of the way these substances enter the body, metabolize, and reach their sites of action. The remainder of the chapter focuses on the receptors that respond to these cannabinoids and the natural substances in the body that work at these same sites.

Marijuana contains more than 60 compounds unique to the plant called cannabinoids. They interact with each other in interesting ways, altering their impact. Cannabinoids appear in a variety of strengths in marijuana, hashish, hash oil, and synthetic medications like nabilone, dronabinol, and levonantradol. People eat or smoke these products, leading to slower or faster absorption of chemicals. The cannabinoids alter the permeability of nerve membranes. They also react with their own special receptors—CB1 in the brain and nervous system and CB2 in the immune system. Researchers have identified substances native to the body that also work on these receptors, including anandamide and arachidonolyl-glycerol. Details of each of these topics appear in the following sections.

Active Ingredients—the Cannabinoids

A first step in understanding marijuana's impact involves identifying its active components. Cannabis contains more than 400 different chemical

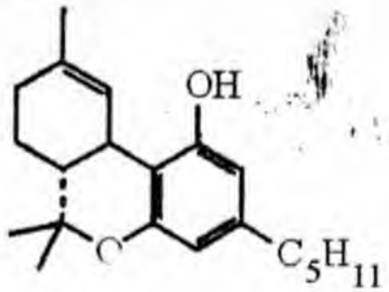


Figure 6.1. Delta-9-THC. This cannabinoid is responsible for most of marijuana's psychoactive effects.

compounds. At least 66 are unique to the plant and receive the name "cannabinoids." The best known cannabinoid is probably delta-9 tetrahydrocannabinol (THC). Considerable research has also examined the related molecule delta-8 THC. Two conventions exist for naming chemicals: formal and monoterpenoid. Thus, delta-9 THC (the formal name) is also called delta-1 THC (the monoterpenoid name). Similarly, delta-8 THC is also known as delta-6 THC. This text uses only the formal names. THC alone refers to the delta-9 variety. Delta-9 THC and delta-8 THC appear to produce the majority of the psychoactive effects of marijuana. As figures 6.1 and 6.2 reveal, the molecules differ only in the location of the double bond in the first carbon ring.

Delta-9 THC is more abundant in the plant, leading researchers to hypothesize that it is the main source of the drug's impact. The liver breaks delta-9 THC down into 11-OH-delta-9 THC (11-hydroxy-delta-

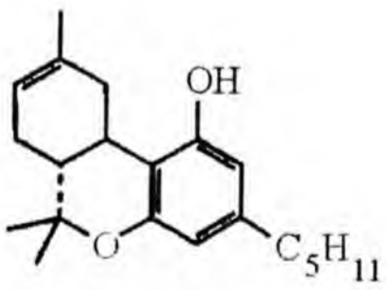


Figure 6.2. Delta-8-THC. This cannabinoid produces some of marijuana's psychoactive effects, but it is less abundant than delta-9-THC.

9-THC). This metabolite also causes psychoactive effects, including changes in subjective sensations. As figure 6.3 reveals, it only differs from THC by a few atoms, but it may be three times as potent because it reaches the brain more readily (Razdan, 1986).

Two other common cannabinoids are cannabinol and cannabidiol, depicted in figures 6.4 and 6.5, respectively. Delta-9-THC, cannabinol, and cannabidiol are the most prevalent psychoactive chemicals in the plant and provide the majority of marijuana's effects. For example, THC and cannabidiol account for 95% of marijuana's active ingredients (Doorenbos, Fetterman, Quimby, & Turner, 1971). Dozens of other cannabinoids exist, but most are variants of delta-9 THC, delta-8 THC, cannabinol, and cannabidiol. Research has uncovered six additional families of molecules unique to marijuana. All begin with the familiar "cannab" prefix. These include cannabichromene, cannabicyclol, cannabielsoin, cannabigerol, cannabinidiol, and cannabitriol. Many differ little from each other. All are lipophilic, meaning that they dissolve in fat, fatty tissue, or fatty fluids. They are not soluble in water. Thus, despite the claims of many aging hippies, teas made from boiled marijuana probably do not create extensive cannabinoid effects.

A great deal of research focuses on THC. Some investigators have turned their attention to the other cannabinoids, particularly cannabinol and cannabidiol. Studies address the activity of each of these chemicals alone and in combination with THC. Cannabinol has generated considerable interest, in part, because THC breaks down into this compound

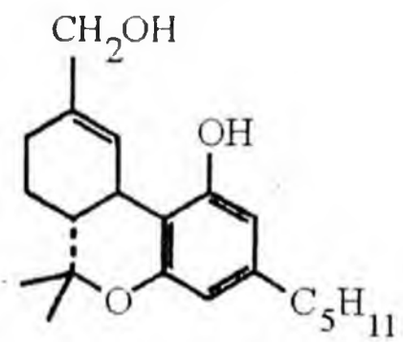


Figure 6.3. 11-hydroxy-delta-9-THC. The liver breaks delta-9-THC into this compound, which reaches the brain faster and may be 3 times as psychoactive.

research has also addressed cannabinol's interaction with THC. Cannabinol diminishes the intensity of THC's subjective effects but prolongs their duration. Cannabinol may also decrease some of the stimulation that THC can produce (Brazis & Mathre, 1997).

Considerable research also focuses on cannabidiol. Cannabidiol becomes THC as the marijuana plant matures, and this THC later breaks down into cannabinol. Up to 40% of the cannabis resin from some marijuana strains is cannabidiol (Grilly, 1998). Yet the amount varies in different plants. Some African varieties contain little of the chemical (Turner & Hadley, 1974). Early studies suggested that cannabidiol administered alone had no impact, much like early studies of cannabinol (Hollister, 1974). Later research, however, revealed its effects only appeared at moderate doses. Too little or too much of the drug created no response. The appropriate dosage, however, can decrease anxiety in healthy people. It also reduces psychotic symptoms such as hearing voices or thinking incoherently. In addition, cannabidiol induces sleepiness and may protect epileptics against seizures (Zuardi & Guimaraes, 1997).

Research has also addressed the impact of cannabidiol on THC's effects. The two cannabinoids in combination may create different experiences from either drug alone. Synergistic interactions like this can be very difficult to study. Drug lore suggests that cannabidiol minimizes THC's psychoactive effects and delays their onset. Yet formal studies reveal that the interaction is not quite so simple. Cannabidiol may exaggerate some of THC's effects while attenuating others. It may increase THC-induced euphoria, but limit the production of anxiety and disordered thinking. Cannabidiol slows THC metabolism in the liver. Thus, a dose of THC combined with cannabidiol will create more psychoactive metabolites than the same dose of THC administered alone (Bornheim, Kim, Perotti, & Benet, 1995). By slowing THC's metabolism, cannabidiol can exaggerate some of its effects, including euphoria and the subjective sense of feeling high.

Although cannabidiol slows THC metabolism, it also may limit the drug's negative side effects. THC alone can produce anxiety, panic, and psychotic symptoms, particularly at high doses. Cannabidiol not only decreases anxiety on its own, but it also buffers against THC-induced panic and discomfort. Cannabidiol minimizes psychotic symptoms like bizarre thoughts or odd perceptions. Thus, it may attenuate these negative aspects of THC intoxication. Strains of marijuana that lack cannabidiol may produce more panic or psychotic effects. These findings may prove par-

ticularly useful given recent research on dronabinol (Marinol), the synthetic version of THC used to treat nausea and weight loss. Negative side effects of this drug might decrease if physicians combined it with cannabidiol (Zuardi & Guimaraes, 1997).

Cannabis Preparations

Users can ingest cannabinoids in a number of forms, including marijuana, hashish, hash oil, and synthetic medications. Nearly all parts of the marijuana plant contain psychoactive ingredients, but most of the cannabinoids appear in the resinous glands and flowering tops. Thus, the price for glands or tops is markedly higher than for other parts of the plant. Different cannabis preparations have different names. "Marijuana," a Spanish word purportedly coined in Mexico, originally meant cheap tobacco. The term may stem from the Portuguese expression "mariguango," which means intoxicant (Maisto et al., 1995). Later the word referred to the dried leaves and flowers of cannabis. Residents of India distinguish among three forms: bhang, ganja, and charas. Bhang is the dried leaves of the plant, comparable to marijuana. People smoke these leaves or combine them with milk and spices to form a drink that is also called bhang. Ganja refers to the sap-carrying tops of female plants in India, but in Jamaica the term applies to the leaves as well. Charas is hashish, the dried resin separated from the flowers and pressed together (McKim, 1997).

Many legends surround hashish. A well-known report concerns an exotic technique for collecting resin. Harvesters allegedly pranced naked through sunny fields of cannabis, gathering shiny sap and scraping it gently from their bodies to form cakes. These tales sound like contemporary urban legends or a marketing strategy for modern dealers. Nevertheless, comparable stories appeared as early as the 1850s. Most reporters from that era found workers who wore leather aprons to catch resin as they ran through fields. These workers then told of naked harvesting in other locations (Johnston, 1855; Von Bibra, 1855).

Stories like these may have been an attempt to fool outsiders, similar to the way children from farms tell children from the city that chasing a cow will turn her milk to cottage cheese. Perhaps poorer gatherers of hashish resin could not afford leather aprons. Whatever the arrangement in the past, modern hashish production does not employ naked trips through fields. Instead, manufacturers shake the resinous glands from the

plants and press it into hash. Others simply form blocks by pressing hash oil into powdered cannabis.

In addition to ganja, bhang, and charas or hashish, hash oil also appears in the illicit drug market. Producers create this viscous liquid by boiling hashish or cannabis in a solvent, straining it through a filter, and then letting the solvent evaporate, leaving the oil. The process can be extremely dangerous given the flammability of the solvents, which usually include alcohol or ether (Gold, 1989). The risk may prove worthwhile because hash oil commands higher prices. The oil has the potential to generate huge profits because it is relatively compact and easy to smuggle. It is often more potent than hashish or cannabis, too. Yet hash oil is not particularly popular. Smoking the oil by itself can require special glass pipes as part of a messy and cumbersome process. The solvents used to form the oil may be unhealthy to smoke. Most users find hashish or cannabis easier to ingest and potent enough to create the effects they desire (Clarke, 1998).

Synthetic cannabinoids also exist; they are usually ingested orally. Dronabinol (Marinol), a synthetic version of THC suspended in sesame oil, can treat poor appetite, nausea, and vomiting (e.g., Lefkowtiz et al., 1995). Current studies also address dronabinol's efficacy as a treatment for spasticity associated with multiple sclerosis and pain after surgery (Hanigan, Destree, & Truong, 1986). Some initial work also suggests that this drug might help disturbed behavior in Alzheimer's patients (Volicer et al., 1997). The abuse potential for this substance appears to be minimal. It is the only cannabinoid approved for medical use in the United States. Nabilone (Cesamet), an analogue of THC available in the United Kingdom, also limits nausea, vomiting, and spasticity (e.g., Steel et al., 1980). Levonantradol, another synthetic THC analogue unavailable in the United States, shows some promise in treating acute surgical pain, nausea, and vomiting (Jain et al., 1981; Tyson et al., 1985). Apparently, no pharmaceutical company has pursued its development as a medication (IOM, 1999). The medicinal uses of these synthetic cannabinoids appear in more detail in chapter 8.

Potency

Cannabis preparations vary dramatically in their effects. The most common indicator of potency is the percentage of delta-9 tetrahydrocannab-

inol (THC). Although THC is not the only source of psychoactive effects in the plant, it is the most abundant chemical that clearly alters subjective experience. Hashish typically contains 20% THC, with some estimates as high as 50%. Hash oil can contain up to 70% THC. Yet each of these products can vary dramatically in potency. Some samples of hash oil and hashish contain no THC at all. These products with no THC obviously create few subjective effects, except for those that arise from expectancy. Hashish and hash oil with the highest potencies often cause the most dramatic experiences of intoxication.

Marijuana also shows considerable variation in potency depending upon the plant strain, growing conditions, and storage. Some varieties of plants contain more THC than others. *Cannabis sativa* used for industrial hemp often contains less than 1% THC. Smoking marijuana this low in potency does not change subjective experience. Marijuana with less than 1% THC has the same effects as a placebo (Zimmer & Morgan, 1997). Thus, hemp products are not psychoactive. No one will grow intoxicated from smoking the various shampoos, soaps, or clothes currently manufactured from these plants. Psychoactive strains of marijuana typically contain 2 to 5% THC, but concentrations as high as 22% have been documented (Iversen, 2000). The moisture and temperature of the growing season can alter potency. Storage in hot environments can degrade the cannabinoids and lower THC content (Clarke, 1998). Exposure to light also accelerates the breakdown of THC. A year of storage in a bright place can produce nearly three times the decrease in THC as a year of storage in a dark place (Brazis & Mathre, 1997).

Many media reports suggest that cannabis has increased in potency quite dramatically in recent years. These reports have generated considerable debate. Yet the magnitude of the increase is difficult to document. In addition, the tacit assumption that increased potency translates into greater danger from the drug may not be true. Reports of a stronger drug actually began over 30 years ago. By the middle of the 1980s, some authors suggested that marijuana's potency had increased by a factor of 100 (MacDonald, 1984). These claims clearly suffered from exaggeration or misinformation. Other arguments about increased potency arose from the University of Mississippi's Potency Monitoring Project. This program reports the average THC content of cannabis taken in drug arrests. Estimates were extremely low in the 1970s, sometimes below 1%. As discussed above, cannabis with this little THC has no impact on subjective experience. The idea that a drug with no effects would increase in pop-

ularity over the years makes little sense. Thus, these estimates from the 1970s were probably poor reflections of the amount of THC in marijuana available at the time.

Investigators hypothesize that the data from the Potency Monitoring Project underestimate the true amount of THC in marijuana from the 1970s. First, the estimates were based on very few samples of seized cannabis. In some years there were no more than 50 samples to analyze (Potency Monitoring Project [PMP], 1974–1996). In addition, police may have stored the marijuana in hot lockers that allowed the THC to degrade rapidly (Mikuriya & Aldrich, 1988). Despite the small samples and poor storage, the average THC content in 1976 was 2% (ElSohly, Holley, & Turner, 1985).

An alternative source of potency information, an independent laboratory in California, analyzed many more samples than the Potency Monitoring Project and found a large range in THC concentration. In 1973, this laboratory tested over 100 samples and found that marijuana had an average THC content of 1.6 % (Ratcliffe, 1974). Later analyses ranged up to almost 8% THC (Perry, 1977). Thus, the idea that all cannabis of the 1970s had less than 1% THC seems unlikely. Ratcliffe's (1974) estimate of 1.6% may be conservative but credible; the 1976 estimate of 2% may be closer to the truth.

Potency data from the 1980s through the middle of the 1990s suggest that THC content continued to vary dramatically from strain to strain and sample to sample. With improved storage techniques and much larger samples, the Potency Monitoring Project found THC concentrations varied from 2% to almost 4%. Average concentrations approached 4% THC in 1984, 1988, 1990, and 1991 (PMP, 1974–1996). Trends in the rest of the 1990s showed comparable THC content, with a peak around 4.5% THC in 1997. Other cannabinoids like cannabinol and cannabidiol have not increased in concentration over the years (ElSohly et al., 2000). Thus, claims of 1,000% (Cohen, 1979) or 10,000% (MacDonald, 1984) increases in marijuana potency are clearly inaccurate. A threefold increase from approximately 1.5% in the early 1970s to 4.5% in the late 1990s may be closer to the truth. A simple doubling from an average of 2% to an average of 4% also seems plausible.

Although many media reports warn that increased potency translates into greater danger, data suggest otherwise. The implications of a two or threefold increase in THC concentration remain unclear. Marijuana with greater amounts of THC may not prove more hazardous than weaker

cannabis. First, acute administration of the drug is essentially nontoxic. No one has ever died from THC poisoning. Smoking enough cannabis to ingest a lethal amount of THC may be physically, if not financially, impossible.

Estimates of a fatal dose of any drug arise from some rather gruesome animal research. Different groups of animals receive large amounts of a drug until a particular dosage kills 50% of them. Researchers refer to the dose that is lethal for 50% of the animals as the LD 50. Investigators then extrapolate from these data to estimate a lethal dose for humans. The LD 50 for THC is approximately 125 mg for every kilogram of body weight (Nahas, 1986). Thus, a 160-pound (approximately 73-kilogram) person would need 9,125 mg of THC to have a 50% chance of dying. A typical marijuana cigarette weighs one gram and contains roughly 20 mg of THC, suggesting that roughly 450 joints would prove fatal. Furthermore, at least 50% of the THC is destroyed in the burning process or lost to sidestream smoke. Given this loss, 900 joints would be a more appropriate estimate of a fatal amount (Doweiko, 1999). The 900 joints would weigh roughly 2 pounds. Although experienced users tell many exaggerated tales about smoking large amounts of cannabis, this dosage exceeds 100 times the quantity typically consumed by the heaviest users.

Given the limited fear of lethal overdose, marijuana with larger percentages of THC may actually have some benefits. Stronger cannabis may lead to smoking smaller amounts in order to achieve desired effects. Smoking smaller quantities could provide some protection against the health problems normally associated with inhaling smoke. Smokers may take smaller, shorter puffs when using more potent marijuana (Heishman, Stitzer, & Yingling, 1989). Smoking less may decrease the amount of tars and noxious gases inhaled, limiting the risk for mouth, throat, and lung damage (Matthias, Tashkin, Marques-Magallanes, Wilkins & Simmons, 1997). Obviously, avoiding smoke completely would eliminate these problems. Thus, eating cannabis products may have fewer negative consequences than smoking them. Comparisons between these two ways of administering the drug appear next.

Cannabinoid Administration

A thorough understanding of marijuana's effects requires some knowledge of how it enters a biological system. Drugs can penetrate the body

in many ways. Humans inject drugs intramuscularly (into muscles) or intravenously (into veins). They also inject subcutaneously (under the skin), a process known as "skin popping." People snort drugs intranasally. Some substances can be absorbed sublingually by placing them under the tongue. A few drugs can dissolve through the skin in transdermal administration, like the ubiquitous nicotine patch. None of these methods is particularly common for marijuana. Cannabis has two popular routes of administration: inhalation (smoking) and oral ingestion (eating). In addition, researchers have examined intravenous injections of THC and rectal administration via the marijuana suppository. Drug companies have also proposed a deep lung aerosol, a nasal spray, a nasal gel, and a sublingual preparation of synthetic THC (IOM, 1999).

All these alternative techniques for administering the drug remain relatively rare, but inhalation is quite common. In addition to cannabis, humans inhale nicotine, opium, crack and freebase cocaine, methamphetamine, glue, gasoline, and anesthetics. Inhalation serves as one of the fastest modes of administration for any drug, and THC is no exception. Smoke held in the lungs contacts the bloodstream directly through a rich network of capillaries. This blood travels almost immediately to the brain, the site of the majority of cannabinoid receptors. Thus, the first hints of intoxication can appear within 10 seconds of exhaling the smoke (Levinthal, 1999). People may reach their peak blood concentration of THC while still smoking. The rapid absorption during smoking parallels the dramatic increases associated with intravenous doses of THC. THC dissolves readily in fatty tissues of all sorts, but eventually travels through the blood to the liver and kidneys. It is subsequently metabolized and excreted.

Several factors influence the amount of THC absorbed during smoking. Larger puffs held deeply in the lungs for a long time create the most dramatic effects. At least 30% of the THC in cannabis disappears in the combustion of smoking. More cannabinoids escape while the marijuana cigarette burns between puffs (Davis, McDaniel, Cadwell, & Moody, 1984). Some studies suggest that experienced smokers can take in more THC than inexperienced ones, that is, they may inhale more efficiently. Experienced smokers seem to know their lung capacity and understand the amount of smoke that they can hold without coughing. In contrast, inexperienced smokers may take larger puffs that they subsequently cough out, or smaller puffs that do not provide much of the psychoactive chemicals.

In laboratory studies, heavy users absorbed approximately 27% of the THC available in a joint; light users absorbed only about 14% (Ohlsson, et al., 1982; Ohlsson, Agurell, Lindgren, Gillespie, & Hollister, 1985). The increased efficiency of inhalation in experienced users may account for a curious phenomenon called reverse tolerance or sensitization. Many regular users of cannabis report rapid effects at extremely low doses of the drug. Researchers once posited that people grew more and more sensitive to the drug with repeated exposure, allowing them to experience the subjective effects with less and less of the substance.

Limited absorption may contribute to the minimal effects that novice smokers report the first few times they try cannabis. Many eventually learn to inhale and report more impact from the drug. Some never learn to inhale and subsequently run for public office. The amount of THC an individual assimilates while smoking can vary dramatically. Yet users rarely complain about an inability to absorb enough THC. The effects of smoking are rapid, and people can modify their doses quite readily. A detectable increase in dosage is usually a mere puff or two away. Instead, complaints related to smoking concern irritation of the mouth, throat, and lungs. These complaints occasionally lead a smoker to eat marijuana or hashish instead.

Oral administration has the longest history of all the techniques for using drugs, beginning with alcohol consumption around 8000 B.C. (Roueche, 1963). Most substances taken by mouth must travel the entire gastrointestinal tract, which contains several natural barriers to absorption. These barriers are important in helping minimize the toxic effects of many substances. The interior of the stomach, a highly acidic environment, can break down a variety of noxious chemicals. Unfortunately, this environment also neutralizes potentially helpful medications. For example, stomach acid destroys insulin, making oral administration of this drug useless.

Drugs that survive the stomach pass to the small intestine. Membranes between the intestinal wall and surrounding blood capillaries include two layers of fat molecules. Thus, only fat-soluble substances pass into these capillaries, which then send the drug to the liver for further metabolism. Those drugs that survive the liver metabolism reach general circulation. Yet entering the bloodstream is no guarantee of reaching the brain. The blood-brain barrier, a tightly knit bed of capillaries, keeps all but a few of the most lipid-soluble substances from reaching the brain. This barrier

separates the brain from the circulatory system, minimizing the impact of any potential toxins.

Given all the natural barriers inherent in oral administration, it remains dramatically slower than inhalation. Eating marijuana may create smaller effects than smoking an equal amount because so much of the drug breaks down in digestion. Eating cannabis or hashish leads to delayed, erratic absorption, depending upon the state of the gut at the time. A gram of cannabis might lead to extreme intoxication when smoked but hardly alter subjective experience if eaten after a full meal.

The concentration of THC also tends to peak much later after oral administration than after smoking. Concentrations peak between 1 and 6 hours after eating THC in chocolate cookies and around 2 hours in sesame oil pills like dronabinol (Ohlsson et al., 1980; Ohlsson et al., 1985; Wall, Sadler, Brine, Harold, & Perez-Reyes, 1983). In one study, marijuana-laced brownies led to some effects in 30 minutes, but peak responses did not occur for 2½ to 3½ hours (Cone, Johnson, Paul, Mell, & Mitchell, 1988). Cannabis resin eaten in a meat sandwich also took at least 2 hours to create peak effects (Law, Mason, Moffat, Gleadle, & King, 1984). Thus, the digestive process decreases the bioavailability of the drug. Bypassing this digestive process via smoking enhances effects. The marijuana suppository also bypasses degradation in the liver and leads to greater availability of THC (Mattes, Shaw, Edling-Owens, Engelman, & ElSohly, 1993).

Despite the potential drawbacks of decreased availability and slower initiation of effects, orally administered marijuana has developed quite a history. Cannabis products heated in oil or butter and combined with sweets have served as confections for centuries (Abel, 1980). Modern recipes for brownies, soup, meatloaf, guacamole, banana bread, and cookies can include cannabis. Hashish recipes for cookies, brownies, and soup are also quite common (Powell, 1971). Tinctures made from marijuana soaked in alcohol also provide a vehicle for oral administration. In addition, dronabinol, the synthetic version of THC dissolved in sesame oil, is marketed in capsules for easy swallowing. Eating the drug avoids the obvious throat and mouth irritation and risk for lung problems that accompany smoking.

THC Metabolism

The amount of time required to metabolize THC has shown considerable variation from person to person and study to study. The period required to eliminate THC from the body should not be confused with the duration of the drug's psychoactive effects. People stop feeling high long before THC has left their bodies. Intoxication rarely last more than a few hours, with orally administered doses lasting longer than smoked cannabis. After an intravenous injection of THC, blood levels peak almost immediately and then decrease by 90% in the first hour. This rapid drop does not mean that the drug has exited the body; it simply leaves the blood to dissolve into fat tissue. THC in the blood partitions into fat tissue, then leaks slowly from fat to be degraded and excreted. Although media accounts of marijuana's effects often treat THC's fat solubility as a novelty, sedatives like the barbiturates and benzodiazapines are stored in fat, too. After the first hour, blood levels of THC do not drop as rapidly. As THC from the blood is eventually excreted in urine and feces, THC stored in fat returns to circulation, but in doses too small to create psychoactive effects.

Researchers express the time required to metabolize a drug as its half-life—the period required to break the dose down to 50% of its original amount. Suppose the half-life of a hypothetical drug was one day. People who absorbed 100 mg of this drug would reduce it to 50 mg in one day. The next day they would again cut the available dose in half, to 25 mg. The next day would decrease the amount to 12.5 mg, and so on. Zeno's paradox would suggest that this consistent splitting in two would actually never lead to a blood level of zero. The amount would decrease by 50% repeatedly, growing smaller and smaller, but it would never disappear. Practically, drugs reach an undetectable concentration after 4.5 or 5 half-lives (Diaz, 1997).

Estimates of the half-life of THC based on urinary excretion show incredible variation. Research estimates of THC's half-life range from as little as 19 hours (Hunt & Jones, 1980) to as much as 4 days (Johansson, Arguell, Hollister, & Halldin, 1988). Early work suggested that users might grow more efficient at metabolizing THC as they gain experience with the drug (Lemberger, Axelrod, & Kopin, 1971). This study found a half-life of 28 hours for chronic smokers, but naive users took 57 hours to metabolize half of the dose. These results had considerable intuitive

appeal because they helped explain marijuana tolerance. The authors of this research implied that people grew tolerant to the drug because they essentially eliminated it more readily.

In contrast to evidence of increased rates of metabolism in experienced users, a later study found that people who had received THC each day for two weeks did not metabolize faster than moderate users who had not ingested daily doses (Hunt & Jones, 1980). In addition, the study with the longest estimated half-life used chronic, regular smokers (Johansson et al., 1988). These results seem confusing in light of the previously reported shorter half-life for heavier users. Thus, THC's rate of metabolism may not increase with repeated use. Most studies show a half-life between 1 and 1.5 days (Ohlsson et al., 1982; Ohlsson et al., 1985; Wall et al., 1983). A recent study using an extremely sensitive measuring technique and a two-week follow-up period found THC half-life ranges up to 2.5 days (Huestis & Cone, 1998). This study used the best methods available and suggests that a dose of THC leaves the body completely after 12 or 13 days.

The extreme variation in the estimates for the half-life of THC may stem from studying small samples of people over relatively short durations, using measurement techniques that vary in sensitivity. This large range of estimates likely reflects individual differences among people. Some simply metabolize more quickly than others. Techniques that do not rely on urine samples suggest THC stays in the body even longer. Analysis of fat cells rather than urine samples has revealed that the drug can remain in the body up to a month in some people (Johansson, Noren, Sjovall, & Halldin, 1989). Popular authors imply that this long elimination period is the norm (DuPont, 1984), but many people metabolize THC faster. Despite all the variability in elimination periods, marijuana does appear to have a longer half-life than some other drugs. For example, nicotine's half-life is about 2 hours; caffeine's is 3 to 6 hours (Henningfield, Cohen, & Pickworth, 1993). However, some sedatives that are more fat soluble show half-lives around 2 days or more (Diaz, 1997). Thus, marijuana takes more time to metabolize than some drugs, but less than others.

Popular authors often misinterpret THC's long half-life by frequently implying that intoxication or some sort of residual effect of the drug remains for weeks at a time. Yet intoxication dissipates in a couple of hours. The amount of THC released gradually from fat cells does not create any subjective, cognitive, or emotional effects but may register on

drug tests. Thus, a person may test positive for cannabis even a week or two after smoking, when all signs of intoxication have clearly terminated (Zimmer & Morgan, 1997). A number of underground legends suggest that goldenseal, cranberry juice, or various other concoctions might shorten this period of testing positive; no systematic research addresses this question. Drinking enormous quantities of fluids may dilute THC metabolites in the urine and alter the outcome of a test, but these fluids do not actually alter metabolic rate (Coombs & West, 1991).

Cannabinoid Receptors

Once cannabinoids enter the body, they must find a site to create their effects. The quest to understand the biological function of cannabinoids has generated a large body of research. Initial studies tracked radioactive THC through the body. This work revealed that THC attached to all the surfaces of the neuron, suggesting that it might alter the permeability of cell membranes to create its impact (Makriyannis & Rapaka, 1990). Researchers were familiar with the idea of drugs altering membrane permeability because some of alcohol's effects may stem from a comparable process (Doweiko, 1999).

Later work revealed that at least some of marijuana's impact could not arise solely from changes in the permeability of cell membranes. Newer studies found that cannabinoids could inhibit the synthesis of an extremely important compound, cyclic adenosine monophosphate (cyclic AMP or cAMP), which helps initiate nerve impulses (Howlett, Johnson, Melvin, & Milne, 1988). Other drugs that work in this way have special receptors that alter the cAMP. These receptors inhibit adenylyl cyclase (AC), the enzyme used to make cAMP. Examinations of every receptor known to inhibit AC revealed that none of them responded to the cannabinoids.

With all these other receptors ruled out, researchers concluded that cannabis must work via its own site. Investigators soon identified the cannabinoid receptor and mapped its distribution in the brain (Bidaut-Russell, Devane, & Howlett, 1990; Devane, Dysarz, Johnson, Melvin, & Howlett, 1988 Herkenham et al., 1990). The cannabinoid receptors in the nervous system, which are known as the CB1 type, are quite numerous. By way of comparison, CB1 receptors are 10 times more abundant than mu opiod receptors, the sites of action for morphine. After

researchers identified the CB1 receptor in the brain, other work revealed a second site of action in the immune system. This receptor was dubbed, surprisingly, CB2.

Contrary to what we all learned in high school courses on biology, receptors are not locks that either open or close in response to some key. The cannabinoid receptors (and all others) are proteins—strings of amino acids that span the membrane of the cell. Some of the amino acids are embedded in the cell membrane; some are implanted inside the cell; others extend outside. Cannabinoids bind with the portion of the receptor outside the cell and trigger activity inside. Different cannabinoids bind in different ways, leading to varied amounts of activity within the nerve cell.

One action triggered by the cannabinoid receptor is the inhibition of AC and subsequent inhibition of cAMP, as mentioned above. Thus, any process that requires cAMP will slow down if the cannabinoid receptor has been activated. The receptor also opens the potassium channels of the neuron, which decreases its rate of firing. Unlike the potassium channels, calcium channels close when the cannabinoid receptor activates. Closed calcium channels decrease the release of neurotransmitters. Thus, by inhibiting cAMP, slowing the nerve's firing rate, and decreasing neurotransmitter release, cannabinoids alter the communication between nerve cells. These actions may account for many of the effects of THC as well as other cannabinoids.

The cannabinoid receptors and their associated brain systems do not work in a vacuum. Any alterations of one neurotransmitter can change the functioning of others. THC clearly creates changes in the dopamine system, as cocaine, amphetamine, nicotine, and alcohol do (Koob & Le Moal, 1997). The cannabinoids can enhance dopamine's activation of movement, suggesting that they might help treat Parkinson's disease (Sanudo-Pena & Walker, 1998). Cannabinoids can inhibit or enhance gamma-aminobutyric acid (GABA), the neurotransmitter that may contribute to alcohol's sedative effects (Pacheco, Ward, & Childers, 1993; Shen, Piser, Seybold, & Thayer, 1996). THC also interferes with acetylcholine, a neurotransmitter involved in memory. The effect on acetylcholine may underlie the memory problems associated with cannabis intoxication. Thus, the cannabinoid receptor and related neurotransmitter systems clearly play an important role in the functioning of the brain.

Human cannabinoid receptors are extremely similar to those found in rodents, suggesting that evidence from animal studies may apply to people (Gerard, Mollereau, Vassart, & Parmentier, 1991). Leeches, mollusks,

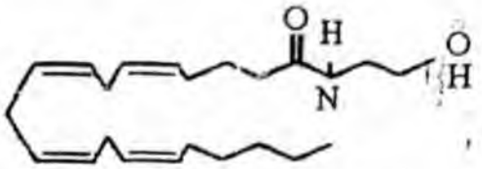


Figure 6.6. Anandamide. This cannabinoid occurs naturally in the body. It is the first endogenous cannabinoid discovered.

chickens, turtles, trout, and fruit flies have cannabinoid receptors, too (Howlett, Evans, & Houston, 1992; Stefano, Salzet, & Salzet, 1997). Even a primitive protozoan, the Hydra, has a cannabinoid receptor that appears to alter its feeding (De Petrocellis, Melck, Bisognor, Milone, & DiMarzo, 1999). The presence of the receptor in such a wide variety of species suggests that it must have an important and universal function. The ubiquitous presence of the CB1 and CB2 receptors inspired a search for substances within the body that might react at these sites.

The Body's Own Cannabinoids

It seems unlikely that so many animals would develop receptors simply to respond to some green weed. The identification of the cannabinoid receptors inspired the search for the body's own substances that might activate them. Studies of the functions of these endogenous cannabinoids could reveal a lot about how marijuana works, as well as how the brain works. Several endogenous chemicals appear to interact with the cannabinoid receptor. The two studied most are arachidonylethanolamine (anandamide) and 2-arachidonolyl-glycerol (2-AG), pictured respectively in figures 6.6 and 6.7.

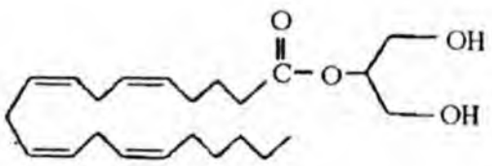


Figure 6.7. 2-arachidonolyl-glycerol (2-AG). This substance is the most abundant endogenous cannabinoid.

The first cannabinoid identified in the body was dubbed anandamide, from the Sanskrit word *ananda*, which means "bliss" or "ecstasy" (Devane et al., 1992). Its actual chemical name is arachidonylethanolamine. As the name suggests, its components include arachidonic acid and ethanolamine. Arachidonic acid serves as the building block of dozens of other chemicals, including some of those involved in the way aspirin works. Ethanolamine is related to alcohol. The anadamide molecule does not particularly resemble THC, but both interact with the cannabinoid receptors. Other natural compounds work on drug receptors but do not share the drug's molecular shape. For example, endorphins, the endogenous opiates, do not look much like opium or morphine. Yet they work at the same sites on the neuron. Clearly, molecules of different shapes may still connect to the same receptor. The critical aspects of the shape of the molecule are not known precisely.

Enzymes metabolize anandamide quite quickly, so its duration of action is shorter than THC's. Anandamide creates less intense effects than THC, perhaps because of this rapid breakdown. It also has only 25 to 50% of THC's affinity for receptors. Still, anandamide creates some of the same reactions. For example, this endogenous cannabinoid induces overeating (Williams & Kirkham, 1999) and lowers activity, body temperature, and pain sensitivity (Fride & Mechoulam, 1993). Researchers find anandamide in many of the brain areas rich in CB1 receptors, including the hippocampus, a structure involved in memory. Thus, this receptor may play a role in the deficits in short-term memory associated with marijuana intoxication. CB1 receptors also appear in the cerebellum, a motor center of the brain. The ability of cannabinoids to relieve spasticity and tremor may involve the receptors in this area (Baker et al., 2000).

Anandamide also appears in the thalamus, a structure involved with pain and emotion. Oddly, the thalamus has relatively few cannabinoid receptors. Perhaps anandamide works on other receptors in this structure. Anandamide works in systems outside the brain as well. It appears in spleen tissue, which has many CB2 receptors, and acts in the immune system (IOM, 1999). Anandamide even inhibits the growth of breast cancer cells (De Petrocellis et al., 1998). Research on anandamide's exact functions in the brain and immune system continues.

Several compounds related to anandamide also bind to cannabinoid receptors, including 2-arachidonolyl-glycerol (2-AG). The compound 2-AG is a prominent constituent of brain tissue, about 170 times more

abundant than anandamide (Stella, Schweitzer, & Piomelli, 1997). It clearly interacts with both the CB1 and CB2 receptors (Sugiura, et al., 1999; Sugiura et al. 2000). It also alters heart rate and blood pressure in mice (Jarai et al., 2000). Its exact role in other cannabinoid effects is not yet clear. Research on the endogenous cannabinoid system progresses rapidly. Studies have already isolated new substances that bind to cannabinoid receptors, but they have not been identified yet. Their precise biological impact remains unknown.

Conclusions

Marijuana contains more than 400 chemical components; at least 66 of them are cannabinoids unique to the plant. The most prevalent ones include delta-9-THC, cannabinol, and cannabidiol. THC causes cannabis's intoxicating effects. Cannabinol has about one-tenth the psychoactive effects of THC. At high doses, it can increase sleep and decrease body temperature. Cannabinol may decrease THC's psychoactive effects, particularly the stimulating aspects of the subjective experience, but it may also extend the duration of intoxication. Cannabidiol may decrease anxiety and psychotic symptoms as well as minimize seizures. In combination with THC, cannabidiol may increase THC concentrations, slow its metabolism, and limit any anxious or paranoid feelings associated with intoxication. Researchers have identified dozens of other cannabinoids, many with shapes similar to these three. All are soluble in fat, but their other chemical properties are not understood completely.

Many different preparations of cannabis exist, including wide varieties of hashish, hash oil, and marijuana. Their potencies can vary dramatically, with hashish containing up to 50% THC and hash oil running as high as 70% THC. Cannabis itself is often between 2 and 4% THC, with some claims of potency reaching markedly higher. Concerns about dramatic increases in potency over the last 30 years may stem from poorly analyzed or misrepresentative samples of cannabis from the 1970s. Assertions about increases in potency of 10 to 100 times seem extremely unlikely. THC concentrations have probably increased by a factor of 2 or 3. These increases may not justify alarm. THC is not toxic at high doses like alcohol, nicotine, or many other common drugs. High-potency marijuana may actually minimize risk for lung problems because less is required to achieve desired effects.

Users often smoke cannabis products and occasionally eat them. Researchers are currently experimenting with other ways to administer THC, including a nasal spray and rectal suppository. Smoke inhalation provides a rapid absorption of THC into the blood and brain, creating striking changes in subjective experience that often last a couple of hours. Ingesting marijuana or hashish requires digestion in the gastrointestinal tract and liver, delaying and reducing effects but lengthening their duration. Although intoxication rarely lasts more than a few hours, the complete elimination of THC clearly takes at least a few days. The chemical can remain in fat cells for up to one month. The fat cells eventually release the THC back into the blood stream, but in quantities too small to have any subjective effect. The liver breaks down this released THC and its metabolites are excreted.

In an effort to understand which neurotransmitter systems create THC's effects, investigators eventually identified two receptors that respond specifically to the cannabinoids. One receptor (CB1) exists in the brain and appears in high concentrations in areas involved with memory and motor control. The other receptor (CB2) is most prevalent in the immune system. The identification of this new neurotransmitter system has generated considerable research and reveals that the brain remains more complex than previously thought. The presence of these receptors inspired a search for the body's own chemicals that may activate them. Research has uncovered two natural cannabinoids; anandamide and 2-AG. These appear to mimic some of THC's effects, though they are less potent and have a shorter duration of action. Future research in this area will likely continue to inform us about the way this drug works as well as how the brain functions.

B

Sénat Senate

CANADA

CANNABIS:

OUR POSITION FOR A CANADIAN PUBLIC POLICY

REPORT OF THE SENATE SPECIAL COMMITTEE ON ILLEGAL DRUGS

SUMMARY REPORT

CHAIR

PIERRE CLAUDE NOLIN

DEPUTY CHAIR

COLIN KENNY

SEPTEMBER 2002

COMMITTEE MEMBERS

SENATORS

Senator Tommy BANKS
Senator Sharon CARSTAIRS, P.C. (ex officio)
Senator Colin KENNY, Deputy Chair
Senator Noel A. KINSELLA (ex officio)
Senator John LYNCH-STAUNTON (ex officio)
Senator Shirley MAHEU
Senator Pierre Claude NOLIN, Chair
Senator Fernand ROBICHAUD, P.C. (ex officio)
Senator Eileen ROSSITER

STAFF

Clerk:	Blair Armitage
Assistant Clerk:	Daniel Charbonneau
Assistant Clerk:	Adam Thompson
Director of Research:	Daniel Sansfaçon
Research assistants :	Gérald Lafrenière
	Chantal Collin
	François Dubois
	Barbara Wheelock
Communication Advisors :	Jean-Guy Desgagné
	David Newman
	Diane Boucher
Administrative Assistants:	Nicole Bouchard
	Martine DeLaunière
	Brigitte Martineau
	Krista Durrell

B

Sénat Senate

CANADA

CANNABIS:

OUR POSITION FOR A CANADIAN PUBLIC POLICY

REPORT OF THE SENATE SPECIAL COMMITTEE ON ILLEGAL DRUGS

SUMMARY REPORT

CHAIR

PIERRE CLAUDE NOLIN

DEPUTY CHAIR

COLIN KENNY

SEPTEMBER 2002

COMMITTEE MEMBERS

SENATORS

Senator Tommy BANKS
Senator Sharon CARSTAIRS, P.C. (ex officio)
Senator Colin KENNY, Deputy Chair
Senator Noel A. KINSELLA (ex officio)
Senator John LYNCH-STAUNTON (ex officio)
Senator Shirley MAHEU
Senator Pierre Claude NOLIN, Chair
Senator Fernand ROBICHAUD, P.C. (ex officio)
Senator Eileen ROSSITER

STAFF

Clerk:	Blair Armitage
Assistant Clerk:	Daniel Charbonneau
Assistant Clerk:	Adam Thompson
Director of Research:	Daniel Sansfaçon
Research assistants :	Gérald Lafrenière
	Chantal Collin
	François Dubois
	Barbara Wheelock
Communication Advisors :	Jean-Guy Desgagné
	David Newman
	Diane Boucher
Administrative Assistants:	Nicole Bouchard
	Martine DeLaunière
	Brigitte Martineau
	Krista Durrell

GLOSSARY OF KEY TERMS

Abuse
Vague term with a variety of meanings depending on the social, medical and legal contexts. Some equate any use of illicit drugs to abuse: for example, the international conventions consider that any use of drugs other than for medical or scientific purposes is abuse. The Diagnosis and Statistical Manual of the American Psychiatric Association defines abuse as a maladaptive pattern of substance use leading to clinically significant impairment or distress as defined by one or more of four criteria (see Chapter 7). In the Report, we prefer the term excessive use (or harmful use).

Acute effects
Refers to effects resulting from the administration of any drug and specifically to its short term effects. These effects are distinguished between central (cerebral functions) and peripheral (nervous system). Effects are dose-related.

Addiction
General term referring to the concepts of tolerance and dependency. According to WHO addiction is the repeated use of a psychoactive substance to the extent that the user is periodically or chronically intoxicated, shows a compulsion to take the preferred substance, has great difficulty in voluntarily ceasing or modifying substance use, and exhibits determination to obtain the substance by almost any means. Some authors prefer the term addiction to dependence, because the former also refers to the evolutive process preceding dependence.

Agonist
A substance that acts on receptor sites to produce certain responses.

Anandamide
Agonist neurotransmitter of the endogenous cannabinoid system. Although not yet fully understood in research, these neurotransmitters seem to act as modulators as THC increases, the liberation of dopamine in nucleus accumbens and in the cerebral cortex.

At-risk use
Use behaviour which makes users at risk of developing dependence to the substance.

Cannabinoids
Endogenous receptors of the active cannabis molecules, particularly Delta 9-THC. Two endogenous receptors have been identified: CB1 densely concentrated in the hippacampus, basal ganglia, cerebellum and cerebral cortex, and CB2, particularly abundant in the immune system. The central effects of cannabis appear to be related only to CB1.

Cannabis
Three varieties of the cannabis plant exist: *cannabis sativa*, *cannabis indica*, and *cannabis ruredalis*. *Cannabis sativa* is the most commonly found, growing in almost any soil condition. The cannabis plant has been known in China for about 6000 years. The flowering tops and leaves are used to produce the smoked cannabis. Common terms used to refer to cannabis are pot, marijuana, dope, ganja, hemp. Hashish is produced from the extracted resin. Classified as a psychotropic drug, cannabis is a modulator of the central nervous system. It contains over 460 known chemicals, of which 60 are cannabinoids. Delta-9-tétrahydrocannabinol, referred to as THC, is

the principal active ingredient of cannabis. Other components such delta-8-tétrahydrocannabinol, cannabinol and cannabidiol are present in smaller quantities and have no significant impacts on behaviour or perception. However, they may modulate the overall effects of the substance.

Commission on narcotic drugs (CND)
The Commission on Narcotic Drugs (CND) was established in 1946 by the Economic and Social Council of the United Nations. It is the central policy-making body within the UN system for dealing with all drug-related matters. The Commission analyses the world drug abuse situation and develops proposals to strengthen international drug control.

Chronic effects
Refers to effects which are delayed or develop after repeated use. In the report we prefer to use the term consequences of repeated use rather than chronic effects.

Decriminalization
Removal of a behaviour or activity from the scope of the criminal justice system. A distinction is usually made between *de jure* decriminalization, which entails an amendment to criminal legislation, and *de facto* decriminalization, which involves an administrative decision not to prosecute acts that nonetheless remain against the law. Decriminalization concerns only criminal legislation, and does not mean that the legal system has no further jurisdiction of any kind in this regard. Other, non-criminal, laws may regulate the behaviour or activity that has been decriminalized (civil or regulatory offences, etc.).

Diversion
The use of measures other than prosecution or a criminal conviction for an act that nonetheless remains against the law. Diversion can take place before a charge is formally laid, for example if the accused person agrees to undergo treatment. It can also occur at the time of sentencing, when community service or treatment may be imposed rather than incarceration.

Depenalization
Modification of the sentences provided in criminal legislation for a particular behaviour In the case of cannabis, it generally refers to the removal of custodial sentences.

Dependence
State where the user continues its use of the substance despite significant health, psychological, relational, familial or social problems. Dependence is a complex phenomenon which may have genetic components. Psychological dependence refers to the psychological symptoms associated with craving and physical dependence to tolerance and the adaptation of the organism to chronic use. The American Psychiatric Association has proposed seven criteria (see Chapter 7).

Dopamine
Neuromediator involved in the mechanisms of pleasure.

Drug
Any chemical agent that alters the biochemical or physiological processes of tissues or organisms. In this sense, the term drug refers better to any substance which is principally used for its psychoactive effects. Also used to refer to illicit rather than licit (such as nicotine, alcohol or medicines) substances.

European Monitoring Centre on Drugs and Drug Addiction (EMCDDA)
The European Monitoring Centre was created in 1993 to provide member states within the EU objective, reliable and comparable information on drugs, drug addictions and their consequences. Statistical information, documents and techniques developed in the EMCDDA are designed to give a broad perspective on drug issues in Europe. The Centre only deals with information. It relies on national focal points in each of the Member States.

Fat soluble
Characteristic of a substance to irrigate the tissues quickly. THC is highly fat-soluble.

Gateway / Gateway Theory
Theory suggesting a sequential pattern in involvement in drug use from nicotine to alcohol, to cannabis and then to "hard" drugs. In regard to cannabis, the theory rests on a statistical association between the use of hard drugs and the fact that these users have generally used cannabis as their first illicit drug. This theory has not been validated by empirical research and is considered outdated.

Half-life
Time needed for the concentration of a particular drug in blood to decline to half its maximum level. The half-life of THC is 4.3 days on average but is faster in regular users than in occasional users. Because it is highly fat soluble, THC is stored in fatty tissues, thus increasing its half-life to as much as 7 to 12 days. Prolonged use of cannabis increases the period of time needed to eliminate it from the system. Even one week after use, THC metabolites may remain in the system. They are gradually metabolised in the urine (one third) and in feces (two thirds). Traces of inactive THC metabolites can be detected as long as 30 days after use.

Hashish
Resinous extract from the flowering tops of the cannabis plant transformed into a paste.

International conventions
Various international conventions have been adopted by the international community since 1912, first under the League of Nations, then under the United Nations, to regulate the possession, use, production, distribution, sale, etc., of various psychotropic substances. Currently, the three main conventions in force are the 1961 Single Convention, the 1971 Convention on Psychotropic Substance and the 1988 Convention against Illicit Traffic. Canada is a signatory to all three conventions. Subject to countries' national constitutions, these conventions establish a system of regulation where only medical and scientific uses are permitted. This system is based on the prohibition of source plants (coca, opium and cannabis) and the regulation of synthetic chemicals produced by pharmaceutical companies.

International Narcotics Control Board (INCB)
The Board is an independent, quasi-judicial organization responsible for monitoring the implementation of the UN conventions on drugs. It was created in 1968 as a follow up to the 1961 Single Convention, but had predecessors as early as the 1930s. The Board makes recommendations to the UN Commission on Narcotics with respect to additions or deletions in the appendices of the conventions.

Intoxication
Disturbance of the physiological and psychological systems through substance use. Pharmacology generally distinguishes four levels of intoxication: light, moderate, serious and fatal.

Joint
Cigarette of marijuana or hashish with or without tobacco. Because joints are never identical, scientific analyses of the effects of THC in their use are more difficult, especially to determine the therapeutic benefits of cannabis and to examine its effects on driving.

League of Nations
International organisation organization of Sstates until in existence until 1938; now the United Nations.

Legalization
Legislating under a regulatory system the culture, production, marketing, sale and use of substances. Although no such provision currently exist in relation to "street-drugs" (as opposed to alcohol or tobacco which are regulated products), a legalization system could take two forms: free of state control (free markets) and with state controls (regulatory regime).

Marijuana
Mexican term originally referring to a cigarette of poor quality. Has now become a synonym for cannabis in popular language usage.

Narcotic
Substance which can induce stupor or artificial sleep. Usually restricted to opiates. Sometimes used incorrectly to refer to all drugs capable of inducing dependence.

Office of National Drug Control Policy (ONDCP) USA
Created in 1984 under the Reagan administration, the Office is under the direct authority of the White House. It coordinates US policy on drugs. Its budget is currently US $18 billion.

Opiates
Substance derived from the opium poppy. The term opiate excludes synthetic opioids such as heroin and methadone.

Prohibition
Historically, the term most often refers to the period of national interdiction of alcohol sales in the United States between 1919 and 1933. By analogy, the term is now used to describe UN and State policies aiming for a drug-free society. Prohibition is based on the interdiction to cultivate, produce, fabricate, sell, possess, use, etc., some substances except for medical and scientific purposes.

Psychoactive substance
Substance which alters mental processes such as thinking or emotions. We prefer to use this term as it is more neutral than the term "drug" and does not refer to the legal status of the substance.

Psychotropic substance (see also psychoactive)
Used synonymously with psychoactive substance, however the term refers to drugs primarily used in the treatment of mental disorders, such as anxiolytics, sedatives, neuroleptics, etc. More specifically,the term refers to the substances covered in the 1971 Convention on Psychotropic Substances.

Regulation
System of control specifying the conditions under which the cultivation, production, marketing, prescription, sales, possession or use of a substance are allowed. Regulatory approaches may rest on interdiction (as for illegal drugs) or controlled access (as for medical drugs or alcohol). Our proposal of an exemption regime under the current legislation is a regulatory regime.

Tetrahydrocannabinol (Δ9-THC)
Main active component of cannabis, Δ9-THC is highly fat-soluble and has a lengthy half-life. Its psychoactive effects are modulated by other active components in cannabis. In its natural state, cannabis contains between 0.5% to 5% THC. Sophisticated cultivation methods and plant selection, especially female plants, lead to higher levels of THC concentration.

Tolerance
Reduced response of an organism and increased capacity to support the effects of a substance after a more or less lengthy period of use. Tolerance levels are extremely variable between substances, and tolerance to cannabis is believed to be lower than for most other drugs,including tobacco and alcohol.

Toxicity
Characteristic of a substance which induces intoxication, i.e., "poisoning". Many substances, including some common foods, have some level of toxicity. Cannabis presents almost no toxicity and cannot lead to an overdose.

United Nations Drug Control Program (UNDCP)
Established in 1991, the Program works to educate the world about the dangers of drug abuse. The Program aims to strengthen international action against drug production, trafficking and drug-related crime through alternative development projects, crop monitoring and anti-money laundering programs. UNDCP also provides accurate statistics through the Global Assessment Programme (GAP) and helps to draft legislation and train judicial officials as part of its Legal Assistance Programme. UNDCP is part of the UN Office for Drug Control and the Prevention of Crime.

World Health Organization (WHO) The World Health Organization, the United Nations' specialized agency for health, was established on April 7, 1948. WHO's objective, as set out in its Constitution, is the attainment by all peoples of the highest possible level of health. Health is defined in WHO's Constitution as a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity.

INTRODUCTION

The **Senate Special Committee on Illegal Drugs** addressed the question of drugs just as everyone else does, with the same preconceptions, attitudes, fears and anxieties we all share. Of course, we had at our disposal the 1996 study our colleagues conducted on government legislation dealing with illegal drugs, which had enabled them to hear a number of witnesses over several months. We also knew at the outset that research expertise would be available to us, but it is still difficult to overcome attitudes and opinions that we have long taken for granted. Whether one is in favour of enhanced enforcement or, on the contrary, greater liberalization, opinions often resist the facts and in a field such as this the production of facts, even through scientific research, is not necessarily a neutral undertaking. We, like you, have our prejudices and preconceptions. Together we must make the effort to go beyond such predispositions. That is one of the objectives of this report.

The public policy regime we propose expresses the fundamental premise underlying our report: *in a free and democratic society, which recognizes fundamentally but not exclusively the rule of law as the source of normative rules and in which government must promote autonomy as far as possible and therefore make only sparing use of the instruments of constraint, public policy on psychoactive substances must be structured around guiding principles respecting the life, health, security and rights and freedoms of individuals, who, naturally and legitimately, seek their own well-being and development and can recognize the presence, difference and equality of others.*

We are aware, as much now as we were at the start of our work, that there is no pre-established consensus in Canadian society on public policy choices in the area of drugs. In fact, our research has shown us that there are few societies where there is a broadly shared consensus among the general public, let alone between the public and experts. We are well aware, perhaps more so than at the outset, that the question of illegal drugs, viewed from the standpoint of public policy, has a broad international context and that we cannot think or act in isolation. We know our proposals are provocative, that they will meet with resistance. However, we are also convinced that Canadian society has the maturity and openness to welcome an informed debate.

PART I – GENERAL ORIENTATION

CHAPTER 1 – OUR MANDATE

"That a special committee of the Senate be struck to examine:

- *the approach taken by Canada to cannabis, its preparations, derivatives and similar synthetic preparations, in context;*
- *the effectiveness of this approach, the means used to implement it and the monitoring of its application;*
- *the related official policies adopted by other countries;*
- *Canada's international role and obligations under United Nations agreements and conventions on narcotics, in connection with cannabis, the Universal Declaration of Human Rights and other related treaties; and*
- *the social and health impacts of cannabis and the possible consequences of different policies;*

That the special committee consist of five senators, three of whom shall constitute a quorum;
That the Honourable Senators Banks, Kenny, Nolin, Rossiter and (a fifth Senator to be named by the Chief Government Whip) be named to the committee;
That the committee be authorized to send for persons, papers and records, to hear witnesses, to report from time to time, and to print from day to day such papers and evidence as may be ordered by it;
That the briefs and evidence heard during consideration of Bill C-8, An Act respecting the control of certain drugs, their precursors and other substances and to amend certain other Acts and repeal the Narcotic Control Act in consequence thereof, by the Standing Senate Committee on Legal and Constitutional Affairs during the 2nd Session of the 35th Parliament be referred to the committee;
That the documents and evidence compiled on this matter and the work accomplished by the Special Senate Committee on Illegal Drugs during the 2nd Session of the 36th Parliament be referred to the committee;
That the committee be empowered to authorize, if deemed appropriate, the broadcasting on radio and/or television and the coverage via electronic media of all or part of its proceedings and the information it holds;
That the committee present its final report no later than August 31, 2002; and that the committee retain the powers necessary to publicize its findings for distribution of the study contained in its final report for 30 days after the tabling of that report;
That the committee be authorized, notwithstanding customary practice, to table its report to the Clerk of the Senate if the Senate is not sitting, and that a report so tabled be deemed to have been tabled in the Senate."

The Committee's mandate is a continuation of the evolution of drug legislation passed by the Parliament of Canada in 1996, the *Controlled Drugs and Substances Act.* While this legislation was being studied by the Sub-Committee on Bill C-7 of the Standing Committee on Health of the House of Commons in 1994 and 1995, the vast majority of witnesses were highly critical of the bill. The most common criticisms concerned three points: first, the lack of basic principles or an expressed statement as to the purpose of the act; second, the fact that the bill perpetuated the prohibition system of the 1920s, and third, the absence of any emphasis on harm reduction and prevention criteria. Despite the amendments made by the Sub-Committee of the House, the testimony heard by the Senate Committee was equally critical. Witnesses noted that the Act did not categorize drugs on the basis of the dangers they represented, that it did not contain any specific, rational criteria and that it was impossible, particularly in view of the Act's complexity, to determine how it would be implemented in practice. All of these criticisms led that Senate Committee to "*propose energetically*" the creation of a Joint Committee of the House of Commons and the Senate that would review all Canadian drug legislation, policies and programs. However, the 1997 federal election intervened. Senator Nolin, convinced of the need for action and faced with the inaction of the House of Commons, tabled his first motion in 1999 - that a Senate Committee be struck and given a mandate to examine the legislation, policies and programs on illegal drugs in Canada. The motion was adopted by the Senate in April 2000.

However, that Committee was dissolved by general election of October 2000, and was restruck on March 15, 2001, with an amended mandate: the scope of its work was now restricted to cannabis "in its context". We chose to interpret this sentence broadly.

CHAPTER 2 – OUR WORK

At the Committee's public hearings, the Chair presented the research program as follows:

> *"In order to fully satisfy the mandate conferred upon the committee, the committee has adopted an action plan. This plan centres around three challenges. The first challenge is that of knowledge. We will be hearing from a wide variety of experts, both from Canada and afar, from academic settings, the police, legal specialists, medical specialists, the government sector and social workers. (...)*
> *The second challenge, surely the most noble challenge, is that of sharing knowledge. The committee hopes that Canadians from coast to coast will be able to learn and share the information that we will have collected. In order to meet this challenge, we will work to distribute this knowledge and make it accessible to all. We would also like to hear the opinions of Canadians on this topic and in order to do so, we will be holding public hearings in the spring of 2000 throughout Canada.*
> *And finally, the third challenge for this committee will be to examine and identify the guiding principles on which Canada's public policy on drugs should be based."*

In view of our mandate, including an obligation to provide Canadians with objective and rigorous information, we have emphasized rigour and openness throughout the entire process, an approach that was all the more important as opinions on all sides of the illegal drugs issue are strong and often categorical. But rigour is not enough. For the information to reach Canadians, we could not reserve it for our exclusive use, hence the second principle that guided us: openness. From the outset, we insisted that all our work be made available as soon as possible on our Web site and we entered into direct dialogue with our fellow citizens as well as with experts.

The Committee approved a research program divided into five major axes of knowledge, sub-dividing each one into specific issues:

- the socio-historical, geopolitical, anthropological, criminological and economic issues of the use and regulation of cannabis;
- the medical and pharmacological aspects of the consumption, use and regulation of cannabis;
- the legal aspects from a national perspective;
- the legal and political issues in an international perspective; and
- the ethical issues and Canadians' moral and behavioural standards.

In an attempt to answer these questions in the most effective and economical manner possible, the Committee agreed to perform two tasks concurrently: conduct a research program and hear expert witnesses–complementary activities. We asked the Parliamentary Research Branch and other researchers to produce syntheses and analyses of the relevant literature. In all, the Committee received 23 reports and benefited from summaries of work conducted in other countries, including attendance at international conferences. In all, the Committee held more than 40 days of public hearings in Ottawa and 10 other Canadian communities, hearing more than 100 witnesses from all backgrounds, from across Canada and abroad.

The second component of our program of work was to examine public opinion. That meant we had two closely related responsibilities. The first was a duty to inform, indeed, to educate. We hope those who are offended by that term will pardon our presumption, but we are convinced that on public policy topics that are societal issues, it is the duty of political leaders to transmit information that educates, not merely convinces. The level of knowledge about drugs, even about cannabis, perhaps the best known drug, is often limited and clouded by myth. Our second responsibility in taking public opinion into account was to go out and discover it. We did so in three ways. We publicized our work as widely and as openly as possible to enable everyone to learn about it and react to it. Many chose to write us, although they were relatively few compared with the number of people in this country. We commissioned a qualitative public opinion study. The focus groups conducted across the country as part of that study are described in detail in Chapter 10. We also held public hearings in eight

communities across the country, enabling citizens to come and tell us what they thought, what they knew and what they had experienced.

In order to be able to interpret all this knowledge and come to conclusions and recommendations, the third component of our work focussed on guiding principles.

CHAPTER 3 – GUIDING PRINCIPLES

It has now been thirty years since the Royal Commission of Inquiry on the Non-Medical Use of Drugs, the Le Dain Commission, studied issues similar to those we are studying today. Its report on cannabis, whose scientific conclusions on the effects of the drug were generally accepted by all members of the Commission, led to three reports: a majority report by three of the members, and two minority reports. Each expressed a different concept of the role of the State and of criminal law, and the roles of science and ethics in the choices that had to be made. Having examined each of these subjects, we have elected to set down the guiding principles that clarify the concept we have of the roles that the state, criminal law, science and ethics must play in the development of a public policy on cannabis.

Ethical considerations take us through what is, that is the realm of facts, to the realm of what should be, what would be desirable, moving from recognized facts to standards, then more importantly to values and finally to the means of passing on and above all implementing these values. This is why ethics was our first subject. As a guideline, we have adopted the principle that an ethical public policy on illegal drugs, and on cannabis in particular, must **promote reciprocal autonomy built through a constant exchange of dialogue within the community.**

We always find ourselves in paradoxical situations where, to a certain degree, each person has the free will to make decisions and makes free decisions for himself, while at the same time rules are established in order to regulate interaction with others, a complex and more or less formal, but appropriate approach. The goal of governance is freedom, and not control. It is a question of defining the goals of society through policies and programs of action that are then implemented through systems and processes and upheld by those who govern that permits the encouragement and affirmation of those goals for human action. The law, as a vehicle of choice of governance, does not merely express rules or limitations passed for the benefit of and on behalf of citizens, but seeks a reciprocal process of building social relationships through which people, citizens and governments, can constantly adjust their expectations of behaviour. We therefore accept as a guiding principle for governance that **all of the means the State has at its disposal must work towards facilitating human action, particularly the processes allowing for the building of arrangements between government of the citizenry and governance of the self.**

On the whole, the legal basis of the criminal law is weak where the prescribed standard first, does not concern a relationship with others and where the characteristics of the relationship do not establish a victim and a perpetrator able to recognize his/her

actions; second, has to find its justification outside fundamental social relationships; and third, results in the form of enforcement, the harmful effects of which undermine and challenge the very legitimacy of the law. Where criminal law is involved in these issues, the very standard prescribed by the law turns the perpetrator into the victim and tries to protect him from himself, something it can do only by producing a never-ending stream of knowledge that remains constantly out of his reach. In this context **only offences involving significant direct danger to others should be matters of criminal law**.

The Committee's Report - especially the second part - puts great emphasis on research-based knowledge. This focus is an attempt to do justice to the knowledge that has been developed over the past few decades. We considered it important and indeed necessary to give it detailed consideration. Indeed, the Committee recommends that the drive to acquire knowledge on specific issues we deem important be continued. We do not claim, however, to have answered the fundamental question of why people consume psychoactive substances, such as alcohol, drugs or medication. We were indeed surprised, given the quantity of studies conducted each year on drugs, that this area has not been covered. It is almost as if the quest for answers to technical questions has caused science to lose sight of the basic issue!

Scientific knowledge cannot replace either personal reflection or the political decision-making process. It supports those processes, science's greatest contribution to public drug policy. Our guiding principle is that **science, which must continue to explore specific areas of key issues and reflect on overarching questions, supports the public policy development process.**

These principles have guided our interpretation of the available information as well as our choice of recommendations; the reader should always keep them in mind when reading our report.

CHAPTER 4 – A CHANGING CONTEXT

This chapter puts the Committee's work in context. In recent years, in fact, in the past few months, events of some significance have taken place; some directly linked to illegal drugs, others far removed from them. Obviously, September 11 comes to mind. In social and political terms, the claims of medical users, of recreational users, within the changing context of drug use and, more generally, inter-generational conflict, have to be taken into account. Legislation passed in the aftermath of September 11, some provisions of which could affect police drug investigations, the fight against organized crime and the trial of the Hells Angels in Quebec, must also be taken into account. In legal terms, court decisions have had a direct effect on medical use and a decision will be rendered in the next few months by the Supreme Court on recreational use. In international terms, the fragility of the UNDCP and the development of a continental drug policy for the Americas are relevant to an understanding of certain issues that may even overdetermine national policy. Finally, globalization and the more extreme forms

of economic liberalism have been factors too, primarily in western societies but worldwide as well, in the increase of addictive behaviours, be they the use of drugs or other substitutes for social life.

PART II – CANNABIS: EFFECTS, TYPES OF USE, ATTITUDES

CHAPTER 5 – CANNABIS: FROM PLANT TO JOINT

This chapter first describes the cannabis plant and the various forms in which it becomes a consumer drug. We then take a brief look at the geographical origin of the cannabis plant and the routes along which it circulates in the modern world, noting at the same time current modes of production (soil-based and hydroponic) that have developed in certain regions of Canada. We then describe the pharmacokinetics of the cannabis plant, in particular its main active ingredients, and their metabolism in the body.

Available information on cannabis markets is weak and contradictory. Since 1997, the RCMP's annual reports on drugs suggest that 800 tons of cannabis circulate in Canada each year. Yet, many people told us that cannabis production has increased significantly and that cannabis has become more available than ever in this country. Data on the economic value of the cannabis market are no more reliable. We noted that:

- The size of the national production has significantly increased, and it is estimated that 50% of cannabis available in Canada is now produced in the country;
- The main producer provinces are British Columbia, Ontario and Quebec;
- Estimates of the monetary value of the cannabis market are unreliable. For example, if 400 tons are grown yearly in Canada, at a street value of $225 per ounce, the total value of the Canadian production would be less than $6 billion per year, less than the often quoted value of the BC market alone;
- An unknown proportion of national production is exported to the United States; and
- A portion of production is controlled by organized crime elements.

We heard many alarmist comments on the increased level of active ingredient (THC) in cannabis, however, it is currently impossible to estimate the average content of cannabis available in the market. More sophisticated growing methods have likely contributed to increasing the THC concentration. We observed that:

- In its natural state, cannabis contains between 0.5% and 3% THC. Sophisticated growing methods and genetic progress have made it possible to increase THC content in recent years, but it is impossible to estimate the average content of cannabis available in the market; it is reasonable to consider that content varies between 6% and 31%.

- THC is fat soluble and readily spreads in the innervated tissues of the brain; it reaches a peak in the blood plasma in less than nine minutes and falls to approximately 5% after one hour.
- The body is slow to eliminate THC and inactive THC metabolites can be detected in urine up to 27 days after use in the case of regular users.
- Psychoactive effects generally last two to three hours and may last as many as five to seven hours after use.

CHAPTER 6 – USERS AND USES: FORM, PRACTICE, CONTEXT

Who uses cannabis? How do the patterns of use in Canada compare to those in other countries? In what context is cannabis used? Why? What populations are most vulnerable? What are the social consequences of cannabis, specifically on delinquency and criminal behaviour? Most important, what trajectories do cannabis users follow, specifically with respect to consumption of other drugs?

At the very least, partial answers to these questions are prerequisite to establishing policy on a substance. In Canada, knowledge of patterns and contexts of cannabis use verges on the abysmal. In the early 1980s, the USA, the United Kingdom, and Australia introduced monitoring systems for the general population and the student population. In the last five years, a number of European countries have introduced data collection systems as part of the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). Canada, by contrast, has carried out only two epidemiological general population surveys specific to drugs (in 1989 and 1994), and only some provinces conduct surveys of the student population, using different methods and instruments that preclude data comparison. Furthermore, few sociological or anthropological studies are conducted on the circumstances or context of illegal drug use, specifically for cannabis. The result is that our pool of knowledge on users and characteristics of use is sorely lacking.

We have no explanation for this situation, at least no satisfactory explanation. In the 1970s, following up on the work done by the Le Dain Commission, Canada could have set up a trend monitoring system. In the 1980s, when Canada's Anti-Drug Strategy was adopted, to which the federal government allocated $210M over five years, a data collection system could well have been created. The fact that it was not could be due to an absence of leadership or vision, a fear of knowing, the division of powers among levels of government, or the absence of a socio-legal research tradition within the departments responsible for justice and health. In fact, all of the above are probable factors. Whatever the case, it is our contention that this situation, unacceptable by definition, requires timely remedial action. We must resign ourselves to working with the scarce Canadian data available, and, more significantly, the virtually non-existent comparable data. We will also look at studies and data from other countries.

The chapter is divided into four sections. The first covers consumption patterns in the population as a whole, then specifically in the 12-18 year age group and compares the patterns in various countries. In the adult population we observed that:

- The epidemiological data available indicates that close to 30% of the population (12 to 64 years old) has used cannabis at least once;
- Approximately 2 million Canadians over age 18 have used cannabis during the previous 12 months, approximately 600,000 have used it during the past month, and approximately 100,000 use it daily. Approximately 10% used cannabis during the previous year; and
- Use is highest between the ages of 16 and 24.

For youth in the 12-17 age group, we observed that:

- Canada would appear to have one of the highest rates of cannabis use among youths;
- Approximately 1 million would appear to have used cannabis in the previous 12 months, 750,000 in the last month and 225,000 would appear make daily use; and
- The average age of introduction to cannabis is 15.

The second section looks at what we know about reasons for and details on use, including origins and cultural differences. The third section deals specifically with cannabis user trajectories, including escalation. We have observed the following:

- Most experimenters stop using cannabis;
- Regular users were generally introduced to cannabis at a younger age. Long-term users most often have a trajectory in which use rises and falls;
- Long-term regular users experience a period of heavy use in their early 20s;
- Most long-term users integrate their use into their family, social and occupational activities; and
- Cannabis itself is not a cause of other drug use. In this sense, we reject the gateway theory.

The fourth and last section covers the relationship between cannabis use and delinquency and crime. Based on research evidence, we concluded that:

- Cannabis itself is not a cause of delinquency and crime; and
- Cannabis is not a cause of violence.

CHAPTER 7 – CANNABIS: EFFECTS AND CONSEQUENCES

When it comes to cannabis, one hears anything and its opposite. While in some areas more research is needed and in others research results are contradictory, there exists nevertheless a strong basis of information contradicting many of the myths that continue to be perpetuated.

This chapter is divided into five sections. The first is a collection of statements on the presumed effects of marijuana that the Committee heard or became aware of through its research. The following three sections examine the acute effects of cannabis, followed in turn by the physiological and neurological consequences, the psychological consequences and the social consequences. Then, because of its significance and the central place it holds in social and political concerns, we turn our attention specifically to the question of any possible dependence arising from prolonged use of cannabis.

With respect to the effects of cannabis, the Committee observed that:

- The immediate effects of cannabis are characterized by feelings of euphoria, relaxation and sociability; they are accompanied by impairment of short-term memory, concentration and some psychomotor skills; and
- Long term effects on cognitive functions have not been established in research.

The Committee has distinguished between use, at-risk use and excessive use. Quantities used, psychosocial characteristics of the users and factors related to use contexts and quality of the substance all come into play to explain the passage from one category to the other. On at-risk use, the Committee observed that:

- Most users are not at-risk users insofar as their use is regulated, irregular and temporary, rarely beyond 30 years of age;
- For users above 16, at-risk use is defined as using between 0.1 to 1 gram per day; and
- Available epidemiological data suggests that approximately 100,000 Canadians might be at-risk users.
- The Committee feels that, because of its potential effects on the endogenous cannabinoid system and cognitive and psychosocial functions, any use in those under age 16 is at-risk use.

With respect to excessive use we observed that:

- More than one gram per day over a long period of time is heavy use, which can have certain negative consequences on the physical, psychological and social well-being of the user. According to the epidemiological data available, there is reason to believe that approximately 80,000 Canadians above age 16 could be excessive users;
- For those between the ages of 16 and 18, heavy use is not necessarily daily use but use in the morning, alone or during school activities;
- Heavy use can have negative consequences for physical health, in particular for the respiratory system (chronic bronchitis, cancer of the upper respiratory tract);
- Heavy use of cannabis can result in negative psychological consequences for users, in particular impaired concentration and learning and, in rare cases and with people already predisposed, psychotic and schizophrenic episodes;
- Heavy use of cannabis can result in consequences for a user's social well-being, in particular their occupational and social situation and their ability to perform tasks; and

- Heavy use of cannabis can result in dependence requiring treatment; however, dependence caused by cannabis is less severe and less frequent than dependence on other psychotropic substances, including alcohol and tobacco.

CHAPTER 8 – DRIVING UNDER THE INFLUENCE OF CANNABIS

If there is one issue, other than the effects of cannabis use on young people or the effects of substance abuse, that is likely to be of concern to society and governments, then it is certainly the effect of the use of cannabis on the ability to drive a vehicle. We are already familiar with the effects of alcohol on driving and the many accidents involving injuries or deaths to young people. In spite of the decreases in use noted in recent years, one fatal accident caused by the use of a substance is one accident too many.

Next to alcohol, cannabis is the most widely used psychoactive substance, particularly among young people in the 16-25 age group. Casual use occurs most often in a festive setting, at weekend parties, often accompanied by alcohol. People in this age group are also the most likely to have a car accident and are also susceptible to having an accident while impaired.

Cannabis affects psychomotor skills for up to five hours after use. The psychoactive effects of cannabis are also dependent on the amount used, the concentration of THC and the morphology, experience and expectations of users. But what are the specific effects of cannabis on the ability to drive motor vehicles? What are the effects of alcohol and cannabis combined? And what tools are available to detect the presence of a concentration of THC that is likely to significantly affect the psychomotor skills involved in vehicle operation?

This chapter is divided into three sections. The first considers the ways of testing for the presence of cannabinoids in the body. The second analyzes studies on the known prevalence of impaired driving, in both accident and non-accident contexts. The third and last summarizes what is known about the effects of cannabis on driving based on both laboratory and field studies. As in the other chapters, the Committee then draw its own conclusions.

The Committee feels it is quite likely that cannabis makes users more cautious, partly because they are aware of their deficiencies and compensate by reducing speed and taking fewer risks. However, because what we are dealing with is no longer the consequences on the users themselves, but the possible consequences of their behaviour on others, the Committee feels that it is important to **opt for the greatest possible caution** with respect to the issue of driving under the influence of cannabis.

Given what we have seen, we conclude the following:

- Between 5% and 12% of drivers may drive under the influence of cannabis; this percentage increases to over 20% for young men under 25 years of age;
- Cannabis alone, particularly in low doses, has little effect on the skills involved in automobile driving. Cannabis leads to a more cautious style of driving. However it has a negative impact on decision time and trajectory. This in itself does not mean that drivers under the influence of cannabis represent a traffic safety risk;
- A significant percentage of impaired drivers test positive for cannabis and alcohol together. The effects of cannabis when combined with alcohol are more significant than is the case for alcohol alone;
- Despite recent progress, there does not yet exist a reliable and non intrusive rapid roadside testing method;
- Blood remains the best medium for detecting the presence of cannabinoids;
- Urine cannot screen for recent use;
- Saliva is promising, but rapid commercial tests are not yet reliable enough;
- The visual recognition method used by police officers has yielded satisfactory results, and
- It is essential to conduct studies in order to develop a rapid testing tool and learn more about the driving habits of cannabis users.

CHAPTER 9 - USE OF MARIJUANA FOR THERAPEUTIC PURPOSES

There has been renewed interest in the issue of the use of marijuana for therapeutic purposes in recent years, particularly in Canada. In the wake of an Ontario Court of Appeal ruling which found the provisions of the *Controlled Drugs and Substances Act* to be unconstitutional pertaining to the therapeutic use of marijuana, the federal Minister of Health made new regulations in July 2001 that give people with specified medical problems access to marijuana under certain conditions.

However, the scientific community, the medical community in particular, is divided on the real therapeutic effectiveness of marijuana. Some are quick to say that opening the door to medical marijuana would be a step toward outright legalization of the substance.

But none of that should matter to physicians or scientists. It is not a question of defending general public policy on marijuana or even all illegal drugs. It is not a question of sending a symbolic message about "drugs". It is not a question of being afraid that young people will use marijuana if it is approved as a medicine. The question, and the only question, for physicians as professionals is whether, to what extent and in what circumstances, marijuana serves a therapeutic purpose. Physicians should have to determine whether people with certain diseases would benefit from marijuana use and weigh the side effects against the benefits. If they do decide the patient should use marijuana, they then have to consider how he or she might get it.

This chapter is devoted to the history of the use of marijuana for therapeutic purposes and the status of contemporary knowledge of marijuana and synthetic cannabinoids. We then give a brief account of compassion clubs and other organizations that supply marijuana for therapeutic use, as well as various public policy regimes. We conclude with our views on medical use of marijuana. In a later chapter, we discuss which public policy regime would be most appropriate given the status of medical use of marijuana

We observed that:

- There are clear, though non-definitive indications of the therapeutic benefits of marijuana in the following conditions: analgesic for chronic pain, antispasm for multiple sclerosis, anticonvulsive for epilepsy, antiemetic for chemotherapy and appetite stimulant for cachexi;
- There are less clear indications regarding the effect of marijuana on glaucoma and other medical conditions;
- Marijuana has not been established as a drug through rigorous, controlled studies.
- The quality and effectiveness of marijuana, primarily smoked marijuana, have not been determined in clinical studies;
- There have been some studies of synthetic compounds, but the knowledge base is still too small to determine effectiveness and safety;
- Generally, the effects of smoked marijuana are more specific and occur faster than the effects of synthetic compounds;
- The absence of certain cannabinoids in synthetic compounds can lead to harmful side effects, such as panic attacks and cannabinoid psychoses;
- Smoked marijuana is potentially harmful to the respiratory system;
- People who smoke marijuana for therapeutic purposes self-regulate their use depending on their physical condition and do not really seek the psychoactive effect;
- People who smoke marijuana for therapeutic purposes prefer to have a choice as to methods of use;
- Measures should be taken to support and encourage the development of alternative practices, such as the establishment of compassion clubs;
- The practices of these organizations are in line with the therapeutic indications arising from clinical studies and meet the strict rules on quality and safety;
- The studies that have already been approved by Health Canada must be conducted as quickly as possible;
- The qualities of the marijuana used in those studies must meet the standards of current practice in compassion clubs, not NIDA standards;
- The studies should focus on applications and the specific doses for various medical conditions; and
- Health Canada should, at the earliest possible opportunity, undertake a clinical study in cooperation with Canadian compassion clubs.

CHAPTER 10 - CANADIANS' OPINIONS AND ATTITUDES

It is always difficult to gauge the public's opinions, attitudes and concerns. The traditional method of surveying a representative sample of the population was too expensive for our resources. Surveys also have limits that we discuss in more detail. However, we did commission a qualitative study using focus groups, the results of which are presented in this chapter. We also report the results of other surveys that we researched and considered. As well, many Canadians wrote to us or sent us e-mails, and others came out to our public hearings to participate. Obviously we cannot draw solid conclusions from this. The people who wrote to us were probably those to whom the issue is very important, regardless of which way they may lean. Some are cited in our Report but we must reiterate that no conclusion should be drawn from these opinions in terms of representativeness. No account of Canadians' opinions on and attitudes toward drugs in general would be complete without an examination of the role of the media in shaping those opinions and attitudes. In recent years, as a result of this Committee's work and other initiatives, various Canadian newspapers and magazines have run stories or have written editorials on the issue. These are the focus of the first part of the chapter. The next part presents the results of surveys and polls, including the survey we commissioned and surveys conducted in different provinces. The last part covers our understanding of what Canadians told us.

We observed the following:

- Public opinion on marijuana is more liberal than it was 10 years ago;
- There is a tendency to think that marijuana use is more widespread and that marijuana is more available than it used to be;
- There is a tendency to think that marijuana is not a dangerous drug;
- The concern about organized crime is significant;
- Support for medical use of marijuana is strong;
- There is a tendency to favour decriminalization or, to a lesser degree, legalization;
- People criticize enforcement of the legislation in regards to simple possession of marijuana; and
- There is a concern for youth and children.

PART III — POLICIES AND PRACTICES IN CANADA

CHAPTER 11 - A NATIONAL DRUG STRATEGY?

Based on the impo tance of the subject, it would probably surprise many Canadians to learn that only from 1987 to 1993 did Canada have a fully funded national drug strategy. It is true that Canada has had legislation dealing with the use of psychoactive substances since the passage of the *Opium Act* in 1908. This Act was followed by several pieces of criminal legislation over the years that increased federal

enforcement powers over psychoactive substances and expanded the list of illicit substances. These pieces of legislation have historically focused on the supply of psychoactive substances, adopting a prohibitionist approach to use. It is widely acknowledged now, however, that a more balanced approach is required if one is to deal effectively with those who abuse psychoactive substances.

This chapter recounts the development and implementation of the 1987 National Drug Strategy, which had as an objective the promotion of a balanced approach to the problem of psychoactive substance abuse. This is followed by a discussion of what became of the national strategy and what goals have been achieved.

We observed the following:

- Canada urgently needs a comprehensive and coordinated national drug strategy for which the federal government provides sound leadership;
- Any future national drug strategy should incorporate all psychoactive substances, including alcohol and tobacco;
- To be successful, a national drug strategy must involve true partnerships with all levels of government and with non-governmental organizations;
- Over the years, the intermittency of funding has diminished the ability to coordinate and implement the strategy; adequate resources and a long-term commitment to funding are needed if the strategy is to be successful;
- Clear objectives for the strategy must be set out, and comprehensive evaluations of these objectives and the results are required;
- At the developmental stage, there is a need to identify clear and shared criteria for "success";
- The core funding for the Canadian Centre on Substance Abuse (CCSA) has been insufficient for it to carry out its mandate; proper funding for the CCSA is essential;
- There is a need for an independent organization – the CCSA – to conduct national surveys at least every second year; there is also a need to achieve some level of consistency, comparability and similar time frames for provincially-based school surveys;
- Coordination at the federal level should be given to a body that is not an integral part of one of the partner departments; and
- Canada's Drug Strategy's should adopt a balanced approach – 90% of federal expenditures are currently allocated to the supply reduction.

CHAPTER 12 - THE NATIONAL LEGISLATIVE CONTEXT

Drugs have been prohibited for fewer than a hundred years; cannabis for slightly more than 75 years. It is tempting to think that the decisions made over the years to use criminal law to fight the production and use of certain drugs are in keeping with social progress and the advancement of scientific knowledge about drugs. But is this really the case? The history of legislation governing illegal drugs in Canada, like the analysis in Chapter 19 of the structure of international conventions, suggests that it is highly

doubtful. To what extent is such reasoning really rational? Is the rationale of the system of controls acceptable in the eyes of civil society, users as well as abstainers? What criteria motivated legislator decisions? Indeed, were there criteria? What motivated parliamentarians from Canada and elsewhere to prohibit certain substances, to control access to certain others, and to permit still others to be sold over the counter?

Knowing where we have been helps in understanding where we are going. That is the goal of this chapter, retracing the evolution of Canadian drug laws from 1908 to the present day. We have identified three legislative periods. The first, and longest, spans 1908 to 1960, the period of hysteria. We were told that drugs were made criminal because they are dangerous. Analysis of debates in Parliament and in media accounts clearly shows how far this is from truth. When cannabis was introduced in the legislation on narcotics in 1923, there was no debate, no justification, in fact many members did not even know what cannabis was.

The second period, much shorter, runs from 1961 to 1975, the search for lost reason. Following the explosion in drug use in the early 1960s and demands for reform from various sectors of society, governments appointed a commission of inquiry in Canada, the Le Dain Commission. Last comes the contemporary period at the beginning of the 1980s. Reform is not on the policy agenda any more and anti-drug policies have forged ahead.

In summary, we observed that:

- Early drug legislation was largely based on a moral panic, racist sentiment and a notorious absence of debate;
- Drug legislation often contained particularly severe provisions, such as reverse onus and cruel and unusual sentences; and
- The work of the Le Dain Commission laid the foundation for a more rational approach to illegal drug policy by attempting to rely on research data. The Le Dain Commission's work had no legislative outcome until 1996 in certain provisions of the *Controlled Drugs and Substances Act*, particularly with regard to cannabis.

CHAPTER 13 - REGULATING THERAPEUTIC USE OF CANNABIS

Cannabis has an extremely long history of therapeutic use, going back several thousands of years. It was often used for the same medical conditions it is used for today. With the development of the pharmaceutical industry in the last century, the medical community has gradually discontinued its use. Various factors may explain this. Developments in the pharmaceutical industry provided the medical community with more stable and better tested medication. The practice of medicine itself has changed and so has our conception of health. Then, at the turn of the 20th century, the plants from which opium, cocaine and cannabis are derived were banned by the international community, except for medical and scientific purposes. In the case of cannabis, no rigorous study had been done until recently.

Further to the social rediscovery of cannabis and the identification of its molecular composition and chemical elements in the 1960s, renewed interest in the therapeutic applications of cannabis grew in the early 1970s. More people began using the plant for its therapeutic benefits and many demanded a relaxation of the prohibitionist rules governing cannabis.

Partly because its safety and effectiveness have yet to be reviewed in clinical trials, cannabis has not been approved for sale in Canada as a medical product. Despite this lack of approval, many use cannabis for its therapeutic purposes without legal authorization. In addition, because of the many claims regarding its therapeutic benefit, a growing number of people have called for a less restrictive approach and are demanding access to cannabis for people who could benefit from its use.

This chapter reviews the events that prompted the recent enactment of the *Marihuana Medical Access Regulations*. One of the objectives of the regulations is to provide a compassionate framework of access to marijuana for seriously ill Canadians while research regarding its therapeutic application continues. Also discussed is the implementation of these regulations, which came into force on 30 July 2001.

We have observed the following:

- The MMAR are not providing a compassionate framework for access to marijuana for therapeutic purposes and are unduly restricting the availability of marijuana to patients who may receive health benefits from its use;
- The refusal of the medical community to act as gatekeepers and the lack of access to legal sources of cannabis appear to make the current regulatory scheme an "illusory" legislative exemption and raises serious Charter implications;
- In almost one year, only 255 people have been authorized to possess marijuana for therapeutic purposes under the MMAR and only 498 applications have been received – this low participation rate is of concern;
- Changes are urgently needed with regard to who is eligible to use cannabis for therapeutic purposes and how such people gain access to cannabis;
- Research on the safety and efficacy of cannabis has not commenced in Canada because researchers are unable to obtain the product needed to conduct their trials;
- No attempt has been made in Health Canada's current research plan to acknowledge the considerable expertise currently residing in the compassion clubs;
- The development of a Canadian source of research-grade marijuana has been a failure.

CHAPTER 14 - POLICE PRACTICES

Views on police priorities regarding enforcement of laws on illicit drugs are, at the very least, inconsistent, if not contradictory. Some believe that too much police time, effort and resources are spent in investigating illicit drug offences and, more specifically, possession offences, even more specifically, cannabis possession offences. Others, including the police themselves, claim that police priorities are already focused

on traffickers and producers, and that possession charges are laid as a result of police presence to deal with other criminal activity. Thus, they maintain that the vast majority of cannabis possession charges are incidental to other police responsibilities.

This chapter reviews the key organizations that are responsible for enforcing Canada's current illicit drugs legislation, the *Controlled Drugs and Substances Act* (CDSA). It includes a discussion of the powers they have been granted, and the investigative techniques used, in relation to illicit drug investigations. Finally, key police-related statistics are explored. This information should help clarify some of the misconceptions related to enforcement of laws on illicit drugs.

The Committee found that:

- The annual cost of drug enforcement in Canada is estimated to be between $700 million and $1 billion;
- Reduced law enforcement activities resulting from amendments to the drug legislation on cannabis could produce substantial savings or a significant reallocation of funds by police forces to other priorities;
- Due to the consensual nature of drug offences, police have been granted substantial enforcement powers and have adopted highly intrusive investigative techniques; these powers are not unlimited, however, and are subject to review by Canadian courts;
- Over 90,000 drug-related incidents are reported annually by police; more than three-quarters of these incidents relate to cannabis and over 50% of all drug-related incidents involve possession of cannabis;
- From 1991 to 2001, the percentage change in rate per 100,000 people for cannabis-related offences is +91.5 – thus, the rate of reported cannabis-related offences has almost doubled in the past decade;
- The number of reported incidents related to the cultivation of cannabis increased dramatically in the past decade;
- Reported incident rates vary widely from province to province;
- Cannabis was involved in 70% of the approximately 50,000 drug-related charges in 1999. In 43% of cases (21,381), the charge was for possession of cannabis.;
- The rate of charges laid for drug offences vary significantly from province to province;
- The uneven application of the law is of great concern and may lead to discriminatory enforcement, alienation of certain groups within society, and creation of an atmosphere of disrespect for the law; in general, it raises the issue of fairness and justice; and
- Statistics on seizure seem to confirm an increase in cannabis cultivation in Canada and also a shift in police priorities regarding this offence.

CHAPTER 15 - THE CRIMINAL JUSTICE SYSTEM

The previous chapter examined how people first come into contact with the criminal justice system through the enforcement of criminal legislation. Several questions remain, however. What happens once a person has been charged with a drug offence? Who is responsible for prosecuting drug cases? What type of punishment do people receive? Who ends up with a criminal record? Have there been any challenges to the constitutional validity of drug legislation? These issues and others related to the criminal justice system are reviewed in this chapter

We have observed the following:

- The cost of prosecuting drug offences in 2000-2001 was $57 million with approximately $5 million or roughly 10% of the total budget relating to prosecuting cannabis possession offences;
- In 1999, it was estimated that Canadian criminal courts heard 34,000 drug cases, which involved more than 400,000 court appearances;
- The Drug Treatment Court initiatives seem very encouraging, although comprehensive evaluations are needed to ensure such programs are effective;
- Disposition and sentencing data with respect to drug-related offences are incomplete and there is an urgent need to correct this situation;
- Correctional Service Canada spends an estimated $169 million annually to address illicit drugs through incarceration, substance abuse programs, treatment programs and security measures; expenditures on substance abuse programs are unreasonably low, given the number of inmates who have substance-abuse dependence problems;
- A criminal conviction can negatively affect a person's financial situation, career opportunities and restrict travel. In addition, it can be an important factor in future dealings with the criminal justice system; and
- Provincial courts of appeal have so far maintained the constitutionality of cannabis prohibition. They have found that because there is some evidence of harm caused by marijuana use that is neither trivial nor insignificant, Parliament has a rational basis to act as it has done, and the marijuana prohibition is therefore consistent with the principles of fundamental justice in section 7 of the Charter. These decisions have been appealed, and the Supreme Court of Canada will soon decide whether cannabis prohibition is constitutionally sound.

CHAPTER 16 - PREVENTION

Viewed in theory, at least, as a public health issue, a policy on illegal drugs should call for a strong prevention strategy. Nothing, however, is more fluid, vague, or even controversial, than prevention. When it comes to illegal drugs, the legal and political context makes the issue of prevention even harder to clarify and actions even harder to define. The national legal context surrounding illegal drugs and the interpretation of international drug policies are such that because they are defined *a priori* as harmful

substances, illegal drugs must not be used. Another way of putting it is that any use is abuse. If use is abuse, if individuals or organizations involved in prevention are unable to make distinctions that are essential in setting objectives and devising preventive measures, what hope is there of establishing successful prevention programs? There are, as this chapter will show, many prevention programs that are not aimed solely or even particularly at the prevention of use, but rather the prevention of at-risk behaviour. Harm reduction, for example, is not only a general strategy for dealing with psychoactive substances, but is also a preventive approach that seeks to lower the risks associated with drugs and drug control without requiring abstinence. However, harm reduction is the subject of much controversy and criticism because it is based on the premise that use of drugs is a social reality. Addressing the issue of prevention means considering at the same time government policies on illegal drugs. Any discussion of prevention entails discussion of the limits of government intervention and of how one conceives of human action. How far should government interventions go in identifying groups at risk without further stigmatizing groups already at risk? To what extent are humans rational beings who act in their best interest provided they are given the right information?

This chapter on prevention begins with a statement that will come as no surprise to health or justice experts: when it comes to prevention, there is lots of talk, but the resources allocated are small and the initiatives weak. The second section asks the question: what prevention? We look at current knowledge of the factors underlying prevention initiatives and the effectiveness of some preventive measures, with special emphasis on one of the most important weapons in the war on drugs, the DARE program. The third section looks at the harm reduction approach to prevention. As in the other chapters, our conclusions are in the form of observations that may serve to guide future actions.

The Committee found that:

- Prevention is not designed to control but rather to empower individuals to make informed decisions and acquire tools to avoid at-risk behaviour;
- A national drug strategy should include a strong prevention component;
- Prevention strategies must be able to take into account contemporary knowledge about drugs;
- Prevention messages must be credible, verifiable and neutral;
- Prevention strategies must be comprehensive, cover many different factors and involve the community;
- Prevention strategies in schools should not be led by police services or delivered by police officers;
- The RCMP should reconsider its choice of the DARE program that many evaluation studies have shown to be ineffective;
- Prevention strategies must include comprehensive evaluation of a number of key elements;

- A national drug strategy should include mechanisms for widely disseminating the results of research and evaluations;
- Evaluations must avoid reductionism, involve stakeholders in prevention be part of the program, and include longitudinal impact assessment;
- Harm reduction strategies related to cannabis should be developed in coordination with educators and the social services sector; and
- Harm reduction strategies related to cannabis should include information on the risks associated with heavy chronic use, tools for detecting at-risk and heavy users and measures to discourage people from driving under the influence of marijuana.

CHAPTER 17 - TREATMENT PRACTICES

With the exception of the treatment given to offenders imprisoned in federal institutions and Aboriginals, the care available to individuals who are substance-dependent is essentially the responsibility of the provinces and territories. This chapter is therefore brief since we received only a few submissions and heard few witnesses on this question.

In Chapter 7 we determined that physical dependency on cannabis was rare and insignificant. Some symptoms of addiction and tolerance can be identified in habitual users but most of them have no problem in quitting and do not generally require a period of withdrawal. As far as forms of psychological dependency are concerned, the studies are still incomplete but the international data tend to suggest that between 5% and 10% of regular users (using at least in the past month) are at risk of becoming dependent on cannabis. We estimated that approximately 3% or 600,000 adult Canadians have consumed cannabis in the past month and that approximately 0.5% or 100,000 use it on a daily basis. This indicates that somewhere between 30,000 and 40,000 people might be at-risk and 5,000 to 10,000 might make excessive use. For those aged 16 and 17, the numbers were between 50,000 and 70,000 at-risk and 8,000 to 17,000 potentially excessive users. The data also indicated that the peak period for intensive use is between the ages of 17 and 25 years. These broad parameters indicate where to look to prevent dependency and offer treatment services for those in need.

What form does cannabis dependency take? Most authors agree that psychological dependency on cannabis is relatively minor. In fact, it cannot be compared in any way with tobacco or alcohol dependency and is even less common than dependency on certain psychotropic medications.

We have observed that:

- The expression 'drug addiction' should no longer be used and we should talk instead of substance abuse and dependency;
- Between 5% and 10% of regular cannabis users are at risk of developing a dependency;
- Physical dependency on cannabis is virtually non-existent;

- Psychological dependency is moderate and is certainly lower than for nicotine or alcohol;
- Most regular users of cannabis are able to diverge from a trajectory of dependency without requiring treatment;
- There are many forms of treatment but nothing is known about the effectiveness of the different forms of treatment for cannabis dependency specifically;
- As a rule, treatment is more effective and less costly than incarceration;
- Studies of the treatment programs should be conducted, including treatments programs for people with cannabis dependency; and
- Studies should be conducted on the interaction of the cannabinoid and the opioid systems.

CHAPTER 18 - OBSERVATIONS ON PRACTICES

Previous chapters have described public action by dividing it into the major sectors of involvement. Before closing the third part of this report, we make some general observations that cut across the individual areas we have examined. The first concerns difficulties in harmonizing the various levels and sectors of involvement; the second, the difficulty in co-ordinating their various approaches; and the third, the costs of drugs and public policy.

A study published by CCSA in 1996 but based on 1992 data had identified the following costs of substance abuse:

- The costs associated with all illegal drugs were $1.4 billion, compared with $7.5 billion in the case of alcohol and $9.6 billion in the case of tobacco.
- Expressed as a percentage of the gross domestic product, the total costs for all substances was 2.67%. Of this, 0.2% was for illegal drugs, 1.09% for alcohol and 1.39% for tobacco.
- The principal costs of illegal drugs are externalities, that is, loss of productivity - $823 million, health care - $88 million, and losses in the workplace - $5.5 million, for a total of about 67% of all costs related to illegal drugs.
- The cost of public policies, or opportunity costs, represent about 33%.
- The cost of enforcing the law represents about 29.2% of all costs, or about 88% of all policy costs. The balance goes to prevention, research and administration.

Previous studies conducted in British Columbia in 1991, in Ontario in 1988 and in Quebec in 1988, using different methodologies, established costs of $388 million, $1.2 billion and $2 billion respectively, for a total cost of $3.5 billion in these three provinces alone. These figures demonstrate the extent to which such estimates can vary, according to the methodology selected and the availability of data.

Nevertheless, with the CCSA study taken as the standard, two comments must be made. First, loss of productivity – the major cost – is measured in mortality - $547 million and morbidity - $275 million. Except in the case of traffic fatalities, cannabis is not a cause of death and involves none of this type of social cost. Morbidity corresponds to losses attributed to problems caused by drug use as measured by the difference between the average annual income of users and of the population in general. Here, two further observations about cannabis should be noted. A large proportion of cannabis users are young people who are not yet part of the workforce and cannabis use involves none of the addiction and attendant problems that follow from heroin or cocaine use. Therefore, the costs that can be attributed to cannabis in this regard are likely minimal. If one accepts the methodology of the authors, **cannabis in itself entails few externalities**, which are the main measures of the social cost of illegal drugs.

However, it should also be noted that the study did not calculate the costs of substance-related crime. Alcohol is well known for its frequent association with crimes of violence (at least 30% of all cases), as well as with impaired driving, which results in major social and economic losses. Crime related to illegal drugs is of several types: organized crime, crimes against property committed in order to pay for drugs, true mainly in the case of heroin and cocaine, and crimes of violence committed under the influence of drugs. With the exception of organized crime and driving under the influence, cannabis involves few of the factors that generate criminal behaviour.

Secondly, according to the CCSA's study, the main cost of illegal drugs, after loss of productivity, is the cost of law enforcement, which the study estimates at approximately $400 million. In Chapters 14 and 15, we note that police and court costs are certainly much higher than this figure, and probably total between $1 and $1.5 billion. The proportion of these costs attributable to cannabis is impossible to determine for certain. But, insofar as 77% of all drug-related offences involve cannabis, and of these 50% simple possession, and given that about 60% of incidents result in a charge, of which some 10% to 15% of cases the accused receives a prison sentence, it is clear that a considerable proportion of the drug-related activity addressed by the penal justice system is concerned with cannabis. While admitting this to be a very rough estimate, we suggest that about 30% of the activity of the justice system is tied up with cannabis. On the basis of our estimates and the lowest cost of law enforcement, or $1 billion, it costs about $300 million annually to enforce the cannabis laws.

In effect, the main social costs of cannabis are a result of public policy choices, primarily its continued criminalization, while the consequences of its use represent a small fraction of the social costs attributable to the use of illegal drugs.

Overall, we observed the following:

- The lack of any real national platform for discussion and debate on illegal drugs prevents the development of clear objectives and measurement indicators;
- The absence of a national platform makes exchange of information and best practices impossible;
- Practices and approaches vary considerably between and within provinces and territories;
- The conflicting approaches of the various players in the field are a source of confusion;
- The resources and powers of enforcement are greatly out of balance compared with those of the health and education fields and the civil society;
- The costs of all illegal drugs had risen to close to $1.4 billion in 1992;
- Of the total costs of illegal drugs in 1992, externalities (social costs) represented 67% and public policy costs 33%;
- The social costs of illegal drugs and the public policy costs are underestimated ;
- The cost of enforcing the drug laws is more likely to be closer to $1 billion to $1.5 billion per annum;
- The principal public policy cost relative to cannabis is that of law enforcement and the justice system; which may be estimated to represent a total of $300 to $500 million per annum;
- The costs of externalities attributable to cannabis are probably minimal - no deaths, few hospitalizations, and little loss of productivity;
- The costs of public policy on cannabis are disproportionately high given the drug's social and health consequences; and
- The Canadian Centre on Substance Abuse is seriously under-funded; its annual budget amounts to barely 0.1% of the social costs of illegal drugs alone (alcohol not included). Its budget should be increased to at least 1%; that is, approximately $15 million per annum.

PART IV-PUBLIC POLICY OPTIONS

CHAPTER 19 - THE INTERNATIONAL LEGAL ENVIRONMENT

This chapter could begin and end with the same words: The international drug control conventions are, at least with respect to cannabis, an utterly irrational restraint that has nothing to do with scientific or public health considerations.

Three points bear making concerning the substance of the current conventions.

The first has to do with the absence of definitions. The terms drugs, narcotics and psychotropics are not defined in any way except as lists of products included in schedules. It follows that any natural or synthetic substance on the list of narcotics is, for the purposes of international law, a narcotic, and that a psychotropic is defined in

international law by its inclusion in the list of psychotropics. The only thing that the 1961 Convention tells us about the substances to which it applies is that they can be abused. The 1971 Psychotropics Convention, which reversed the roles in that the synthetic drug producing countries wanted narrower criteria, indicates that the substances concerned may cause dependence or central nervous system stimulation or depression and may give rise to such abuse as to "constitute a public health problem or a social problem that warrants international control."

The second point, following from the first, relates to the arbitrary nature of the classifications. While cannabis is included, along with heroin and cocaine, in Schedules I and IV of the 1961 Convention, which carry the most stringent controls, it is not even mentioned by name in the 1971 Convention, though THC is listed as a Schedule I psychotropic along with mescaline, LSD and so on. The only apparent criterion is medical and scientific use, which explains why barbiturates are in Schedule III of the 1971 Convention and therefore subject to less stringent controls than natural hallucinogens. These classifications are not just arbitrary, but inconsistent with the substances' pharmacological classifications and their danger to society.

Third, if there was so much concern about public health based on how dangerous "drugs" are, one has to wonder why tobacco and alcohol are not on the list of controlled substances.

We conclude from these observations that the international regime for the control of psychoactive substances, beyond any moral or even racist roots it may initially have had, **is first and foremost a system that reflects the geopolitics of North-South relations in the 20th century**. Indeed, the strictest controls were placed on organic substances – the coca bush, the poppy and the cannabis plant – which are often part of the ancestral traditions of the countries where these plants originate, whereas the North's cultural products, tobacco and alcohol, were ignored and the synthetic substances produced by the North's pharmaceutical industry were subject to regulation rather than prohibition. It is in this context that the demand made by Mexico on behalf of a group of Latin American countries during the negotiations leading up to the 1988 Convention, that their use be banned, must be understood. It was a demand that restored the balance to a degree, as the countries of the South had been forced to bear the full brunt of the controls and their effects on **their own people** since the inception of drug prohibition. The result may be unfortunate, since it reinforces a prohibitionist regime that history has been shown to be a failure, but it may have been the only way, given the mood of the major Western powers, to demonstrate the irrationality of the entire system in the longer term. In any case, it is a short step from there to question the legitimacy of instruments that help to maintain the North-South disparity yet fail miserably to reduce drug supply and demand.

We make the following observations:

- The series of international agreements concluded since 1912 have failed to achieve their ostensible aim of reducing the supply of drugs;
- The international conventions constitute a two-tier system that regulates the synthetic substances produced by the North and prohibits the organic substances produced by the South, while ignoring the real danger the substances represent for public health;
- When cannabis was included in the international conventions in 1925, there was no knowledge of its effects;
- The international classifications of drugs are arbitrary and do not reflect the level of danger they represent to health or to society;
- Canada should inform the international community of the conclusions of our report and officially request the declassification of cannabis and its derivatives.

CHAPTER 20 - PUBLIC POLICIES IN OTHER COUNTRIES

The vast majority of Canadians have heard about the "war on drugs" which the USA is conducting and about its prohibitionist approach, but many would be surprised to see the major variations between states, indeed between cities, within that country. Even fewer know that Sweden enforces a prohibitionist policy at least as strict as that of the US, but through other means. Many of us have, in one way or another, heard about the "liberal" approach introduced in the Netherlands in 1976. Fewer people know of the Spanish, Italian, Luxembourg or Swiss approaches, which are even more liberal in certain respects. More recently, Canadians learned of the decision by the UK's Minister of the Interior to reclassify cannabis as a Class C drugs, but it is not clear that we know precisely what that means. In view of the preconceptions that many may have in relation to France with regard to wine, many may be surprised to learn that its policy on cannabis appears more "conservative" than that of neighbouring Belgium, for example. As may be seen, after the overall framework of the puzzle has been established by the international community, the ways the pieces are put together vary widely among states, and at times among the regions of a single state.

That is why, in order to learn about the experience and approaches of other countries, the Committee commissioned a number of research reports on the situations in other countries and heard representatives of some of those countries in person. We of course had to make some choices, such as limiting ourselves to the western countries of the northern hemisphere. This is a weak point in our Report, we agree, but our resources were limited. In addition, as we wanted to compare public policies with data on use trends and judicial practices, we were forced to choose countries with an information base. In our hearings with representatives of those countries, we were mainly limited by time and cost.

In this chapter, we describe the situations in five European countries — France, the Netherlands, the United Kingdom, Sweden and Switzerland — and in Australia and the United States.

CHAPTER 21 - PUBLIC POLICY OPTIONS

Public policy is not just a matter of enabling legislation, in this case criminal legislation. Nonetheless, when it comes to illegal drugs, criminal legislation occupies a symbolic and determinative place. It is as if this legislation is the backbone of our public policy. Public discussions of cannabis do not deal so much with such matters as public health, user health, prevention of at-risk or excessive use, but with such questions as the pros and cons of decriminalization, establishing a civil offence or maintaining a criminal offence, or possible legalization and the extent thereof.

In respect of illegal drugs, where the key issues are, first and foremost, matters of public health and culture (including education and research), and where criminal law should be used only as a last resort, public policy must be based primarily on clear principles and objectives. For this to come about, public policy must be equipped with a set of tools designed to deal with the various issues that drugs represent to societies. Legislation is only one such tool. The social and economic costs of illegal drugs affect many aspects of society through lower productivity and business loss, hours of hospitalization and medical treatment of all kinds, police time and prison time, and broken or lost lives. Even if no one can pinpoint the exact figures, a portion of these costs arise, not from the substances themselves, but from the fact that they are criminalized. In fact, more than for any other illegal drug, its criminalization is the principal source of social and economic costs. However, in spite of the fact that the principal social costs of drugs affect business, health and family, the emphasis on the legal debate tips the scales of public action in favour of law enforcement agencies. No one can deny that their work is necessary to ensure public order and peace and fight organized crime. At the same time, over 90% of resources are spent on enforcing the law, the most visible actions with respect to drugs in the public sphere are police operations and court decisions and, at least with respect to cannabis, the law lags behind individual attitudes and opinions, thus creating a huge gap between needs and practice.

Most national strategies display a similar imbalance. The national strategies that appear to have the greatest chance of success, however, are those that strive to correct the imbalance. These strategies have introduced knowledge and observation tools, identified indicators of success with respect to their objectives, and established a veritable nerve centre for implementing and monitoring public policy. The law, criminal law especially, is put in its proper place as one method among many of reaching the defined objectives, not an aim in itself.

This chapter is divided into three sections. The first examines the effectiveness of legal measures for fighting drugs, and shows that legal systems have little effect on consumption or supply. The second section describes the various components of a public policy. The third considers the direction of criminal policy, and defines the main terms used: decriminalization, depenalization, diversion, legalization, and regulation.

In our view, it is clear that if the aim of public policy is to diminish consumption and supply of drugs, specifically cannabis, all signs indicate

complete failure. One might think the situation would be worse if not for current anti-drug action. This may be so. Conversely, one might also think that the negative impact of anti-drug programs that are currently centre stage are greater than the positive effect, specifically non-compliance with laws that are inconsistent with majority attitudes and behaviour. One of the reasons for this failure is the excessive emphasis placed on criminal law in a context where prohibition of use and a drug-free society appear to remain the omnipresent and determining direction of current public policies.

We think that a public policy **on psychoactive substances must be both integrated and adaptable, target at-risk uses and behaviours and abuses based on a public health approach that neither trivializes nor marginalizes users**. Implementation of such a policy must be multifaceted.

Some say that decriminalization is a step in the right direction, one that gives society time to become accustomed to cannabis, to convince opponents that chaos will not result, to adopt effective preventive measures. We believe however that **this approach is in fact the worst case scenario, depriving the State of a necessary regulatory tool for dealing with the entire production, distribution, and consumption network, and delivering hypocritical messages at the same time.**

In our opinion, the data we have collected on cannabis and its derivatives provide sufficient grounds for our general conclusion that the **regulation of the production, distribution and consumption of cannabis, inasmuch as it is part of an integrated and adaptable public policy, is best able to respond to the principles of autonomy, governance that fosters human responsibility and limitation of penal law to situations where there is demonstrable harm to others. A regulatory system for cannabis should permit, specifically:**

- *more effective targeting of illegal traffic and a reduction in the role played by organized crime;*
- *prevention programs better adapted to the real world and better able to prevent and detect at-risk behaviour;*
- *enhanced monitoring of products, quality and properties;*
- *better user information and education; and*
- *respect for individual and collective freedoms, and legislation more in tune with the behaviour of Canadians.*

In our opinion, Canadian society is ready for a responsible policy of cannabis regulation that complies with these basic principles.

CONCLUSIONS AND RECOMMENDATIONS

The Senate Special Committee on Illegal Drugs' mandate was to examine Canada's public policy approach in relation to cannabis and assess its effectiveness and impact in light of the knowledge of the social and health-related effects of cannabis and the international context. Over the past two years, the Committee has heard from Canadian and foreign experts and reviewed an enormous amount of scientific research. The Committee has endeavoured to take the pulse of Canadian public opinion and attitudes and to consider the guiding principles that are likely to shape public policy on illegal drugs, particularly cannabis. Our report has attempted to provide an update on the state of knowledge and the key issues, and sets out a number of conclusions in each chapter.

This final section sets out the main conclusions drawn from all this information and presents the resulting recommendations derived from the thesis we have developed namely: *in a free and democratic society, which recognizes fundamentally but not exclusively the rule of law as the source of normative rules and in which government must promote autonomy as far as possible and therefore make only sparing use of the instruments of constraint, public policy on psychoactive substances must be structured around guiding principles respecting the life, health, security and rights and freedoms of individuals, who, naturally and legitimately, seek their own well-being and development and can recognize the presence, difference and equality of others.*

LE DAIN – THIRTY YEARS AGO ALREADY

Thirty years ago, the Le Dain Commission released its report on cannabis. This Commission had far greater resources than we did. However, we had the benefit of Le Dain's work, a much more highly developed knowledge base since then and of thirty years' historical perspective.

The Commission concluded that the criminalization of cannabis had no scientific basis. Thirty years later, we confirm this conclusion and add that continued criminalization of cannabis remains unjustified based on scientific data on the danger it poses.

The Commission heard and considered the same arguments on the dangers of using cannabis: apathy, loss of interest and concentration, learning difficulties. A majority of the Commissioners concluded that these concerns, while unsubstantiated, warranted a restrictive policy. Thirty years later, we assert that the studies done in the meantime have not confirmed the existence of the so-called amotivational syndrome

and add that most studies rule out this syndrome as a consequence of the use of cannabis.

The Commission concluded that not enough was known about the long-term and excessive use of cannabis. We assert that these types of use exist and may present some health risks; excessive use, however, is limited to a minority of users. Public policy, we would add, must provide ways to prevent and screen for at-risk behaviour, something our policies have yet to do.

The Commission concluded that the effects of long-term use of cannabis on brain function, while largely exaggerated, could affect adolescent development. We concur, but point out that the long-term effects of cannabis use appear reversible in most cases. We note also that adolescents who are excessive users or become long-term users are a tiny minority of all users of cannabis. Once again, we would add that a public policy must prevent use at an early age and at-risk behaviour.

The Commission was concerned that the use of cannabis would lead to the use of other drugs. Thirty years' experience in the Netherlands disproves this clearly, as do the liberal policies of Spain, Italy and Portugal. And here in Canada, despite the growing increase in cannabis users, we have not had a proportionate increase in users of hard drugs.

The Commission was also concerned that legalization would mean increased use, among the young in particular. We have not legalized cannabis, and we have one of the highest rates in the world. Countries adopting a more liberal policy have, for the most part, rates of usage lower than ours, which stabilized after a short period of growth.

Thirty years later, we note that:

- Billions of dollars have been sunk into enforcement without any greater effect. There are more consumers, more regular users and more regular adolescent users;
- Billions of dollars have been poured into enforcement in an effort to reduce supply, without any greater effect. Cannabis is more available than ever, it is cultivated on a large scale, even exported, swelling coffers and making organized crime more powerful; and
- There have been tens of thousands of arrests and convictions for the possession of cannabis and thousands of people have been incarcerated. However, use trends remain totally unaffected and the gap the Commission noted between the law and public compliance continues to widen.

It is time to recognize what is patently obvious: our policies have been ineffective, because they are poor policies.

INEFFECTIVENESS OF THE CURRENT APPROACH

No clearly defined federal or national strategy exists. Some provinces have developed strategies while others have not. There has been a lot of talk but little significant action. In the absence of clear indicators accepted by all stakeholders to assess Canadian public policy, it is difficult to determine whether action that has been taken is effective.

Given that policy is geared to reducing demand (i.e. drug-use rates) and supply (by reducing the availability of drugs and pushing up drug prices), both these indicators may be used. A look at trends in cannabis use, both among adults and young people, **forces us to admit that current policies are ineffective**. In Chapter 6, we saw that trends in drug-use are on the increase. If our estimates do indeed reflect reality, no fewer that 2million Canadians aged between 18 and 65 have used cannabis at least once over the past 12 months, while at least 750,000 young people between the ages of 14 and 17 use cannabis at least once per month, one third of them on a daily basis. This proportion appears, at least in the four most highly-populated provinces, to be increasing. Statistics suggest that both use and at-risk use is increasing.

Of course, we must clearly establish whether the ultimate objective is a drug-free society, at least one free of cannabis, or whether the goal is to reduce at-risk behaviour and abuse. This is an area of great confusion, since Canadian public policy continues to use vague terminology and has failed to establish whether it focuses on substance abuse as the English language terminology used in several documents seems to suggest or on drug-addiction as indicated by the French language terminology.

It is all very well to criticize the "trivialization" of cannabis in Canada, to "explain" increases in use, but it must also be established why, if this is indeed the case, this trivialization has occurred. It is also important to identify the root cause of this trivialization against a backdrop of mainly anti-drug statements. The courts and their lenient attitude might be blamed for this. Perhaps the judiciary is at the forefront of those responsible for cannabis policies and the enforcement of the law. It must also be determined whether sentences are really as lenient as some maintain. A major issue to be addressed is whether harsher sentences would indeed be an effective deterrent given that the possibility of being caught by the police is known to be a much greater deterrent. Every year, over 20,000 Canadians are arrested for cannabis possession. This figure might be as high as 50,000 depending on how the statistics are interpreted. No matter what the numbers, they are too high for this type of conduct. However, even those numbers are laughable number when compared to the three million people who have used cannabis over the past 12 months. We should not think that the number of arrests could be significantly increased even if billions more dollars were allocated to police enforcement. Indeed, such a move should not even be considered.

A look at the availability and price of drugs, **forces us to admit that supply-reduction policies are ineffective**. Throughout Canada, above all in British Columbia

and Quebec, the cannabis industry is growing, flooding local markets, irritating the United States and lining the pockets of criminal society. Drug prices have not fallen but quality has improved, especially in terms of THC content – even if we are sceptical of the reported scale of this improvement. Yet, police organizations already have greater powers and latitude – especially since the September 11, 2001 tragedy – in relation to drugs than in any other criminal matter. In addition, enforcement now accounts for over 90 % of all spending related to illegal drugs. To what extent do we want to go further down this road?

Clearly, current approaches are ineffective and inefficient. Ultimately, their effect amounts to throwing taxpayers' money down the drain in a crusade that is not warranted by the danger posed by the substance. It has been maintained that drugs, including cannabis, are not dangerous because they are illegal but rather are illegal because they are dangerous. This is perhaps true of other types of drugs, but not of cannabis. We should state this clearly once and for all, for public good: it is time to stop this crusade.

PUBLIC POLICY BASED ON GUIDING PRINCIPLES

However much we might wish good health and happiness for everyone, we all know how fragile they are. Above all, we realize that health and happiness cannot be forced on a person, especially not by criminal law based on a specific concept of what is morally 'right'. No matter how attractive calls for a drug-free society might be, and even if some people might want others to stop smoking, drinking alcohol, or smoking joints, we all realize that these activities are part of our social reality and the history of humankind.

Consequently, what role should the State play? It should neither abdicate responsibility and allow drug markets to run rife, nor should it impose a particular way of life on people. We have opted, instead, for a concept whereby public policy **promotes and supports freedom for individuals and society as a whole**. For some, this would undoubtedly mean avoiding drug use. However, for others, the road to freedom might be via drug use. For society as a whole, in practice, this concept means a State that does not dictate what should be consumed and under what form. Support for freedom necessarily means flexibility and adaptability. It is for this reason that public policy on cannabis has to be clear while at the same time tolerant, to serve as a guide while at the same time avoiding imposing a single standard. This concept of the role of the State is based on the **principle of autonomy and individual and societal responsibility.** Indeed, it is much more difficult to allow people to make their own decisions because there is less of an illusion of control. It is just that: an illusion. We are all aware of that. It is perhaps sometimes comforting, but is likely to lead to abuse and unnecessary suffering. An ethic of responsibility teaches social expectations, expectations not to use drugs in public or sell them to children and responsible

behaviour, recognizing at-risk behaviour and being able to use moderately, and supports people facing hardship by providing a range of treatment.

From this concept of government action ensues a limited role for criminal law. As far as cannabis is concerned, **only behaviour causing demonstrable harm to others should be prohibited**: illegal trafficking, selling to minors and impaired driving.

Public policy shall also draw on available knowledge and scientific research but without expecting science to provide the answers to political issues. Indeed, scientific knowledge does have a major role to play **in supporting decision-making,** at both the individual and government levels. But science should play no greater role. It is for this reason that the Committee considers that a drug and dependency monitoring agency and a research program should be set up to help future decision-makers.

A CLEAR AND COHERENT FEDERAL STRATEGY

Although the Committee has focused on cannabis, we have nevertheless observed inherent shortcomings in the federal drug strategy. Quite obviously, there is no real strategy or focused action. Behind the assumed leadership provided by Health Canada there emerges a lack of necessary tools for action, a patchwork of ad hoc approaches varying from one substance to another and piecemeal action by various departments. Of course, co-ordinating bodies do exist, but lack real tools and clear objectives, each focusing its action according to its own particular priorities. This state of affairs has resulted in a whole series of funded programs being developed without any tangible cohesion.

Many stakeholders have expressed their frustration to the Committee at the apparently vanishing pieces of the puzzle and at the whole gamut of incoherent decisions, that cause major friction on the front lines. Various foreign observers also expressed their surprise that a country as rich as Canada, which is not immune to psychoactive substance-related problems, did not have a "champion", a spokesperson or a figure of authority able to fully grasp the real issues and obtain genuine cooperation from all of the stakeholders.

It is for this reason that we are recommending the creation of the position of National Advisor on Psychoactive Substances and Dependency to be attached to the Privy Council. We do not envisage this as a superstructure responsible for managing budgets and action related to psychoactive substances. We favour an approach similar to that of the *Mission interministérielle à la drogue et à la toxicomanie* in France over one modelled on that of the United States' Office of National Drug Control Policy. The Advisor would have a small dedicated staff, the majority of whom would be on assignment from various federal departments and bodies involved in drug issues.

The Advisor would be responsible: for advising the Cabinet and the Prime Minister on national and international psychoactive substance-related issues; for ensuring coordination between federal departments and agencies; for overseeing the

development of federal government psychoactive substance-related objectives and ensuring these objectives are satisfied; and to serve as a Canadian government spokesperson on issues related to psychoactive substances at an international level.

Recommendation 1

The Committee recommends that the position of National Advisor on Psychoactive Substances and Dependency be created within the Privy Council Office; that the Advisor be supported by a small secretariat and that the necessary staff be assigned by federal departments and agencies involved with psychoactive substances on request.

NATIONAL STRATEGY SUSTAINED BY ADEQUATE RESSOURCES AND TOOLS

A federal policy and strategy do not in themselves make a national strategy. Provinces, territories, municipalities, community organizations and even the private sector all have a role to play in accordance with their jurisdiction and priorities. This is necessary and this diversity is worth encouraging. However some harmonization and meaningful discussion on practices and pitfalls, on progress and setbacks, and on knowledge are to be encouraged. Apart from those provided by the resource-starved piecemeal actions of the Canadian Centre on Substance Abuse, there are all too few opportunities and schemes to promote exchanges of this type. **The current and future scale of drug and dependency-related issues warrants that the Canadian government earmark the resources and establish the tools with which to develop fair, equitable and considered policies**.

Like the majority of Canadian and foreign observers of the drug situation, we were struck by the relative lack of tools and measures for determining and following up on the objectives of public psychoactive substance policy. One might not agree with the numbers-focused goals set out by the Office of National Drug Control Policy for the reduction of drug use or for the number of drug treatment programs set up and evaluated. However, we have to admit that at least these figures serve as guidelines for all stakeholders and as benchmarks against which to measure success.

Similarly, one might not feel totally comfortable with the complex Australian goal-definition process, whereby the whole range of partners from the various levels of government, organizations and associations meet at a conference every five years to review goals. However, at least those goals agreed upon by the various stakeholders constitute a clear reference framework and enable better harmonization of action.

The European monitoring system with its focal points in each country of the European Union under the European Monitoring Centre for Drugs and Drug Addiction umbrella might seem cumbersome; and the American system of conducting various annual epidemiological studies might appear expensive. We might even

acknowledge that there are problems with epidemiological studies, which are far from providing a perfect picture of the psychoactive substance use phenomena. However, at least these tools, referred to and used throughout the western world, permit the development of a solid information base with which to analyse historical trends, identify new drug-use phenomena and react rapidly. In addition, it allows for an assessment of the relevance and effectiveness of action taken. No system of this type exists in Canada, which is the only industrialized western country not to have such a knowledge structure.

It is for these reasons that the Committee recommends that the Government of Canada support various initiatives to develop a genuine national strategy. Firstly, the Government should call a national conference of the whole range of partners with a view to setting out goals and priorities for action over a five-year period. This conference should also identify indicators to be used in measuring progress at the end of the five-year period. Secondly, the Canadian Centre on Substance Abuse needs to be renewed. Not only does this body lack resources but it is also subject to the vagaries of political will of one Minister, the Minister of Health. The Centre should have a budget in proportion with the scale of the psychoactive substance problem and should have the independence required to address this issue. Lastly, a Canadian Monitoring Agency on Drugs and Dependency should be created within the Centre.

Recommendation 2

The Committee recommends that the Government of Canada mandate the National Advisor on Psychoactive Substances and Dependency to call a high-level conference of key stakeholders from the provinces, territories, municipalities and associations in 2003, to set goals and priorities for action on psychoactive substances over a five-year period.

Recommendation 3

The Committee recommends that the Government of Canada amend the enabling legislation of the Canadian Centre on Substance Abuse to change the Centre's name to the *Canadian Centre on Psychoactive Substances and Dependency*; make the Centre accountable to Parliament; provide the Centre with an annual basic operating budget of $15 million to be increased annually; require the Centre to table an annual report on actions taken, key issues, research and trends in Parliament and in the provincial and territorial legislatures; mandate the Centre to ensure national coordination of research on psychoactive substances and dependency and to conduct studies into

specific issues; and mandate the Centre to undertake an assessment of the national strategy on psychoactive substance and dependency every five years.

Recommendation 4

The Committee recommends that, in the legislation creating the Canadian Centre on Psychoactive Substances and Dependency, the Government of Canada specifically include provision for the setting up of a Monitoring Agency on Psychoactive Substances and Dependency within the Centre; provide that the Monitoring Agency be mandated to conduct studies every two years, in cooperation with relevant bodies, on drug-use trends and dependency problems in the adult population; work with the provinces and territories towards increased harmonization of studies of the student population and to ensure they are carried out every two years; conduct ad hoc studies on specific issues; and table a bi-annual report on drug-use trends and emerging problems.

A PUBLIC HEALTH POLICY

When cannabis was listed as a prohibited substance in 1923, no public debate or discussion was held on the known effects of the drug. In fact, opinions expressed were disproportionate to the dangers of the substance. Half a century later, the Le Dain Royal Commission of Inquiry on the Non-Medical Use of Drugs held a more rational debate on cannabis and took stock of what was known about the drug. Commissioners were divided not so much over the nature and effects of the drug but rather over the role to be played by the State and criminal law in addressing public health-related goals. Thirty years after the Le Dain Commission report, we are able to categorically state that, **used in moderation, cannabis in itself poses very little danger to users and to society as a whole, but specific types of use represent risks for users**.

In addition to being ineffective and costly, criminalization leads to a series of harmful consequences: users are marginalized and exposed to discrimination by the police and the criminal justice system; society sees the power and wealth of organized crime enhanced as criminals benefit from prohibition; and governments see their ability to prevent at-risk use diminished.

We would add that, **even if cannabis were to have serious harmful effects, one would have to question the relevance of using the criminal law to limit these effects**. We have demonstrated that criminal law is not an appropriate governance tool for matters relating to personal choice and that prohibition is known to result in harm

which often outweighs the desired positive effects. However, current scientific knowledge on cannabis, its effects and consequences are such that this issue is not relevant to our discussion.

Indeed available data indicate that the scale of the cannabis use phenomenon can no longer be ignored. Chapter 6 indicated that no fewer than 30% of Canadians (12 to 64 years old) have experimented with cannabis at least once in their lifetime. In all probability, this is an underestimation. We have seen that approximately 50% of high school students have used cannabis within the past year. Nevertheless, a high percentage of them stop using, and the vast majority of those who experiment do not go on to become regular users. Even among regular users, only a small proportion develop problems related to excessive use, which may include some level of psychological dependency. Consumption patterns among cannabis users do not inevitably follow an upward curve but rather a series of peaks and valleys. Regular users also tend to have a high rate of consumption in their early twenties, which then either drops off or stabilizes, and in the vast majority of cases, most often ceasing altogether in their thirties.

All of this does not in any way mean, however, that cannabis use should be encouraged or left unregulated. Clearly, it is a psychoactive substance with some effects on cognitive and motor functions. When smoked, cannabis can have harmful effects on the respiratory airways and is potentially cancerous. Some vulnerable people should be prevented, as much as possible, from using cannabis. This is the case for young people under [illegible] years of age and those people with particular conditions that might make them vulnerable, for example those with psychotic predispositions. As with alcohol, adult users should be encouraged to use cannabis in moderation. Given that, as for any substance, at-risk use does exist, preventive measures and detection tools should be established and treatment initiatives must be developed for those who use the drug excessively. Lastly, it goes without saying that education initiatives and severe criminal penalties must be used to deter people from operating vehicles under the influence of cannabis.

As for any other substance, there is at-risk use and excessive use. There is no universally accepted criterion for determining the line between regular use, at-risk use and excessive use. The context in which use occurs, the age at which users were introduced to cannabis, substance quality and quantity are all factors that play a role in the passage from one type of use to another. Chapters 6 and 7 identified various criteria, which we have collated in table form below.

Proposed Criteria for Differentiating Use Types

	Environment	Quantity	Frequency	Period of use and intensity
	Curiosity	Variable	A few times over lifetime	None
	Recreational, social Mainly in evening Mainly in a group	A few joints Less than one gram per month	A few times per month	Spread over several years but rarely intensive
	Recreational and occupational (to go to school, to go to work, for sport...) Alone, in the morning Under 16 years of age	Between 0.1 and 1 gram per day	A few times per week, evenings, especially weekends	Spread over several years with high intensity periods
	Occupational and personal problems No self regulation of use	Over one gram per day	More than once per day	Spread over several years with several months at a time of high intensity use

Even if **cannabis itself poses very little danger to the user and to society as a whole, some types of use involve risks**. It is time for our public policy to recognize this and to **focus on preventing at-risk use and on providing treatment for excessive cannabis users**.

Recommendation 5

The Committee recommends that the Government of Canada adopt an integrated *policy on the risks and harmful effects of psychoactive substances* covering the whole range of substances (medication, alcohol, tobacco and illegal drugs). With respect to cannabis, this policy should focus on educating users, detecting and preventing at-risk use and treating excessive use.

A REGULATORY APPROACH TO CANNABIS

The **prohibition of cannabis does not bring about the desired reduction in cannabis consumption or problematic use**. However, this approach does have a whole series of harmful consequences. Users are marginalized, and over 20,000 Canadians are arrested each year for cannabis possession. Young people in

schools no longer enjoy the same constitutional and civil protection of their rights as others. Organized crime benefits from prohibition and the criminalization of cannabis enhances their power and wealth. Society will never be able to stamp out drug use – particularly cannabis use.

Some might believe that an alternative policy signifies abandoning ship and giving up on promoting well-being for Canadians. Others might maintain that a regulatory approach would fly in the face of the fundamental values of our society. We believe, however, that the continued prohibition of cannabis jeopardizes the health and well-being of Canadians much more than does the substance itself or the regulated marketing of the substance. In addition, we believe that the continued criminalization of cannabis undermines the fundamental values set out in the *Canadian Charter of Rights and Freedoms* and confirmed in the history of a country based on diversity and tolerance.

We do not want to see cannabis use increase, especially among young people. Of note, the data from other countries that we compared in Chapters 6 and 20 indicate that countries such as the Netherlands, Australia and Switzerland, which have put in place a more liberal approach, have not seen their long-term levels of cannabis use rise. The same data also clearly indicate that countries with a very restrictive approach, such as Sweden and the United States, are poles apart in terms of cannabis use levels and that countries with similar liberal approaches, such as the Netherlands and Portugal, are also at opposite ends of the spectrum, falling somewhere between Sweden and the United States. We have concluded that public policy itself has little effect on cannabis use trends and that other more complex and poorly understood factors play a greater role in explaining the variations.

An exemption regime making cannabis available to those over the age of 16 could probably lead to an increase in cannabis use for a certain period. Use rates would then level off as interest wanes and as effective prevention programs are set up. A roller coaster pattern of highs and lows would then follow, as has been the case in most other countries.

This approach is neither one of total abdication nor an indication of abandonment but rather a vision of the role of the State and criminal law as **developing and promoting but not controlling human action** and as **stipulating only necessary prohibitions** relating to the fundamental principle of respect for life, other persons and a harmonious community, and as **supporting and assisting others, not judging and condemning difference**.

We might wish for a drug-free world, fewer smokers or alcoholics or less prescription drug dependency, but we all know that we shall never be able to eliminate these problems. More importantly, we should not opt to criminalize them. The Committee believes that the same healthy and respectful approach and attitude should be applied to cannabis.

It is for this reason that the Committee recommends that the Government of Canada amend the *Controlled Drugs and Substances Act* to create a criminal exemption scheme, under which the production and sale of cannabis would be licensed. Licensing

and the production and sale of cannabis would be subject to specific conditions, which the Committee has endeavoured to specify. For clarity's sake, these conditions have been compiled at the end of this section. It should be noted at the outset that the Committee suggests cigarette manufacturers should be prohibited from producing and selling cannabis.

Recommendation 6

The Committee recommends that the Government of Canada amend the *Controlled Drugs and Substances Act* to create a criminal exemption scheme. This legislation should stipulate the conditions for obtaining licences as well as for producing and selling cannabis; criminal penalties for illegal trafficking and export; and the preservation of criminal penalties for all activities falling outside the scope of the exemption scheme.

Recommendation 7

The Committee recommends that the Government of Canada declare an amnesty for any person convicted of possession of cannabis under current or past legislation.

A COMPASSION-BASED APPROACH FOR THERAPEUTIC USE

In Chapter 9, we noted that cannabis has not been approved as a medicinal drug in the pharmacological sense of the word. In addition to the inherent difficulties in conducting studies on the therapeutic applications of cannabis, there are issues arising from the current legal environment and the undoubtedly high cost to governments of conducting such clinical studies.

Nevertheless, we do not doubt that for some medical conditions and for certain people cannabis is indeed an effective and useful therapy. Is it more effective than other types of medication? Perhaps not. Can physicians currently prescribe cannabis at a known dosage? Undoubtedly not. Should persons suffering from certain physical conditions diagnosed by qualified practitioners be permitted to use cannabis if they wish to do so? Of this, we are convinced.

The regulations made in 2001 by Health Canada, even though they are a step in the right direction, are fundamentally unsatisfactory. They do not facilitate access to therapeutic cannabis. They do not consider the experience and expertise available in compassion clubs. These regulations only govern marijuana and do not include cannabis derivatives such as hashish and cannabis oils.

It is for these reasons that the Committee recommends that Health Canada amend the *Marihuana Medical Access Regulations* in order to allow compassionate access to cannabis and its derivatives. As in the previous chapter, proposed rules have been compiled at the end of this chapter.

Recommendation 8

The Committee recommends that the *Marijuana Medical Access Regulations* be amended to provide new rules regarding eligibility, production and distribution with respect to cannabis for therapeutic purposes. In addition, research on cannabis for therapeutic purposes is essential.

PROVISIONS FOR OPERATING A VEHICLE UNDER THE INFLUENCE OF CANNABIS

In Chapter 8, we discussed the fact that research has not clearly established the effects of cannabis when taken alone on a person's ability to operate a vehicle. Nevertheless, there is enough evidence to suggest that operating a vehicle while under the influence of cannabis alters motor functions and affects a person's ability to remain in his or her lane. We have also established that the combined effects of cannabis and alcohol impair faculties even more than does alcohol taken alone. Epidemiological studies have shown that a certain number of cannabis users do drive under the influence of the substance and that a large proportion of these people, mainly the young, appear to believe that cannabis does not impair their ability to drive.

This chapter also indicated that no reliable and non-intrusive roadside detection tools exist. Saliva-based equipment is a promising development but for the time being, provide random results. We have also established that a visual recognition system, which has mainly been developed and assessed in the United States, is a reliable way of detecting drug-induced impaired driving faculties.

Recommendation 9

The Committee recommends that the Criminal Code be amended to lower permitted alcohol levels to 40 milligrams of alcohol per 100 millilitres of blood, in the presence of other drugs, especially, but not exclusively cannabis; and to admit evidence from expert police officers trained in detecting persons operating vehicles under the influence of drugs.

RESEARCH

Research on psychoactive substances, and particularly on cannabis, has undergone a boom over the past 20 years. The Committee was able to fully grasp the actual extent of this increase since we faced the challenge of summarizing it. Not all research is of the same quality and the current political and legal climate governing cannabis hampers thorough and objective studies. Nevertheless, a solid fact base was available to the Committee, on which to establish its conclusions and recommendations.

However, more research needs to be done in a certain number of specific areas. In Chapter 6, we established that a lack of practical research on cannabis users has resulted in only a limited amount of information on contexts of use being available. It is also currently difficult to establish criteria on the various types of cannabis use in order to guide those responsible for prevention. The Committee suggests that cannabis use of over one gram per day constitutes excessive use and that between 0.1 and one gram per day equates to at-risk use. We also suggest that any use below 16 years of age is at-risk use. This is of course enlightened speculation, but speculation nevertheless, which remains to be explored.

In Chapters 16 and 17, we referred to the fact that we know very little about the most effective prevention practices and treatment. Here also, the current context hindered. As far as prevention is concerned, the more or less implicit "*just say no*" message and the focus on cannabis use prevention are strategies that have been dictated by the prohibition-based environment. In terms of treatment for problem users, abstinence-based models have long been the dominant approach and continue to sit very poorly with harm-reduction-based models. Thorough assessment studies are required.

The Canadian Centre on Psychoactive Substances and Dependency must play a key role in co-ordinating and publishing the results of studies. The Centre does not have to conduct research itself. This can and indeed must sometimes be carried out by academics. The Health Research Institutes are also natural players. However, it is important to clearly identify a single central body to collect research information. This will enable the information to be distributed as widely possible and, we hope, used.

Recommendation 10

The Committee recommends that the Government of Canada create a national fund for research on psychoactive substances and dependency to fund research on key issues, more particularly on various types of use, on the therapeutic applications of cannabis, on tools for detecting persons operating vehicles under the influence of drugs and on effective prevention and treatment programs; that the Government of Canada mandate the Canadian Centre on

Psychoactive Substances and Dependency to co-ordinate national research and serve as a resource centre.

CANADA'S INTERNATIONAL POSITION

The Committee is well aware that were Canada to choose the rational approach to regulating cannabis we have recommended, it would be in contravention of the provisions of the various international conventions and treaties governing drugs. We are also fully aware of the diplomatic implications of this approach, in particular in relation to the United States.

We are keen to avoid replicating, at the Canada - US border, the problems that marked relations between the Netherlands, France, Belgium and Germany over the issue of drug tourism between 1985 and 1995. This is one of the reasons that justifies restricting the distribution of cannabis for recreational purposes to Canadian residents.

We are aware of the fact that a proportion of the cannabis produced in Canada is exported, mainly to the United States. We are also aware that a considerable proportion of heroin and cocaine comes into Canada via the United States. We are particularly cognisant of the fact that Canadian cannabis does not explain the increase in cannabis use in the United States. It is up to each country to get its own house in order before criticizing its neighbour.

Internationally, Canada will either have to temporarily withdraw from the conventions and treaties or accept that it will be in temporary contravention until the international community accedes to its request to amend them. The Committee opts for the second approach, which seems to us to be more consistent with the tradition and spirit of Canadian foreign policy. In addition, we have seen that international treaties foster the imbalanced relationship between the northern and southern hemispheres by prohibiting access to plants, including cannabis, produced in the southern hemisphere, while at the same time developing a regulatory system for medication manufactured by the pharmaceutical industry in the northern hemisphere. Canada could use this imbalanced situation to urge the international community to review existing treaties and conventions on psychoactive substances.

Canada can and indeed should provide leadership on drug policy. Developing a national information and action infrastructure would undoubtedly be key to this. **Canada must also play a leading role in the Americas.** We believe that Canada enjoys a favourable international reputation and that it can promote the development of fairer and more rational drug, in particular cannabis policies. We also contend that Canada should strive for the creation of a European observatory style Drug and Dependency Monitoring Agency for the Americas within the Organization of American States.

Recommendation 11

The Committee recommends that the Government of Canada instruct the Minister of Foreign Affairs and International Trade to inform the appropriate United Nations authorities that Canada is requesting an amendment to the conventions and treaties governing illegal drugs; and that the development of a Drugs and Dependency Monitoring Agency for the Americas be supported by the Government of Canada.

PROPOSALS FOR IMPLEMENTING THE REGULATION OF CANNABIS FOR THERAPEUTIC AND RECREATIONAL PURPOSES

Amendments to the
Marijuana Medical Access Regulations
(Production and sale of cannabis for therapeutic purposes)

A. Eligible person

A person affected by one of the following: wasting syndrome; chemotherapy treatment; fibromyalgia; epilepsy; multiple sclerosis; accident-induced chronic pain; and some physical condition including migraines and chronic headaches, whose physical state has been certified by a physician or an individual duly authorized by the competent medical association of the province or territory in question, may choose to buy cannabis and its derivatives for therapeutic purposes. The person shall be registered with an accredited distribution centre or with Health Canada.

B. Licence to distribute

A Canadian resident may obtain a licence to distribute cannabis and its derivatives for therapeutic purposes. The resident must undertake to only sell cannabis and its derivatives to eligible persons; to only sell cannabis and its derivatives purchased from producers duly licensed for this purpose; to keep detailed records on the medical conditions and their development, consumption and the noted effects on patients; to take all measures needed to ensure the safety of the cannabis products and to submit to departmental inspections.

C. Licence to produce

A Canadian resident may obtain a licence to produce cannabis and its derivatives for therapeutic purposes. The resident must undertake: to not hold a licence to produce cannabis for non therapeutic purposes; to take the measures necessary to ensure the consistency, regularity and quality of crops; to take the measures necessary to ensure the security of production sites; to know and document the properties and concentrations of each harvest with respect to Delta 9 THC; to sell only to accredited distribution centres and to submit to departmental inspections.

D. Other proposals

- Ensure that expenses relating to the use of cannabis for therapeutic purposes will be eligible for a medical expenses tax credit;
- Establish a program of research into the therapeutic applications of cannabis, by providing sufficient funding; by mandating the Canadian Centre on Psychoactive Substances and Dependency to co-ordinate the research program; and by providing for the systematic study of clinical cases based on the documentation available in organizations currently distributing cannabis for therapeutic purposes and in future distribution centres; and
- Ensure that the advisory committee on the therapeutic use of cannabis represents all players, including distribution centres and users.

Amendment to the *Controlled Drugs and Substances Act* (CDSA) (Production and sale of cannabis for non therapeutic purposes)

A. General aims of the bill

- To reduce the injurious effects of the criminalization of the use and possession of cannabis and its derivatives;
- To permit persons over the age of 16 to procure cannabis and its derivatives at duly licensed distribution centres; and
- To recognize that cannabis and its derivatives are psychoactive substances that may present risks to physical and mental health and, to this end, to regulate the use and trade of these substances in order to prevent at-risk use and excessive use.

B. Licence to distribute

Amend the Act to create a scheme providing for exemption to the criminal offences provided in the CDSA with respect to the distribution of cannabis. A Canadian resident may obtain a licence to distribute cannabis. The resident must undertake **not to distribute to persons under the age of 16; must never have been sentenced for a criminal offence, with the exception of offences related to the possession of cannabis, for which an amnesty will be declared**; and must agree to procure cannabis only from duly licensed producers. In addition, in accordance with potential restrictions under the *Canadian Charter of Rights and Freedoms*, licensed distributors shall not display products explicitly and shall not advertise in any manner.

C. Licence to produce

Amend the Act to create an exemption to the criminal offences provided in the CDSA with respect to the production of cannabis. A Canadian resident may obtain a licence to produce cannabis. The resident must undertake to only sell to duly licensed distributors; to sell only marijuana and hashish with a THC content of 13% or less; to limit production to the quantity specified in the licence; to take the measures needed to ensure the security of production sites; to keep detailed records of quantities produced, crops, levels of THC concentration and production conditions; and to submit to departmental inspections. No person charged with and sentenced for criminal offences, with the exception of the possession of cannabis, for which an amnesty will be declared, shall be granted a licence. No person or legal entity, directly or indirectly associated with the production, manufacture, promotion, marketing or other activity connected with tobacco products and derivatives shall be granted a licence. In accordance with potential restrictions under the *Canadian Charter of Rights and Freedoms*, cannabis products and their derivatives shall not be advertised in any manner.

D. Production for personal use

Amend the Act to create an exemption to the criminal offences provided in the CDSA in order to permit the personal production of cannabis so long as it is not sold for consideration or exchange in kind or other and not advertised or promoted in any other way. In addition, quantities shall be limited to ensure production is truly for personal consumption.

E. Consumption in public

Consumption in public places frequented by young people under 16 years of age shall be prohibited.

F. International trade

All forms of international trade, except those explicitly permitted under the Act shall be subject to the penalties provided in the CDSA for illegal trafficking.

G. Other proposals

- Ensure the establishment of a National Cannabis Board with duly mandated representatives of the federal government and the governments of the provinces and territories. The Board would keep a national register on the production and sale of cannabis and its derivatives, set the amount and distribution of taxes taken on the sale of cannabis products and ensure the taxes collected on the production and sale of cannabis and derivatives are

directed solely to prevention of at-risk use, treatment of excessive users, research and observation of trends and the fight against illegal trafficking.

- The provinces and territories would continue to develop prevention measures that should be directed at at-risk use, as a priority. The Canadian Centre on Psychoactive Substances and Dependency should be mandated to collect best treatment practices and ensure an exchange of information on effective practices and their evaluation.
- The provinces and territories would continue to develop support and treatment measures that should be directed at excessive use, as a priority. The Canadian Centre on Psychoactive Substances and Dependency should be mandated to collect best prevention practices and ensure an exchange of information on effective practices and their evaluation.
- Resources available to police and customs to fight smuggling, export in all its forms and cross-border trafficking should be increased.

CHAPTER 5

CANNABIS: FROM PLANT TO JOINT

Cannabis, marijuana, pot, grass, kif, grifa, ganja–from so many cultures, so many names for the drug made from *cannabis sativa indica*, one of the two main varieties of hemp. Beyond these various names are also different ways in which the drug is used and the context of those various usages: here marijuana is rolled with cigarette tobacco in a cigarette paper (joint), there kif is smoked in a pipe and elsewhere *ganja* is smoked in a water pipe. Sometimes it is baked into cookies or cakes. The French *pétard*, the English joint or the Indian *bangh* are all names for the product consumed and, at the same time designate different usages: marijuana is most often composed of the plant's flowering tops and dried, powdered leaves; *sinsemilla* is a preparation consisting of female tops of a private variety of seeds, whereas Indian ganja consists solely of fertilized flowering tops.[1]

These names are not mere accidents of folklore: like other substances, cannabis has codified uses that vary across cultures. The words used to name the same drug refer to a set of relations that populations of various cultures maintain with it, a kind of code of manners, but also of reasons to use the drug. In North America (United States and Canada), marijuana has long been identified with youth and the sexual liberation of the 1960s; in India and Jamaica, *ganja* has religious aspects which it does not necessarily possess in the West; and this same drug has still other cultural meanings in the Maghreb. We return to this question in Chapter 6.

This chapter first describes the cannabis plant and the various forms in which it becomes a consumer drug. We then take a brief look at the geographical origin of the cannabis plant and the routes along which it circulates in the modern world, noting at the same time its current modes of production (soil-based and hydroponic) which have developed in certain regions of Canada. We then describe the pharmacokinetics of the cannabis plant, in particular its main active ingredients and their metabolism in the body.

---

[1] See in particular INSERM (2001) *Cannabis. Quels effets sur le comportement et la santé ?* Paris: Les Éditions Inserm, page 143 passim; Ben Amar (in preparation); Wheelock, B.B. (2002) *Physiological and Psychological Effects of Cannabis: Review of the Findings.* Report prepared for the Senate Special Committee on Illegal Drugs, Ottawa: Senate of Canada.

ONE PLANT, VARIOUS DRUGS[2]

There are a number of varieties of cannabis. The best known are *Cannabis sativa, Cannabis indica* and *Cannabis ruderalis. Cannabis sativa* is the main variety which grows in virtually any climate. In dry, sandy and slightly alkaline soils, it yields plants that can reach up to seven meters in height. In Canada, the preferred variety for soil-based cultivation is *Cannabis indica*, which is a shorter plant, but with higher concentrations of Δ^9-THC (the main active ingredient of cannabis, discussed more fully below). There are male and female plants. In general, female plants are richer in Δ^9-THC than the males, which are often smaller and bare of leaves. Δ^9-THC is mainly found in the resin secreted by the flowering tops.



Flowering tops and leaves of cannabis

It appears that cannabis was first known in China some 6,000 years ago, then subsequently in India, then the Middle East, Africa, Mexico and South America. Cannabis can be cultivated in a number of ways, in greenhouses or hydroponically, which makes it possible to increase plant productivity and achieve high Δ^9-THC levels. Methods for genetically selecting the best greenhouse varieties and crops have also made it possible to increase the active ingredient content.

---

[2] This section draws freely on various papers, in particular those by Ben Amar (in preparation), of INSERM, *op. cit*, and Pelc, I., (2002) (ed.) *International Scientific Conference on Cannabis*, Brussels. In particular, we wish to thank Professor Ben Amar for his permission to reproduce the plates.



Male and female cannabis plants

Marijuana, which is a Mexican term initially used in reference to cheap tobacco, but which subsequently designated certain parts of the cannabis plant, is generally green or brown in colour and produces a characteristic odour when burned. It resembles oregano or coarse tea.[3] Marijuana comes from all the parts of the plant once dried. In this form, its THC content is lower; THC content is increased by selecting the flowering tops of the female plant. Dried and coarsely powdered, marijuana is most often rolled into thin cigarettes together with cigarette tobacco (joint), and sometimes smoked in a pipe or, less frequently, in cigar form. A typical joint contains between 0.5 and 1 g of cannabis. Like hash, it can also be baked into cookies and cakes, and be drunk as an herbal tea as well. A number of specialists told us that domestic cannabis made through controlled greenhouse production costs approximately $100 an ounce, and is then sold on the street at average prices ranging between $200 and $250. While we consider this estimated production cost high, the only other available studies concern production costs in developing countries such as Morocco.



Marijuana and joints

[3] On these questions, see in particular: McKim W.A. (2000) "Cannabis" in McKim, W.A. (ed.) *Drugs and Behaviour. An Introduction to Behavioral Pharmacology.* Upper Saddle River: Prentice Hall; Health Canada (1990) *Straight Facts About Drugs and Drug Abuse.* Ottawa: Department of Supply and Services; and Comité permanent de lutte à la toxicomanie (2001) *Drogues. Savoir plus. Risquer Moins.* (Édition québécoise) Montréal: Stanké.

Hashish, also known as hash, shit, kif (in North Africa) and *charas* (in India), is the viscous resin produced by the marijuana plant and obtained by pounding then compressing the dried leaves and flowering tops to obtain what, in France, is called a "barrette" or here a cube or block. It takes approximately 45 to 75 kg of cannabis to produce 1 kg of hash, which is sold in light brown to black pieces of hard or soft consistency. It is frequently smoked, alone or mixed with tobacco or marijuana, in a cigarette (joint), pipe or, more rarely, cigar. It may also be baked into cookies or cakes. The Δ^9-THC content of hash is generally between 3% and 6% in normal production. As is the case for cannabis, Δ^9-THC content can be increased through growing methods and resin concentrations to achieve levels of more than 10% on average. Slightly more expensive than marijuana, hashish sells for approximately $300 to $350 an ounce on the street.



Haschich

There are two other cannabis-based products, marijuana and hashish oils, which are extracted from resin using 90-proof alcohol, which is subsequently evaporated through exposure to the sun. These oils are viscous, greenish brown to blackish, foul-smelling liquids, with generally higher cannabinoid concentrations of up to 30% to 60% Δ^9-THC. Oils are generally dripped onto cigarette paper or tobacco then smoked. They are scarce and more expensive than other products.



Cannabis oils

The following passage from a report prepared by Labrousse and Romero for the *Observatoire français des drogues et des toxicomanies* (OFDT; French Monitoring Centre for Drugs and Drug Addictions) in 2001 on cannabis production in Morocco describes the various stages of production very clearly.

From Cannabis to Oil – The Production Process in Morocco

Kif is the name given to the cannabis plant as a whole. (...) Cut and dried in the sun (generally on rooftops) for at least a month and a half, it is preserved in houses for several months under plastic tarpaulins. Chopped by hand with a special knife on a board, it is then mixed with tobacco for smoking. The traditional mixture consists of one-third kif, two-thirds tobacco and is smoked in a *sebsi*, a long wooden pipe with a terracotta or stone pipe bowl.

Chira is the powder resulting from solidification of the small resin drops exuded by the flowering tops of the female plants. To separate the resin from the dried plants, processors pound or shake the plants over a stretched thin nylon veil that serves as a screen. The first powder to fall, golden beige in colour, is called *zgirma*. This is the top quality, so-called double-zero powder which is said to contain as much as 20% THC. The next powder to fall is called *hamda*, which is mixed with plant waste giving it a greenish colour. *Hamda* is lightly screened to yield various product qualities: zero, no. 1, no. 2, no. 3 and no. 4 (the lowest quality), containing respectively from 10% to 2% THC. (...) It takes approximately 100 kg of kif to obtain 1 kg of top-quality hashish.

Peasants (...) told us that the rest of the operation, when carried out by traffickers, took place in ostensibly secret buildings isolated in the mountains. (...) There the powder is placed in cellophane bags, then heated and compressed to yield resin or hashish, readied for the market in the form of small bars (generally 250 grams) called *tbiba* or "little plate". (...) The "double zero" quality, which derives its name from the two holes made in the bar with the end of a lit cigarette, is reserved for domestic consumption and preferred customers. Misinformed foreign customers often receive hash that has been cut with black polish, glue, henna, fig, earth or even medication.

(...) Cannabis oil is derived from no. 3 and no. 4 quality resins and produced by diluting hashish in a container with pharmaceutical alcohol. After six to eight hours of distillation, the liquid is filtered and stirred until all the alcohol has evaporated. Local production of this high value-added liquid (it takes 10 kg of hashish to produce one liter of oil) is less marginal than is generally thought.

Labrousse, A. and L. Romero (2001). *Rapport sur la situation du cannabis dans le Rif marocain*. Paris: OFDT.

CANNABIS ROADS

Where does the cannabis and hashish available in Canada come from? What quantities are imported and how much is produced locally? What routes are used to transport the drugs between provinces? What quantities are exported to other countries? What is the monetary value of this market? These are constantly recurring questions. They serve various purposes: to underline the scope of the drug "problem" generally, to explain the power of organized crime which makes money from drugs, as well as to substantiate the discrepancy between the size of the problem and the limited resources governments allocated to reducing supply. But this information can also assist in better understanding the extent of the problem experienced by peasants in the

various producer countries, the ecological issues raised by the cultivation of drugs, as well as the strategic position of drugs in geopolitics.

The cultivation of cannabis is the most widespread of all illegal drugs, which is not surprising since, not only does the plant grow readily in a number of climates, but it also requires little processing before becoming marijuana. According to the 2000 report of the *United Nations Drug Control Program* (UNDCP):

> *Over the last decade, 120 countries reported illicit cultivation of cannabis in their territory. Interpol identifies 67 source countries for cannabis through seizures made in 1998. (...) Estimating the extent of illicit cannabis cultivation, production and trafficking is much more difficult than for other plant-based drugs because of the significant amount of wild cannabis growth, the diverse nature of cultivation and the sheer magnitude of trafficking. In contrast to other plant-based narcotic drugs, illicit cannabis products can originate from three qualitatively distinct sources of supply: outdoor illicit cultivation; naturalized cannabis plant populations (wild growing cannabis); and plants cultivated indoors by means of sophisticated growing technology. (...) The large number of countries reporting an increase in cannabis consumption (two-thirds of all countries reporting drug abuse trends in 1996) would suggest that overall production must have increased; but this is only partly confirmed by seizure data. (...) Cultivation estimated (including wild growth), based on reports from Member States in the 1990s, ranges from 670,000 hectares to 1,850,000 hectares. Production estimates vary by a factor of 30, from 10,000 tonnes to 300,000 tonnes. Linking production and consumption estimates, UNDCP estimates world wide cannabis production to be at about 30,000 tonnes.*[4]

As may be seen, estimates vary greatly and are enormously difficult to validate. How can anyone estimate the number of cannabis plants that are transformed into marijuana? The data provided by the governments of various countries on cultivated areas are themselves only approximations. As to the number of greenhouses and other forms of production, there is quite literally no way of knowing.

The work of the team at France's *Observatoire géopolitique des drogues*, under the direction of Alain Labrousse, is exemplary in the field. The box from the same report produced for the OFDT in 2001, describes a three-month field project in which the authors cross-checked data from various sources.

Variable Estimates – The Case of Morocco

In their study, Labrousse and Romero state that, according to the Department of Agriculture, cannabis was produced on 75,000 hectares in 2000. (By comparison, in its 2000 report, the ODCCP cites the figure of 50,000 hectares in cannabis production in Morocco, an official figure provided by the Department of the Interior.)

Based on their own work in the field, they estimate that 90,000 hectares were in production in 1999 and between 110,000 and 120,000 in 2001. That production involved approximately 200 000 families, between one and one and a half million persons. Based on those areas, production would be between 1,600 and 3,000 tonnes, after deducting the quantities of kif set aside for national consumption.

Labrousse and Romero, *op. cit.*

[4] United Nations Office for Drug Control and Crime Prevention (2001) *World Drug Report 2001.* Oxford: Oxford University Press, pages 30-32. Available on line at http://www.undcp.org/adhoc/world_drug_report_2000/report_2001-01-22_1.pdf.

In particular, it has been observed that, when linked to the population of potential cannabis users (which the Centre estimates at some 120 million persons), the estimated global production of 30,000 tonnes is much nearer the 10,000 tonne floor than the 300,000 tonne ceiling.

According to the UNDCP, the main producers are Colombia and Mexico (marijuana) and Morocco (hashish). According to the International Criminal Police Organization (Interpol), Morocco, Afghanistan and Pakistan are the main sources of hashish and Colombia, Niger and South Africa of cannabis. Lastly, according to Labrousse, marijuana production is exploding, with Colombia becoming again the major producer it was in the 1970s, and production rapidly increasing in West Africa (Nigeria, Ghana, Congo, Ivory Coat, Senegal), although the great steppes of the Commonwealth of Independent States (Kazakhstan, Kirghizistan, Ukraine, Belarus and Azerbaijan) have virtually unlimited export potential, while Afghanistan and Pakistan likely produce 2,000 tonnes of hashish, the equivalent of Morocco's production.[5] In addition, Canada has been a cannabis exporting country for a number of years now.[6]

Traditionally, the cannabis available in Canada comes mainly from Mexico, Jamaica and the countries of the horn of Africa, while hashish originates mainly in Asia and the Middle East:

> *The hashish market in Central Eastern Canada is known world-wide. U.S. criminals are among the international traffickers who orchestrate multi-tonne shipments of this drug from Pakistan directly to Montreal by mothership or container. In 2001, some shipments transited the United Arab Emirates, Africa and Europe before reaching Canada. Multi-kilo quantities are also imported from Jamaica by couriers travelling on board commercial airlines.*[7]

While a large portion of cannabis sold in the Canadian market was of foreign origin until the 1980s, the situation has radically changed since that time. It is estimated that national production has now supplanted imports. In its 1999 report, the Royal Canadian Mounted Police writes:

> *It is estimated that more than 50% of the marihuana available in Canada is produced domestically. Of the foreign marihuana seized in or en route to Canada in 1999, at least 5,535 kilograms originated from Jamaica, 825 kilograms from South Africa and 860 kilograms from Mexico. Foreign shipments arrive directly into Canadian ports of entry or transit through the United States before reaching Canada. On June 11, 1999, U.S. Customs intercepted 2,464 kg of Jamaican marihuana and 141 kg of hash oil at Newark, New Jersey in a marine container bound for Montreal. Furthermore in Project JOULE*

---

[5] Labrousse, A. (2000) *Drogues. Un marché de dupes.* Paris: éditions alternatives; see also "L'approvisionnement des marchés des drogues dans l'espace Schengen." *Les Cahiers de la Sécurité Intérieure*, 32, 2e trimestre 1998.

[6] See, for example, in OGD (1996) *Atlas mondial des drogues.* Paris: PUF.

[7] Royal Canadian Mounted Police (2002) *Drug Situation in Canada (2001).* Ottawa: author.

on June 20, 1999, 2,617 kg of Jamaican marihuana destined for Canada were seized in Stuart, Florida.[8]

How much cannabis and hashish are available in Canada? What is the monetary value of those drugs? It is in fact impossible to answer these questions, for obvious reasons, since the drugs are illegal. While we know the amount of tobacco produced and sold in cigarette form, and the volume of alcohol produced or imported and consumed, and sales turnover can be calculated in both cases on the basis of those volumes, it is impossible to do this for illegal drugs.

For a time, the United Nations International Drug Control Program suggested that the total value of the illegal drug "industry" was approximately US $400 billion, greater than the oil industry.[9] The total value of cannabis obviously cannot be separated from that amount, even though we know that the largest number of persons who use drugs use cannabis. No one really knows how or on what basis these figures are advanced, whether they were produced using a rigorous calculation method or merely noted down on a napkin over a meal.[10] And yet they often serve as a reference. In a series of articles published on the illicit drug issue in 2001, *The Economist* cited the $400 billion amount before suggesting a more conservative estimate of US $150 billion.[11] By comparison, the value of the pharmaceutical industry is near US $300 billion, that of the tobacco industry $204 billion and that of the alcoholic beverages industry $250 billion.

Since the authors provide itemized accounts of their calculation methods, we will now continue our analysis of the Moroccan example.

---

[8] Royal Canadian Mounted Police (2000) *Drug Situation in Canada (1999).* Ottawa: author.

[9] UNDCP (2000) *op. cit.*

[10] The Committee invited the Executive Director of UNDCP or a delegate to testify before it, but the invitation was turned down.

[11] "Stumbling in the Dark", *The Economist*, July 28 - August 3, 2001.

Yields and Returns from Cannabis – The Case of Morocco

Cannabis is a not very demanding plant that grows in poor soils, which it quite quickly renders unfit for any other form of agriculture. As a result of the illegal nature of this crop, the income it generates is disproportionately high compared to that from legal food and cash crops. It is also a non-perishable product that can be sold from the home, into an ever certain market and on credit. In particular, it enables local populations to improve their living conditions and opens the way to initiatives by the peasants themselves.

Estimates of per-hectare cannabis income vary with soil type, rainfall, degree of irrigation, whether the cannabis is processed into chira (powder), period of sale and other factors. In addition, researchers give various estimates based on the same criteria. This is due to the fact that it is difficult to obtain reliable data from mistrustful peasant farmers. Income from the production of unprocessed kif varies, depending on sources, from 12,450 to 210,000 French francs per hectare.

(...) while cannabis is highly profitable on irrigated perimeters, it is much less so on pluvial lands, particularly in poor years (...) Many peasant farmers who likely cultivate only 1.5 ha to 3 ha (non irrigated) of cannabis, earn, in poor years, only 20,000 F to 40,000 F from that crop to support families of, in many cases, more than 10 persons.

(But) cannabis is 12 to 46 times more profitable than grain crops.

In 1997, based on production of 1,397 tonnes of hashish for the Rif as a whole, Pascual Moreno estimated the return for Moroccan producers (from the peasant farmer to the major traffickers) at $1.816 billion. Since a certain number of Moroccan traffickers operate outside the country, Moreno estimated the return to the Moroccan economy from cannabis profits at $2 billion, compared to $750 million for textile exports, $460 million from foreign investments and $1.26 billion for tourism. He also estimated the profits of European traffickers at $3 billion (apparently not including street sales).

However, since cannabis is more profitable than any other crop, peasant farmers tend to abandon food crops and to supply themselves from the market. As a result, there is a growing food shortage in the region.

Labrousse and Romero (2001) *op. cit.*: 12-15.

We know of no similar field work for Canada or Mexico. In addition, in Canada, climatic conditions have stimulated development of greenhouse and hydroponic crops, and the ratio of these cultivation methods to soil cultivation methods is not known.

We therefore use the following figures and data on cannabis production, cannabis and hashish imports and the monetary value of those drugs in the Canadian market, with considerable reservation and prudence.

According to the RCMP, "*the annual production of marijuana in Canada [is] at least in the 800 tonne range. This estimate appears overwhelming, however investigators believe it is quite conservative, and it is supported by intelligence and seizures of marijuana in plant and bulk forms.*"[12] The same figures are stated in the 1998 and 2002 reports. Note as well that, at 800 tonnes, Canadian production represents approximately 2.5% of global production, as stated by the UNDCP.

In its 1998-1999 annual report, the Observatoire géopolitique des drogues stated that, based on police sources, the value of the illegal drug market in Canada was $7 billion to $10 billion a year.[13] For 2001, the RCMP estimated that the market value

[12] Royal Canadian Mounted Police (2000), *op.cit.*

[13] World Geopolitics of Drugs (1999) *Annual Report 1998/1999.* Paris: WGD, page 178.

of all illegal drugs was $18 billion.[14] It is impossible to estimate the share of cannabis and hashish in that total. As we most often do not know the calculation basis for these estimates, they must also be prudently considered. As the Assistant Deputy Solicitor General stated in his appearance before the Committee, the calculation methods, based on the assumption that police and customs organizations seize 10% of all drugs, are unscientific and unreliable.[15] We nevertheless note an apparent inconsistency: the seeming stagnation of cannabis production at 800 tonnes and of hashish imports at 100 tonnes since 1998, as well as the declining prices of heroin and cocaine in a stable, even declining market (RCMP reports) are not consistent with the presumed doubling in total value of the drug market. As a result, in dealing with these various estimates of the quantity of drugs produced and monetary value of the drug market, the Committee often had the impression that, ultimately, no one really knew how big it was.

With regard to hashish, the RCMP believes that it

> *is easier to estimate the quantity of hashish entering the Canadian market annually than the quantity of any other illegal drug. Unlike what is observed for other drugs, such as cocaine and marijuana, that can be found across Canada and the United States, hashish use in North America is a localized phenomenon. The drug is very popular in Quebec, Ontario and the Atlantic Provinces, whereas demand is limited elsewhere in Canada and supply is sporadic at best in the northeastern United States. Consequently, Montreal organized criminal groups are specialized in the massive importing of hashish and have a monopoly on its distribution in bulk. In view of these facts and of information on multi-tonne hashish shipments seized in Canada and abroad and on those we know have entered the Canadian market, RCMP analysts estimate that at least 100 tonnes of the drug are imported into Canada each year.*[16]

Canada is also an in-transit country for drugs to the United States, and a significant portion of Canadian cannabis is intended for export, in particular to that country.

> *Smuggling of Canadian marihuana to the United States remains a source of concern for enforcement officials on both sides of the border. Though this activity is particularly noticeable on the British Columbia–U.S. border, it is not limited to that province. There is intelligence that the Hell's Angels in Quebec are supplying marihuana to their U.S. counterparts. Intelligence also indicates that there is marihuana smuggling activity across the Great Lakes. Despite the foregoing, few U.S. marihuana seizures can be traced back to Canada.*[17]

In 1999, Washington officials suggested that Canada could be placed on the list of countries suspected of a soft stance in the fight against drug production and trafficking.

---

[14] Greater Toronto Area Combined Forces Special Unit (2002) *Fact Sheet - Heroin.* Available on line at: http://www.cfseu.org/heroin.html

[15] Mr. Paul Kennedy, Testimony before the Senate Special Committee on Illegal Drugs, June 10, 2002.

[16] *Ibid.*

[17] Royal Canadian Mounted Police (2000) *op. cit.*

More recently, officials of the Drug Enforcement Administration repeated that Canada's trafficking in cannabis toward the United States was a significant problem. One RCMP officer told a national newspaper that approximately 70% of marijuana grown in Canada wound up in the United States,[18] whereas, according to the 2002 report of the International Drug Control Agency, the figure was approximately 60%.[19] We have heard, and RCMP officers confirmed it, that cannabis from British Columbia has such a high value that it was traded on par with cocaine. According to those police officers specialized in the war on drugs, British Columbia's triple A quality cannabis is worth approximately $4,000 a pound in Canada and one kilogram of cocaine is currently worth US $11,000. However, while reference is made to this supposition in the annual report for 1999, it is not confirmed:

> *Canadian marihuana is sometimes used as a currency to purchase cocaine that is warehoused in the U.S.A. The exchange ratio is about three to one. Exchanges of one to one have been rumoured but never substantiated. Furthermore, such a rate of exchange does not make sound commercial sense considering that a kilo of cocaine sells for $13,000 U.S. (in lots of 50 kilos or more) while the wholesale price of a kilo of marihuana ranges around $6,000 or $8,000 U.S.*[20]

In its 2002 report, the RCMP merely mentions the fact that Canadian cannabis is exchanged for cocaine, without saying whether it is on an equal weights basis. We also note a certain inconsistency here as the price of a kilogram of cocaine is expressed in US dollars, whereas that of a kilogram of marijuana is expressed sometimes in Canadian dollars, at other times in US dollars.

British Columbia, Ontario and Quebec are the main producers in Canada. British Columbia's large production can be attributed in particular to suitable climatic conditions, but there are probably also sociocultural explanations, as the Pacific Coast mentality explains in part why cannabis appears to have taken root there to a greater extent.

Cannabis production in British Columbia appears to have increased significantly over the past 10 years, becoming, according to some analysts, one of the province's biggest industries in terms of monetary value, which some analysts set at $6 billion, whereas, according to some police officers, a conservative estimate would be $4 billion.[21] If marijuana sells for $225 an ounce, at 16 ounces a pound, British Columbia would appear to produce the equivalent of 550 tonnes of cannabis a year, more than two-thirds of the total amount of cannabis circulating in Canada.

---

[18] National Post, May 17, 2002. The Committee is interested, and somewhat amused, to note that this article and a previous report on the Global television network on May 13, 2002, outlining the concerns of American representatives, followed the Committee's publication of its Discussion Paper.

[19] International Narcotics Control Board (2001) *Report of the International Narcotics Control Board for 2000.* Available on line at: http://www.incb.org.

[20] Royal Canadian Mounted Police (2000) *op. cit.*

[21] RCMP, private meeting.

Testifying in Richmond, B.C., on 14 May 2002, RCMP Superintendent Clapham said there were between 15,000 and 20,000 illegal cannabis production sites in British Columbia (figures from the Drug Enforcement Administration), while RCMP narcotics specialists, the next day, put the figure at 7,000. Regardless of the true number, the figures, as may be seen, must necessarily be considered very carefully.

As to growing methods, soil-based production is still the most popular, but the more sophisticated, hydroponic and aeroponic,[22] methods are expanding, particularly among criminal gangs that have the necessary infrastructure.

> *It is not uncommon to find indoor grow operations involving over 3,000 plants. Those figures vary considerably from one province to another, overall less than 10 percent of all marihuana seized in Canada was grown using hydroponics (a method of growing plants with the roots in nutrient mineral solutions rather than in soil). Indoor grow operations still rely mostly on soil-based organic cultivation but hydroponics is gaining in popularity. Despite the availability of highly sophisticated technologies designed to increase the yield even more, most growers do not bother to go to such lengths, preferring simpler and proven methods. Marihuana remains the most popular illicit drug, both in terms of consumption and trafficking. The annual marihuana production has been estimated to be around five million plants. Given the relatively low cost of setting up a grow operation and the considerable profits it generates, this activity has become increasingly attractive, even to otherwise law-abiding citizens. In the majority of regions, large operations are invariably run by outlaw motorcycle gangs, although Asian-based organizations have been making inroads in British Columbia and Alberta. More and more groups are using "crop sitters" and other go-betweens to tend their plantations. This hands-off approach makes it difficult for police to link the operation to the people who are actually behind it. Outdoor crops are often grown on Crown lands located in remote areas in order to reduce the risk of detection.*[23]

In all, with considerable reservations as to the validity of the data, the Committee submits the following:

	Marijuana	Hashish
[illegible]	800 tonnes	100 tonnes
[illegible]	approximately 50%	?
[illegible]	National production (British Columbia, Ontario, Quebec) Imports: Mexico, Jamaica	Imports: Pakistan, Afghanistan, Morocco
[illegible]	$2,000 to $4,000/pound	?
Retail value (ounce)	$225 to $250	$325 to $350

[22] Technique whereby the roots are suspended and sprayed regularly with water enriched with nutrient material, still very rare and the effectiveness of which remains to be proven. (Source: RCMP (2002)).

[23] RCMP, Drug Situation in Canada (1999) *op. cit.*

PROPERTIES OF CANNABIS

Classified in the pharmacopoeia as a hallucinogenic, psychodysleptic or psychotomimetic, cannabis is a disrupter or modulator, that is to say that it alters perceptions and emotions. Classified in the international conventions and national legislation as a narcotic, cannabis belongs to the class of psychotropics which comprises five major groups: depressants (alcohol, Valium), stimulants, minor (coffee, nicotine) and major (cocaine, amphetamines), disrupters (cannabis, LSD), antipsychotics and medication for mood disorders (lithium).

More than 460 known chemical constituents are present in cannabis.[24] Of that number, more than 60 are identified as cannabinoids. The main active ingredient in cannabis, which was identified by the team of Dr. Mechoulam in 1964,[25] is Δ^9-tetrahydrocannabinol, common called THC. Other cannabinoids present in Indian hemp include delta-8-tetrahydrocannabinol, cannabinol and cannabidiol, but they are present in small quantities and have no significant effect on behaviour, compared to Δ^9-THC,[26] although they can modulate the product's overall effect.[27] Cannabinol also has anti-inflammatory effects.

For a better understanding of the effects of cannabis discussed in the following chapters, we will first consider its pharmacological properties. Consequently, readers may skip this technical section without risk of not properly understanding the rest of the report. In the following paragraphs, we first discuss Δ^9THC levels and, second, specifically examine the pharmacological properties of that substance.

---

[24] See in particular Grinspoon, L. and J.B. Bakalar (1997) *Marijuana. The Forbidden Medicine.* New Haven and London: Yale University Press; Clark P.A. (2000) "The ethics of medical marijuana: government restrictions vs. medical necessity", *Journal of Public Health Policy*, 21: 40-60; as well as Wheelock (2002) for the Senate Committee.

[25] Gaoni, Y. and R. Mechoulam (1964) "Isolation, structure and partial synthesis of an active constituent of hashish", *Journal of the American Chemistry Society*, 86: 1646-1647; and Mechoulam, R. and Y. Gaoni (1965) "A total synthesis of delta-9-tetrahydrocannabinol, the active constituent of hashish", *Journal of the American Chemistry Society*, 87: 3273-3275.

[26] Smith, D.E. (1998) "Review of the American Medical Association Council on Scientific Affairs Report on Medical Marijuana", *Journal of Psychoactive Drugs.* 30: 127-136; McKim W.A. (2000) "Cannabis", in McKim, W.A. (ed.) *Drugs and Behavior. An introduction to behavioral pharmacology.* Upper Saddle River: Prentice Hall.

[27] Ashton, C.H. (2001) "Pharmacology and effects of cannabis: a brief review", *British Journal of Psychiatry.* 178: 101-106.

Δ^9THC Concentrations

The Δ^9THC content of marijuana generally varies in natural growing conditions from 0.5 to 4%.[28] Δ^9THC content serves first as a basis for distinguishing the drug type of plant from the fibre type: permitted concentrations vary by country - in Canada, as in France, it is 0.3% for the fibre type. For more than a decade now, techniques for selecting powerful strains and cultivation (in greenhouses and hydroponically) have made it possible to achieve Δ^9THC concentrations of 15% or more. Δ^9THC content is also used to distinguish between various cannabis products and thus to determine their price: the content of sinsemilla, for example, generally varies between 7% and 14% and is more expensive than "regular" cannabis.

The question of Δ^9THC content, its variability, how it is determined and its effects has raised numerous issues. While all specialists agree that maximum active ingredient concentrations have increased over the past 20 years, opinion is divided on average concentrations in cannabis available on the market. Estimates vary as to the preponderance and consequences of Δ^9THC concentrations.

First, it should be emphasized that studies show that concentrations are subject to extreme variability, for a number of reasons. First, failing a control system at source, the Δ^9THC content of marijuana is estimated on the basis of police seizures. However, only a portion of the drug seized is analyzed for THC content,[29] and analyses are not all equally reliable, depending on how police or customs officials conducted the seizures and how the products were preserved and transported to the lab. In addition, between a seized product in clandestine lab or at a customs post and the product sold on the street, a number of changes can be made: tobacco, herbs and other products can be added to the gram of "pot" sold at a school which alter the nature of the drug and thus the quantity of active ingredient. This is even truer for hashish, as seen above in the example on processing in Morocco.

Second, since cannabis is a widespread illegal product, it is impossible to take a representative sample of the drug available on the market at a given time for analysis. Thus it is impossible to measure the difference between the Δ^9THC content of cannabis seized at the production or delivery site and that of cannabis used by individuals. And third, the active ingredient concentration varies with the geographical area of origin, climatic conditions and production conditions. Likely circulating in the

---

[28] Huestis, M.A *et al.* (1992) "Characterization of the absorption phase of marijuana smoking", *Clinical Pharmacology and Therapeutics*, 52: 31-41.

[29] Note, for example, that, in the United States, there is no systematic method for measuring THC. As emphasized in a comparative analysis of changes in price of heroin, cocaine and marijuana, "Another problem is that the DEA does not test marijuana for THC content, so there is no marijuana counterpart to the pure grams reported for cocaine and heroin. The difficulty this causes is the STRIDE data provide no basis for adjusting price changes for marijuana's quality." Abt Associates (2001) *The Price of Illicit Drugs: 1981 through the Second Quarter of 2000.* Washington, DC. Report prepared for the Office on National Drug Control Policy.

market at any given time is a significant variety of cannabis products reflecting the diverse conditions in which they were produced. It follows that two samples seized in Vancouver in the same week could have very different concentrations, as would be the case for samples seized the same week in Vancouver, Montreal and St. John's.

Experts told the Committee that cannabis in the Canadian market was 700% more powerful than the same drug in the 1970s. Some suggested that the average Δ^9THC content of cannabis on the market is approximately 30%, compared to 3% to 4% in the 1970s.

> *The cannabis used today is up to 500 percent higher in THC - that is a range between five percent to 31 percent - than the cannabis most adults remember from the 1960s and 1970s.*[30]

In its 1999 annual report, the Royal Canadian Mounted Police estimated the average content of seizures at 6%.[31] In Quebec, the Montreal Police Department asserted that the THC content of cannabis is now 25%. In a private meeting with Committee members, RCMP narcotics experts in British Columbia emphasized that it is *impossible in the current state of affairs to determine the average content of cannabis in the country* or in a given province, in particular as a result of the extreme variability of seizures and methods of analysis. The officers who conduct the seizures do not always pay attention to the manner in which they preserve the product, such that it may lose its Δ^9THC content: heat, light and humidity affect the stability of cannabis. Lastly, the experts providing cannabis for therapeutic purposes whom we met said they kept various grades of cannabis, based in particular on Δ^9THC concentrations, and that, in certain cases, the products offered to patients reached concentrations of 27%.

The most exhaustive studies on changes in Δ^9THC levels in cannabis have been conducted in Australia, the Netherlands, France and the United States. They show, first, that more powerful products have appeared in the market beside the traditional forms of cannabis: "skunk" (a variety originating in the United States and the Netherlands), "super-skunk" and "pollen" (stamens of male plants). Canada has not lagged behind, with *BC Bud* and *Quebec Gold* in particular.

More specifically, the studies on Δ^9THC concentrations show similar trends:

- In Australia, a study by Wayne and Wendy on 31,000 seizures conducted between 1980 and 1997 shows that average content varied little over the period and was between 0,6 % and 13 %. Among other things, it appears that the main development has been a more significant selection than

---

[30] Testimony of Mchael J. Boyd, Chair of the Drug Abuse Committee and Deputy Chief of the Toronto Police Service, for the Canadian Association of Chiefs of Police, Senate Special Committee on Illegal Drugs, Issue No. 14, page 74.

[31] Royal Canadian Mounted Police (1999), *Annual Report*.

previously of the parts of the plant with the highest concentrations.[32] The authors of this study make the following observation which applies equally to Canada:

A number of factors probably explain the persistence of the belief that the THC content of cannabis plants in Australia has increased 30 fold in the absence of any supporting data. First, defenders of the claim often point to reports of single samples with unusually high THC content tested by the police. At best, such samples indicate the maximum THC content that has been achieved (assuming that there were no errors in the test results) but they do not tell us what the THC content is in the cannabis that is typically used by consumers. Second, biases in the sampling of tested cannabis are amplified by the attention that the print and electronic media give to unusually potent samples, creating the false impression that cannabis with exceptionally high THC is the norm. Third, uncontested repetition of these assertions in the media has established them as "facts"; those who contest these claims are asked to prove that they are false rather than the (usually nameless) proponents being asked to provide evidence that they are true. Fourth, an increase in average THC content seems to explain an apparent increase in the number of cannabis users who experience problems as a consequence of their use.[33]

- In the Netherlands, the *Drug Information Monitoring System* of the Trimbos Institute has conducted various studies since 2000 on average Δ^9THC content. The local variety, *Nether-Weed*, contained an average of 8.6% THC in 2000 and 11.3% in 2001, whereas imported varieties were stable at approximately 5%. One of the reasons given for this difference was that the local variety was fresher and contained a lower ratio of cannabinol to Δ^9THC. In addition, *Nether-Weed* resembles sinsemilla, which comes from the unfertilized flowers of the female plant and is cultivated in greenhouses.
- In France, the Roques report referred to concentrations of up to 20% in the case of certain Dutch hydroponic varieties.[34] In its recent report, France's *Institut national de la santé et de la recherche médicale* notes a toxicological study conducted by Mura on the Δ^9THC concentrations of seizures since 1993. From 1993 to 1995, the average concentration was 5.5%, but approximately 8% since 1996, with spikes of up to 22%.[35] In 2000, 3% of marijuana samples analyzed contained Δ^9THC levels of more than 15%.
- Lastly, in the United States, data for 2000 show an average concentration of 6%, compared to 4.1% in 1997. In fact, recalling a study recently conducted in Mississippi, Dr. John Morgan noted:

---

[32] Wayne, H. and S. Wendy (2000) "The THC content of cannabis in Australia: evidence and implications", *Australian and New Zealand Journal of Public Health*. 24: 503-508.

[33] *Ibid*, page 504.

[34] Roques, B. (1999) *La dangerosité des drogues*. Paris: Odile Jacob.

[35] INSERM (2001) *Cannabis: quels effets sur le comportement et la santé?* Paris: Les Éditions Inserm.

(...) in the midst of this furore over the remarkable increases in marijuana potency, it is interesting that the potency of the commercial crop sold in the United States has not varied enormously over the 30 years that potency has been assessed by the analysis of THC content in criminally seized marijuana. In fact, I recently looked at the report, which also comes from Mississippi, that the mean THC content of some 40,000 seizures since 1974 is about three percent. It has gone up in the last 10 years. In fact, in the last 10 years I believe the arithmetic mean is more than four percent while in the 10 years before that it was about 3.5 percent. [36]

The following table summarizes some of the data on a historical basis for certain countries.

Year analysed	Domestic Marijuana, USA			Sinsemilla, USA		
	= 3 %	= 5 %	= 9 %	= 3 %	= 5 %	= 9 %
	63%	25%	3%	93%	77%	49%
	63%	29%	6%	96%	85%	64%
	Average of 6.07% (DEA)			Average of 13,65% (DEA)		
	75%	48%	7%	93%	87%	35%
	80%	55%	4%	100%	99%	78%
	Between 0.6% and 13%					
	Average of 3,8%					
[illegible] 1999	Average of 6%			Not available		

(1) Source: Rigter H. and M. von Laar (2002) " Epidemiological Aspects of Cannabis Use", International Scientific Conference on Cannabis, Brussels, page 32

(2) Drug Enforcement Administration, http://www.usdoj.gov/dea/concern/marijuana.html

(3) Source: Hall, W. and W. Swift (2000) *op. cit.*, page 505

(4) Source: RCMP, Annual Report for 1999

In short, it appears that the main change has been in maximum concentrations obtained as a result of sophisticated cross-breeding and cultivation methods, whereas average concentrations have not significantly changed over the past 30 years.[37] What conclusion can be drawn from this? In the minds of some, if cannabis could still be called a "soft drug" in the 1970s, that is no longer the case today. Some are not reluctant to say it is a drug comparable to heroin or cocaine in its addictive power. As an example, the Canadian Police Association has issued the following opinion on the risks associated with cannabis.

Generally, marijuana and its derivative products are described [as soft drugs] to distance the drug from the recognized harm associated with other illegal drugs. This has been a successful yet dangerous approach

---

[36] Dr. John Morgan, Professor at the City University of New York Medical School, testimony before the Senate Special Committee on Illegal Drugs, June 11, 2001, Issue No. 4, page 29.

[37] ElSohly, M.A., *et al.* (2000) "Potency trends of delta9-THC and other cannabinoids in confiscated marijuana from 1980-1997", *Journal of Forensic Sciences*, 45(1): 24-30.

and contributes to the misinformation, misunderstanding and increasing tolerance associated with marijuana use. Marijuana is a powerful drug with a variety of effects. (...) Marijuana use is associated with poor work and school performance and learning problems for younger users. Marijuana is internationally recognized as a gateway drug for other drug use. Risk factors for marijuana dependence are similar to those of other forms of drug abuse. [38]

Others associated the increase in demand for treatment for cannabis dependence with the increase in active ingredient concentrations. As the National Post reported:

The potent BC Bud, which has a THC content as high as 25% compared to the 2% typical in the 1970s, is also leading to health concerns in the United States. Admissions for marijuana drug treatment in Washington State now exceed the rate for treatment of alcoholism. Cannabis admissions in Cook County, Ill., have risen by 400% in the last year. [39]

Can it be said that cannabis has in fact become a "hard" drug like cocaine and heroin? Apart from the validity of the effects of cannabis itself as described by the Police Association, and as will be discussed in detail in the Chapter 7, that contention does not take into account the way in which the drug is used or the lack of knowledge of the effects of Δ^9THC concentrations. Studies on the ways in which cannabis is used, considered in Chapter 6, show that regular users appear to prefer medium to mild cannabis, and that they adjust their use to the strength of the drug. Interviews with individuals who use cannabis for medical purposes tend moreover to confirm this perception. More significantly, for lack of any specific studies on the question, the effects of higher Δ^9THC concentrations are simply not known. Lastly, as will be shown in the following section, the bio-availability of Δ^9THC, that is to say the proportion that is actually absorbed by the body following combustion, is highly variable. As emphasized in the report of the World Health Organization (WHO) on cannabis, considering all these factors, the actual quantity of THC absorbed by the cannabis user is difficult to estimate.[40] Ultimately, while it can be a legitimate preoccupation, the real issue of Δ^9THC content has more to do with our ability to control it and better know its effects, rather than making all kinds of alarmist and unfounded statements about its level.

---

[38] Sergeant Dale Orban, Regina Police, at the Senate Committee hearing on May 28, 2001.

[39] National Post, May 17, 2002.

[40] World Health Organization (1997) *Cannabis: a health perspective and research agenda.* Geneva: WHO, 1997. On line at: www.who.org.

Pharmacokinetics [41]

Upon inhalation, and depending on the smoker's way of smoking and smoking experience, between 15% and 50% of the Δ^9THC present in the smoke is absorbed into the bloodstream. The percentage also depends on the Δ^9THC concentration in the smoked product. The substance is absorbed very quickly, and maximum blood concentrations are achieved in less than 15 minutes after the start of inhalation. The effects felt almost immediately after absorbing the smoke diminish gradually over the next 60 minutes and generally last a maximum of three hours after inhalation. In other words, THC levels in the blood plasma are highest immediately after absorption, whereas maximum effects are felt approximately 30 to 40 minutes later. The following table reproduced from the ISERM collective assessment, shows the time to appearance and duration of detection of cannabinoids in the blood.[42]

Concentration, time to appearance[1] and duration of detection[2] of cannabinoids in the blood after smoking a marijuana cigarette containing 15.8 mg or 33.8 mg of Δ^9THC

Component	Maximum concentration	Time to appearance of peak (hr)	Duration of detection (hr)
[illegible]	84.3 (50-129)[3]	0.14 (0.10-0.17)	7.3 (3-12)
	162.2 (76-267)[4]	0.14 (0.08-0.17)	12.5 (6-27)
[illegible] Δ^9THC	6.7 (3.3-10.4)	0.25 (0.15-0.38)	4.5 (0.54-13)
	7.5 (3.8-16.0)	0.20 (0.15-0.25)	11.2 (2.2-27)
[illegible] Δ^9THC-COOH	24.5 (15-54)	2.43 (0.8-4.0)	84.0 (48-168)
	54.0 (22-101)	1.35 (0.54-2.21)	152.0 (72-168)

(1) average interval between start of consumption and appearance of a concentration peak
(2) average interval between start of consumption and moment when lowest concentration of component is detected (> 0.5 mg/ml)
(3) cigarette containing 13.8 mg (1.75%) of Δ^9THC
(4) cigarette containing 33.8 mg (3.55%) of Δ^9THC

Bio-availability of Δ^9THC is slower and weaker when the drug is ingested orally (cookies, cakes, herbal teas): approximately 4% to 12%; although slower to be felt and different in quality, its effects are longer lasting.

In all, we do not know how the effects of THC (concentration) interact with personal factors (way of smoking, health status, alcoholism or medication). However, it is likely that the same THC concentration does not have the same effect on all smokers, which moreover tend to be confirmed by the plasticity of cannabis in the hormonal stream (see below).

---

[41] This section is based to a large extent on the INSERM 2001 report as well as the European scientific report 2002 and the survey work done by Wheelock 2002 for the Committee.

[42] INSERM (2001) *Cannabis. Quels effets sur le comportement et la santé?* Paris: author, page 340.

Δ^9THC is highly lipophilic and is quickly distributed to all fatty tissues, including the brain. It is also characterized by an entero-hepatic cycle and renal reabsorption which results in persistent effects. In a driving simulator study, a significant linear correlation was found up to seven hours following absorption, particularly on the trajectory control.

Δ^9THC undergoes oxydative metabolism resulting in the production of various elements, in particular 11-hydroxy-tetrahydrocannabinol (11-OH Δ^9THC) a psychoactive metabolite which, transported by albumin, whereas Δ^9THC attaches mainly to lipoproteins, penetrates the brain more deeply than Δ^9THC; 8 β-hydroxy-Δ^9-tetrahydrocannabinol, potentially psychoactive but whose action would be negligible; and various other components not known for their psychoactive effects. In addition to the potentially psychoactive elements, cannabis contains approximately 200 derivatives of combustion and pyrolysis comparable to those found in tobacco, though some of which are highly carcinogenic and are more concentrated in cannabis smoke than tobacco smoke.

Cannabinoids are eliminated in various ways: through digestion, the kidneys and perspiration. Approximately 15% to 30% of Δ^9THC in the blood is eliminated in urine, 30% to 65% through stools. Because it binds strongly to tissues, Δ^9THC is eliminated slowly in urine: the urine of regular heavy users contains traces of Δ^9THC-COOH 27 days after they have last used cannabis.

Regular users metabolize Δ^9THC up to twice as fast as individuals who have never previously used the drug. One study showed, in particular, that the intravenous administration of one 5 mg dose of Δ^9THC resulted in higher blood levels in regular users than occasional users.[43]

Cannabinoids act on the body through the endogenous cannabinoid system, consisting of neurochemical substances (endogenous ligands) and specific receptors. The behavioural and central effects of cannabis are due to the agonistic action of its main ingredients (in particular Δ^9THC, exogenous cannabinoid), on the endogenous cannabinoid receptors (anandamide, 2-arachidonoylglycerol) present in the nervous tissues of the brain.

Although the chemical structure of Δ^9THC was identified by Mechoulam in 1964,[44] it wasn't until very recently that the characteristics and location of the endogenous cannabinoid system was determined.[45] Two types of cannabinoid receptors have been isolated: CB1 in 1990[46] and CB2 in 1993.[47] CB1 is mainly expressed in the

---

[43] Cited in INSERM (2001) *op. cit.*, page 148.

[44] Guoli and Mechoulam (1964) *op. cit.*

[45] Devane, W.A. *et al.* (1992) "Isolation and structure of a brain constituent that binds to the cannabinoid receptor", *Science*, 258 (5090): 1946-1949.

[46] Matsuda, L.A. *et al.* (1990) "Structure of a cannabinoid receptor and functional expression of the cloned DNA", *Nature*, 346(6284) 5561-564.

central and peripheral nervous system. CB2 is expressed essentially in the cells of the immune system. It follows from this distribution that CB1 is essentially involved in psychotropic effects and CB2 in immunomodulatory effects.

The main endocannabinoids are arachidonoylethanolamide (also called anandamide - a word derived from Sanskrit, literally meaning congratulated) and 2-arachidonoylglycerol (2-AG). These are the only two endogenous molecules known to be capable of binding to cannabinoids receptors CB1 and CB2 and replicating the pharmacological and behavioural effects of Δ^9THC. Anandamide levels in the brain are comparable to those of other neurotransmitters such as dopamine and serotonine. The highest levels corresponding to high CB1 density areas, that is to say the hippocampus, striatum, the cerebellum and the cortex. Like anandamide, 2-AG reproduces all the behavioural effects of Δ^9THC or anandamide, but its action is less powerful.

The CB1 receptors are among the most abundant neuronal receptors in the central nervous system, and their distribution correlates remarkably with the behavioural effects of cannabinoids on memory, sensory perception and control of movements, as shown in the table below.

Location of CB1 receptors in the CNS and correlated pharmacological effects [48]

Structures	Marking	Physiological consequences	References
			Herkenham et al., 1990
	+		Herkenham, 1992
	+		Tsou et al., 1998, 1999
	++	Cognitive effects	Katona et al., 1999
	++	Locomotive effects	Rinaldi-Carmona et al.,
	++	Cognitive effects (short-term memory inhibition), antiepileptic action	1996 Matsuda et al., 1990, 1993 Hohmann, 1999
	+	Endocrine and antinociceptive effects	Marsicano and Lutz, 1999 Westlake et al., 1994
	-		
	-		
	-		
	-		
	+	Antinociceptive effects	
	-		
	-		

[47] Munro, S. *et al.* (1993) "Molecular characterization of a peripheral receptor for cannabinoids", *Nature*, 365: 61-65. Note that a recent scientific conference of the National Institute on Drug Abuse in the United States reported on the work of researchers on the hypothesis that there are additional receptors and other ligands. To our knowledge, the latter have not yet been formally identified in the research setting.

[48] Table reproduced from INSERM (2001), *op. cit.*, page 298.

Structures	Marking	Physiological consequences	References
Bridged nuclei	–		
Brainstem	–	No lethal dose, no acute mortality	
Cerebellum	++	Motor effects (balance)	

++: abundant marking; +: intermediate marking; –: little or no marking.

This concentration of CB1 receptors largely explains the effects of Δ^9THC. Intense expression of CB1 receptors in the basal nucleus and molecular layer of the cerebellum is thus consistent with the inhibiting effects of cannabinoids on psychomotor performance and motor coordination. Their expression in the cortex and hippocampus is consistent with the modulation of elementary forms of learning, explaining in particular the reversible deleterious effects on short-term memory and cognitive function. Their lack of marking in the brainstem explains the absence of acute toxicity or lethal doses of cannabis derivatives. The CB1 receptors in the thalamocortical system participate in the sensory disturbances and analgesic properties of cannabis. Similarly, the presence of receptors in the periaqueductal area and the dorsal horn of the spinal cord contribute to its antinociceptive power.

We also note that the CB1 receptors do not merely inhibit brain function. As a result of circuit effects, cannabinoids can stimulate certain neuron populations, in particular dopaminergic cells in the mesolimbic pathway. Together with the observation that prolonged treatment with cannabis (at doses corresponding to the equivalent of 575 cannabis cigarettes a day!) appears to induce lasting adaptive changes to the central nervous system and to the positive relationship between cannabinoids and stress hormones (corticotrophine), this explains the difficulties (irritability, sleep disorders and so on) observed in regular users when they have stopped using cannabis. We return to this issue in the Chapter 7 in the discussion on cannabis tolerance and dependence.

Lastly, recent works suggest there are significant interindividual variations in the effects of cannabinoids depending on sex steroid hormones in men and women: it appears that the effects of exogenous and endogenous cannabinoids can be modulated by the hormonal state of each individual and that, in exchange, the CB1 receptors and endocannabinoids are able to regulate hormonal activity.

As was observed in the WHO report in 1997, various research questions remain unanswered, in particular how and to what extent cannabis use alters the endogenous cannabinoid and what the relationship is between blood plasma cannabinoid levels and induced behavioural effects.

CONCLUSIONS

In conclusion, the Committee makes the following findings:

Conclusions of Chapter 5

- The size of the cannabis market is estimated at 800 tonnes a year.
- The size of the national production has significantly increased, and it is estimated that 50% of cannabis available is now produced in the country.
- The main producer provinces are British Columbia, Ontario and Quebec.
- Estimates of the monetary value of the cannabis market are unreliable. For example, if 400 tons are grown yearly in Canada, at a street value of $225 per ounce, the total value of the Canadian production would be less than $6 billion per year, less than the often quoted value of the BC market alone.
- An unknown proportion of national production is exported to the United States.
- A portion of production is controlled by organized crime elements.

- THC is the main active ingredient of cannabis; in its natural state, cannabis contains between 0.5% and 3% THC.
- Sophisticated growing methods and genetic progress have made it possible to increase THC content in recent years, but it is impossible to estimate the average content of cannabis available in the market; it is reasonable to consider that content varies between 6% and 31%.
- THC is fat soluble and readily spreads in the innervated tissues of the brain; it reaches a peak in the blood plasma in less than nine minutes and falls to approximately 5% after one hour.
- The body is slow to eliminate THC and inactive THC metabolites can be detected in urine up to 27 days after use in the case of regular users.
- Psychoactive effects generally last two to three hours and as many as five to seven hours after use.

References

A. C. Nielson Co. (1998). TV statistics. Available: http://www.tvta.org/stats.html.

Abel, E. (1977). The relationship between cannabis and violence: A review. *Psychological Bulletin, 84,* 193–211.

Abel, E. (1980). *Marijuana: The first twelve thousand years.* New York: Plenum.

Abrahamov, A., Abrahamov, A., & Mechoulam, R. (1995). An efficient new cannabinoid antiemetic in pediatric oncology. *Life Sciences, 56,* 2097–2102.

Adamec, C., Pihl, R. O., & Leiter, L. (1976). An analysis of the subjective marijuana experience. *International Journal of the Addictions, 11,* 295–307.

Adams, A. J., Brown, B., Haegerstrom-Portnoy, G., & Flom, M. C. (1976). Evidence for acute efffects of alcohol and marijuana on color discrimination. *Perception and Psychophysics, 20,* 119–124.

Adelman, S. A., & Weiss, R. D. (1989). What is therapeutic about inpatient alcoholism treatment? *Hospital and Community Psychiatry, 40,* 515–519.

Alcott, L. M. (1869/1976). *Plots and counterplots: More unknown thrillers of Louisa May Alcott.* M. Stern (Ed.). New York: William Morrow.

Aldrich, M. R. (1997). History of therapeutic cannabis. In M. L. Mathre (Ed.), *Cannabis in medical practice* (pp. 35–55). London: McFarland.

Aldrich, M. R., & Mikuriya, T. (1988). Savings in California marijuana law enforcement costs attributable to the Moscone Act of 1976—A summary. *Journal of Psychoactive Drugs, 20,* 75–81.

Ali, R., Christie, P., Hawks, D., Lenton, S., Hall, W., Donnelly, N., et al. (1998). *The social impacts of the cannabis expiation notice scheme in South Australia.* Canberra, Australia: Department of Health and Family Services.

American Management Association. (1998). *Drug testing and monitoring survey*. New York: Author.

American Psychiatric Association (APA). (1952). *Diagnostic and statistical manual of mental disorders* (1st ed.). Washington, DC: Author.

American Psychiatric Association (APA). (1968). *Diagnostic and statistical manual of mental disorders* (2nd ed.). Washington, DC: Author.

American Psychiatric Association (APA). (1994). *Diagnostic and statistical manual of mental disorders* (4th ed.). Washington, DC: Author.

Ames, F. R. (1986). Anticonvulsant effect of cannabidiol. *South African Medical Journal, 69*, 14.

Andreasson, S., Allebeck, P., & Rydberg, U. (1989). Schizophrenia in users and non-users of cannabis. *Acta Psychiatrica Scandinavica, 79*, 505–510.

Andreoli, T. E., Carpenter, C. C., Bennet, C. J., & Plum, F. (Eds.). (1997). *Cecil essentials of medicine*. Philadelphia: Saunders.

Armor, D. J., Polich, J. M. & Stambul, H. B. (1978). *Alcoholism and treatment*. New York: Wiley.

Baker, D., Pryxe, G., Croxford, J. L., Brown, P., Pertwee, R. G., Huffman, J. W., et al. (2000). Cannabinoids control spasticity and tremor in a multiple sclerosis model. *Nature, 404*, 84–87.

Balzac, H. (1900). *Letters to Madame Hanska*. Boston: Little, Brown.

Basavarajappa, B. S., & Hungund, B. L. (1999). Chronic ethanol increases the cannabinoid receptor agonist anandamide and its precursor N-arachidonoylphosphatidylethanolamine in SK-N-SH cells. *Journal of Neurochemistry, 72*, 522–528.

Basu, D., Malhotra, A., Bhagat, A., & Varma, V. K. (1999). Cannabis psychosis and acute schizophrenia: A case control study from India. *European Addiction Research, 5*, 71–73.

Bates, M. N., & Blakely, T. A. (1999). Role of cannabis in motor vehicle crashes. *Epidemiological Reviews, 21*, 222–232.

Baudelaire, C. (1861/1989). *The flowers of evil*. M. Mathews & J. Mathews (Eds.). New York: New Directions.

Beal, J. E., Olson, R., Laubenstein, L., Morales, J. O., Bellman, P., Yangco, B., et al. (1995). Dronabinol as a treatment for anorexia associated with weight loss in patients with AIDS. *Journal of Pain and Symptom Management, 10*, 89–97.

Beal, J. E., Olson, R., Lefkowitz, L., Laubenstein, L., Bellman, P., Yangco, B., et al. (1997). Long-term efficacy and safety of dronabinol for Acquired Immunodeficiency Syndrome–associated anorexia. *Journal of Pain and Symptom Management, 14*, 7–14.

Bech, P., Rafaelsen, L., & Rafaelsen, O. J. (1973). Cannabis and alcohol: Ef-

fects on estimation of time and distance. *Psychopharmacologia, 32,* 373–381.

Beck, A. T., Wright, F. D., Newman, C. F., & Liese, B. S. (1993). *Cognitive therapy of substance abuse.* New York: Guilford.

Bell, J. (1857). On the haschish or Cannabis Indica. *Boston Medical and Surgical Journal, 56,* 209–216.

Bello, J. (1996). *The benefits of marijuana: Physical, psychological, and spiritual.* Boca Raton, FL: Lifeservices.

Benet, S. (1975). Early diffusion and folk uses of hemp. In V. Rubin (Ed.), *Cannabis and culture* (pp. 39–50). The Hague: Mouton.

Benjamin, D. K., & Miller, R. L. (1991). *Undoing drugs.* New York: Basic Books.

Bennett, W. (1991). The plea to legalize drugs is a siren call to surrender. In M. Lyman & G. Potter (Eds.), *Drugs in society* (p. 339). Cincinnati: Anderson.

Bidaut-Russell, M., Devane, W. A., & Howlett, A. C. (1990). Cannabinoid receptors and modulation of cyclic AMP accumulation in the rat brain. *Journal of Neurochemistry, 55,* 21–55.

Bishop, J. L. (1966/1868). *A history of American manufactures.* New York: Kelley.

Blank, D., & Fenton, J. (1991). Early employment testing for marijuana. In S. Guse & J. Walsh (Eds.), *Drugs in the workplace* (monograph 91, pp. 151–167). Rockville, MD: National Institute on Drug Abuse.

Blaze-Temple, D., & Lo, S. K. (1992). Stages of drug use: A community survey of Perth teenagers. *British Journal of Addiction, 87,* 215–225.

Bleiberg, J. L., Devlin, P., Croan, J., & Briscoe, R. (1994). Relationship between treatment length and outcome in a therapeutic community. *International Journal of the Addictions, 29,* 729–740.

Block, R. I., Erwin, W. J., Farinpour, R., & Braverman, K. (1998). Sedative, stimulant, and other subjective effects of marijuana: Relationships to smoking techniques. *Pharmacology, Biochemistry and Behavior, 59,* 405–412.

Block, R. I., Farinpour, R., & Braverman, K. (1992). Acute effects of marijuana on cognition: Relationships to chronic effects and smoking techniques. *Pharmacology, Biochemistry and Behavior, 43,* 907–917.

Block R. I., & Ghoneim, M. M. (1993). Effects of chronic marijuana use on human cognition. *Psychopharmacology, 110,* 219–228.

Block, R. I., O'Leary, D. S., Ehrhardt, J. C., Augustinack, J. C., Ghoneim, M. M., Arndt, S., et al. (2000). Effects of frequent marijuana use on brain tissue volume and composition. *NeuroReport, 11,* 491–496.

Block, R. I., O'Leary, D. S., Hichwa, R. D., Augustinack, J. C., Ponto, L. L. B., Ghoneim, M. M., et al. (2000). Cerebellar hypoactuvity in frequent marijuana users. *NeuroReport, 11*, 749–753.

Block, R. I. & Wittenborn, J. R. (1984a). Marijuana effects on semantic memory: Verification of common and uncommon category members. *Psychological Reports, 55*, 503–512.

Block, R. I. & Wittenborn, J. R. (1984b). Marijuana effects on visual imagery in a paired-associate task. *Perceptual & motor skills, 58*, 759–766.

Block, R. I., & Wittenborn, J. R. (1986). Marijuana effects on the speed of memory retrieval in the letter-matching task. *International Journal of the Addictions, 21*, 281–285.

Bloom, J. W., Kaltenborn, W. T., Paoletti, P., Camilli, A., & Leibowitz, M. S. (1987). Respiratory effects of non-tobacco cigarettes. *British Medical Journal, 295*, 516–518.

Blum, R. H. (1984). *Handbook of abusable drugs*. New York: Gardner.

Boire, R. G. (1992). *Marijuana law*. Berkeley, CA: Ronin.

Bonnie, R. J., & Whitebread, C. H. (1974). The marijuana conviction: A history of marihuana prohibition in the United States. Charlottesville: University Press of Virginia.

Borg, J., Gershon, S., & Alpert, M. (1975). Dose effects of smoked marijuana on human cognitive and motor functions. *Psychopharmacologia, 42*, 211–218.

Bornheim, L. M., Kim, K. Y., Li, J., Perotti, B. Y., & Benet, L. Z. (1995). Effect of cannabidiol pretreatment on the kinetics of tetrahydrocannabinol metabolites in mouse brain. *Drug Metabolism & Disposition, 23*, 825–831.

Bowman, M., & Pihl, R. O. (1973). Cannabis: Psychological effects of chronic heavy use: A controlled study of intellectual functioning in chronic users of high potency cannabis. *Psychopharmacologia, 29*, 159–170.

Braden, W., Stullman, R. C., & Wyatt, R. J. (1974). Effects of marijuana on contingent negative variation and reaction time. *Archives of General Psychiatry, 31*, 537–541.

Brazis, M.-Z., & Mathre, M. L. (1997). Dosage and administration of cannabis. In M. L. Mathre (Ed.), *Cannabis in medical practice* (pp. 142–156). London: McFarland.

Brecher, E. M. (1972). *Licit and illicit drugs*. Boston: Little, Brown.

British Medical Association. (1997). Therapeutic uses of cannabis. Amsterdam: Harwood.

Bromberg, W. (1939). Marihuana: A psychiatric study. *Journal of the American Medicol Association, 113*, 4–12.

Bromberg, W., & Rodgers, T. C. (1946). Marihuana and aggressive crime. *American Journal of Psychiatry, 102,* 825–827.

Brown, E. J., Flanagan, T. J., & McLeod, M. (Eds.) (1984). *Sourcebook of criminal justice statistics–1983.* Washington DC: U.S. Government Printing Office, U.S. Department of Justice, Bureau of Justice Statistics.

Brown, S. A. (1993). Recovery patterns in adolescent substance abuse. In J. S. Baer, G. A. Marlatt, & R. J. McMahon (Eds.), *Addictive behaviors across the life span* (pp. 161–183). Newbury Park: Sage.

Bruce, T. J., Spiegel, D. A., & Hegel, M. T. (1999). Cognitive-behavioral therapy helps prevent relapse and recurrence of panic disorder following alprazolam discontinuation: A long-term follow-up of the Peoria and Dartmouth studies. *Journal of Consulting and Clinical Psychology, 67,* 151–156.

Bruera, E., & Higginson, I. (Eds.) (1996). *Cachexia-anorexia in cancer patients.* New York: Oxford University P

Bureau of Census. (1999). *Statistical ab: .ct of the U.S.* Washington, DC: Congressional Information Services.

Burish, T. G., & Tope, D. M. (1992). Psychological techniques for controlling the adverse side effects of cancer chemotherapy: Findings from a decade of research. *Journal of Pain and Symptom Management, 7,* 287–301.

Burke, J. (1999). It's not how hard you work but how you work hard: Evaluating workaholism components. *International Journal of Stress Management, 6,* 225–239.

Burton, R. (1621/1977). *Anatomy of melancholy.* New York: Vintage.

Cabral, G. A. (1999). Cannabinoid receptors in sperm. In G. G. Nahas, K. M. Sutin, D. J. Harvey, & S. Agurell (Eds.), *Marijuana and medicine* (pp. 317–326). Totowa, NJ: Humana.

Callahan, E. J. (1980). Alternative strategies in the treatment of narcotic addiction: A review. In W. R. Miller (Ed.), *The addictive behaviors* (pp. 143–168). New York: Pergamon.

Cami, J., Guerra, D., Ugena, B., Segura, J., & De La Torre, R. (1991). Effects of subject expectancy on THC intoxication and disposition from smoked hashish cigarettes. *Pharmacology, Biochemistry and Behavior, 40,* 115–119.

Campbell, A. M. G., Evans, M., Thomson, J. L. G., & Williams, M. J. (1971). Cerebral atrophy in young cannabis smokers. *Lancet, 2,* 1219–1224.

Canadian Centre on Substance Abuse. (1998). *Cannabis control in Canada: Options regarding possession.* Ottawa, Canada: Author.

Caplan, P. J. (1995). *They say you're crazy.* Reading, MA: Addison-Wesley.

Cappell, H. D., & Pliner, P. L. (1973). Volitional control of marijuana intox-

ication: A study of the ability to "come down" on command. *Journal of Abnormal Psychology, 82,* 428–434.

Carlin, A. S., Bakker, C. B., Halpern, L., & Post, R. D. (1972). Social facilitation of marijuana intoxication: Impact of social set and pharmacological activity. *Journal of Abnormal Psychology, 80,* 132–140.

Carlin, A. S., Post, R. D., Bakker, C. B., & Halpern, L. M. (1974). The role of modeling and previous experience in the facilitation of marijuana intoxication. *Journal of Nervous and Mental Disease, 159,* 275–281.

Carlin, A. S., & Trupin, E. W. (1977). The effect of long-term chronic marijuana use on neuropsychological functioning. *International Journal of the Addictions, 12,* 617–624.

Carlini, E. A., & Cunha, J. M. (1981). Hypnotic and antiepileptic effects of cannabidiol. *Journal of Clinical Pharmacology, 21,* 417S–427S.

Carrier, L. (1962). *The beginnings of agriculture in America.* New York: Johnson Reprint Co.

Carter, T. F. (1968). *The invention of paper in China.* New Haven: Yale University Press.

Carter, W. E. (1980). *Cannabis in Costa Rica.* Philadelphia: Institute of the Study of Human Issues.

Caspari, D. (1999). Cannabis and schizophrenia: Results of a follow-up study. *European Archives of Psychiatry and Clinical Neuroscience, 249,* 45–49.

Casswell, S. (1975). Cannabis intoxication: Effects of monetary incentive on performance, a controlled investigation of behavioural tolerance in moderate users of cannabis. *Perceptual and Motor Skills, 41,* 423–434.

Casswell, S., & Marks, D. F. (1973). Cannabis and temporal disintegration in experienced and naive subjects. *Science, 179,* 803–805.

Casto, D. M. (1970). Marijuana and the assassins—An etymological investigation. *International Journal of the Addictions, 5,* 747–757.

Center on Addiction and Substance Abuse (CASA). (1996). National survey of American attitudes on substance abuse: II. Teens and their parents. New York: CASA at Columbia University.

Chait, L. D. (1990). Subjective and behavioral effects of marijuana the morning after smoking. *Psychopharmacology, 100,* 328–333.

Chait, L. D., Fischman, M. W., & Schuster, C. R. (1985). Hangover effects the morning after marijuana smoking. *Drug & Alcohol Dependence, 15,* 229–238.

Chait, L. D., & Pierri, J. (1992). Effects of smoked marijuana on human performance: A critical review. In L. Murphy & A. Bartke (Eds.), *Marijuana/cannabinoids: Neurobiology and neurophysiology* (pp. 387–423). Boca Raton: CRC.

Chandler, L. S. Richardson, G. A., Gallagher, J. D., & Day, N. L. (1996). Prenatal exposure to alcohol and marijuana: Effects on motor development of preschool children. *Alcoholism: Clinical and Experimental Research, 20,* 455–461.

Chang, K. (1968). The archeology of ancient China. New Haven: Yale University Press.

Chen, J., Marmur, R., Pulles, A., Paredes, W., & Gardner, E. L. (1993). Ventral tegmental microinjection of delta-9-tetrahydrocannabinol enhances ventral tegmental somatodendritic dopamine levels but not forebrain dopamine levels: Evidence for local neural action by marijuana's psychoactive ingredient. *Brain Research, 621,* 65–70.

Cherek, D. R., Moeller, F. G., Schnapp, W., & Dougherty, D. M. (1997). Studies of violent and nonviolent male parolees: I. Laboratory and psychometric measurements of aggression. *Biological Psychiatry, 41,* 514–522.

Cherek, D. R., Roache, J. D., Egli, M. Davis, C., et al. (1993). Acute effects of marijuana smoking on aggressive escape, and post-maintained responding of male drug users. *Psychopharmacology, 111,* 163–168.

Chopra, I. C., & Chopra, R. N. (1957). The use of cannabis drugs in India. *Bulletin on Narcotics, 1,* 4–29.

Chowdhury, A. N., & Bagchi, D. J. (1993). Koro in heroin withdrawal. *Journal of Psychoactive Drugs, 25,* 257–258.

Chowdhury, A. N., & Bera, N. K. (1994). Koro following cannabis smoking: Two case reports. *Addiction, 89,* 1017–1020.

Clark, I. D., & Nakashima, E. N. (1968). Experimental studies of marijuana. *American Journal of Psychiatry, 125,* 379–384.

Clark, W. C., Janal, M. N., Zeidenberb, P., & Nahas, G. (1981). Effects of moderate and high doses of marijuana on thermal pain: A sensory decision analysis. *Journal of Clinical Pharmacology, 21,* 299S–310S.

Clarke, R. C. (1998). *Hashish!* Los Angeles: Red Eye.

Clifford, D. B. (1983). Tetrahydrocannabinol for tremor in multiple sclerosis. *Annals of Neurology, 13,* 669–671.

Co, B. T., Goodwin, D. W., Gado, M., Mikhael, M., & Hill, S. Y. (1977). Absence of cerebral atrophy in chronic cannabis users: Evaluation by computerized transaxial tomography. *Journal of the Amereican Medical Association, 237,* 1229–1230.

Coates, R. A., Farewell, V. T., Raboud, J., Read, S. E., MacFadden, D. K., Calzavara, L. M., et al. (1990). Cofactors of progression to acquired immunodeficiency syndrome in a cohort of male sexual contacts of men with immunodeficiency virus disease. *American Journal of Epidemiology, 132,* 717–722.

Cohen, J. (1990). *Statistical power analysis for the behavioral sciences*. Hillsdale, NJ: Lawrence Erlbaum.

Cohen, M. J., & Rickles, W. H., Jr. (1974). Performance on a verbal learning task by subjects of heavy past marijuana usage. *Psychopharmacologia, 37* 323–330.

Cohen, S. (1976). The 94 day cannabis study. *Annals of the New York Academy of Sciences, 282,* 211–220.

Cohen, S. (1979). Marihuana: A new ball game? *Drug Abuse and Alcoholism Newsletter, 8,* 4.

Comitas, L. (1976). Cannabis and work in Jamaica: A refutation of the amotivational syndrome. *Annals of the New York Academy of Sciences, 282,* 24–34.

Cone, E. J., Johnson, R. E., Paul, B. D., Mell, L. D., & Mitchell, J. (1988). Marijuana-laced brownies: Behavioral effects, physiologic effects, and urinalysis in humans following ingestion. *Journal of Analytic Toxicology, 12,* 169–175.

Consroe, P., Laguna, J., Allender, J., Snider, S., Stern, L., Sandyk, R., et al. (1991). Controlled clinical trial of cannabidiol in Huntington's disease. *Pharmacology, Biochemistry and Behavior, 40,* 701–708.

Consroe, P., Musty, R., Rein, J., Tillery, W., & Pertwee, R. G. (1997). The perceived effects of smoked cannabis on patients with multiple sclerosis. *European Neurology, 38,* 44–48.

Consroe, P., Sandyk, R., & Snider, S. R. (1986). Open label evaluation of cannabidiol in dystonic movement disorders. *International Journal of Neuroscience, 30,* 277–282.

Coombs, R. H., & West, L. J. (1991). Drug testing: Issues and options. New York: Oxford University Press.

Cornish, J. W., McNicholas, L. F., & O'Brien, C. P. (1995). Treatment of substance related disorders. In A. F. Schatzberg & C. B. Nemeroff (Eds.), *Textbook of psychopharmacology* (pp. 575–637). Washington, DC: American Psychiatric Association.

Cosgrove, J., & Newell, T. G. (1991). Recovery of neuropsychological functions during reduction in use of phencyclidine. *Journal of Clinical Psychology, 47,* 159–169.

Cousens, K., & DiMascio, A. (1973). Delta-9-THC as an hypnotic: An experimental study of three dose levels. *Psychopharmacologia, 33,* 355–364.

Crane v. Campbell, 245 U.S. 304; 38 S. Ct. 98 (1917).

Creason, C. R., & Goldman, M. (1981). Varying levels of marijuana use by adolescents and the amotivational syndrome. *Psychological Reports, 48,* 447–454.

Culver, C. M., & King, F. W. (1974). Neuropsychological assessment of un-

dergraduate marihuana and LSD users. *Archives of General Psychiatry, 31,* 707–711.

Cunha, J. M., Carlini, E. A., Pereira, A. E., Ramos, O. L., Pimental, C., Gagliardi, R., et al. (1980). Chronic administration of cannabidiol to healthy volunteers and epileptic patients. *Pharmacology, 21,* 175–185.

da Orta, G. (1563/1913). *Colloquies on the simples & drugs of India (Goa).* (Sir Clements Markham, Trans.). London: Henry Sotheran.

Dansak, D. A. (1997). As an antiemetic and appetite stimulant for cancer patients. In M. L. Mathre (Ed.), *Cannabis in medical practice* (pp. 69–83). London: McFarland.

Davidson, E. S. & Schent, S. (1994). Variability in subjective responses to marijuana: Initial experiences of college students. *Addictive Behaviors, 19,* 531–538.

Davis, K. H., Jr., McDaniel, I. A., Jr., Cadwell, L. W., & Moody, P. L. (1984). Some smoking characteristics of marijuana cigarettes. In S. Agurell, W. L. Dewey, & R. E. Wilette (Eds.), *Cannabinoids: Chemical, pharmacologic, and therapeutic aspects* (pp. 97–110). New York: Academic.

Dawes, R. M. (1994). *House of cards.* New York: Free Press.

Day, N. L., Richardson, G. A., Geva, D., & Robles, N. (1994). Alcohol, marijuana, and tobacco: Effects of prenatal exposure on offspring growth and morphology at age six. *Alcoholism: Clinical and Experimental Research, 18,* 786–794.

De Petrocellis, L., Melck, D., Bisogno, T., Milone, A. & Di Marzo, V. (1999). Finding of the endocannabinoid signalling system in Hydra, a very primitive organism: Possible role in the feeding response. *Neuroscience, 92,* 377–387.

De Petrocellis, L., Melck, D., Palmisano, A., Bisogno, T., Laezza, C., Bifulco, M., et al. (1998). The endogenous cannabinoid anandamide inhibits human breast cancer cell proliferation. *Proceedings of the National Academy of Sciences, 95,* 8375–8380.

De Quincy, T. (1966). *Confessions of an opium eater.* New York: American Library.

de Zwart, W. M., Stam, H., & Kuiplers, S.B.M. (1997). *Key data—smoking, drinking, drug use, and gambling among pupils aged 10 years or older.* Netherlands: Netherlands Institute of Health and Addiction.

Dennis, R. J. (1990). The American people are starting to question the drug war. In A. S. Trebach & K. B. Zeese (Eds.), *The great issues in drug policy* (pp. 141–186). Washington, DC: Drug Policy Foundation.

Department of Health and Human Services (DHHS). (1998). *National household survey on drug abuse: Population estimates, 1997.* Washington, DC: U.S. Government Printing Office.

Devane, W. A., Dysarz, F. A., Johnson, M. R., Melvin, L. S., & Howlett, A. C. (1988). Determination and characterization of a cannabinoid receptor in rat brain. *Molecular Pharmacology, 34,* 605–613.

Devane, W. A., Hanus, L., Breuer, A., Pertwee, R. G., Stevenson, L. A., Griffin, G., et al. (1992). Isolation and structure of a brain constituent that binds to the cannabinoid receptor. *Science, 258,* 1946–1949.

Di Marzo, V., Sepe, N., De Petrocellis, L., Berger, A., Crozier, G., Fride, E., et al. (1998). Trick or treat from food cannabinoids? *Nature, 396,* 636.

Diaz, J. (1997). *How drugs influence behavior.* Upper Saddle River, NJ: Prentice Hall.

Dixon, L., Haas, G., Weiden, P. J., Sweeney, J., & Frances, A. J. (1991). Drug abuse in schizophrenic patients: Clinical correlates and reasons for use. *American Journal of Psychiatry, 148,* 224–230.

Doblin, R. (1994). The MAPS/California NORML marijuana waterpipe/vaporizer study. *Newsletter of the Multidisciplinary Association for Psychedelic Studies, 5,* 19–22.

Donaldson, S. I., Sussman, S., MacKinnon, D. P., Severson, H. H., Glynn, T., Murray, D. M., et al. (1996). Drug abuse prevention programming: Do we know what content works? *American Behavioral Scientist, 39,* 868–883.

Donovan, J. E. (1996). Problem behavior theory and the explanation of adolescent marijuana use. *Journal of Drug Issues, 26,* 379–404.

Donovan, J. E., & Jessor, R. (1983). Problem drinking and the dimension of involvement with drugs: A Guttman scalogram analysis of adolescent drug use. *American Journal of Public Health, 73,* 543–552.

Doorenbos N., Fetterman, P., Quimby, M., & Turner, C. (1971). Cultivation, extraction, and analysis of *Cannabis sativa L. Annals of the New York Academy of Sciences, 191,* 3–14.

Dornbush, R. L. (1974). Marijuana and memory: Effects of smoking on storage. *Transactions of the New York Academy of Science, 36,* 94–100.

Dornbush, R. L., Fink, M., & Freedman, A. M. (1971). Marijuana, memory, and perception. *American Journal of Psychiatry, 128,* 194–197.

Doweiko, H. E. (1999). *Concepts of chemical dependency.* New York: Brooks Cole.

Dreher, M. C. (1997). Cannabis and pregnancy. In M. L. Mathre (Ed.), *Cannabis in medical practice* (pp. 159–170). London: McFarland.

Dreher, M. C., Nugent, K., & Hudgins, R. (1994). Prenatal marijuana exposure and neonatal outcomes in Jamaica: An ethnographic study. *Pediatrics, 93,* 254–260.

Drug Watch Oregon. (1996). *Marijuana research review.* Portland, OR: Author.

Drummer, O. H. (1994). Drugs in drivers killed in Australian road traffic accidents. (Report no. 0594). Melbourne, Australia: Monash University, Victorian Institute of Forensic Pathology.

Du Toit, B. M. (1975). Dagga: The history and ethnographic setting of *Cannabis sativa* in Southern Africa. In V. Rubin (Ed.), *Cannabis and culture* (pp. 51–62). The Hague: Mouton.

Du Toit, B. M. (1980). *Cannabis in Africa*. Rotterdam: Balkema.

Dumas, A. (1844/1998). *The Count of Monte Cristo*. New York: Oxford University Press.

Duncan, D. F. (1987). Lifetime prevalence of "amotivational syndrome" among users and non-users of hashish. *Psychology of Addictive Behaviors, 1*, 114–119.

Dunn, M., & Davis, R. (1974). The perceived effects of marijuana on spinal cord injured males. *Paraplegia, 12*, 175.

DuPont, R. (1984). *Getting tough on gateway drugs*. Washington, DC: American Psychiatric Association.

Dutch Ministry of Health, Welfare, and Sport. (1995). *Drug policy in the Netherlands—continuity and change*. Netherlands: Author.

Earleywine, M., & Finn, P. R. (1991). Sensation seeking explains the relation between behavioral inhibition and drinking. *Addictive Behaviors, 16*, 123–128.

Earleywine, M., Finn, P. R., & Martin C. S. (1990). Personality risk for alcoholism and alcohol consumption: A latent variable analysis. *Addictive Behaviors, 15*, 183–187.

Earleywine, M., & Newcomb, M. (1997). Concurrent versus simultaneous polydrug use: Prevalence, correlates, discriminant validity, and prospective effects on health outcomes. *Experimental and Clinical Psychopharmacology, 5*, 353–364.

Eaton, C. (1966). *A history of the old south*. New York: Macmillan.

Eddy, N. B., Halbach, H., Isbell, H., & Seevers, M. H. (1965). Drug dependence: Its significance and characteristics. *Bulletin of the World Health Organization, 32*, 721–733.

Elmore, A. M., & Tursky, B. (1981). A comparison of two psychophysiological approaches to the treatment of migraine. *Headache, 21*, 93–101.

ElSohly, M. A. Holley, J. H., & Turner, C. E. (1985). Constituents of *Cannabis sativa L.* XXVI. The delta-9-tetrahydrocannabinol content of confiscated marijuana, 1974–1983. In D. J. Harvey (Ed.), *Marijuana '84* (pp. 233–247). Oxford: IRL.

ElSohly, M. A., Ross, S. A., Mehmedic, Z., Arafat, R., Yi, B., & Banahan, B. F. (2000) Potency trends of delta-9-THC and other cannabinoids in

confiscated marijuana from 1980–1997. *Journal of Forensic Sciences, 45,* 24–30.

Employment Division v. Smith, 494 U.S. 872 (1990).

Emrich, H. M., Weber, M. M., Wendl, A., Zihl, J., Von Meyer, L., & Hanishc, W. (1991). Reduced binocular depth inversion as an indicator of cannabis induced censorship impairment. *Pharmacology, Biochemistry and Behavior, 40,* 689–690.

Ennett, S. T., Tobler, N. S., Ringwalt, C. L., & Flewelling, R. L. (1994). How effective is drug abuse resistance education? A meta-analysis of Project DARE outcome evaluations. *American Journal of Public Health, 84,* 1394–1401.

Entin, E. E., & Goldzung, P. J. (1973). Residual effects of marijuana use on learning and memory. *Psychological Record, 23,* 169–178.

Evans, L. (1999). Last words: Wedding day dreams. *Hemp Times, 3,* 90.

Evans, M. A., Martz, R., Brown, D. J., Rodda, B. E., Kiplinger, G. F., Lemberger, L., et al. (1973). Impairment of performance with low doses of marihuana. *Clinical Pharmacology and Therapeutics, 14,* 936–940.

Evans, M. A., Martz, R., Rodda, B. E., Lemberger, L., & Forney, R. B. (1976). Effects of marihuana-dextroamphetamine combination. *Clinical Pharmacology and Therapeutics, 20,* 350–361.

Evans, M. D., Hollon, S. D., Derubeis, R. J., Pinsecki, J. M., Grove, W. M., Garvey, J. J., et al. (1992). Differential relapse following cognitive therapy and pharmacotherapy for depression. *Archives of General Psychiatry, 49,* 802–808.

Evans, R. M. (1998). What is "legalization"? What are "drugs"? In J. M. Fish (Ed.), *How to legalize drugs* (pp. 369–387). Northvale, NJ: Jason Aronson.

Federal Bureau of Investigation. (1997). *Crime in the United States, 1996, FBI uniform crime report.* Washington, DC: U.S. Government Printing Office.

Ferguson, T. J., Rule, B. G., & Lindsay, R. C. (1982). The effects of caffeine and provocation on aggression. *Journal of Research in Personality, 16,* 60–71.

Fiore, M. C., Smith, S. S., Jorenby, D. E., & Baker, T. B. (1994). The effectiveness of the nicotine patch for smoking cessation. *Journal of the American Medical Association, 271,* 1940–1947.

Fiorentine, R., & Anglin, M. D. (1997). Does increasing the opportunity for counseling increase the effectiveness of outpatient drug treatment? *American Journal of Drug and Alcohol Abuse, 23,* 369–382.

Fish, J. M. (Ed.) (1998). *How to legalize drugs.* Northvale, NJ: Jason Aronson.

Fletcher, J. M., & Satz, P. (1977). A methodological commentary on the Egyptian study of chronic hashish use. *Bulletin on Narcotics, 29,* 29–34.

Foltin, R. W., Fischman, M. W., Brady, J. V., Bernstein, D. J., Capriotti, R. M., Nellis, M. J., et al. (1990). Motivational effects of smoked marijuana: Behavioral contingencies and low-probability activities. *Journal of the Experimental Analysis of Behavior, 53,* 5–19.

Foltin, R. W., Fischman, M. W., Brady, J. V., Kelly, T. H., Bernstein, D. J., & Nellis, M. J. (1989). Motivational effects of smoked marijuana: Behavioral contingencies and high-probability recreational activities. *Pharmacology, Biochemistry and Behavior, 34,* 871–877.

Foltin, R. W., Fischman, M. W., & Byrne, M. F. (1988). Effects of smoked marijuana on food intake and body weight of humans living in a residential laboratory. *Appetite, 11,* 1–14.

Fossier, A. E. (1931). The marijuana menace. *New Orleans Medical and Surgical Journal, 84,* 247–252.

Foucault, M. (1973). *Madness and civilization: A history of insanity in the age of reason.* New York: Random House.

Frankel, J. P., Hughes, A., Lees, A. J., & Stern, G. M. (1990). Marijuana for parkinsonian tremor. *Journal of Neurology, Neurosurgery and Psychiatry, 53,* 436.

Franklin, D. (1990). Hooked-not hooked. Why isn't everyone an addict? *Health, 9,* 39–52.

Franzini, L. R., & Grossberg, J. M. (1995). *Eccentric and bizarre behaviors.* New York: Wiley.

Fride, E., & Mechoulam, R. (1993). Pharmacological activity of the cannabinoid receptor agonist, anandamide, a brain constituent. *European Journal of Pharmacology, 231,* 313–314.

Fried, P. A., Watkinson, B., & Gray, R. (1992). A follow-up study of attentional behavior in 6-year-old children exposed prenatally to marijuana, cigarettes, and alcohol. *Neurotoxicology and Teratology, 14,* 299–311.

Fried, P. A., Watkinson, B., & Willan, A. (1984). Marijuana use during pregnancy and decreased length of gestation. *American Journal of Obstetrics and Gynecology, 150,* 23–27.

Fuentes, J. A., Ruiz-Gayo, M., Manzanares, J., Vela, G., Reche, I., & Corchero, J. (1999). Cannabinoids as potential new analgesics. *Life Sciences, 65,* 675–685.

Garraty, J. A. & Gay, P. (1981). *The Columbia history of the world.* New York: Harper and Row.

Gautier, T. (1846/1966). The hashish club. In D. Solomon (Ed.), *The marijuana papers* (pp. 121–135). New York: Bobbs-Merrill.

Gerard, C. M., Mollereau, C., Vassart, G., & Parmentier, M. (1991). Molecular cloning of a human cannabinoid receptor which is also expressed in testis. *Biochemistry Journal, 279*, 129–134.

Gergen, M. K., Gergen, K. J., & Morse, S. J. (1972). Correlates of marijuana use among college students. *Journal of Applied Social Psychology, 2*, 1–16.

Gianutsos, R., & Litwack, A. R. (1976). Chronic marijuana smokers show reduced coding into long-term storage. *Bulletin of the Psychonomic Society, 7*, 277–279.

Gieringer, D. (1996). Marijuana water pipe and vaporizer study. *Newsletter of the Multidisciplinary Association for Psychedelic Studies, 6*, 5–9.

Ginsberg, A. (1966). First manifesto to end the bringdown. In D. Solomon (Ed.), *The marijuana papers* (pp. 183–200). New York: Bobbs-Merrill.

Godwin, H. (1967). The ancient cultivation of hemp. *Antiquity, 41*, 42–49.

Gold, D. (1989). *Cannabis alchemy: The art of modern hashmaking*. Berkeley: Ronin.

Goldberg, L., Bents, R., Bosworth, E., Trevistan, L., & Elliot, D. C. (1991). Anabolic steroid education and adolescents: Do scare tactics work? *Pediatrics, 87*, 283–286.

Goldberg, R. (1997). *Drugs across the spectrum*. Englewood, CO: Morton.

Goldschmidt, L., Day, N. L., & Richardson, G. A. (2000). Effects of prenatal marijuana exposure on child behavior problems at age 10. *Neurotoxicology and Teratology, 22*, 325–336.

Golub, A. & Johnson, B. D. (1994). The shifting importance of alcohol and marijuana as gateway substances among serious drug abusers. *Journal of Studies on Alcohol, 55*, 607–614.

Goode, E. (1971). Drug use and grades in college. *Nature, 239*, 225–227.

Gordon, D. R. (1994). *The return of the dangerous classes—drug prohibition and policy politics*. New York: W. W. Norton.

Gorenstein, E. E. (1987). Cognitive-perceptual deficits in an alcoholism spectrum disorder. *Journal of Studies on Alcohol, 48*, 310–318.

Gorenstein, E. E., Mammato, C. A., & Sandy, J. M. (1989). Performance of inattentive-overactive children on selected measures of prefrontal-type function. *Journal of Clinical Psychology, 45*, 619–632.

Gorman, T. J. (1996). *Marijuana is NOT medicine*. Santa Clarita, CA: California Narcotic Officers' Association.

Gorter, R. (1991). Management of anorexia-cachexia associated with cancer and HIV infection. *Oncology (Supplement), 5*, 13–17.

Gougeon, D. (1984–1985). CEEB SAT mathematics scores and their correlation with college performance in math. *Educational Research Quarterly, 9*, 8–11.

Gralla, R. J., Tyson, L. B., Bordin, L. A., Clark, R. A., Kelsen, D. P., Kris,

M. G., et al. (1984). Antiemetic therapy: A review of recent studies and a report of a random assignment trial comparing metoclopramide with delta-9-tetrahydrocannabinol. *Cancer Treatment Reports, 68,* 163–172.

Grant, B. F., & Pickering, R. (1998). The relationship between cannabis use and DSM-IV cannabis abuse and dependence: Results from the national longitudinal alcohol epidemiological survey. *Journal of Substance Abuse, 10,* 255–264.

Grant, I., Rochford, J., Fleming, T., & Stunkard, A. (1973). A neuropsychological assessment of the effects of moderate marihuana use. *Journal of Nervous and Mental Disease, 156,* 278–280.

Grattan, J. H. G., & Singer, C. (1952). *Anglo-Saxon magic and medicine.* London: Oxford University Press.

Gray, L. C. (1958). *History of agriculture in the Southern United States.* Gloucester, MA: Peter Smith.

Green, B. E., & Ritter, C. (2000). Marijuana use and depression. *Journal of Health and Social Behavior, 41,* 40–49.

Greenfield, S. F., & O'Leary, G. (1999). Sex differences in marijuana use in the United States. *Harvard Review of Psychiatry, 6,* 297–303.

Greenwald, M. K., & Stitzer, M. L. (2000). Antinoceptive, subjective and behavioral effects of smoked marijuana in humans. *Drug and Alcohol Dependence, 59,* 261–275.

Grigor, J. (1852). Indian hemp as an oxytocic. *Monthly Journal of Medical Science, 15,* 124–125.

Grilly, D. M. (1998). *Drugs and human behavior.* Boston: Allyn and Bacon.

Grinspoon, L. (1971). *Marijuana reconsidered.* Cambridge: Harvard University Press.

Grinspoon, L., & Bakalar, J. B. (1997). *Marijuana, the forbidden medicine.* New Haven: Yale University Press.

Gross, H., Egbert, M. H., Faden, V. B., Godberg, S. C., Kaye, W. H., Caine, E. D., et al. (1983). A double-blind trial of delta-9-THC in primary anorexia nervosa. *Journal of Clinical Psychopharmacology, 3,* 165–171.

Gruber, A. J., Pope, H. G., & Oliva, P. (1997). Very long-term users of marijuana in the United States: A pilot study. *Substance Use and Misuse, 32,* 249–264.

Grun, B. (1982). *The timetables of history.* New York: Touchstone.

Halikas, J. A., Goodwin, D. W., & Guze, S. B. (1971). Marijuana effects: A survey of regular users. *Journal of the American Medical Association, 217,* 692–694.

Halikas, J. A., Weller, R. A. & Morse, C. L. (1982). Effects of regular marijuana use on sexual performance. *Journal of Psychoactive Drugs, 14,* 59–70.

Halikas, J. A., Weller, R. A., Morse, C. L., & Hoffmann, R. G. (1985). A longitudinal study of marijuana effects. *International Journal of the Addictions, 20,* 701–711.

Hall, W., " Solowij, N. (1998). Adverse effects of cannabis. *Lancet, 352,* 1611–1616.

Hall, W., Solowij, N., & Lennon, J. (1994). *The health and psychological consequences of cannabis use.* Canberra: Australian Government Publication Services.

Haney, M., Ward, A. S., Comer, S. D., Foltin, R. W., & Fischman, M. W. (1999a). Abstinence symptoms following oral THC administration to humans. *Psychopharmacology, 141,* 385–394.

Haney, M., Ward, A. S., Comer, S. D., Foltin, " W., & Fischman, M. W. (1999b). Abstinence symptoms following smoked marijuana in humans. *Psychopharmacology, 141,* 395–404.

Hanigan, W. C., Destree, R., & Truong, X. T. (1986). The effect of delta-9-THC on human spasticity. *Clinical Pharmacology and Therapeutics, 39,* 198.

Hannerz, J., & Hindmarsh, T. (1983). Neurological and neuroradiological examination of chronic cannabis smokers. *Annals of Neurology, 13,* 207–210.

Hansen, W. B. (1992). School-based substance abuse prevention: A review of the state of the art in curriculum, 1980–1990. *Health Education Research: Theory and Practice, 7,* 403–430.

Harris, L. S., Munson, A. E., & Carchman, R. A. (1976). Antitumor properties of cannabinoids. In M. C. Braude and S. Szara (Eds.), *The pharmacology of marijuana* (Vol. 2, pp. 773–776). New York: Raven.

Hartley, J. P., Nogrady, S. G., & Seaton, A. (1978). Bronchodilator effect of delta-1-tetrahydrocannabinol. *British Journal of Clinical Pharmacology, 5,* 523–525.

Hasan, K. A. (1974). Social aspects of the use of cannabis in India. In V. Rubin (Ed.), *Cannabis and culture* (pp. 235–246). The Hague: Mouton.

Hayes, J. S., Lampart, R., Dreher, M. C., & Morgan, L. (1991). Five-year follow-up of rural Jamaican children whose mothers used marijuana during pregnancy. *West Indian Medical Journal, 40,* 120–123.

Heishman, S. J., Huestis, M. A., Henningfield, J. E., & Cone, E. J. (1990). Acute and residual effects of marijuana: Profiles of plasma THC levels, physiological, subjective and performance measures. *Pharmacology, Biochemistry and Behavior, 34,* 561–565.

Heishman, S. J., Stitzer, M. L., & Yingling, J. E. (1989). Effects of tetrahydrocannabinol content on marijuana smoking behavior, subjective reports, and performance. *Pharmacology, Biochemistry & Behavior, 34,* 173–179.

Hembree, W. C., Nahas, G. G., Zeidenberg, P., & Huang, H. F. S. (1979). Changes in human spermatozoa associated with high-dose marijuana smoking. In G. G. Nahas & W. D. M. Paton (Eds.), *Marijuana: Biological effects, analysis, metabolism, cellular responses* (pp. 429–439). New York: Pergamon.

Hemming, M., & Yellowlees, P. M. (1993). Effective treatment of Tourette's syndrome with marijuana. *Journal of Psychopharmacology, 7,* 389–391.

Henningfield, J., Cohen, C., & Pickworth, W. (1993). Psychopharmacology of nicotine. In C. Orleans & J. Slade (Eds.), *Nicotine addiction: Principle and management* (pp. 24–45). New York: Oxford University Press.

Hepler, R. S., & Petrus, R. (1971). Experiences with administrations of marijuana to glaucoma patients. In S. Cohen and R. Stillman (Eds.), *The therapeutic potential of marijuana* (pp. 63–76). New York: Plenum.

Herer, J. (1999). *The emperor wears no clothes.* Van Nuys, CA: HEMP Publishing.

Herkenham, M., Lynn, A. B., Little, M. D., Johnson, M. R., Melvin, L. S., De Costa, B. R., et al. (1990). Cannabinoid receptor localization in brain. *Proceedings of the National Academy of Sciences, 87,* 1932–1936.

Herodotus (1999/5th Century B.C.). *The histories.* C. Dewald (Ed.). (R. A. Waterfield, Trans.). New York: Oxford University Press.

Hill, S. Y., Schwin, R., Goodwin, D. W., & Powell, B. J. (1974). Marijuana and pain. *Journal of Pharmacology and Experimental Therapeutics, 188,* 415–418.

Hilts, P. J. (1994, August 2). Is nicotine addictive? It depends on whose criteria you use. *New York Times,* p. C3.

Himmelstein, J. L. (1986). The continuing career of marijuana: Backlash . . . within limits. *Contemporary Drug Problems, 13,* 1–21.

Hochman, J. S., & Brill, N. Q. (1973). Chronic marijuana use and psychosocial adaptation. *American Journal of Psychiatry, 130,* 132–139.

Hoefler, M., Lieb, R., Perkonigg, A., Schuster, P., Sonntag, H., & Wittchen, H. U. (1999). Covariates of cannabis use progression in a representative population sample of adolescents: A prospective examination of vulnerability and risk factors. *Addiction, 94,* 1679–1694.

Hollister, L. E. (1974). Structure-activity relationships in man of cannabis constituents, and homologs and metabolites of delta-9 tetrahydrocannabinol. *Pharmacology, 11,* 3–11.

Holloway, M. (1991). Rx for addiction. *Scientific American, 264,* 94–103.

Holly, E. A., Lele, C., Bracci, P. M., & McGrath, M. S. (1999). Case-control study of non-Hodgkin's lymphoma among women and heterosexual men in the San Francisco Bay area. *American Journal of Epidemiology, 150,* 375–389.

Hooker, W. D., & Jones, R. T. (1987). Increased susceptibility to memory intrusions and the Stroop interference effect during acute marijuana intoxication. *Psychopharmacology, 91,* 20–24.

Hope, D. A., & Heimberg, R. G. (1993). Social phobia and social anxiety. In D. Barlow (Ed.), *Clinical handbook of psychological disorders* (pp. 99–136). New York: Guilford.

Horton, J. P., Nogrady, S. G., & Seaton, A. (1978). Bronchodilator effect of delta-1-tetrahydrocannabinol. *British Journal of Clinical Pharmacology, 5,* 523–525.

House of Lords—Select Committee on Science and Technology (1998). *Cannabis—The scientific and medical evidence.* London: The Stationery Office.

How much marijuana do Americans really smoke? (1995). *Forensic Drug Abuse Advisor, 7,* 7–8.

Howlett, A. C., Evans, D. M., & Houston, D. B. (1992). The cannabinoid receptor. In L. Murphy & A. Bartke (Eds.), *Marijuana/cannabinoids: Neurobiology and neurophysiology* (pp. 387–423). Boca Raton, FL: CRC.

Howlett, A. C., Johnson, M. R., Melvin, L. S., & Milne, G. M. (1988). Nonclassical cannabinoid analgesics inhibit adenylate cyclase: Development of a cannabinoid receptor model. *Molecular Pharmacology, 33,* 297–302.

Hser, Y. I., Grella, C., Chou, C. P., & Anglin, M. D. (1998). Relationships between drug treatment careers and outcomes: Findings from the National Drug Abuse Treatment Outcome Study. *Evaluation Review, 22,* 496–519.

Huestis, M. A., & Cone, E. J. (1998). Urinary excretion half-life of 11-Nor-9-carboxy-DELTA-9-tetrahydrocannabinol in humans. *Proceedings of the Fifth International Congress of Therapeutic Drug Monitoring and Clinical Toxicology, 20,* 570–576.

Hume, D. (1739/1978). *A treatise on human nature.* New York: Oxford University Press.

Hunt, C. A., & Jones, R. T. (1980). Tolerance and disposition of tetrahydrocannabinol in man. *Journal of Pharmacology and Experimental Therapeutics, 215,* 35–44.

Hunt, W. A., Barnett, L. W., & Branch, L. G. (1971). Relapse rates in addiction programs. *Journal of Clinical Psychology, 27,* 455–456.

Husak, D. (1992). *Drugs and rights.* New York: Cambridge University Press.

Husak, D. (1998). Two rationales for drug policy: How they shape the content of reform. In J. M. Fish (Ed.), *How to legalize drugs* (pp. 29–60). Northvale, NJ: Jason Aronson.

Hymowitz, N., Feuerman, J., Hollander, M., & Frances, R. J. (1993). Smok-

ing deterrence using silver acetate. *Hospital and Community Psychiatry, 44,* 113–116.

Indian Hemp Drugs Commission (IHDC). (1894). Report of the Indian hemp drugs commission. Simla, India: Government Central Printing Office.

Indiana Prevention Resource Center. (1998). *Factline on marijuana.* Bloomington: The Trustees of Indiana University.

Institute of Medicine (IOM). (1999). *Marijuana and medicine: Assessing the science base.* Washington, DC: National Academy.

Iversen, L. L. (2000). *The science of marijuana.* New York: Oxford University Press.

Jain, A. K., Ryan, J. R., McMahon, F. G., & Smith, G. (1981). Evaluation of intramuscular levonantradol and placebo in acute postoperative pain. *Journal of Clinical Pharmacology, 21,* 320S–326S.

Jarai, Z., Wagner, J. A., Goparaju, S. K., Wang, L., Razdan, R. K., Sugiura, T., et al. (2000). Cardiovascular effects of 2-AG in anesthetized mice. *Hypertension, 35,* 679–684.

Jarbe, T. U., & Hiltunen, A. J. (1987). Cannabimimetic activity of cannabinol in rats and pigeons. *Neuropharmacology, 26,* 219–228.

Jessor, R. (1998). *New perspective on adolescent risk behaviors.* Cambridge: Cambridge University Press.

Jessor, R., & Jessor, S. L. (1977). *Problem behavior and psychosocial development: A longitudinal study of youth.* New York: Academic Press.

Joesof, M. R., Beral, V., Aral, S. O., Rolfs, R. T., & Cramer, D. W. (1993). Fertility and use of cigarettes, alcohol, marijuana, and cocaine. *Annals of Epidemiology, 3,* 592–594.

Johansson, E., Arguell, S., Hollister, L., & Halldin, M. (1988). Prolonged apparent half-life of delta-1-tetrahydrocannabinol in plasma of chronic marijuana users. *Journal of Pharmacy and Pharmacology, 40,* 374–375.

Johansson, E., Noren, K., Sjovall, J., & Halldin, M. M. (1989). Determination of delta-1-tetrahydrocannabinol in human fat biopsies from marihuana users by gas chromatography-mass spectrometry. *Biomedical Chromatography, 3,* 35–38.

Johnston, J. F. (1855). *Chemistry of common life.* New York: Appleton.

Johnston, L., Bachman, J., & O'Malley, P. (1981). Marijuana decriminalization: The impact on you, 1975–1980. *Monitoring the Future Occasional Paper, 13,* 27–29.

Johnston, L., Bachman, J., & O'Malley, P. (1996). *National survey results on drug use from the Monitoring the Future study, 1975–1995.* Washington, DC: U.S. Government Printing Office.

Kabilek, J., Krejci, Z., & Santavy, F. (1960). Hemp as a medicament. *Bulletin on Narcotics, 12,* 5–22.

Kaestner, R. (1991). The effects of drug use on the wages of young adults. *Journal of Labor Economics, 9,* 381–412.

Kaestner, R. (1994a). The effect of illicit drug use on the labor supply of young adults. *Journal of Human Resources, 29,* 123–136.

Kaestner, R. (1994b). New estimates of the effect of marijuana and cocaine on wages: Accounting for unobserved person specific effects. *Industrial and Labor Relations Review, 47,* 454–470.

Kandel, D. B., & Davies, M. (1992). Progression to regular marijuana involvement: Phenomenology and risk factors for near-daily use. In M. Glantz & R. Pickens (Eds.), *Vulnerability to drug abuse* (pp. 211–253). Washington, DC: American Psychological Association.

Kandel, D. B., & Davies, M. (1996). High school students who use crack and other drugs. *Archives of General Psychiatry, 53,* 71–80.

Kandel, D. B., Yamaguchi, K., & Chen, K. (1992). Stages of progression in drug involvement from adolescence to adulthood: Further evidence for the gateway theory. *Journal of Studies on Alcohol, 53,* 447–457.

Kaplan, J. (1970). *Marijuana—The new prohibition.* New York: Wald.

Karacan, D. B., Fernandez-Salas, A., Coggins, W. J., Carter, W. E., Williams, R. L., Thornby, J. I., et al. (1976). Sleep electroencephalagraphic–electrooculographic characteristics of chronic marijuana users. *Annals of the New York Academy of Sciences, 282,* 348–374.

Karniol, I. G., Shirakawa, I., Takahashi, R. N., Knobel, E., & Musty, R. E. (1975). Effects of delta-9-tetrahydrocannabinol and cannabinol in man. *Pharmacology, 13,* 502–512.

Kaslow, R. A., Blackwelder, W. C., Ostrow, D. G., Yerg, D., Palenicek, J., Coulson, A. H., et al. (1989). No evidence for a role of alcohol or other psychoactive drugs in accelerationg immunodeficiency in HIV-1-positive individuals. *Journal of the American Medical Association, 261,* 3424–3429.

Kattlove, H. (1995). Antiemetic properties of granisetron. *New England Journal of Medicine, 332,* 1653.

Kirk, D. (1999). From Hungary with love. *Hemp Times, 3,* 44–88.

Kirk, J. M., Doty, P., & de Wit, H. (1998). Effects of expectancies on subjective responses to oral delta-9-tetrahydrocannabinol. *Pharmacology, Biochemistry and Behavior, 59,* 287–293.

Kleiman, M.A.R. (1992). *Against excess: Drug policy for results.* New York: Basic Books.

Kleinhenz, J., Streitberger, K., Windeler, J., Gussbacher, A., Mavridis, G., & Martin, E. (1999). Randomised clinical trial comparing the effects of acu-

puncture and a newly designed placebo needle in rotator cuff tendinitis. *Pain, 83,* 235–241.

Koob, G. F., & Le Moal, M. (1997). Drug abuse: Hedonic homeostatic dysregulation. *Science, 278,* 52–58.

Koski, P. R., & Eckberg, D. L. (1983). Bureaucratic legitimation: Marihuana and the Drug Enforcement Administration. *Sociological Focus, 16,* 255–273.

Kotler, D. P., Tierney, A. R., Wang, J., & Pierson, R. N. (1989). Magnitude of body-cell-mass depletion and the timing of death from wasting in AIDS. *American Journal of Clinical Nutrition, 53,* 149–154.

Kouri, E., Pope, H. G., & Lukas, S. E. (1999). Changes in aggressive behavior during withdrawal from long-term marijuana use. *Psychopharmacology, 143,* 302–308.

Kouri, E., Pope, H. G., Yurgelun-Todd, D., & Gruber, S. (1995). Attributes of heavy vs. occasional marijuana smokers in a college population. *Biological Psychiatry, 38,* 475–481.

Krampf, W. (1997). AIDS and the wasting syndrome. In M. L. Mathre (Ed.), *Cannabis in medical practice* (pp. 84–93). London: McFarland.

Kuehnle, J., Mendelson, J. H., & David, K. R. (1977). Computed tomographic examination of heavy marijuana users. *Journal of the American Medical Association, 237,* 1231–1232.

Kung, C. T. (1959). *Archaeology in China.* Toronto: University of Toronto Press.

Kutchins, H., & Kirk, S. A. (1997). *Making us crazy.* New York: Free Press.

Labouvie, E., Bates, M. E., & Pandina, R. J. (1997). Age of first use: Its reliability and predictive utility. *Journal of Studies on Alcohol, 58,* 638–643.

LaBrie, J., & Earleywine, M. (2000). Sexual risk behaviors and alcohol: Higher base rate estimates revealed using the unmatched count technique. *Journal of Sex Research, 37,* 321–326.

Laird-Clowes, W. (1877). An amateur assassin. *Belgravia, 31,* 353–359.

Lapey, J. D. (1996). *Marijuana update 1995.* Omaha: Drug Watch International.

Lapp, W. M., Collins, R. L., Zywiak, W. H., & Izzo, C. V. (1994). Psychopharmacological effects of alcohol on time perception: The extended balanded placebo design. *Journal of Studies on Alcohol, 55,* 96–112.

Law, B., Mason, P. A., Moffat, A. C., Gleadle, R. I., & King, L. J. (1984). Forensic aspects of the metabolism and excretion of cannabinoids following oral ingestion of cannabis resin. *Journal of Pharmacy and Pharmacology, 36,* 289–294.

Leary v. U.S., 383 F.2d 851 (5th Cir. 1967).

Leary, T. (1997). *Flashbacks: A personal and cultural history of an era*. Los Angeles: J. P. Tarcher.

Leirer, V. O., Yesavage, J. A., & Morrow, D. G. (1991). Marijuana carryover effects on aircraft pilot performance. *Aviation Space and Environmental Medicine, 62,* 221–227.

Lemberger, L., Axelrod, J., & Kopin, I. J. (1971). Metabolism and disposition of tetrahydrocannabinol in naive subjects and chronic marijuana users. *Pharmacological Reviews, 23,* 371–380.

Lemberger, L., & Rowe, H. (1975). Clinical pharmacology of nabilone, a cannabinol derivative. *Clinical Pharmacology & Therapeutics, 18,* 720–726.

Lenson, D. (1995). *On drugs*. Minneapolis: University of Minnesota Press.

Leuchtenberger, C. (1983). Effects of marijuana (cannabis) smoke on cellular biochemistry on In Vitro test systems. In K. O. Fehr and K. Kalant (Eds.), *Cannabis and health hazards* (pp. 177–224). Toronto: Addiction Research Foundation.

Levey, M. (1966). Medieval Arabic toxicology. *Transactions of the American Philosophical Society, 56,* 5–43.

Levinthal, C. (1999). *Drugs, behavior, and modern society*. Boston: Allyn and Bacon.

Leweke, F. M., Giuffrida, A., Wurster, U., Emrich, H. M., & Piomelli, D. (1999). Elevated endogenous cannabinoids in schizophrenia. *NeuroReport, 10,* 1665–1669.

Li, H. L. (1974). An archeological and historical account of cannabis in China. *Economic Botany, 28,* 437–448.

Li, H. L. (1975). The origin and use of cannabis in Eastern Asia: Their linguistic-cultural implications. In V. Rubin (Ed.), *Cannabis and culture* (pp. 51–62). The Hague: Mouton.

Light, G. A., Geyer, M. A., Clementz, B. A., Cadenhead, K. S., & Braff, D. L. (2000). Normal P50 suppression in schizophrenia patients treated with atypical antipsychotic medications. *American Journal of Psychiatry, 157,* 767–771.

Linn, S., Schoenbaum, S. C., Monson, R. R., Rosner, R., Stubblefield, P. C., & Ryan, K. J. (1983). The association of marijuana use with outcome of pregnancy. *American Journal of Public Health, 73,* 1161–1164.

Linzen, D. H., Dingemans, P. M., & Lenior, M. E. (1994). Cannabis abuse and the course of recent-onset schizophrenic disorders. *Archives of General Psychiatry, 51,* 273–279.

Low, M. D., Klonoff, H., & Marcus, A. (1973). The neurophysiological basis of the marijuana experience. *Canadian Medical Association Journal, 108,* 157–165.

Ludlow, F. H. (1857). *The hasheesh eater: Being passages from the life of a Pythagorean*. New York: Harper.

Lukas, S. E., Mendelson, J. H., & Benedikt, R. (1995). Electroencephalographic correlates of marijuana-induced euphoria. *Drug and Alcohol Dependence, 37*, 131–140.

Lyketsos, C. G., Garrett, E., Liang, K. Y., & Anthony, J. C. (1999). Cannabis use and cognitive decline in persons under 65 years of age. *American Journal of Epidemiology, 149*, 794–800.

Lynam, D. R., Milich, R., Zimmerman, R., Novak, S. P., Logan, T. K., Martin, C., et al. (1999). Project DARE: No effects at 10-year follow-up. *Journal of Consulting and Clinical Psychology, 67*, 590–593.

Lyons, M. J., Toomey, R., Meyer, J. M., Green, A. I., Eisen, S. A., Goldberg, J., et al. (1997). How do genes influence marijuana use? The role of subjective effects. *Addiction, 92*, 409–417.

Maccannell, K., Milstein, S. L., Karr, G., & Clark, S. (1977). Marijuana-produced impairments in form perception: Experienced and non-experienced subjects. *Progress in Neuro-Psychopharmacology, 1*, 339–343.

MacCoun, R. J. (1993). Drugs and the law: A psychological analysis of drug prohibition. *Psychological Bulletin, 113*, 497–512.

MacCoun, R., & Reuter, P. (1997). Interpreting Dutch cannabis policy: Reasoning by analogy in the legalization debate. *Science, 278*, 47–52.

MacDonald, D. I. (1984). *Drugs, drinking, and adolescents*. Chicago: Year Book Medical Publishers.

Mackesy-Amiti, M. E., Fendrich, M., & Goldstein, P. J. (1997). Sequence of drug use among serious drug users: Typical vs. atypical progression. *Drug and Alcohol Dependence, 45*, 185–196.

Mahdi, M. (Ed.). (1992). *The Arabian nights*. New York: Knopf.

Maisto, S. A., Galizio, M., & Connors, G. J. (1995). *Drug use and abuse*. New York: Harcourt.

Makriyannis, A., & Rapaka, R. S. (1990). The molecular basis of cannabinoid activity. *Life Sciences, 47*, 2173–2184.

Malec, J., Harvey, R. F., & Cayner, J. J. (1982). Cannabis effect on spasticity in spinal cord injury. *Archives of Physical Medicine and Rehabilitation, 63*, 116–118.

Maloff, D. (1981). A review of the effects of the decriminalization of marijuana. *Contemporary Drug Problems, 10*, 306–340.

Maltby, L. L. (1999). *Drug testing: A bad investment*. New York: American Civil Liberties Union.

Mandel, J. (1988). Is marijuana law enforcement racist? *Journal of Psychoactive Drugs, 20*, 83–91.

Mann, P. (1985). *Marijuana alert*. New York: McGraw-Hill.

Manno, J. E., Kiplinger, G. F., Haine, S. E., Bennett, I. F., & Forney, R. B. (1970). Comparative effects of smoking marihuana or placebo on human motor and mental performance. *Clinical Pharmacology and Therapeutics, 11*, 808–815.

Margolin, B. (1998). *Guide to state and federal marijuana laws*. Los Angeles: Chuck Alton.

Marijuana Anonymous (1995). *Life with hope*. Van Nuys, CA: Marijuana Anonymous World Services.

Marlatt, A. (Ed.). (1998). *Harm reduction*. New York: Guilford.

Marlatt, G. A., Demming, B., & Reid, J. B. (1973). Loss of control drinking in alcoholics: An experimental analogue. *Journal of Abnormal Psychology, 81*, 233–241.

Marlatt, G. A., & Gordon, J. R. (1985). *Relapse prevention: Maintenance strategies in the treatment of addictive behaviors*. New York: Guilford.

Marlatt, G. A., & Rohsenow, D. J. (1980). Cognitive process in alcohol use: Expectancy and the balanced placebo design. In N. K. Mello (Ed.), *Advances in substance abuse*. (Vol. 1, pp. 159–199). Greenwich, CT: JAI.

Mathew, R. J., & Wilson, W. H. (1992). The effects of marijuana on cerebral blood flow and metabolism. In L. Murphy & A. Bartke (Eds.), *Marijuana/cannabinoids: Neurobiology and Neuro-physiology* (pp. 337–386). Boca Raton FL: CRC.

Mathew, R. J., Wilson, W. H., Chiu, N. Y., Turkington, T. G., Degrado, T. R., & Coleman, R. E. (1999). Regional cerebral blood flow and depersonalization after tetrahydrocannabinol administration. *Acta Psychiatrica Scandinavica, 100*, 67–75.

Mattes, R. D., Engelman, K., Shaw, L. M., & ElSohly, M. A. (1994). Cannabinoids and appetite stimulation. *Pharmacology, Biochemistry and Behavior, 49*, 187–195.

Mattes, R. D., Shaw, L. M., Edling-Owens, J., Engelman, K., & ElSohly, M. A. (1993). Bypassing the first-pass effect for the therapeutic use of cannabinoids. *Pharmacology, Biochemistry and Behavior, 44*, 745–747.

Mattes, R. D., Shaw, L. M., & Engelman, K. (1994). Effects of cannabinoids (marijuana) on taste intensity and hedonic ratings and salivary flow of adults. *Chemical Senses, 19*, 125–140.

Matthias, P., Tashkin, D. P., Marques-Magallanes, J. A., Wilkins, J. N., & Simmons, M. S. (1997). Effects of varying marijuana potency on deposition of tar and delta9-THC in the lung during smoking. *Pharmacology, Biochemistry and Behavior, 58*, 1145–1150.

Mc Daniel, M. A. (1988). Does pre-employment drug use predict job suita-

bility? In S. Guse & J. Welsh (Eds.), *Drugs in the workplace* (monograph 91, pp. 151–167). Rockville, MD: National Institute on Drug Abuse.

McGee, R., Williams, S. A., Poulton, R., & Moffitt, T. (2000). A longitudinal study of cannabis use and mental health from adolescence to early adulthood. *Addiction, 95,* 491–503.

McGeorge, J., & Aitken, C. K. (1997). Effects of cannabis decriminalization in the Australian Capital Territory on university students' patterns of use. *Journal of Drug Issues, 27,* 785–793.

McGlothlin, H. W., & West, L. J. (1968). The marijuana problem: An overview. *American Journal of Psychiatry, 125,* 1126–1134.

McKim, W. A. (1997). *Drugs and behavior: An introduction to behavioral pharmacology 1.* Englewood Cliffs, NJ: Prentice Hall.

McMeens, R. R. (1860). Report of the committee on *Cannabis Indica*. In *Transactions of the 15th Annual Meeting of the Ohio State Medical Society*. Columbus, OH: Follett, Foster & Co. (Reprinted from *Marijuana: Medical papers, 1839–1972,* pp. 117–140, by T. H. Mikuriya, Ed., 1973, Oakland: Medi-Comp.)

McQuay, H., Carroll, D., & Moore, A. (1995). Variation in the placebo effect in randomized controlled trials of analgesics: All is as blind as it seems. *Pain, 64,* 331–335.

Mechoulam, R., Fride, E., Hanus, L., Sheskin, T., Bisogno, T., Di Marzo, V., et al. (1997). Anandamide may mediate sleep induction. *Nature, 389,* 25–26.

Meinck, H. M., Schonle, P. W., & Conrad, B. (1989). Effect of cannabinoids on spasticity and ataxia in multiple sclerosis. *Journal of Neurology, 236,* 120–122.

Mellaart, J. (1967). *Catal Huyuk: A neolithic town in Anatolia*. New York: McGraw-Hill.

Menhiratta, S. S., Wig, N. N., & Verma, S. K. (1978). Some psychological correlates of long-term heavy cannabis users. *British Journal of Psychiatry, 132,* 482–486.

Mikulas, W. L. (1996). Sudden onset of subjective dimensionality: A case study. *Perceptual and Motor Skills, 82,* 852–854.

Mikuriya, T. H. & Aldrich, M. R. (1988). Cannabis 1988: Old drug, new dangers, the potency question. *Journal of Psychoactive Drugs, 20,* 47–55.

Miles, C. G., Congreve, G. R. S., Gibbins, R. J., Marshman, J., Devenyi, P., & Hicks, R. C. (1974). An experimental study of the effects of daily cannabis smoking on behavior patterns. *Acta Pharmacologica et Toxicologica, 34*(Suppl. 7), 1–43.

Miller, C. & Wirtshafter, D. (1991). *The hemp seed cookbook*. Athens, OH: Hempery.

Miller, D. S., & Miller, T. Q. (1997). A test of socioeconomic status as a predictor of initial marijuana use. *Addictive Behaviors, 22,* 479–489.

Miller, L., & Cornett, T. (1978). Marijuana: Dose-response effects on pulse rate, subjective estimates of intoxication, free recall and recognition memory. *Pharmacology, Biochemistry and Behavior, 9,* 573–579.

Miller, L., Cornett, T., Drew, W., McFarland, D., Brightwell, D., & Wikler, A. (1977). Marijuana: Dose-response effects on pulse rate, subjective estimates of potency, pleasantness, and recognition memory. *Pharmacology, 15,* 268–275.

Miller, L., Cornett, T., & Wikler, A. (1979). Marijuana: Dose-response effects on pulse rate, subjective estimates of intoxication and multiple measures of memory. *Life Sciences, 25,* 1325–1350.

Miller, N. S., Gold, M. S., & Pottash, C. (1989). A 12-step treatment approach for marijuana (cannabis) dependence. *Journal of Substance Abuse Treatment, 6,* 241–250.

Miller, N. S., Gold, M. S., & Smith, D. E. (1997). *Manual of therapeutics for addictions.* New York: Wiley.

Miller, T. Q. (1994). A test of alternative explanations for the stage-like progression of adolescent substance use in four national samples. *Addictive Behaviors, 19,* 287–293.

Miller, W. R. (1999). *Integrating spirituality into treatment: Resources for practitioners.* Washington DC: American Psychological Association.

Miller, W. R., & Hester, R. K. (1986). Inpatient alcoholism treatment: Who benefits? *American Psychologist, 41,* 794–805.

Miller, W. R., & Rollnick, S. (1991). *Motivational interviewing.* New York: Guilford.

Miron, J. A. (1999). *Violence and the U.S. prohibition of drugs and alcohol.* (NBER Working Paper No. 6950. JEL No. K42).

Moeller, G. F., Dougherty, D. M., Lane, S. D., Steinberg, J. L., & Cherek, D. R. (1998). Antisocial personality disorder and alcohol-induced aggression. *Alcoholism: Clinical and Experimental Research, 22,* 1898–1902.

Molnar, J., Szabo, D., Pusztai, R., Mucsi, I., Berek, L., Ocsovszki, I., et al. (2000). Membrane associated antitumor effects of crocine-, ginsenoside, and cannabinoid derivatives. *Anticancer Research, 20,* 861–867.

Moos, R. H., King, M. J., & Patterson, M. A. (1996). Outcomes of residential treatment of substance abuse in hospital and community-based programs. *Psychiatric Services, 46,* 66–72.

Moreau, J. J. (1845/1973) *Hashish and mental illness.* New York: Raven.

Morganstern, J., Labouvie, E., McCrady, B. S., Kahler, C. W., & Frey, R. M. (1997). Affiliation with alcoholics anonymous after treatment: A study of

its therapeutic effects and mechanisms of action. *Journal of Consulting and Clinical Psychology, 65,* 768–777.

Morley, S. (1997). Pain management. In A. Baum, S. Newman, J. Weinman, R. West, & C. McManus (Eds.), *Cambridge handbook of psychology, health, and medicine* (pp. 234–237). Cambridge: Cambridge University Press.

Morningstar, P. J. (1985). Thandai and Chilam: Traditional Hindu beliefs about the proper use of cannabis. *Journal of Psychoactive Drugs, 17,* 141–165.

Mueller, B. A., Daling, J. R., Weiss, N. S., & Moore, D. E. (1990). Recreational drug use and the risk of primary infertility. *Epidemiology, 1,* 195–200.

Muller-Vahl, K. R., Kolbe, H., & Dengler, R. (1997). Gilles de la Tourette syndrome: Influence of nicotine, alcohol, and marijuana on the clinical symptoms. *Der Nervenarzt, 68,* 985–989.

Musto, D. F. (1999). *The American disease: Origins of narcotic control.* New York: Oxford University Press.

Musty, R. E., & Kaback, L. (1995). Relationships between motivation and depression in chronic marijauna users. *Life Sciences, 56,* 2151–2158.

Myerscough, R., & Taylor, S. (1985). The effects of marijuana on human physical aggression. *Journal of Personality and Social Psychology, 49,* 1541–1546.

Nadelmann, E. A. (1992). Thinking seriously about alternatives to drug prohibition. *Daedalus, 121,* 87–132.

Nahas, G. G. (1986). Cannabis: Toxicological properties and epidemiological aspects. *Medical Journal of Australia, 145,* 82–87.

Nahas, G. G. (1990). *Keep off the grass.* Middlebury, VT: Paul S. Erickson.

Nahas, G. G., Suciv-Foca, G., Armand, J-P., & Morishima, A. (1974). Inhibition of cellular mediated immunity in marihuana smokers. *Science, 183,* 419–420

Nakamura, E. M., da Sikes, E. A., Concho, G. K., Wilkinson, D. A., & Masur, J. (1991). Reversible effects of acute and long-term administration of delta 9 THC on memory in the rat. *Drugs and Alcohol Dependence, 28,* 167–175.

Narcotics Anonymous. (1988). *Narcotics anonymous.* Van Nuys, CA: World Services Office.

Nathan, P. (1988). The addictive personality is the behavior of the addict. *Journal of Consulting and Clinical Psychology, 56,* 183–188.

National Drug Strategy Household Survey Report (1995). Canberra: Australian Government Publishing Service.

National Institute on Drug Abuse (NIDA). (1991). *NIDA capsules: Summary of findings from the 1990 Household Survey on Drug Abuse*. Rockville, MD: U.S. Department of Health and Human Services.

National Institute on Drug Abuse (NIDA). (1997). *Monitoring the future study*. Washington, DC: U.S. Department of Health and Human Services. [December 20th press release].

National Institute on Drug Abuse (NIDA). (1998). *Marijuana: Facts parents need to know*. Washington, DC: U.S. Department of Health and Human Services.

National Organization for the Reform of Marijuana Laws (NORML). (1996a). Principles of responsible cannabis use. Available: http://www.natlnorml.org/about/responsible.shtml.

National Organization for the Reform of Marijuana Laws (NORML). (1996b). Crop earnings in the United States. Available: www.norml.org / facts /crop /report.shtml #croprank.

Needham, J. (1974). *Science and civilization in China*. Cambridge: Cambridge University Press.

Newcomb, M. & Earleywine, M. (1996). The willing host: Intrapersonal contributors to substance abuse. *American Behavioral Scientist, 7*, 823–837.

Newcomb, M. D., McCarthy, W. J., & Bentler, P. M. (1989). Cigarette smoking, academic lifestyle, and self-efficacy: An eight-year study from early adolescence to young adulthood. *Journal of Applied Social Psychology, 19*, 251–281.

Neylan, T. C., Fletcher, D. J., Lenoci, M., McCallin, K., Weiss, D. S., Schoenfeld, F. B., et al. (1997). Sensory gating in chronic post-traumatic stress disorder: Reduced auditory P50 suppression in combat veterans. *Biological Psychiatry, 46*, 1656–1664.

Ng, S. K. C., Brust, J. C. M., Hauser, W. A., & Susser, M. (1990). Illicit drug use and the risk of new-onset seizures. *American Journal of Epidemiology, 132*, 47–57.

Normand, J., Lempert, R. O., & O'Brien, C. (1994). *Under the influence? Drugs and the American workforce*. Washington, DC: National Academy.

Normand, J. S., Salyards, S., & Mahoney, J. (1990). An evaluation of preemployment drug testing. *Journal of Applied Psychology, 75*, 629–639.

NORML v. Bell, 488 F. Supp. 123 (D.D.C. 1980).

Nowinski, J. (1996). Facilitation 12-step recovery from substance abuse and addiction. In F. Rotgers, D. S. Keller, & J. Morganstern (Eds.), *Treating substance abuse: Theory and technique* (pp. 13–37). New York: Guilford.

Nowinski, J., & Baker, S. (1992). *The twelve-step facilitation handbook*. New York: Lexington Books.

Noyes, R., Brunk, S. F., Avery, D. H., & Canter, A. (1975). The analgesic properties of delta-9-tetrahydrocannabinol and codeine. *Clinical Pharmacology and Therapeutics, 18,* 84–89.

Noyes, R., Brunk, S. F., Baram, D. A., & Canter, A. (1975). Analgesic effects of delta-9-tetrahydrocannabinol. *Journal of Clinical Pharmacology, 15,* 139–143.

Office of the National Drug Control Policy. (1997a). *National drug control strategy.* Washington, DC: Author.

Office of the National Drug Control Policy. (1997b). *State and local spending on drug control activities, Report from the National Survey on local and state governments.* Washington, DC: Author.

Ohlsson, A., Agurell, S., Lindgren, J-E., Gillespie, H. K., & Hollister, L. E. (1985). Pharmacokinetic studies of delta-1-tetrahydrocannabinol in man. In G. Barnett & C. N. Chiang (Eds.), *Pharmacokinetics and pharmacodynamics of psychoactive drugs* (pp. 824–840). Foster City, CA: Biomedical Publications.

Ohlsson, A., Lindgren, J-E., Wahlen, A., Agurell, S., Hollister, L. E., & Gillespie, H. K. (1980). Plasma delta-9-tetrahydrocannabinol concentrations and clinical effects after oral and intravenous administration and smoking. *Clinical Pharmacology and Therapeutics, 28,* 409–416.

Ohlsson, A., Lindgren, J-E., Wahlen, A., Agurell, S., Hollister, L. E., & Gillespie, H. K. (1982). Single-dose kinetics of deuterium-labelled delta-1-tetrahydrocannabinol in heavy and light cannabis users. *Biomedical Mass Spectrometry, 9,* 6–10.

Olsen v. DEA, 878 F.2d 1458 (D.C.C. 1989).

Olsen v. DEA, No. 96–1058, 519 U.S. 1118; 117 S. Ct. 964 U.S. LEXIS 837; 136 L. Ed. 2d 849 U.S.L.W. 3569.

O'Shaughnessy, W. B. (1842). On the preparation of the Indian hemp or gunjah (*Cannabis Indica*). The effects on the animal system in health, and their utility in the treatment of tetanus and other convulsive diseases. *Transactions of the Medical and Physical Society of Bombay, 8,* 421–461.

Ostrowski, J. (1998). Drug prohibition muddles along: How a failure of persuasion has left us with a failed policy (pp. 352–368). In J. M. Fish (Ed.), *How to legalize drugs.* Northvale, NJ: Jason Aronson.

Overholser, J. C. (1987). Clinical utility of the Socratic method. In C. Stout (Ed.), *Annals of clinical research* (pp. 1–7). Des Plaines, IL: Forest Institute.

Pacheco, M. A., Ward, S. J., & Childers, S. R. (1993). Identification of cannabinoid receptors in cultures of rat cerebellar granule cells. *Brain Research, 603,* 102–110.

Packer, H. L. (1968). *The limits of criminal sanction*. Palo Alto, CA: Stanford University Press.

Page, B. J. (1983). The amotivational syndrome hypothesis and the Costa Rica study: Relationships between methods and results. *Journal of Psychoactive Drugs, 15*, 261–267.

Page, B. J., Fletcher, J. M., & True, W. R. (1988). Psychosociocultural perspectives on chronic cannabis use: The Costa Rican follow-up. *Journal of Psychoactive Drugs, 20*, 57–65.

Parish, D. (1989). Relation of pre-employment drug testing result to employment status: A one-year follow-up. *Journal of General Internal Medicine, 4*, 44–47.

Parker, C. S., & Wrigley, F. W. (1950). Synthetic cannabis preparations in psychiatry: I. Synhexyl. *Journal of Mental Science, 96*, 276–279.

Patrick, G., Straumanis, J. J., Struve, F. A., Fitz-Gerald, M. J., Leavitt, J., & Manno, J. E. (1999). Reduced P50 auditory gating response in psychiatrically normal chronic marijuana users: A pilot study. *Biological Psychiatry, 45*, 1307–1312.

Pearl, J., Domino, E., & Rennick, P. (1973). Short-term effects of marijuana smoking on cognitive behavior in experienced male users. *Psychopharmacologia, 31*, 13–24.

Peeke, S. C., Jones, R. T., & Stone, G. C. (1976). Effects of practice on marijuana-induced changes in reaction time. *Psychopharmacology, 48*, 159–163.

Peele, S., with Brodsky, A. (1975). *Love and addiction*. New York: Taplinger.

Peele, S. (1998). *The meaning of addiction*. San Francisco: Josey Bass.

Peels, S. (1989). *The diseasing of America*. Boston: Houghton Mifflin.

Perez-Reyes, M., Timmons, M. C., Davis, K. H., & Wall, E. M. (1973). A comparison of the pharmacological activity in man of intravenously administered delta-9-tetrahydrocannabinol, cannabinol and cannabidiol. *Experientia, 29*, 1368–1369.

Perkins, H. W., Meilman, P. W., Leichliter, J. S., Cashin, J. R., & Presley, C. A. (1999). Misperceptions of the norms for the frequency of alcohol and other drug use on college campuses. *Journal of American College Health, 47*, 253–258.

Perry, D. (1977). Street drug analysis and drug use trends, Part II, 1969–1976. *PharmChem Newsletter, 6*, 4.

Petro, D. J. (1980). Marijuana as a therapeutic agent for muscle spasm or spasticity. *Psychosomatics, 21*, 81–85.

Petro, D. J. (1997a). Pharmacology and toxicity of cannabis. In M. L. Mathre (Ed.), *Cannabis in medical practice* (pp. 56–66). London: McFarland.

Petro, D. J. (1997b). Seizure disorders. In M. L. Mathre (Ed.), *Cannabis in medical practice* (pp. 112–124). London: McFarland.

Petro, D. J. (1997c). Spasticity and chronic pain. In M. L. Mathre (Ed.), *Cannabis in medical practice* (pp. 112–124). London: McFarland.

Petro, D. J., & Ellenberger, C. (1981). Treatment of human spasticity with delta-9-tetrahydrocannabinol. *Journal of Clinical Pharmacology, 21*, 413S–416S.

Pihl, R. O., & Sigal, H. (1978). Motivation levels and the marihuana high. *Journal of Abnormal Psychology, 87*, 280–285.

Plato. (1999). *Great dialogues of Plato*. (W. H. D. Rouse, Trans.). New York: Mass Market Paperback.

Plinv the Elder. (1999). *The natural history*. (H. Rachham, Trans.). Cambridge: Harvard University Press.

Polen M. R. (1993). Health care use by frequent marijuana smokers who do not smoke tobacco. *Western Journal of Medicine, 158*, 596–601.

Pond, D. A. (1948). Psychological effects in depressive patients of the marijuana homologue synhexyl. *Journal of Neurology, Neurosurgery, and Psychiatry, 11*, 279.

Pope, H. G., & Yurgelun-Todd, D. (1996). The residual cognitive effects of heavy marijuana use in college students. *Journal of the American Medical Association, 275*, 521–527.

Potency Monitoring Project (PMP). (1974–1996). Quarterly Reports. University of Mississippi: Research Institute of Pharmaceutical Sciences.

Powell, W. (1971). *The anarchist cookbook*. Secaucus, NJ: Barricade.

Powers-Lagac, V. (1991). Values clarification approaches to pre-teen substance-abuse prevention. In B. Forster and J. C. Salloway (Eds.), *Prevention and treatments of alcohol and drug abuse* (pp. 119–140). Lewiston, NY: Edwin Mellen.

Prochaska, J. O., & DiClemente, C. C. (1983). Stages and processes of self-change in smoking: Toward an integrative model of change. *Journal of Consulting and Clinical Psychology, 5*, 390–395.

Prochaska, J. O., Norcross, J. C., & DiClemente, C. C. (1994). *Changing for good*. New York: Avon Books.

Project MATCH Research Group. (1998). Matching patients with alcohol disorders to treatments: Clinical implications from project MATCH. *Journal of Mental Health UK, 7*, 589–602.

Quigley, H. A. (1996). Number of people with glaucoma worldwide. *British Journal of Ophthamology, 80*, 389–393.

Rabelais F. (1991). *Gargantua and Pantagruel*. (B. Raffel, Trans.). New York: W. W. Norton.

Raft, D., Gregg, J., Ghia, J., & Harris, L. (1977). Effects of intravenous tet-

rahydrocannabinol on experimental and surgical pain: Psychological correlates of the analgesic response. *Clinical Pharmacology and Therapeutics, 21*, 26–33.

Rainone, G. A., Deren, S., Kleinman, P. H., & Wish, E. D. (1987). Heavy marijuana users not in treatment: The continuing search for the "pure" marijuana user. *Journal of Psychoactive Drugs, 19*, 353–359.

Randall, R. C., & O'Leary, A. M. (1998). *Marijuana Rx: The patients' fight for medicinal pot*. New York: Thunder's Mouth.

Raspberry, W. (1996, July 15–21). Prevention and the power of persuasion. *Washington Post National Weekly Edition*, p. 29.

Ratcliffe, D. (1974). Summary of street drug results, 1973. *PharmChem Newsletter, 3*, 3.

Ravin v. State, 537 P.2d 494 (Alaska 1975).

Ray, R., Prabhu, G. G., Mohan, D., Nath, L. M., & Neki, J. S. (1979). Chronic cannabis use and cognitive functions. *Indian Journal of Medical Research, 69*, 996–1000.

Razdan, R. K. (1986). Structure-activity relationships in cannabinoids. *Pharmacology Review, 38*, 75–149.

Reilly, D., Didcott, P., Swift, W., & Hall, W. (1998). Long-term cannabis use: Characteristics of users in an Australian rural area. *Addiction, 93*, 837–846.

Reynolds, J. R. (1890). On the therapeutic uses and toxic effects of *Cannabis Indica*. *Lancet, 1*, 637–638.

Richter, A., & Loscher, W. (1994). (+)-WIN55,212-2 A novel cannabinoid receptor agonist, exerts antidystonic effects in mutant dystonic hamsters. *European Journal of Pharmacology, 264*, 371–377.

Riedel, W. J., Vermeeren, A., Van Boxtel, M. P. J., Vuurman, E. F. P. M., Verhey, F. R. J., Jolles, J., et al. (1998). Mechanisms of drug-induced driving impairment: A dimensional approach. *Human Psychopharmacology, 13*, S49–S63.

Robbe, H. (1998). Marijuana's impairing effects on driving are moderate when taken alone but severe when combined with alcohol. *Human Psychopharmacology: Clinical and Experimental, 13*, S70–S78.

Robinson, J. (1994). Why Germans get six weeks off and you don't. *Escape*, Winter. Available: http://www.escapemag.com/home/sub_3c.htm.

Rochford, J., Grant, I., & LaVigne, G. (1977). Medical students and drugs: Further neuropsychological and use pattern considerations. *International Journal of the Addictions, 12*, 1057–1065.

Roffman, R. A. (1982). *Marijuana as medicine*. Seattle: Madrona Publishers.

Roffman, R. A., & Barnhart, R. (1987). Assessing need for marijuana depen-

dence treatment through an anonymous telephone interview. *International Journal of the Addictions, 22,* 639–651.

Roffman, R. A., Klepsch, R., Wertz, J. S., Simpson, E. E., & Stephens, R. S. (1993). Predictors of attrition from an outpatient marijuana-dependence counseling program. *Addictive Behaviors, 18,* 553–566.

Roffman, R. A., & Stephens, R. S. (1993). Cannabis dependence. In D. L. Dunner (Ed.), *Current psychiatric therapy* (pp. 105–109). Philadelphia: Saunders.

Rogers, C. (1950). A current formulation of client-centered therapy. *Social Service Review, 24,* 442–450.

Rohrich, J., Zorntlein, S., Potsch, L., Skopp, G., & Becker, J. (2000). Effect of the shampoo Ultra Clean on drug concentrations in human hair. *International Journal of Legal Medicine, 113,* 102–106.

Rosenkrantz, H. (1976). The immune response and marijuana. In G. Nahas, W. D. Paton, and J. Idanpaan-Heikkila (Eds.), *Marihuana: Chemistry, biochemistry and cellular effects* (pp. 441–456). New York: Springer-Verlag.

Rosenthal, E., Gieringer, D., & Mikuriya, T. (1997). *Marijuana medical handbook.* Oakland: Quick American Archives.

Rosenthal, E. & Kubby, S. (1996). *Why marijuana should be legal.* New York: Thunder's Mouth.

Rosenthal, F. (1971) *The herb.* Leiden: E. J. Brill.

Rosenthal, M. S., & Kleber, H. D. (1999). Making sense of medical marijuana. *Proceedings of the Association of American Physicians, 111,* 159–165.

Roth, M. D., Arora, A. Barsky, S. H., Kleerup, E. C., Simmons, M., & Tashkin, D. P. (1998). Airway inflammation in young marijuana and tobacco smokers. *American Journal of Respiratory and Critical Care Medicine, 157,* 928–937.

Roth, M. D., Kleerup, E. C., Arora, A., Barsky, S. H., & Tashkin, D. P. (1996). Endobronchial injury in young tobacco and marijuana smokers as evaluated by visual, pathologic and molecular criteria. *American Journal of Respiratory and Critical Care Medicine, 153,* 100A.

Rosenthal, R., & Rosnow, R. L. (1991). *Essentials of behavioral research.* New York: McGraw-Hill.

Roueche, B. (1963). Alcohol in human culture. In S. P. Lucia (Ed.), *Alcohol and civilization* (pp. 167–182). New York: McGraw-Hill.

Rowell, E. A., & Rowell, R. (1939). *On the trail of marijuana, the weed of madness.* Mountain View, CA: Pacific.

Rubin, V. (Ed). (1975). *Cannabis and culture.* The Hague: Mouton.

Rubin, V., & Comitas, L. (1975). *Ganja in Jamaica, a medical anthropological study of chronic marihuana use.* The Hague: Mouton.

Rudenko, S. I. (1970). *Frozen tombs of Siberia*. Berkeley: University of California Press.

Russell, J. M., Newman, S. C., & Bland, R. C. (1994). Drug abuse and dependence. *Acta Psychiatrica Scandinavica, 376*(Suppl.), 54–62.

Russo, E. (1998). Cannabis for migraine treatment: The once and future prescription? An historical and scientific review. *Pain, 76*, 3–8.

Sallan, S. E., Zinberg, N. E., & Frei, E. (1975). Antiemetic effects of delta-9-tetrahydrocannabinol in patients receiving cancer chemotherapy. *New England Journal of Medicine, 293*, 795–797.

Sandyk, R., & Awerbuch, G. (1988). Marijuana and Tourette's syndrome. *Journal of Clinical Psychopharmacology, 8*, 444–445.

Sanudo-Pena, M. C., & Walker, J. M. (1997). Role of subthalamic nucleus in cannabinoid action in the substantia nigra of the rat. *Journal of Neurophysiology, 77*, 1635–1638.

Sanudo-Pena, M. C., & Walker, J. M. (1998). Effects of intrastitial cannabinoids on rotational behavior in rats: Interactions with the dopaminergic system. *Synapse, 30*, 221–226.

Satz, P., Fletcher, J. M., & Sutker, L. S. (1976). Neuropsychologic, intellectual and personality correlates of chronic marijuana use in native Costa Ricans. *Annals of the New York Academy of Sciences, 282*, 266–306.

Schaeffer, J., Andrysiak, T., & Ungerleider, J. T. (1981). Cognition and long-term use of Ganja (cannabis). *Science, 213*, 465–466.

Schenk, S., & Partridge, B. (1999). Cocaine-seeking produced by experimenter-administered drug injections: Dose-effect relationships in rats. *Psychopharmacology, 147*, 285–290.

Schinke, S. P., Botvin, G. J., & Orlandi, M. A. (1991). *Substance abuse in children and adolsecents: Evaluation and intervention*. Newbury Park, CA: Sage.

Schmitz, J. M., Oswald, L. M., Jacks, S. D., Rustin, T., [illegible]ades, H. M., & Grabowski, J. (1997). Relapse prevention treatment for cocaine dependence: Group vs. individual format. *Addictive Behaviors, 22*, 405–418.

Schneider, A., & Flaherty, M. P. (1991, August 11). Presumed guilty: The law's victims in the war on drugs. *The Pittsburgh Press*. Available: http://www.taima.org/wod/wod.htm.

Schneier, F. R., & Siris, S. G. (1987). A review of psychoactive substance use and abuse in schizophrenia: Patterns of drug choice. *Journal of Nervous and Mental Disease, 175*, 641–652.

Schuckit, M. A., Daeppen, J. B., Danko, G. P., Tripp, M. L., Smith, T. L., Li, T. K., et al. (1999). Clinical implications for four drugs of the DSM-IV distinction between substance dependence with and without a physiological component. *American Journal of Psychiatry, 156*, 41–49.

Schuel, H., Chang, M. C., Burkman, L. J., Picone, R. P., Makriyannis, A., Zimmerman, A. M., et al. (1999). Cannabinoid receptors in sperm. In G. G. Nahas, K. M. Sutin, D. J. Harvey, & S. Agurell (Eds.), *Marijuana and medicine* (pp. 335–346). Totowa, NJ: Humana.

Schultes, R. E., Klein, W. M., Plowman, T., & Lockwood, T. E. (1975). Cannabis: An example of taxonomic neglect. In V. Rubin (Ed.), *Cannabis and culture* (pp. 21–38). The Hague: Mouton.

Schwartz, R. H. (1984). Marijuana: A crude drug with a spectrum of unappreciated toxicity. *Pediatrics, 73,* 457.

Schwartz, R. H. (1991). Heavy marijuana use and recent memory impairment. *Psychiatric Annals, 21,* 80–82.

Schwartz, R. H., Gruenewald, P. J., Klitzner, M., & Fedio, P. (1989). Short-term memory impairment in cannabis-dependent adolescents. *American Journal of Diseases of Children, 143,* 1214–1219.

Scott, J. M. (1969). *The white poppy: A history of opium.* New York: Funk and Wagnalls.

Shahar, A., & Bino, T. (1974). In vitro effects of delta-9-tetrahydrocannabinol (THC) on bull sperm. *Biochemical Pharmacology, 23,* 1341–1342.

Sharma, S., & Moskowitz, H. (1974). Effects of two levels of attention demand on vigilance performance under marihuana. *Perceptual and Motor Skills, 38,* 967–970.

Shedler, J., & Block, J. (1990). Adolescent drug use and psychological health: A longitudinal inquiry. *American Psychologist, 45,* 612–630.

Shen, M., Piser, T. M., Seybold, V. S., & Thayer, S. A. (1996). Cannabinoid receptor agonists inhibit glutamatergic synaptic transmission in rat hippocampal cultures. *Journal of Neuroscience, 16,* 4322–4334.

Shope, J. T., Copeland, L. A., Kamp, M. E., & Lang, S. W. (1998). Twelfth grade follow-up of the effectiveness of a middle school-based substance abuse prevention program. *Journal of Drug Education, 28,* 185–197.

Sidney, S., Quesenberry, C. P., Friedman, G. D., & Tekawa, I. S. (1997). Marijuana use and cancer incidence (California, United States). *Cancer Cause and Control, 8,* 722–728.

Simon, T. R., Stacy, A. W., Sussman, S., & Dent, C. W. (1994). Sensation seeking and drug use among high risk Latino and Anglo adolescents. *Personality and Individual Differences, 17,* 665–672.

Simonds, J. F., & Kashani, J. (1980). Specific drug use and violence in delinquent boys. *American Journal of Drug and Alcohol Abuse, 7,* 305–322.

Simons, J., Correia, C. J., Carey, K. B., & Borsari, B. E. (1998). Validating a five-factor marijuana motives measure: Relations with use, problems, and alcohol motives. *Journal of Counseling Psychology, 45,* 265–273.

Slikker, W., Paule, M. G., Ali, S. F., Scallett, A. C., & Bailey, J. R. (1992). Behavioral, neurochemical, and neurohistological effects of chronic marijuana smoke exposure in the nonhuman primate. In L. Murphy & A. Bartke (Eds.), *Marijuana/cannabinoids: Neurobiology and neurophysiology* (pp. 387–423). Boca Raton, FL: CRC.

Sloman, L. (1998). *Reefer madness: A history of marijuana*. New York: St. Martin's Griffin.

Smiley, A. (1986). Marijuana: On-road and driving simulator studies. *Alcohol, Drugs, and Driving, 2*, 121–134.

Smith, C. G., Almirez, R. G., Scher, P. M., & Asch, R. H. (1984). Tolerance to the reproductive effects of delta-9-tetrahydrocannabinol. In S. Agurell, W. Dewy, and R. Willette (Eds.), *The cannabinoids: Chemical, pharmacologic, and therapeutic aspects* (pp. 471–485). New York: Academic.

Smith, D. E. (1968). The acute and chronic toxicity of marijuana. *Journal of Psychedelic Drugs, 2*, 37–48.

Smith, F. L., Fujimori, K., Lowe, J., & Welch, S. P. (1998). Characterization of delta-9-tetrahydrocannabinol and anandamide antinociception in non-arthritic and arthritic rats. *Pharmacology, Biochemistry and Behavior, 60*, 183–191.

Sobell, L. C., Sobell, M. B., Cunningham, J. A., & Toneatto, T. (1993). A life-span perspective on natural recovery (self-change) from alcohol problems. In J. S. Baer, G. A. Marlatt, & R. J. McMahon (Eds.), *Addictive behaviors across the life span* (pp. 34–68). Newbury Park, CA: Sage.

Solomon, D. (1966). *The marijuana papers*. New York: Bobbs-Merrill.

Solowij, N. (1998). *Cannabis and cognitive functioning*. Cambridge: Cambridge University Press.

Soueif, M. I. (1976). Some determinants of psychological deficits associated with chronic cannabis consumption. *Bulletin on Narcotics, 28*, 25–42.

Spunt, B., Goldstein, P., Brownstein, H., & Fendrich, M. (1994). The role of marijuana in homicide. *International Journal of the Addictions, 29*, 195–213.

Staquet, M., Gantt, C., & Machlin, D. (1978). Effect of nitrogen analog of tetrahydrocannabinol on cancer pain. *Clinical Pharmacology and Therapeutics, 23*, 397–401.

Steele, N., Gralla, R. J., & Braun, D. W. (1980). Double-blind comparison of antiemetic effects of nabilone and prochlorperazine on chemotherapy-induced emesis. *Cancer Treatment Reports, 64*, 219–224.

Stefanis, C. (1976). Biological aspects of cannabis use. In R. C. Petersen (Ed.), *The international challenge of drug abuse* (pp. 149–178). Rockville, MD: National Institute of Drug Abuse.

Stefanis, C., Ballas, C., & Madianou, D. (1975). Sociocultural and epidemio-

logical aspects of hashish use in Greece. In V. Rubin (Ed.), *Cannabis and culture* (pp. 303–326). The Hague: Mouton.

Stefano, G., Salzet, B., & Salzet, M. (1997). Identification and characterization of the leech CNS cannabinoid receptor: Coupling to nitric oxide release. *Brain Research, 753,* 219–224.

Stein, J. A., Newcomb, M. D., & Bentler, P. M. (1996). Initiation and maintenance of tobacco smoking: Changing determinants and correlates in adolescence and young adulthood. *Journal of Applied Social Psychology, 26,* 160–187.

Stella, N., Schweitzer, P., & Piomelli, D. (1997). A second endogenous cannabinoid that modulates long-term potentiation. *Nature, 388,* 773–778.

Stephens, R. S., Curtin, L., Simpson, E. E., & Roffman, R. A. (1994). Testing the abstinence violation effect construct with marijuana cessation. *Addictive Behaviors, 19,* 23–32.

Stephens, R. S., Roffman, R. A., & Simpson, E. E. (1993). Adult marijuana users seeking treatment. *Journal of Consulting and Clinical Psychology, 61,* 1100–1104.

Stephens, R. S., Roffman, R. A., & Simpson, E. E. (1994). Treating adult marijuana dependence: A test of the relapse prevention model. *Journal of Consulting and Clinical Psychology, 62,* 92–99.

Stiglick, A., & Kalant, H. (1982a). Residual effects of prolonged cannabis administration on exploration and DRL performance in rats. *Psychopharmacology, 77,* 124–128.

Stiglick, A., & Kalant, H. (1982b). Learning impairment in the radial-arm maze following prolonged cannabis treatment in rats. *Psychopharmacology, 77,* 117–23.

Stockings, G. T. (1947). A new euphoriant for depressive mental states. *British Medical Journal, 1,* 918–922.

Stoltenberg, J. (1988). *Refusing to be a man: Essays on sex and justice.* New York: Meridian.

Strohmetz, D. B., Alterman, A. I., & Walter, D. (1990). Subject selection bias in alcoholics volunteering for a treatment study. *Alcoholism: Clinical and Experimental Research, 14,* 736–738.

Strupp, H. H. (1989). Psychotherapy: Can the practitioner learn from the researcher? *American Psychologist, 44,* 717–724.

Seruve, F., Straurmanis, J. J., Patrick, G., Leavitt, J., Manno, J. E., & Manno, B. R. (1999). Topographic quantitative EEG sequelae of chronic marijuana users. *Drug and Alcohol Dependence, 56,* 167–179.

Substance Abuse and Mental Health Services Administration (SAMHSA). (1997). *National Household Survey on Drug Abuse: Population estimates, 1996.* Rockville, MD: U.S. Department of Health and Human Services.

Substance Abuse and Mental Health Services Administration (SAMHSA). (2000). *Summary of findings from the 1999 National Household Survey on Drug Abuse*. Rockville, MD: SAMHSA.

Sugiura, T., Kodaka, T., Nakane, S., Miyashita, T., Kondo, S., Suhara, Y., et al. (1999). Evidence that the cannabinoid CB1 receptor is a 2-arachidonoylglycerol receptor. Structure-activity relationship of 2-arachidonoylglycerol, ether-linked analogues, and related compounds. *Journal of Biological Chemistry, 274*, 2794–2781.

Sugiura, T., Kondo, S., Kishimoto, S., Miyashita, T., Nakan, S., Kodaka, T., et al. (2000). Evidence that 2-arachidonoylglycerol but no N-palmitoylethanolamine or anadamide is the physiological ligand for the cannabinoid CB2 receptor. Comparison of the agonistic activities of various cannabinoid receptor ligands in HL-60 cells. *Journal of Biological Chemistry, 275*, 605–612.

Sussman, S., Dent, C. W., Stacy, A. W., & Craig, S. (1998). One-year outcomes of Project Towards No Drug Abuse. *Preventive Medicine, 27*, 632–642.

Sussman, S., Simon, T. R., Dent, C. W., Steinberg, J. M., & Stacy, A. W. (1999). One-year prediction of violence perpetration among high-risk youth. *American Journal of Health Behavior, 23*, 332–344.

Sussman, S., Stacy, A. W., Dent, C. W., Simon, T. R., & Johnson, C. A. (1996). Marijuana use: Current issues and new research directions. *Journal of Drug Issues, 26*, 695–733.

Sutherland, G., Stapleton, J. A., Russell, M. A. H., Jarvis, J. J., Hajek, P., Belcher, M., et al. (1992). Randomized controlled trial of nasal nicotine spray in smoking cessation. *Lancet, 340*, 324–329.

Swan, N. (1994). A look at marijuana's harmful effects. *NIDA Notes, 9*, 17–42.

Szasz, T. S. (1961). *The myth of mental illness*. New York: Hoeber-Harper.

Szasz, T. (1992). *Our right to drugs*. New York: Praeger.

Tart, C. T. (1971). *On being stoned*. Palo Alto, CA: Science and Behavior Books.

Tashkin, D. P. (1999). Marijuana and the lung. In G. G. Nahas, K. M. Sutin, D. J. Harvey, & S. Agurell (Eds.), *Marijuana and medicine* (pp. 279–288). Totowa, NJ: Humana.

Tashkin, D. P., Coulson, A. H., Clark, V. A., Simmons, M., Bourque, L. B., Duann, S., et al. (1987). Respiratory symptoms and lung function in habitual, heavy smokers of marijuana alone, smokers of marijuana and tobacco, smokers of tobacco alone, and nonsmokers. *American Review of Respiratory Disease, 135*, 209–216.

Tashkin, D. P., Simmons, M. S., Sherrill, D. L., & Coulson, A. H. (1997). Heavy habitual marijuana smoking does not cause an accelerated decline in FEV1 with age. *American Journal of Respiratory and Critical Care Medicine, 155,* 141–148.

Taylor, B. (1854). *A journey to central Africa.* New York: Putnam.

Taylor, B. (1855). *The land of the Saracens; or pictures of Palestine, Asia Minor, Sicily and Spain.* New York: Putnam.

Taylor, S., Vardaris, R., Rawitch, A., Gammon, C., Cranston, J., & Lubetkin, A. (1976). The effects of marijuana on human physical aggression. *Aggressive Behavior, 2,* 153–161.

Terhune, K. W., Ippolito, C. A., & Crouch, D. J. (1992). *The incidence and role of drugs in fatally injured drivers* (DOT HS Report No. 808 065). Washington DC: U.S. Department of Transportation, National Highway Traffic Safety Administration.

Thistle, J., & Cook, J. P. (1972) *Seventeenth-century economic documents.* Oxford: Clarendon Press.

Thornicroft, G. (1990). Cannabis and psychosis: Is there epidemiological evidence for an association? *British Journal of Psychiatry, 157,* 25–33.

Timpone, J. G., Wright, D. J., Li, N., Egorin, M. J., Enama, M. E., Mayers, J., et al. (1997). The safety and pharmacokinetics of single-agent and combination therapy with megesterol acetate and dronabinol for the treatment of HIV wasting syndrome. *AIDS Research and Human Retroviruses, 13,* 305–315.

Tinklenberg, J. R., Murphy, P., Murphy, P. L., & Pfefferbaum, A. (1981). Drugs and criminal assaults by adolescents: A replication study. *Journal of Psychoactive Drugs, 13,* 277–287.

Trent, L. K. (1998). Evaluation of a four- versus six-week length of stay in the Navy's alcohol treatment program. *Journal of Studies on Alcohol, 59,* 270–279.

Truong, X. T., & Hanigan, W. C. (1986). Effect of delta-9-THC on EMG measurements in human spasticity. *Clinical Pharmacology and Therapeutics, 39,* 232.

Tucker, J. A., Donovan, D. M., & Marlatt, G. A. (Eds.). (1999). *Changing addictive behavior: Bridging clinical and public health strategies.* New York: Guilford.

Tunving, K., Thulin, O., Risberg, J., & Warkentin, S. (1986). Regional cerebral blood flow in long-term heavy cannabis use. *Psychiatry Research 17,* 15–21.

Turner, C. E., & ElSohly, M. A. (1981). Biological activity of cannabichromene, its homologs and isomers. *Journal of Clinical Pharmacology, 21,* 283S–291S.

Turner, C. E., & Hadley, K. W. (1974). Chemical analysis of cannabis sativa of distinct origin. *Archivos de Investigacion Medica, 5*, 141–150.

Tusser, T. (1580). *Five hundred points of good husbandrie*. London: Henrie Denham.

Tyson, L. B., Gr[illegible]a, R. J., Clark, R. A., Kris, M. G., Bordin, L. A., & Bosl, G. J. (1985). Phase 1 trial of levonantradol in chemotherapy-induced emesis. *American Journal of Clinical Oncology, 8*, 528–532.

Uestuen, B., Compton, W., Mager, D., Babor, T., Baiyewu, O., Chatterji, S., et al. (1997). WHO study on the reliability and validity of the alcohol and drug use disorder instruments: Overview of methods and results. *Drug and Alcohol Dependence, 47*, 161–169.

Urquhart, D. (1855). *The pillars of Hercules; or a narrative of travels in Spain and Morocco in 1848*. New York: Harper.

Vachon, L., Sulkowski, A., & Rich, E. (1974). Marihuana effects on learning, attention and time estimation. *Psychopharmacologia, 39*, 1–11.

Vaillant, G. E. (1983). *The natural history of alcoholism*. Cambridge: Harvard University Press.

Van Tulder, M. W., Cherkin, D. C., Berman, B., Lao, L., & Koes, B. W. (1999). The effectiveness of acupuncture in the management of acute and chronic low back pain. *Spine, 24*, 1113–1123.

Van der Merwe, N. J. (1975). Cannabis smoking in 13th–14th century Ethiopia. In V. Rubin (Ed.), *Cannabis and culture* (pp. 77–80). The Hague: Mouton.

Vinciguerra, V., Moore, T., & Brennan, E. (1988). Inhalation marijuana as an antiemetic for cancer chemotherapy. *New York State Journal of Medicine, 88*, 525–527.

Volicer, L., Stelly, M., Morris, J., McLaughlin, J., & Volicer, B. J. (1997). Effects of dronabinol on anorexia and disturbed behavior in patients with Alzheimer's disease. *International Journal of Geriatric Psychiatry, 12*, 913–919.

Volkow, N. D., Gillespie, H., Mullani, N., Tancredi, L., Grant, C., Valentine, A., et al. (1996). Brain glucose-metabolism in chronic marijuana users at baseline and during marijuana intoxication. *Psychiatry Research: Neuroimaging, 67*, 29–38.

Volpicelli, J. R., Alterman, A. I., Hayashida, M., & O'Brien, C. P. (1992). Naltrexone in the treatment of alcohol dependence. *Archives of General Psychiatry, 49*, 876–880.

Von Bibra, E. (1855/1994). *The narcotic luxury: Hemp and humans*. Lohrbach: Werner Piper's Medien Xperimente.

Wall, M. E., Sadler, B. M., Brine, D., Harold, T., & Perez-Reyes, M. (1983). Metabolism, disposition, and kinetics of delta-9-tetrahydrocannabinol

in men and women. *Clinical Pharmacology and Therapeutics, 34,* 352–363.

Wallace, J. (1990). Controlled drinking, treatment effectiveness, and the disease model of addiction: A commentary on the ideological wishes of Stanton Peele. *Journal of Psychoactive Drugs, 22,* 281–284.

Wallace, J. (1996). Theory of 12-step oriented treatment. In F. Rotgers, D. S. Keller, & J. Morganstern (Eds.), *Treating substance abuse: Theory and technique* (pp. 13–37). New York: Guilford.

Wallnofer, H., & Von Rottauscher, A. (1965). *Chinese folk medicine and acupuncture.* New York: Bell.

Wampold, B. E., Mondin, G. W., Moody, M., Stich, F., Benson, K., & Ahn, H. (1997). A meta-analysis of outcome studies comparing bona fide therapies: Empirically, "all must have prizes." *Psychological Bulletin, 122,* 203–215.

Weckowicz, T. E., Collier, G., & Spreng, L. (1977). Field dependence, cognitive functions, personality traits, and social values in heavy cannabis users and nonuser controls. *Psychological Reports, 41,* 291–302.

Weisheit, R. A. (1992). *Domestic marijuana: A neglected industry.* New York: Greenwood.

Weller, R. A., & Halikas, J. A. (1980). Objective criteria for the diagnosis of marijuana abuse. *Journal of Nervous and Mental Disease, 176,* 719–725.

Weller, R. A., & Halikas, J. A. (1982). Change in effects from marijuana: A five- to six-year follow-up. *Journal of Clinical Psychiatry, 43,* 362–365.

Weller, R. A., & Halikas, J. A. (1984). Marijuana use and sexual behavior. *Journal of Sex Research, 20,* 186–193.

Welte, J. W., & Barnes, G. M. (1985). Alcohol: The gateway to other drug use among secondary-school students. *Journal of Youth and Adolescence, 14,* 487–498.

Werner, J. (1964). Frankish royal tombs in the cathedrals of Cologne and Saint Denis. *Antiquity, 38,* 201–216.

West, M. (1997). The use of certain cannabis derivatives (Canasol) in glaucoma. In M. L. Mathre (Ed.), *Cannabis in medical practice* (pp. 103–111). London: McFarland.

Wetzel, C. D., Janowsky, D. S., & Clopton, P. L. (1982). Remote memory during marijuana intoxication. *Psychopharmacology, 76,* 278–281.

White, H. R., & Hansell, S. (1998). Acute and long-term effects of drug use on aggression from adolescence into adulthood. *Journal of Drug Issues, 28,* 837–858.

White, H. R., Loeber, R., Stouthamer-Loeber, M., & Farrington, D. (1999). Developmental associations between substance use and violence. *Development and Psychopathology, 11,* 785–803.

Whittier, J. G. (1854/1904). *The Compleat Poetical Works of John Greenleaf Whittier*. Boston: Houghton Mifflin.

Wig, N. N., & Varma, V. K. (1977). Patterns of long-term heavy cannabis use in north India and its effects on cognitive functions: A preliminary report. *Drug and Alcohol Dependence, 2,* 211–219.

Wiley, J. L. (1999). Cannabis: Discrimination of "internal bliss"? *Pharmacology, Biochemistry and Behavior, 64,* 257–260.

Williams, A. F., Peat, M. A., & Crouch, D. J. (1985). Drugs in fatally injured young male drivers. *Public Health Reports, 100,* 19–25.

Williams, C. M., & Kirkham, T. C. (1999). Anandamide induces overeating: Mediation by central cannabinoid (CB1) receptors. *Psychopharmacology, 143,* 315–317.

Wilson, W., Mathew, R., Turkington, T., Hawk, T., Coleman, R. E., & Provenzale, J. (2000). Brain morphological changes and early marijuana use: A magnetic resonance and positron emission tomography study. *Journal of Addictive Diseases, 19,* [illegible] 22.

Wimbush, J. C., & Dalton, D. R. (1997). Base rate of employee theft: Convergence of multiple methods. *Journal of Applied Psychology, 82,* 756–763.

Wirtshafter, D. (1997). Nutritional value of hemp seed and hemp seed oil. In M. L. Mathre (Ed.), *Cannabis in medical practice* (pp. 181–191). London: McFarland.

Witter, F. R., & Niebyl, J. R. (1990). Marijuana use in pregnancy and pregnancy outcome. *American Journal of Perinatology, 7,* 36–38.

Wood, G. B., & Bache, F. (1868). *The dispensatory of the United States of America* (18th ed.) (pp. 379–382). Philadelpia: Lippincott.

Woody, G. E., & MacFadden, W. (1995). Cannabis related disorders. In H. I. Kaplan & B. J. Sadock (Eds.), *Comprehensive textbook of psychiatry* (6th ed.) (pp. 810–817). Baltimore: Williams & Wilkins.

Yonkers, K. A., Warshaw, M. G., Massion, A. O., & Keller, M. B. (1996). Phenomenology and course of generalised anxiety disorder. *British Journal of Psychiatry, 168,* 308–313.

Yoshida, H., Usami, N., Ohishi, Y., Watanabe, K., Yamamoto, I., & Yoshimura, H. (1995). Synthesis and pharmacological effects in mice of halogenated cannabinol derivatives. *Chemical and Pharmaceutical Bulletin, 42,* 335–337.

Yuille, J. C., Tollestrup, P. A., Marxsen, D., Porter, S., & Herve-Hugues, F. M. (1998). An exploration on the effects of marijuana on eyewitness memory. *International Journal of Law & Psychiatry, 21,* 117–128.

Zacny, J. P., & Chait, L. D. (1989). Breathhold duration and response to marijuana smoke. *Pharmacology, Biochemistry and Behavior, 33,* 481–484.

Zacny, J. P., & Chait, L. D. (1991). Response to marijuana as a function of potency and breathhold duration. *Psychopharmacology, 103,* 223–226.

Zeese, K. (1997). Legal issues related to the medical use of marijuana. In M. L. Mathre (Ed.), *Cannabis in medical practice* (pp. 20–32). London: McFarland.

Zias, J., Stark, H., Seligman, J., Levy, R., Werker, E., Breur, A., et al. (1993). Early medical use of cannabis. *Nature, 363,* 215.

Zimmer, L., & Morgan, J. P. (1997). *Marijuana myths marijuana facts.* New York: The Lindesmith Center.

Zimmerman, A. M., Zimmerman, S., & Raj, A. Y. (1979). Effects of cannabinoids on spermatogenesis in mice. In G. G. Nahas and W. D. M. Paton (Eds.), *Marijuana: Biological effects, analysis, metabolism, cellular responses, reproduction, and brain* (pp. 407–418). New York: Pergamon.

Zinberg, N. E. (1984). *Drug set and setting: The basis for controlled intoxicant use.* New Haven: Yale University Press.

Zuardi, A. W., Cosme, R. A., Graeff, F. G., & Guimaraes, F. S. (1993). Effects of ipsapirone and cannabidiol on human experimental anxiety. *Journal of Psychopharmacology, 7,* 82–88.

Zuardi, A. W. & Guimaraes, F. S. (1997). Cannabidiol as an anxiolytic and antipsychotic. In M. L. Mathre (Ed.), *Cannabis in medical practice* (pp. 133–141). London: McFarland.

Zwerling, C., Ryan, J., & Orav, E. J. (1990). The efficacy of preemployment drug screening for marijuana and cocaine in predicting employment outcomes. *Journal of the American Medical Association, 264,* 2639–2643.

E

NBER WORKING PAPER SERIES

MARIJUANA AND CRIME: IS THERE A CONNECTION BEYOND PROHIBITION?

Rosalie Liccardo Pacula
Beau Kilmer

Working Paper 10046
http://www.nber.org/papers/w10046

NATIONAL BUREAU OF ECONOMIC RESEARCH
1050 Massachusetts Avenue
Cambridge, MA 02138
October 2003

Research presented in this paper was supported by a grant from the National Institute on Drug Abuse (R01DA12724) to RAND. The opinions expressed in this paper are those of the authors and do not reflect the opinions of the author's institutions or funding agencies. Contact person: Rosalie Liccardo Pacula, RAND, 1700 Main St., P.O. Box 2138, Santa Monica, CA 90407-2138. Email: Pacula@rand.org. The views expressed herein are those of the authors and not necessarily those of the National Bureau of Economic Research.

©2003 by Rosalie Liccardo Pacula and Beau Kilmer. All rights reserved. Short sections of text, not to exceed two paragraphs, may be quoted without explicit permission provided that full credit, including © notice, is given to the source.

Marijuana and Crime: Is There a Connection Beyond Prohibition?
Rosalie Liccardo Pacula and Beau Kilmer
NBER Working Paper No. 10046
October 2003
JEL No. K14, K42, I18

ABSTRACT

We examine the relationship between marijuana use and non-drug related crime using data on arrests from the Arrestee Drug Abuse Monitoring (ADAM) Program and Uniform Crime Reports. There is a positive association between self-reported use at the time of the offence and non-drug related violent, property and income-producing crime even after accounting for other substance use in the ADAM data. Reduced form equations using both data sets only provide evidence supporting a causal mechanism for property and income-producing crime. In the case of violent crime, we find a statistically significant association with arrests but not reported crime, suggesting that marijuana use may just influence the likelihood of getting caught committing these crimes.

Rosalie Liccardo Pacula
RAND
1700 Main Street
P.O. Box 2138
Santa Monica, CA 90407-2138
and NBER
pacula@rand.org

Beau Kilmer
Kennedy School of Government
Harvard University
John F. Kennedy Street
Cambridge, MA 02138
beau_kilmer@kgsphd.harvard.edu

I. Introduction

An extensive literature exists examining the relationship between substance abuse and crime, the focus of which has typically centered on cocaine, heroin, and alcohol. Few studies specifically examine the relationship between marijuana and crime despite consistent findings that marijuana is the most commonly identified drug among arrestees. Reports from the United States, England, and Australia, for example, all show that approximately 60% of arrestees test positive for marijuana use and that marijuana is the drug whose metabolites are most frequently found in arrestees' urine (Taylor and Bennett, 1999; Makkai et al., 2000).

There are two good reasons why inferences should not be made about the relationship between marijuana and crime on the basis of urine tests of arrestees. First, very few arrestees who test positive for marijuana have only used marijuana. Most of those who test positive for marijuana also use other illicit drugs or alcohol (NIJ, 2000)[1]. The use of these other substances may be what motivated the criminal behavior rather than marijuana. Second, unlike other illegal substances, a positive urine sample for THC only indicates use in the past month; it does not indicate that marijuana was used immediately prior to the offence taking place. Hence, a positive urine test in the case of marijuana cannot be interpreted as evidence that the crime was committed under the influence of marijuana.

Despite its frequent use among arrestee populations, marijuana has generally been shown to inhibit aggressive behavior and violence in humans and thus it is believed not to be a major contributor to crime (Miczek et al., 1994; White and Gorman, 2000). However, in their review of the literature on the topic, the National Research Council concluded that the long-term use of marijuana may alter the nervous system in ways that do promote violence (National Research

[1] Data from the 1999 ADAM sample suggests this figure could exceed 70%. Of the 16,684 arrestees who tested positive for marijuana, 7,748 (46.4%) tested also tested positive for another illicit drug and another 4,436 (26.6%) reported use of alcohol in the previous 72 hours.

E

NBER WORKING PAPER SERIES

MARIJUANA AND CRIME: IS THERE A CONNECTION BEYOND PROHIBITION?

Rosalie Liccardo Pacula
Beau Kilmer

Working Paper 10046
http://www.nber.org/papers/w10046

NATIONAL BUREAU OF ECONOMIC RESEARCH
1050 Massachusetts Avenue
Cambridge, MA 02138
October 2003

Research presented in this paper was supported by a grant from the National Institute on Drug Abuse (R01DA12724) to RAND. The opinions expressed in this paper are those of the authors and do not reflect the opinions of the author's institutions or funding agencies. Contact person: Rosalie Liccardo Pacula, RAND, 1700 Main St., P.O. Box 2138, Santa Monica, CA 90407-2138. Email: Pacula@rand.org. The views expressed herein are those of the authors and not necessarily those of the National Bureau of Economic Research.

©2003 by Rosalie Liccardo Pacula and Beau Kilmer. All rights reserved. Short sections of text, not to exceed two paragraphs, may be quoted without explicit permission provided that full credit, including © notice, is given to the source.

Marijuana and Crime: Is There a Connection Beyond Prohibition?
Rosalie Liccardo Pacula and Beau Kilmer
NBER Working Paper No. 10046
October 2003
JEL No. K14, K42, I18

ABSTRACT

We examine the relationship between marijuana use and non-drug related crime using data on arrests from the Arrestee Drug Abuse Monitoring (ADAM) Program and Uniform Crime Reports. There is a positive association between self-reported use at the time of the offence and non-drug related violent, property and income-producing crime even after accounting for other substance use in the ADAM data. Reduced form equations using both data sets only provide evidence supporting a causal mechanism for property and income-producing crime. In the case of violent crime, we find a statistically significant association with arrests but not reported crime, suggesting that marijuana use may just influence the likelihood of getting caught committing these crimes.

Rosalie Liccardo Pacula
RAND
1700 Main Street
P.O. Box 2138
Santa Monica, CA 90407-2138
and NBER
pacula@rand.org

Beau Kilmer
Kennedy School of Government
Harvard University
John F. Kennedy Street
Cambridge, MA 02138
beau_kilmer@kgsphd.harvard.edu

I. Introduction

An extensive literature exists examining the relationship between substance abuse and crime, the focus of which has typically centered on cocaine, heroin, and alcohol. Few studies specifically examine the relationship between marijuana and crime despite consistent findings that marijuana is the most commonly identified drug among arrestees. Reports from the United States, England, and Australia, for example, all show that approximately 60% of arrestees test positive for marijuana use and that marijuana is the drug whose metabolites are most frequently found in arrestees' urine (Taylor and Bennett, 1999; Makkai et al., 2000).

There are two good reasons why inferences should not be made about the relationship between marijuana and crime on the basis of urine tests of arrestees. First, very few arrestees who test positive for marijuana have only used marijuana. Most of those who test positive for marijuana also use other illicit drugs or alcohol (NIJ, 2000)[1]. The use of these other substances may be what motivated the criminal behavior rather than marijuana. Second, unlike other illegal substances, a positive urine sample for THC only indicates use in the past month; it does not indicate that marijuana was used immediately prior to the offence taking place. Hence, a positive urine test in the case of marijuana cannot be interpreted as evidence that the crime was committed under the influence of marijuana.

Despite its frequent use among arrestee populations, marijuana has generally been shown to inhibit aggressive behavior and violence in humans and thus it is believed not to be a major contributor to crime (Miczek et al., 1994; White and Gorman, 2000). However, in their review of the literature on the topic, the National Research Council concluded that the long-term use of marijuana may alter the nervous system in ways that do promote violence (National Research

[1] Data from the 1999 ADAM sample suggests this figure could exceed 70%. Of the 16,684 arrestees who tested positive for marijuana, 7,748 (46.4%) tested also tested positive for another illicit drug and another 4,436 (26.6%) reported use of alcohol in the previous 72 hours.

Council, 1993). Further, a consistent link between frequent cannabis use and violent crime and property damage has been identified among juveniles (Dembo et al., 1991; Salmelainen, 1995; Baker, 1998). Thus the issue of whether marijuana use *causes* crime, even if limited to a small segment of the population, remains in question.

The assumption that drugs and crime are causally related is a major reason for prohibiting the use of illicit drugs in many developed countries. If marijuana use is not the *cause* of crime, but merely *defined* as a crime, then one must consider all the criminal justice resources dedicated to arresting, processing, and adjudicating marijuana offenders as a cost of prohibition when weighing the cost and benefits of our current marijuana policy.

In this paper, we begin to investigate the causal association between marijuana use and crime. Using individual-level data from the Arrestee Drug Abuse Monitoring (ADAM) Program, we examine the relationship between marijuana use and the probability of getting arrested for a violent, property and income-producing and crime while controlling for concurrent use of alcohol and cocaine. Models consider the sensitivity of results when marijuana use is measured by a positive urine test, self-reported use in the past 3 days, and self-reported use at time of the offence. We find that marijuana use is positively associated with the likelihood of being arrested for a property and income-producing crime, with reduced form models supporting the conclusion that at least some of the association is causal in nature. This finding is further supported by additional analyses of the number of property and income-producing offence arrests measured in the Uniform Crime Reports (UCR). Models estimating the likelihood of being arrested for a violent crime using reduced form models are mixed, with no statistical association found in the ADAM sample and a positive association between marijuana use and violent crime arrests in the UCR sample.

The rest of the paper is organized as follows. In the next section we provide some background on the hypothesized relationship between marijuana and crime and the findings to date. In section III we present the theoretical framework. In Section IV, we discuss the empirical model and the primary data sets used to estimate our models. In Section V we present our results and in Section VI we offer some discussion and conclusions.

II. Background and Significance

Surprisingly few studies have explicitly examined the relationship between cannabis use and crime. Those studies that have been done generally examine the association within the context of four alternative hypotheses based on Goldstein's (1985) tripartite framework, where the association between marijuana use and crime is explained by either psychopharmacological factors, economic-compulsive behavior, systemic violence or common factors.

The psychopharmacological model hypothesizes that drug users engage in violent and/or non-violent crime because of the acute psychoactive effects of the substance (Goldstein, 1985). There is very little support for this model in the case of marijuana, except for adolescents. Laboratory studies generally show that marijuana, unlike alcohol, temporarily inhibits aggression and violence (Mizcek et al, 1994; White and Gorman, 2000), raising doubt that any association identified in the data is causal in nature. Still, there is some evidence showing a correlation between chronic marijuana use and increased risk of violent behavior (White and Hansell, 1998; Kaplan and Damphousse, 1995).

Although cannabis use may temporarily inhibit aggression in the general population, it is possible that cannabis use increases aggression in some individuals. In controlled laboratory studies, for example, the relationship between alcohol use and aggression is influenced by

subject characteristics, such as gender, aggressive tendencies and cognitive abilities, as well as experimental conditions, such as whether the subject was provoked (Bushman, 1997). Indeed, Bushman's (1990) meta-analysis found more aggression among marijuana smokers than placebo controls in laboratory experiments, although he notes that the placebo controls showed significantly less aggression than nondrug controls highlighting the importance of individual heterogeneity in general tendencies toward aggression. Nonetheless, it may be the case, as suggested by the US National Research Council (1993), that prolonged use of cannabis promotes violent or aggressive behavior because of changes in the nervous system.

There is far more convincing evidence of a link between frequent cannabis use and violent crime and nonviolent delinquency among juveniles (Salmelainen, 1995; Fergusson and Horwood, 1997; Baker, 1998). In a study of 10,441 secondary students in New South Wales, Australia, students who were frequent cannabis users were two times more likely to participate in assault and malicious damage of property than students who did not use cannabis. The relationship persisted after adjusting for differences in developmental characteristics, demographics and other substance use (Baker, 1998).[2] In a longitudinal analysis of a New Zealand birth cohort, Fergusson and Horwood (1997) considered four measures of delinquency in their analysis of the consequences of adolescent marijuana use: three or more violent offences, three or more property offences, arrested by police, and convicted of an offence in court. There was a dose-response relationship between each of these outcomes and frequency of marijuana use by age 16. This persisted after adjustment for covariates, suggesting that it was not wholly explained by the characteristics of adolescents who become regular marijuana users by age 16. It

[2] The developmental factors controlled for in the model included parental supervision, family structure, school performance and truancy. The demographic factors accounted for were gender and Aboriginality. Other substance use indicators accounted for were infrequent and frequent use of alcohol and any use of opiates, stimulants, and steroids.

also persisted after adjustment for drug use and criminal behaviour in the user's peer group, indicating that it was not explained by affiliating with delinquent and drug using peers.

Economic crime is that which is motivated by the need to generate income to fund one's own drug use (Goldstein, 1985). By comparison with other illicit drugs, marijuana consumption does not typically produce compulsive patterns of criminal behavior among users and it is not as expensive as other illicit drugs. However, studies suggest that there may be some economically motivated crime at least among youth. In studies of juvenile offenders in the United States and Australia, young offenders who reported frequent use of marijuana reported greater involvement in theft than non-users (Dembo, et al. 1991; Salmelainen 1995; Stevenson and Forsythe 1998). In addition, among juvenile offenders higher marijuana involvement was significantly correlated with higher rates of offending for specific property crimes (Salmelainen, 1995; Stevenson and Forsythe, 1998). The relationship was supported by B. .er's (1998) study of secondary students from New South Wales, in which he found that frequent marijuana users were almost five times more likely to report participation in acquisitive property crime than non-users, even after controlling for individual characteristics, family background, and other substance use (Baker, 1998).[3] What is perhaps most surprising about this study is the fact that frequent marijuana use was found to have a larger effect on participation in property crime than frequent alcohol use or any other illicit drug use.

Systemic violence is that which arises when violence is used to enforce contracts or to resolve "turf wars" in illicit drug markets. Such violence is motivated by the enormous profits that are generated by illicit drug sales and by the absence of legitimate law enforcement to resolve disputes. For a number of reasons it is doubtful that the experience of violence in heroin

[3] The author of the report defines acquisitive property crime as motor vehicle theft, breaking and entering, receiving or selling stolen goods, and shoplifting goods worth $20 or more.

and cocaine markets is applicable to marijuana markets. There is some evidence that violence has been generated by marijuana markets in a few places in the United States, but this has been extremely rare and very localized (Goldstein et al., 1989; ONDCP, 2001). For example, Goldstein et al (1989) found in their assessment of 414 drug-related homicides in New York City that only 6 were related to marijuana. Ethnographic work examining the drug market in New York City showed that although marijuana dealers dominated outdoor parks and streets during the early 1980s, the marijuana market was not associated with the violence seen in the crack market. In the United States today, the majority of marijuana sales are done in private so dealers do not see even see their competitors (ONDCP 2001, Taylor et al. 2001). Even the majority of arrestees report purchasing marijuana indoors (median was 71%). The proportion of arrestees who made outdoor purchases of marijuana exceeded 50 percent in only 4 sites (Taylor et al., 2001).

Marijuana use and criminal behavior may also be associated because both behaviors are driven by a common cause, such as personal characteristics of individuals that motivate them to become involved in both behaviors (Hirschi and Gottfredson, 1988; Fagan, 1990; White 1990). Among the third factors that have been hypothesized to generate the association are: gang involvement (Fagan, 1990), peer effects (Gorman and White, 1995), general problem behavior during adolescence (Jessor and Jessor, 1977), and common environments or situational causes. (Skogan, 1990; Fagan, 1993). There is evidence that substance use and delinquent behavior share many common causes or predictors. For example, many of the childhood risk factors for violence, such as hyperactivity, impulsiveness, risk taking, early school failure, peer rejection, and inability to delay gratification, have been identified as risk factors for teenage drug use and adult drug problems (Hawkins, Catalano, and Miller, 1992. Brook, Whiteman and Cohen, 1995).

Although the common factor model is the model most commonly believed for marijuana there is evidence supporting a causal mechanism and thus the question regarding a causal link even if limited to specific populations remains unanswered. In this paper we explore the relationship between marijuana use and criminal activity using data from two different data sources on crime, the Arrestee Drug Abuse Monitoring program (ADAM) and Uniform Crime Reports (UCR). Reduced form models are used to test the appropriateness of conclusions regarding the association between an individual's marijuana use and the likelihood of getting arrested for a violent, property, and income-producing crime.

III. The Theoretical Framework

Following the theoretical work of Ehrlich (1973), we assume that criminals are risk-neutral expected utility maximizers and make decisions about whether to commit specific crimes based on whether the expected reward (benefit) is greater than the expected cost. The use of mind-altering substances, including marijuana, may influence one's perceptions of the expected payoff or expected cost of engaging in specific crimes or it may reduce one's natural inhibitions for engaging in criminal activity. The direct mechanism through which marijuana and other substances influences the individual's decision to commit an offense is not of immediate interest in this paper because the data are not sufficient to empirically test alternative causal mechanisms. We therefore focus on a reduced-form equation of the number of offences that individual i living in jurisdiction j chooses to become involved in at time t (O_{ijt}), which can be specified as follows:

(1) $O_{ijt} = O(E_{jt}, Y_{it}, Z_{jt}, A_{it}, MJ_{it}, OD_{it})$.

Here E_{jt} is a vector of variables representing the enforcement risk (expected cost) of committing those offences in jurisdiction j at time t, Y_{it} represents a vector of individual-level variables

influencing the marginal benefit of committing the offence at time t, and Z_{jt} represents other community economic factors that may influence either the marginal benefit or marginal cost of committing an offence in jurisdiction j at time t. The variables A_{it}, M_{it}, and OD_{it}, represent the amount of alcohol, marijuana and other drugs, respectively, consumed by individual i during time t. Reduced form demand functions for each of these substances are derived from constrained maximization of the individual's expected utility function, and can be represented as follows:

(2) $A_{it} = A\ (P_{Ajt}, P_{Mjt}, P_{ODjt}, Y_{it})$

(3) $MJ_{it} = MJ\ (P_{Ajt}, P_{Mjt}, P_{ODjt}, Y_{it})$

(4) $OD_{it} = OD\ (P_{Ajt}, P_{Mjt}, P_{ODjt}, Y_{it})$

where P_A, P_M, and P_{OD} represent the price of alcohol, marijuana and other illicit drugs, respectively. Substituting equations (2) – (4) into equation (1) yields the following reduced-form equation:

(5) $O_{ijt} = O(E_{jt}, Y_{it}, Z_{jt}, P_{Ajt}, P_{Mjt}, P_{ODjt})$

If marijuana use does influence one's willingness to engage in crime, either by reducing one's natural inhibitions or by changing one's perceptions of the expected costs or benefits, then we would expect that an increase in the price of marijuana, which reduces the consumption of marijuana, would be negatively associated with the number of offences committed, or $\partial O_{ijt}/\partial P_{Mjt} < 0$.[4] It is quite plausible in light of physiological properties of marijuana, however, that marijuana use only influences one's willingness to engage in certain types of crimes. Thus, in our empirical specification of the model, we separately examine the relationship between this substance and violent, property and income-producing crimes.

[4] As the literature review above shows, there is basically no evidence that marijuana markets themselves generate violence or crime, unlike the market for cocaine. Hence, we are implicitly assuming here that higher marijuana prices do not have a direct association with criminal behavior due to the need to protect territory or market share.

IV. The Data and Empirical Models

Two different data sets are used to explore the relationship between marijuana use and crime. The first source of data is the Arrestee Drug Abuse Monitoring (ADAM) Program (formerly Drug Use Forecasting System). Since 1987, the U.S. Department of Justice has interviewed arrestees in urban booking facilities about their drug use patterns as well as tested them for drug use. The purpose of the study is to provide local law enforcement and other local officials with reliable estimates of the prevalence of drug abuse and related problems in the population of arrestees in their jurisdiction. Sites were originally selected through applications from those jurisdictions interested in participating, but the number of sites increased substantially during the 1990s from 23 in 1996 to 35 in 1998 (See Appendix for complete list of sites).

Prior to 1998 the data generally reflect convenience samples, as they were collected from recent arrestees in the largest booking facility in the county. Since 1998, the sampling methodology has been modified so that the sampling frame now represents all arrestees within a county, not just those booked at the central booking facility. Data collection takes place four times a year (once each calendar quarter) at each site. Arrestees are approached within 48 hours of their arrest and asked to participate in the study. Although participation in ADAM is strictly voluntary, response rates hover around 80 to 90 percent (U.S. Department of Justice, 2000).

Although the data are non-representative of the overall arrestee population, they are the only data source where information on the offender's substance use near the time of the arrest is available. Self-reported use of various legal and illicit substances in the past year, past month and past 72 hours are obtained and validated through analysis of urine specimen. The urinanalyses can identify any of ten substances (including the NIDA-5: cocaine, opiates, marijuana, methamphetamine and PCP), but the results should be interpreted with caution since

some drugs are detectable in the body for up to a month after consumption. Between 1995 and 1999, the survey also included questions pertaining to whether the offender was "under the influence" of specific drugs at the time of the offence. Given that marijuana is one of the drugs that remains detectable in the body for longer periods of time, knowledge of use of marijuana at the time of the offence is extremely important for validating a causal connection. Hence, we use information from the 1996 through 1999 ADAM data for our current analysis. Data from 1995 were not included because of a change in the method for evaluating a positive urine test during that year that resulted in an increase in the number of marijuana detections (NIJ, 1999).

ADAM reports up to three charges for each arrestee and classifies these into more than fifty offenses, ranging from murder to unlicensed vending. We aggregate the most serious offence into three broad categories: violent crime, property crime, and income producing crime.[5] Violent crime includes murder, forcible rape, robbery and aggravated assault. Property crimes include burglary, larceny-theft, motor vehicle theft and arson. Income-producing crimes are defined as robbery, burglary, motor vehicle theft, forgery, embezzlement, stolen goods, and prostitution. For each type of crime in the ADAM data, we estimate the following regression model:

(6) $\Pr(O_{cijt} = 1) =$

$$\Phi(\alpha_0 + \alpha_1 P_{Aji} + \alpha_2 P_{Mji} + \alpha_3 P_{ODji} + \alpha_4 E_{ji} + \alpha_5 Y_{it} + \alpha_6 Z_{jt} + \alpha_7 W_j + \alpha_8 Year + \varepsilon_{it}).$$

where c = violent crime, property crime and income producing crime, Φ is the cumulative distribution function of the univariate normal distribution, W_j is a series of dummy variable for each ADAM site that pick up time invariant unobservable factors that are unique to each

[5] We group people by their most serious arrest charge for two main reasons. First, most arrestees are only charged with one offense. Second, the crime data from the FBI only report the arrest for the most serious charge (the hierarchy rule) and since this analysis utilizes both of these data sets it is useful to make them as consistent as possible.

location, ε_{it} is an individual random error term which is assumed to be normally distributed, and the other variables are as specified previously.[6] Our measure of local enforcement (E_{jt}) is the number of full time sworn officers per capita, which was obtained from estimates reported in the Justice Expenditure and Employment Abstracts. These data are extracted from the Census Bureau's Annual Government Finance Survey and Annual Survey of Public Employment and includes the same jurisdictions covered by ADAM sites.[7]

Individual-level characteristics (Y_{it}) that are collected in the ADAM survey include age, gender, race, ethnicity, marital status, educational attainment, and income. In the case of income, two separate questions are included about legal and illegal income earned in the previous month.[8] Other community factors (Z_{jt}) also controlled for in these models include real per capita income and the local unemployment rate, obtained from the Census Bureau and Bureau of Labor Statistics, respectively.

Information on the monetary price of marijuana comes from various publications of the Illegal Drug Price/Purity Report, (IDPPR) published by the DEA Office of Intelligence or Intelligence Division of the U.S. Department of Justice. Although other sources of marijuana price data are available, the IDPPR published data represents the only source we are aware of in which it is possible to distinguish high and low quality marijuana consistently over time for the same locations. The IDPPR report the minimum and maximum retail (ounce) and wholesale (pound) price of commercial-grade and sinsemilla marijuana in 19 cities located in 16 states. These 19 cities represent main branch offices for the DEA. The price and quality information

---

[6] Year dummy variables were also explored but the dummies indicated a linear trend. Hence the linear trend was employed in all of the models.

[7] We also considered a measure of the relative crime per officers by constructing a measure of the total crime per number of full-time sworn officers. Results are qualitatively similar to those presented here.

[8] Individuals with missing information for either of these income measures, approximately 20% of our ADAM sample, were dropped from the current analysis.

are obtained for purchases made by undercover police officers and DEA agents that are sent to a laboratory for analysis. For the purposes of this analysis, we focus on the quarterly prices for commercial marijuana sold at the retail level. Predicted quarterly prices are obtained using data from 1982 through 2001 to predict the natural logarithm of real price using indicators for the location of the DEA field office, year, interaction terms of the DEA field office and the year of purchase, and year squared.[9] We match the predicted price to the ADAM data set based on quarter and to the UCR data based on year. Each ADAM site is assigned the predicted price of the closest within-state branch office that reported to one of the 19 main field offices.

Cocaine and alcohol prices are included to ensure that the estimated marijuana price effects do not reflect indirect effects through alcohol and cocaine consumption. Similar to previous studies, we use information about the price of cocaine from the DEA's STRIDE data. STRIDE contains records on acquisitions of cocaine (and other illicit drugs) made by undercover agents and informants of the DEA. For each cocaine acquisition, information is recorded about the type of cocaine (e.g. cocaine base (crack), cocaine hydrochloride (powder cocaine), and others), the quantity acquired, its purity (in percent), the cost (if the cocaine was purchase rather than seized), along with the DEA field office responsible for the acquisition and the date that it took place. In addition to cost differences arising from the form of cocaine, the cost of purchases may vary due to the weight and/or purity of the purchase. One method to account for differences in the weight purchased is to divide the (CPI deflated) cost of purchase by its weight to obtain a price per gram. However, this method ignores the quantity discounting evident in these data as well as differences due to actual purity. To overcome these issues, we follow the economics literature and form a predicted price of a pure gram of cocaine for each year and

[9] It is necessary to use predicted prices instead of actual prices because of missing data for particular cities and quarters.

city.[10] City-specific predicted quarterly and annual prices for one pure gram of cocaine were matched to the ADAM site on the basis of the closest city for which we had price data.

Information on the monetary cost of alcohol is represented by the CPI deflated sum of federal and state taxes on a twelve-ounce can of beer. These data are published annually in the Beer Institute's Brewers' Almanac. Information on state and local taxes is used for these analyses instead of city-level alcohol prices because city-specific prices are not consistently available through ACCRA for the ADAM locations in our sample. However, supplemental regressions using this alternative measure for alcohol price resulted in similar findings.

The ADAM data obviously represent a selective population in that we only observe individuals in these data if they committed an offence, were caught, and were sent to a booking facility that participates in the ADAM survey. Probabilistic samples were not drawn from most jurisdictions until 1998. Hence, there are numerous reasons to be concerned about the generalizability of findings obtained from these data. Therefore, we also examine reduced form models using data from the Federal Bureau of Investigation's Uniform Crime Reports (UCR) to test the robustness of our findings. The UCR system collects information on the number of crimes reported to the police in specific crime categories each year for every city in the country. Arrests are also reported for each jurisdiction by criminal offence. While the shortcomings of these data are well documented (e.g. O'Brien, 1985), they remain the only source of geographically disaggregated crime and arrest data in the United States.

---

[10] The model used to predict price is based on regressing the log of the real cost of purchase on the log of the weight of the purchase, the log of the purity of the purchase, indicators for the city of purchase, interactions between the city and year of purchase, the square of the year of purchase, and a set of indicators for the quarter of purchase. In order to address the issue of uncertainty of purity at the time of purchase, we replace actual purity with the predicted purity based on a model containing the regressors included in the model for the predicted price (except the year squared term and quarter dummies). The effect of (the log of) purity is identified in the cost model by constraining its coefficient to be equal to the coefficient on the (log of) weight of the purchase. We then predict the log of the price of a pure gram of cocaine for each city and year, and exponentiate this quantity to get the real price of a gram of cocaine. City-specific prices were estimated for those cities where at least 40 observations were observed over the period 1985-2000 to reduce the noise in the series.

Because we are primarily concerned about ADAM's reliance on convenience sampling during the 1996-1999 time period, we restrict our UCR data to reflect the same 35 counties included in our ADAM sample. Further, we restrict the UCR time period to 1994 through 2000 so that it overlaps with our ADAM sample; thus we can reduce the number of plausible explanations for differences in results that might emerge across these two data sets.[11]

Publicly available data from the UCR provide information on crime and arrest rates, but no information is available on individual characteristics or whether crimes were committed under the influence of alcohol or illicit drugs. At best we can infer an association between crime and marijuana use from the UCR by using a reduced form model to determine if decreases in marijuana prices are associated with increases in particular types of crime. Using data from ADAM, we are able to confirm that use of marijuana among the arrestee population is price responsive (see Table A1 in the Appendix).[12] Preliminary examination and statistical testing of the UCR data suggests that the appropriate empirical specification of equation (5) using these data varied by type of offence.[13] In the case of violent crimes, we model the data using a general linear model with log-link function and nonconstant variance, or:

(7) E [(violent crime arrests/10,000 population)$_{jt}$] =

$$\exp(\beta_0 + \beta_1 P_{Ajt} + \beta_2 P_{Mjt} + \beta_3 P_{OOjt} + \beta_4 E_{jt} + \beta_5 Z_{jt} + \beta_6 W_j + \beta_7 Year_t + v_{jt}).$$

(8) V[(violent crime arrests/10,000 population)$_{jt}$]=

$$E^2[(\text{violent crime arrests/10,000 population})_{jt}].$$

---

[11] It was necessary to expand the time horizon in the UCR data because our unit of observation in the UCR is a county-year. Thus a sample from 1996-1999 would have little statistical power. We chose the years 1994-2000 because trends in crime rates in these locations during that time period were consistent with what occurred during 1996-1999.

[12] The probability of using marijuana, as measured by all three indicators of use in our ADAM sample, is negatively associated with changes in price.

[13] The specific functional form was determined by empirically testing alternative functional forms suggested by box-cox transformations. The variance structure was determined through a modified Park Test (Deb, Manning, and Norton, 2003).

In the case of property and income-producing crimes, we model these outcomes using general linear models with log-link functions and constant coefficient of variation, or:

(9) E [(property crime arrests/10,000 population)$_{it}$] =

$$exp\,(\delta_0 + \delta_1 P_{Nit} + \delta_2 P_{Mit} + \delta_3 P_{ODit} + \delta_4 E_{jt} + \delta_5 Z_{it} + \delta_6 W_j + \delta_7 Year_t + \mu_{it}).$$

(10) V [(property crime arrests/10,000 population)$_{it}$] = 1.

Because individual-level demographic information is not available in the public use UCR data we exclude Y_{it} from the equations above. County-level demographics, income and unemployment rates are included as components of the Z_{it} matrix, however. In addition, we account for county-level income and unemployment rates, obtained from the Bureau of Economic Analysis and Bureau of Labor Statistics, respectively.[14]

In our UCR analyses, we include an additional measure of local enforcement (E_{jt}) so that we can account for the prominence of drug crime and drug enforcement activity in the area. In addition to a measure of the local crime per number of officers, we construct the ratio of local drug arrests to total reported crime from UCR data. Both our measures of enforcement are likely to be endogeneous in the UCR analyses. However, we are unable to identify variables that allow us to uniquely identify variation in law enforcement independent of arrests. Thus, to test the sensitivity of our main marijuana findings to the inclusion of these endogenous variables, we run two sets of models for each outcome. One set of models excludes these enforcement measures and one set includes them.

Descriptive statistics for the ADAM and UCR samples employed for all regression analyses are included in Table 1. Looking only at violent, property, and income-producing

[14] Unemployment figures were not available for the Anchorage FIPS so unemployment data for the Anchorage MSA are substituted (http://www.economagic.com/em-cgi/data.exe/blsla/lausm0380000003).

crimes, there is a larger share of income-producing crimes in the ADAM sample than in the UCR. And for both samples, violent crimes are the least common of the three categories. The predicted prices for cocaine and marijuana, on average, are slightly higher in the UCR sample, in part because the UCR data include data on all 35 locations going back to 1994. The ADAM data only have information for 23 of the 35 cities until 1998. The difference in county characteristics between the two samples therefore, can partially be explained by the inclusion of all cities for more years in the UCR and the fact that the ADAM sample draws a different number of observations from each jurisdiction. To adjust for the unequal weight attributed to various jurisdictions within the ADAM sample, all models are run using a Huber/White correction of the standard errors using the "robust" option in STATA 7.0.

V. Results

Table 2 provides a preliminary look at the association between marijuana use and specific types of crime for the full ADAM sample. When individuals charged with a drug offence are included in the sample, then marijuana users—identified through urine tests or self-reported use—are generally found to be less likely to be charged of a violent, property or income-producing crime than non-users. The notable exception are those individuals who reported use in the past three days who are statistically more likely to be arrested for property and income producing crime, but the finding of a positive association contradicts the result of a negative association for those self-reporting that they were under the influence at the time of the arrest.

Individuals who report being under the influence of alcohol at the time of the offence are more likely to be charged with a violent crime and less likely to be charged with a property or income-producing crime. Not surprisingly, the data show that marijuana users, regardless of

how it is measured, are statistically more likely to be charged with a drug crime. Those under the influence of alcohol, however, are less likely to be charged of a drug-involved crime.

Given that we are only looking at those arrested, it is not surprising that marijuana users are more likely to be charged with a drug-related crime and less likely to be charged with other crimes simply because many marijuana users are picked up on drug charges. Once we take individuals arrested on drug charges out of the sample, however, we should not expect to see any sort of systematic relationship between marijuana use and specific arrest charges unless there is some sort of association (spurious or real) between marijuana use and these specific offences.

When we remove those arrested on drug charges from the sample, we see some interesting changes. In the case of violent crime, we find that those who report use of marijuana in the past three days or being under the influence at the time of the crime are no longer less likely to be charged with a violent crime than non-marijuana users. In fact, those with a positive urine test for marijuana are statistically more likely to be charged with a violent crime than those testing negative. Given that marijuana can be identified in urine for up to 30 days past the time of consumption, this suggests that individuals who engage in violent crimes are also likely to engage in marijuana use but the marijuana use is not necessarily related to their decision to engage in crime.

In the case of property and income-producing crime we find a more consistent story across different measures of marijuana use. Here we see that marijuana users, regardless of how it is measured, are more likely to be arrested for property and income-producing crime. Interestingly, this is the opposite of what we find for those who report being under the influence of alcohol. Those who report being under the influence of alcohol at the time of the offence are less likely to be in either property or income producing crimes than non-alcohol users.

None of the previous findings control for observable factors that may be driving these associations. In Table 3 we present the marginal effects from a probit specification of the likelihood of being charged with a violent crime controlling for individual demographics, sources of income, county demographics, unemployment rates, and county law enforcement.[15] Given the previous table demonstrated differences in findings based on the measure of marijuana that was employed, we decide to estimate each of the models using the three different measures of marijuana use as well as the price of marijuana so we could have a better understanding of how to interpret results from the models including price. Results from the first two models (M1 and M2) suggest that marijuana users are less likely to be charged with a violent arrest than non-users. However, this finding does not hold in model 3 (M3), where use is measured at the time of the offence suggesting that the association identified in the first two models may not be causal in nature. Indeed, our reduced form specification of the model (M4) shows a positive but statistically insignificant relationship between marijuana price and the probability of a violent crime offence, reinforcing the conclusion that marijuana use is not causally related to violent criminal behavior.

Neither the beer tax nor the price of cocaine is statistically significant in these models, contrary to findings from previous studies (DeSimone, 2001; Lott and Mustard, 1997; Cook and Moore, 1993). Although this might appear to be somewhat surprising, it is easily explained by the limited longitudinal variation in these variables during the time period being evaluated and the inclusion of county fixed effects. Cross-sectional variation in the beer tax is captured by county-specific dummies that are included in the regression; the only independent variation that can be identified from the beer tax is the within state variation in real taxes over time. During

[15] Note that all individuals arrested on drug charges are removed from the sample used in this and all subsequent analyses.

In Table 4 we present findings from similar models of the probability of getting arrested for a property crime. Here our different measures of marijuana use generate some conflicting findings. When marijuana use is measured in terms of a positive urine sample (indicating use at some point in the previous thirty days), we find no statistical association between marijuana use and the likelihood of getting arrested for a property crime. If we instead use a more proximal measure of use (M2 and M3), we find that marijuana use is positively associated with the probability of getting arrested for a property crime although the finding with respect to use at the time of offence is only statistically significant at the 10% level. This positive association between marijuana use and property crime is confirmed in the reduced form version of the model (M4), where marijuana prices are found to have a negative and statistically significant association with the probability of arrest for a property crime, suggesting the association may be causal in nature. The positive association between recent marijuana use and property crime is invariant to the inclusion of self-reported alcohol use at the time of the offence (Models M6 through M8).

Contrary to what is found by DeSimone (2001), these models suggest that there is a negative association between powder cocaine use and property crime as higher powder cocaine prices (associated with lower cocaine use) are positively associated with property crime. The finding is fairly robust to variation in the measure of marijuana use and alcohol use. There are at least two plausible explanations for the difference in findings across studies. First, as was already stated, our model has limited variation in the price of cocaine because of our relatively short time period being evaluated and the inclusion of county-fixed effects. Thus, findings obtained from this relatively short panel may not be robust if evaluated over longer periods. Second, our method for predicting the price of cocaine differs substantially from that employed

by DeSimone (2001).[17] For example, we do not include measures of crime and drug arrests when predicting cocaine prices and we exclude crack observations from our price regression so that our price series only reflects changes in the price of powder cocaine.[18] Thus, we are cautious not to place too much importance on this finding.

In Table 5 we present results from models estimating the probability of being arrested for an income-producing crime. The results presented in these models again suggest that marijuana use is causally linked to crime as self-reported measures of marijuana use near the time of the arrest (Models M2 and M3) are positively and significantly associated with property crime and the price of marijuana is inversely related to income-producing crime at conventional levels of significance. The fact that the results from models M2 through M4 are substantially different than those implied by model M1, which relies on urinalysis for identification of use, suggests that we should be cautious drawing conclusions from associations identified off this measure of use.

As was the case in Table 4, we again see in Table 5 a positive association between cocaine prices and income-producing crime, but the same interpretation applies. An intriguing puzzle is presented in Table 5 by the different implied relationship between alcohol and income-producing crimes based on our two different measures of alcohol use. When the beer tax is used to capture the influence of alcohol consumption, we find that higher beer taxes, indicating less alcohol use, is associated with a lower likelihood of being arrested for an income-producing crime, consistent with results obtained elsewhere in the literature (DeSimone 2001, Gyimah-

[17] As indicated in the prior section, we use a much more restricted subset of the STRIDE data and do not include measures of arrest or crime in our estimation of the price of cocaine.

[18] There is a significant literature demonstrating an association between crack cocaine use and crime (Grogger and Willis, 2000; Inciardi, 1990; Fagan and Chin, 1990). It may be the case that by narrowing our focus to powder cocaine in the 1990s, we identify a different relationship between cocaine and crime. Future research will explore this hypothesis.

Brempong, 2001). This contradicts findings obtained from models M5 through M8, however, where alcohol intoxication is shown to be negatively associated with getting arrested for income-producing crimes. The contradiction may simply be caused by an endogencity bias that is generated from the inclusion of self-reported alcohol measures, but it is difficult to know for sure given the limited variability in the beer tax measure.

Overall the findings from the reduced form models would suggest that marijuana use is positively associated with property and income-producing crimes and that no causal association exists between marijuana use and violent crime. However, one must be careful drawing these conclusions based on analysis that only considers the likelihood of getting arrested for a specific criminal offence among a nonrandom sample of arrestees. Results from these models may not hold in the general population because this sample is not representative of the general arrestee population, the criminally involved population, or the general population.

To test the generalizability of these findings to the arrestee population, we estimated models of the number of arrests for violent, property and income producing crimes in the same geographic locations over a similar time period using county-level data from Uniform Crime Reports. Results from these models are presented in Table 6. In the case of the number of property crimes and income-producing crimes we obtain results that are consistent with those presented in Tables 4 and 5. Higher marijuana prices, indicative of lower marijuana use, are negatively and statistically associated with the number of property and income producing criminal arrests per capita, suggesting that marijuana use is positively associated with these measures of arrest. This finding is not sensitive to the inclusion of the endogenous enforcement measures (Column M2).

We find a new result when the dependent variable is the number of violent arrests per capita. In the ADAM analysis (Table 2) we saw no statistical relationship between marijuana prices and the probability of an arrest for a violent offence. Here in Table 6 we see that marijuana prices are negatively and statistically associated with violent crime arrest rates, suggesting that marijuana use may be positively associated with violent crime as well. The result is robust to the inclusion of the endogenous enforcement measures.

It is important to consider the differences in the samples employed for these two analyses before interpreting these findings. The UCR and ADAM samples employed in Tables 2 and 6 differ in the following ways: the representativeness of the data samples; the inclusion of three extra years of data in the UCR analysis; the exclusion of individual demographics in the UCR analysis; and the presence of data for all thirty-five cities for all years in the UCR sample.[19] We ran additional analyses exploring the influence of omitted demographics, the extra years, and the presence of cities in additional years and none of these factors led to a change in the statistical significance of the marijuana price variable, suggesting that the cause for the differential findings across the UCR and ADAM analysis is who is represented in the data.

Findings with respect to the beer tax and cocaine price also differ across the ADAM and UCR analysis. For example, beer taxes are shown in Table 6 to be positively associated with higher levels of all three arrests, which is inconsistent with the previous tables. Our supplemental analyses reveal that this finding is driven by the inclusion of all thirty-five counties in all years. When we restrict the UCR sample to just those counties that are in the sample ADAM sample in each year, we again see that there is no statistical association between the beer tax and any of the arrest rates. The sensitivity of the finding to the inclusion of additional counties in some years reinforces our concern regarding how to properly interpret any findings

[19] The ADAM sample grew from 23 cities in 1996 and 1997 to 35 cities in 1998 and 1999.

from this variable. The findings with respect to the price of cocaine in Table 6 are much more consistent with the existing literature and are robust to changes in the county and years of data included. Thus, we believe that this difference in results pertaining to the cocaine price measure on crime rates identified across the different studies is largely being driven by a difference in the representativeness of the two alternative samples.

VI. Discussion

Results from reduced form specifications of models of the number (UCR) and type (ADAM) of arrest suggest that marijuana use may actually be causally associated with specific types of crime, even for the general population of arrestees. Evidence from both sets of analyses suggest that higher marijuana use, as indicated by lower marijuana prices, is positively associated with property arrests and income-producing criminal arrests. There is also evidence from the UCR analysis that marijuana use might be positively associated with the number of violent arrests.

A significant limitation of the results so far is that we do not know the extent to which those arrested for crimes are behaviorally similar to those who commit crimes. It may be the case that substance use reduces an individual's ability to get away with a crime rather than influencing the likelihood of committing a crime. To consider this possibility, we re-ran our basic reduced form model using crime rates instead of arrest rates for the same locations in our ADAM sample. Although we recognize that crimes reported may not accurate reflect actual crimes committed, these are the only source of crime for all the locations in our ADAM sample. Results from these additional specifications are included in Table 7. Note that we are unable to estimate a model for the number of income-producing arrests per 10,000 residents because the data were not available at a disaggregated level.

Results from our reduced form models predicting violent crime per 10,000 residents in the ADAM locations reinforce the original findings presented in Table 2 that marijuana use is not causally linked to violent criminal behavior. The marijuana price variable, although negative, is statistically insignificant at conventional levels and this null finding is invariant to the inclusion of general enforcement measures. The results from our models predicting property crime are more mixed, as the marijuana price variable is only negative and statistically significant when endogenous measures of enforcement are included in the model. Future work will need to carefully consider the proper treatment of these endogenous variables to fully understand the nature of the relationship between marijuana use and known property crimes.

The results from reduced form models tell a fairly consistent story across all of the tables. The positive association between marijuana use and arrests for property and income-producing crimes is not driven by a spurious correlation; these findings suggest a causal interpretation. These results are consistent with models using more proximate measures of use, including use of marijuana at the time of the offence. However, the proper interpretation of the result is still unclear. It may be the case that marijuana use causes individuals to participate in these crimes or it may be the case that marijuana use increases the likelihood that offenders get arrested for these crimes. Further investigation of this important distinction with other data sets will be necessary.

The results pertaining to the relationship between marijuana use and violent crime are a bit more complex to interpret. Evidence from the ADAM sample of arrestees suggests that the positive association identified between marijuana use and violent crime is not causal in nature. This result is not confirmed in analyses using all known arrests from the ADAM cities, however. When UCR arrest data are employed a causal interpretation is supported. But the finding disappears again when crime is measured in terms of known offences as opposed to arrests.

suggesting that the positive association identified in the UCR analysis may be driven by the fact that marijuana users who participate in crime are more likely to get arrested. Future work will need to consider the extent to which these current findings hold in a nationally representative sample of arrests and crime in order for us to clearly understand whether the criminal justice costs of marijuana prohibition are partially reimbursed through a reduction in crime.

References

Baker, J. (1998). *Juveniles in Crime - Part 1: Participation Rates and Risk Factors.* Sydney: New South Wales Bureau of Crime Statistics and Research and New South Wales Crime Prevention Division.

Bushman, B.J. (1997). Effects of alcohol on human aggression: validity of proposed explanations. In *Recent Developments in Alcoholism*, Vol. 13, ed. M. Galanter, pp. 227-43. New York: Plenum Press.

Bushman, B.J. (1990). Human aggression while under the influence of alcohol and other drugs: An integrative research review. *Psychological Science*, 2, 148–152.

Cook, PJ and M.J. Moore. (1993). "Violence reduction through restrictions on alcohol availability." *Alcohol, Health and Research World*, 17(2): 151-156.

Deb, P., Manning W., and E Norton. (2003). "Modeling Health Care Costs and Counts" Pre-conference workshop held before the *International Health Economics Association* 2003 Meeting (San Francisco, CA).

Dembo, R., Williams, L., Schmeidler, J., Wish, E.D., Getreu, A. and Berry, E. (1991). Juvenile crime and drug abuse: a prospective study of high risk youth. *Journal of Addictive Disorders*, 11 (2), 5-31.

DeSimone, J. (2001). The Effect of Cocaine Prices on Crime. Economic Inquiry. 39(4): 627-643.

Ehrlich, I. (1973). Participation in Illegitimate Activities: A Theoretical and Empirical Investigation. *The Journal of Political Economy* 81(3): 521-565.

Fagan, J. (1990). Intoxication and aggression. Drugs and crime. In *Crime and Justice, A Review of Research*, Vol. 13, ed. M. Tonry and J. Q. Wilson, pp. 241-320. Chicago: The University of Chicago Press.

Fagan, J.A. (1993). The political economy of drug dealing among urban gangs. In *Drugs and Community*, ed. R. Davis, A. Lurigio and D. P. Rosenbaum, pp. 19-54. Springfield, IL: Charles Thomas.

Fagan, J.A. and K.L. Chin. (1990). "Violence as Regulation and Social Control in the Distribution of Crack," *National Institute on Drug Abuse Research Monograph Series* 103: 8-43.

Fergusson, D. M., & Horwood, L. J. (1997). Early onset cannabis use and psychosocial adjustment in young adults. *Addiction, 92*(3). 279-296.

Goldstein, P. (1985). The drugs/violence nexus: a tripartite conceptual framework. *Journal of Drug Issues*, 15 (Fall), 493-506.

Goldstein, P.J., Brownstein, H.H., Ryan, P.J. and Bellucci, P.A. (1989). Crack and homicide in New York City, 1988: a conceptually based event analysis. *Contemporary Drug Problems*. 16, 651-87.

Gorman, D.M. and White, H.R. (1995). You can choose your friends, but do they choose your crime? Implications of differential association theories for crime prevention policy. In *Crime and Public Policy: Putting Theory to Work*, ed. H. D. Barlow, pp. 131-55. Boulder, CO: Westview.

Grogger, J. and M. Willis. (2000). "The Emergence of Crack Cocaine and the Rise in Urban Crime Rates." *The Review of Economics and Statistics*, 82(4): 51..-529.

Gyimah-Brempong, K. (2001). "Alcohol Availability and Crime: Evidence from Census Tract Data" *Southern Economic Journal* 68(1): 2-21.

Hirschi, T. and Gottfredson, M. (1988). Towards a general theory of crime. In *Explaining Criminal Behaviour: Interdisciplinary Approaches*, ed. W. Buikhuisen and S. A. Mednick, pp. 8-26. Leiden; New York: E.J. Brill.

Inciardi, J.A. (1990). "The Crack-Violence Connection Within a Population of Hard-Core Adolescent Offenders," *National Institute on Drug Abuse Research Monograph Series* 103: 92-111.

Jessor, R. and Jessor, S.L. (1977). *Problem Behavior and Psychosocial Development: A Longitudinal Study of Youth*, New York: Academic Press.

Johnston, L.D., O'Malley, P.M. and Bachman, J.G. (2000). *National Survey Results on Drug Use from the Monitoring the Future Study, 1975-1999 Volume II: College Students and Young Adults*, Rockville, MD: National Institute on Drug Abuse.

Kaplan, Howard B. and Kelly R. and Damphousse 1995. Self-attitudes and antisocial personality as moderators of the drug use-violence relationship. In *Drugs, crime and other deviant adaptions: Longitudinal studies*, edited by Howard B. Kaplan. New York: Plenum Press.

Lott, JR. and DB Mustard. (1997). Crime, Deterrence, and Right-to-Carry Concelaed Handguns." *Journal of Legal Studies*, 26: 1-68.

MacCoun, R. and Reuter, P. (2001). *Drug War Heresies: Learning from Other Vices, Times and Places*, Cambridge: Cambridge University Press.

Makkai, T., Fitzgerald, J. and Doak, P. (2000). *Drug use among police detainees*, Contemporary Issues in Crime and Justice, Vol. 49, Sydney: NSW Bureau of Crime Statistics and Research.

Markowitz, S. (2000). *An Economic Analysis of Alcohol, Drugs and Crime in the National Criminal Victimization Survey*, National Bureau of Economic Research Working Paper 7982. Cambridge, MA: National Bureau of Economic Research.

Miczek, K.A., DeBold, J.F., Haney, M., Tidey, J., Vivan, J. and Weerts, E.M. (1994). Alcohol, drugs of abuse, aggression, and violence. In *Understanding and preventing violence*, Vol. 3, ed. A. J. Reiss and J. A. Roth, pp. 377-570. Washington, DC: National Academy Press.

National Institute of Justice. (1999). *1998 Annual report on marijuana use among arrestees.* http://www.adam-nij.net/files/175658.pdf

National Institute of Justice. (2000). *1999 Annual report on marijuana use among arrestees.*

National Research Council (1993). *Understanding and Preventing Violence*, Washington, DC: National Academy Press.

O'Brien, Robert. Crime and Victimization Data (Beverly Hills, CA: Sage). 1985.

Salmelainen, P. (1995). *The correlates of offending frequency: a study of juvenile theft offenders in detention*, Sydney: New South Wales Bureau of Crime Statistics and Research.

Skogan, W. (1990). *Disorder and Decline: Crime and the Spiral Decay in American Neighbourhoods*, New York: Free Press.

Stevenson, R. and Forsythe, L. (1998). *The Stolen Goods Market in New South Wales: An Interview Study with Imprisoned Burglars*, Sydney: NSW Bureau of Crime Statistics and Research.

Taylor, B. and Bennett, T. (1999). *Comparing Drug Use Rates of Detained Arrestees in the United States and England*, Washington, DC: U.S. Department of Justice.

Taylor, B.G., Fitzgerald, N., Hunt, D., Reardon, J.A. and Brownstein, H.H. (2001). *ADAM Preliminary 2000 Findings on Drug Use and Drug Markets - Adult Male Arrestees*: National Institute of Justice.

United States Office of National Drug Control Policy (2001). *Pulse Check: Trends in Drug Abuse. November 2001*, Washington, DC: Office of National Drug Control Policy.

White, H.R. (1990). The drug use-delinquency connection in adolescence. In *Drugs, Crime and the Criminal Justice System*, ed. R. A. Weisheit, pp. 215-56. Cincinnati, OH: Anderson Publishing.

White, Helene Raskin and Stephen Hansell. 1998. Acute and long-term effects of drug use on aggression from adolescence into adulthood. *Journal of Drug Issues*. 28: 837-858.

White, H.R. and Gorman, D.M. (2000). Dynamics of the drug-crime relationship. In *The Nature of Crime: Continuity and Change*, ed. G. LaFree, pp. 151-218. Washington, DC: U.S. Department of Justice.

White, Helene Raskin and Stephen Hansell. 1998. Acute and long-term effects of drug use on aggression from adolescence into adulthood. *Journal of Drug Issues*. 28: 837-858.

FROM :
FAX NO. : 4155527170
Jan. 14 2004 03:12PM P33

Table 1

Means of Primary Data Sets

ADAM Analysis N = 101,990					UCR Analysis N = 188				
Variable	Mean	Std. Dev	Min	Max	Variable	Mean	Std. Dev	Min	Max
Positive Urine Test	0.349	0.477	0	1	Violent arrests per capita	33.030	20.773	7.071	113.250
Use in past 3 days	0.268	0.442	0	1	Log(violent arrests per capita)	3.327	0.576	1.956	4.730
Under the inf: MJ	0.051	0.220	0	1	Property arrests per capita	94.870	29.607	27.546	188.901
Under the inf: Alc	0.211	0.408	0	1	Log(property arrests per capita)	4.500	0.333	3.316	5.241
Arrested for violent crime	0.183	0.387	0	1	Income arrests per capita	52.937	27.000	13.153	186.691
Arrested for property crime	0.246	0.431	0	1	Log(income arrests per capita)	3.861	0.460	2.577	5.229
Arrested for income crime	0.320	0.467	0	1					
Real predicted price of MJ	55.21	18.940	20.37	101.02	Real predicted price of MJ	58.539	19.024	23.839	98.268
Real beer tax	2.32	1.972	0.59	10.76	Real beer tax	2.462	1.863	0.577	11.454
Real predicted price of cocaine	85.76	14.730	34.34	105.85	Real predicted price of cocaine	68.699	14.558	34.944	103.710
Male	0.753	0.431	0	1	Match dummy	0.938	0.243	0	1
Black	0.465	0.499	0	1					
Hispanic	0.214	0.410	0	1	% male	0.484	0.012	0.463	0.514
Other race	0.031	0.173	0	1	% pop less than 18	0.257	0.032	0.180	0.366
Education >= 12	0.420	0.494	0	1	% pop 18-24	0.099	0.011	0.071	0.128
Age 18-24	0.264	0.441	0	1	% white	0.762	0.160	0.320	0.991
Age 25-34	0.295	0.456	0	1	% black	0.182	0.170	0.002	0.649
Age > 34	0.299	0.458	0	1	% other	0.056	0.046	0.007	0.228
Real income - illegal sources	180.80	1185.47	0	63734	% hispanic	0.175	0.200	0.005	0.953
Real income - legal sources	573.64	1423.63	0	63734	unemployment rate	4.911	1.932	1.900	15.400
Year	1997.60	1.145	1996	1999	Real per capita income (in $1000	18.294	5.533	7.959	49.019
Unemployment rate	4.700	1.580	1.9	9.2	Log(county pop)	13.852	0.826	12.000	16.049
FTE police per capita	0.004	0.006	0.001	0.030	Year	1997	1.712	1994	1999
Real per capita income (in $1000)	19483	7213	8471	49019	Index Crime	94384.5	89798.9	9447	591795
% male	0.484	0.01	0.463	0.513	FTE sworn officers	4178.9	7576.1	250	46158
% pop < 18	0.252	0.029	0.182	0.366	total drug arrests/index crime	0.117	0.068	0.020	0.430
% pop 18-24	0.098	0.011	0.074	0.126	index crime/ FTE sworn officers	0.569	0.542	0.009	2.725
% black	0.216	0.173	0.002	0.642					
% other	0.060	0.050	0.007	0.228					
% hisp	0.199	0.176	0.006	0.953					

Table 2
Descriptive Statistics
1996 - 1999 ADAM data

	# of Obs	Full Sample	Non User	User	P-value for diff ~=0
PANEL A : Includes those charged of a drug offence					
Violent Crime					
MJ: Positive urine test	137409	0.148	0.148	0.147	0.544
MJ: Use in past 3 days	137091	0.148			
MJ: under influence	136496	0.148			
ALC: under influence	136497	0.148			
Property Crime					
MJ: Positive urine test	137409	0.197			
MJ: Use in past 3 days	137091	0.197			
MJ: under influence	136496	0.196			
ALC: under influence	136497	0.196			
Income Crime					
MJ: Positive urine test	137409	0.255			
MJ: Use in past 3 days	137091	0.255			
MJ: under influence	136496	0.255			
ALC: under influence	136497	0.255			
Drug-involved Crime					
MJ: Positive urine test	137409	0.187			
MJ: Use in past 3 days	137091	0.187			
MJ: under influence	136496	0.187			
ALC: under influence	136497	0.187			
PANEL B: Excludes those charged with a drug offence					
Violent Crime					
MJ: Positive urine test	111721	0.182			
MJ: Use in past 3 days	111459	0.182	0.181	0.183	0.382
MJ: under influence	110969	0.182	0.181	0.189	0.156
ALC: under influence	110970	0.182			
Property Crime					
MJ: Positive urine test	111721	0.242			
MJ: Use in past 3 days	111459	0.242			
MJ: under influence	110969	0.242			
ALC: under influence	110970	0.242			
Income Crime					
MJ: Positive urine test	111721	0.314			
MJ: Use in past 3 days	111459	0.314			
MJ: under influence	110969	0.314			
ALC: under influence	110970	0.314			

Table 3

Marginal Effects and Robust Standard Errors from Probit Estimation of Prob(Arrested for a Violent Crime)[a]
ADAM 1998 - 1999, Non-drug offenders

	M1		M2		M3		M4	
MJ: positive urine	-0.0054	**						
	(0.003)							
MJ in past 3 days			-0.0111	***				
			(0.003)					
MJ: under influence					-0.0084			
					(0.005)			
Real price of MJ							0.0002	
							(0.001)	
Real beer tax	-0.0112		-0.0122		-0.0113		-0.0136	
	(0.041)		(0.041)		(0.041)		(0.042)	
Real price of cocaine	-0.0002		-0.0002		-0.0002		-0.0002	
	(0.001)		(0.001)		(0.001)		(0.001)	
County Fixed Effects	Yes		Yes		Yes		Yes	
# of Observations	101,960		101,960		101,960		101,960	
Pseudo-R2	0.051		0.051		0.051		0.051	
	M5		**M6**		**M7**		**M8**	
MJ: positive urine	-0.0066	**						
	(0.003)							
MJ in past 3 days			-0.0144	***				
			(0.003)					
MJ: under influence					-0.0191	***		
					(0.005)			
Real price of MJ							0.0002	
							(0.001)	
ALC: under influence	0.0493	***	0.0503	***	0.0506	***	0.0490	***
	(0.003)		(0.003)		(0.003)		(0.003)	
Real price of cocaine	-0.0002		-0.0001		-0.0002		-0.0001	
	(0.001)		(0.001)		(0.001)		(0.001)	
County Fixed Effects	Yes		Yes		Yes		Yes	
# of Observations	101,960		101,960		101,960		101,960	
Pseudo-R2	0.053		0.054		0.053		0.053	

[a] Models include as additional regressors gender, ethnicity, race, education, age categories, legal and illegal income, quarter dummies, time trend, county unemployment rate, the number of police per capita, real county income, % county population that male, black and other race, and age demographics of the county. Statistical significance is designated as follows: *** indicates significance at the 1% level (2-tailed test), ** indicates significance at the 5% level , and * indicates significance at the 10% level.

Table 4

Marginal Effects and Robust Standard Errors from Probit Estimation of Prob(Arrested for a Property Crime)[a]
ADAM 1996 - 1999, Non-drug offenders

	M1		M2		M3		M4	
MJ: positive urine	-0.0036							
	(0.003)							
MJ in past 3 days			0.0211	***				
			(0.003)					
MJ: under influence					0.0109	*		
					(0.006)			
Real price of MJ							-0.0034	**
							(0.001)	
Real beer tax	-0.0369		-0.0357		-0.0378		-0.0065	
	(0.047)		(0.047)		(0.047)		(0.049)	
Real price of cocaine	0.0051	***	0.0051	***	0.0051	***	0.0053	***
	(0.001)		(0.001)		(0.001)		(0.001)	
County Fixed Effects	Yes		Yes		Yes		Yes	
# of Observations	101,960		101,960		101,960		101,960	
Pseudo-R2	0.032		0.032		0.032		0.032	
	M5		**M6**		**M7**		**M8**	
MJ: positive urine	-0.0017							
	(0.003)							
MJ in past 3 days			0.0267	***				
			(0.003)					
MJ: under influence					0.0300	***		
					(0.006)			
Real price of MJ							-0.0036	***
							(0.001)	
ALC: under influence	-0.0772	***	-0.0792	***	-0.0792	***	-0.0773	***
	(0.003)		(0.003)		(0.003)		(0.003)	
Real price of cocaine	0.0053	***	0.0053	***	0.0053	***	0.0053	***
	(0.001)		(0.001)		(0.001)		(0.001)	
County Fixed Effects	Yes		Yes		Yes		Yes	
# of Observations	101,960		101,960		101,960		101,960	
Pseudo-R2	0.036		0.037		0.036		0.036	

[a] Models include as additional regressors gender, ethnicity, race, education, age categories, legal and illegal income, quarter dummies, time trend, county unemployment rate, the number of police per capita, real county income, % county population that male, black and other race, and age demographics of the county. Statistical significance is designated as follows: *** indicates significance at the 1% level (2-tailed test), ** indicates significance at the 5% level , and * indicates significance at the 10% level.

Table 5

Marginal Effects and Robust Standard Errors from Probit Estimation of Prob(Arrested for an Income-Producing Crime)[a]

ADAM 1996 - 1999, Non-drug offenders

	M1		M2		M3		M4	
MJ: positive urine	0.0023							
	(0.003)							
MJ in past 3 days			0.0361	***				
			(0.004)					
MJ: under influence					0.0236	***		
					(0.007)			
Real price of MJ							-0.0047	***
							(0.001)	
Real beer tax	-0.1007	*	-0.0983	*	-0.1018	**	-0.0574	
	(0.052)		(0.052)		(0.052)		(0.054)	
Real price of cocaine	0.0045	***	0.0045	***	0.0045	***	0.0047	***
	(0.001)		(0.001)		(0.001)		(0.001)	
County Fixed Effects	Yes		Yes		Yes		Yes	
# of Observations	101,960		101,960		101,960		101,960	
Pseudo-R2	0.049		0.050		0.049		0.049	
	M5		**M6**		**M7**		**M8**	
MJ: positive urine	0.0046							
	(0.003)							
MJ in past 3 days			0.0432	***				
			(0.004)					
MJ: under influence					0.0479	***		
					(0.007)			
Real price of MJ							-0.0053	***
							(0.001)	
ALC: under influence	0.0961	***	0.0993	***	0.0992	***	0.0960	***
	(0.004)		(0.004)		(0.004)		(0.004)	
Real price of cocaine	0.0052	***	0.0051	***	0.0052	***	0.0051	***
	(0.001)		(0.001)		(0.001)		(0.001)	
County Fixed Effects	Yes		Yes		Yes		Yes	
# of Observations	101,960		101,960		101,960		101,960	
Pseudo-R2	0.054		0.055		0.054		0.054	

[a] Models include as additional regressors gender, ethnicity, race, education, age categories, legal and illegal income, quarter dummies, time trend, county unemployment rate, the number of police per capita, real county income, % county population that male, black and other race, and age demographics of the county. Statistical significance is designated as follows: *** indicates significance at the 1% level (2-tailed test), ** indicates significance at the 5% level , and * indicates significance at the 10% level.

Table 6
GLM Estimates of Log Arrest Rates from UCR: 1994 -1999

	M1		M2	
	OLS Coefficient	Robust Std. Err	OLS Coefficient	Robust Std. Err
Log (# of violent crime arrests/ 10K pop)				
Real price of MJ	-0.017 ***	0.006	-0.022 ***	0.004
Real price of Cocaine	0.002	0.003	-0.001	0.003
Real beer tax	0.215 ***	0.079	0.256 ***	0.087
log(county pop)	-1.853 ***	0.452	-0.447	0.627
% of county pop < 18	11.059 ***	3.809	4.536	4.182
% of county pop black	1.390	5.636	-0.318	4.289
% of county pop other race	34.256 ***	10.077	42.310 ***	8.264
% of county pop Hispanic	-8.914 *	5.122	-13.333 ***	3.971
Real per capita income	-3.59E-05 ***	1.21E-05	-8.51E-05 ***	1.51E-05
Unemployment rate	0.013	0.014	0.007	0.012
Year	-0.037 *	0.019	-0.059 ***	0.015
Crime per officer			0.440 ***	0.128
Drug arrests/total crime			3.342 ***	0.888
Constant	97.940 ***	38.451	126.071 ***	29.710
Log (# of property crime arrests / 10 K pop)				
Real price of MJ	-0.010 **	0.005	-0.013 ***	0.005
Real price of Cocaine	-0.002	0.002	-0.004 **	0.002
Real beer tax	0.177 ***	0.066	0.151 **	0.066
log(county pop)	-0.482	0.336	0.023	0.398
% of county pop < 18	15.342 ***	3.704	15.407 ***	3.751
% of county pop black	1.032	4.223	0.472	4.023
% of county pop other race	8.091	8.343	16.737 **	8.068
% of county pop Hispanic	-5.199	4.505	-8.291 *	4.371
Real per capita income	-1.18E-05	1.35E-05	-3.36E-05 ***	1.19E-05
Unemployment rate	0.013	0.009	0.007	0.009
Year	-0.049 ***	0.015	-0.063 ***	0.017
Crime per officer			0.341 ***	0.083
Drug arrests/total crime			1.562 ***	0.420
Constant	106.099 ***	33.664	125.901 ***	32.365
Log(# of income arrests/ 10K pop)				
Real price of MJ	-0.011 **	0.005	-0.017 ***	0.004
Real price of Cocaine	-0.004	0.003	-0.005 **	0.003
Real beer tax	0.154 *	0.084	0.238 ***	0.072
log(county pop)	-1.008 ***	0.378	0.303	0.490
% of county pop < 18	20.707 ***	3.867	17.411 ***	3.946
% of county pop black	7.775	4.904	6.447 *	3.743
% of county pop other race	13.805	9.064	19.349 **	8.662
% of county pop Hispanic	-3.963	4.033	-10.916 ***	3.708
Real per capita income	-1.43E-05	1.45E-05	-5.63E-05 ***	1.78E-05
Unemployment rate	0.017	0.018	0.011	0.015
Year	-0.057 ***	0.017	-0.063 ***	0.018
Crime per officer			0.328 ***	0.127
Drug arrests/total crime			2.722 ***	0.656
Constant	122.440 ***	35.204	118.105 ***	37.157

All models include as additional regressors city fixed effects.
*** Indicates significance at 1% level (two-tailed test), ** indicates significance at 5% level (two-tailed test) and * indicates significance at the 10% level (two-tailed test)

Table 7
GLM Estimates of Log Crime Rates from UCR: 1994 -1999

	M1		M2	
	OLS Coefficient	Robust Std. Err	OLS Coefficient	Robust Std. Err
Log (# of violent crimes/ 10K pop)				
Real price of MJ	-0.009	0.006	-0.005	0.003
Real price of Cocaine	0.004	0.003	0.000	0.003
Real beer tax	0.286 ***	0.069	0.172 **	0.070
log(county pop)	-1.123 **	0.497	-1.831 ***	0.443
% of county pop < 18	7.929 **	3.796	4.942	3.190
% of county pop black	4.621	3.537	12.023 ***	2.995
% of county pop other race	20.524 *	12.237	9.770	8.906
% of county pop Hispanic	-3.279	6.029	2.631	3.432
Real per capita income	-2.72E-02 ***	1.03E-02	-2.00E-02 *	1.14E-02
Unemployment rate	0.013	0.016	0.008	0.016
Year	-0.047 ***	0.013	-0.054 ***	0.015
Crime per officer			0.518 ***	0.101
Drug arrests/total crime			-0.578 *	0.326
Constant	108.014 ***	30.087	129.284 ***	34.111
Log (# of property crimes / 10 K pop)				
Real price of MJ	-0.003	0.003	-0.005 *	0.003
Real price of Cocaine	0.003	0.002	0.003	0.002
Real beer tax	0.186 ***	0.045	0.026	0.053
log(county pop)	0.718 *	0.418	0.057	0.299
% of county pop < 18	0.092	3.026	9.524 ***	2.537
% of county pop black	0.151	3.146	-2.015	2.840
% of county pop other race	-6.555	5.029	-5.729	3.816
% of county pop Hispanic	-6.965 **	3.139	-9.127 ***	2.355
Real per capita income	-1.44E-02 **	7.16E-03	4.33E-03	7.54E-03
Unemployment rate	0.013	0.013	0.006	0.009
Year	0.002	0.015	0.026 **	0.013
Crime per officer			0.467 ***	0.064
Drug arrests/total crime			-1.704 ***	0.324
Constant	-8.122	30.964	-48.733	26.608

All models include as additional regressors city fixed effects.
*** Indicates significance at 1% level (two-tailed test), ** indicates significance at 5% level (two-tailed test) and * indicates significance at the 10% level (two-tailed test).

Table 7
GLM Estimates of Log Crime Rates from UCR: 1994 -1999

	M1		M2	
	OLS Coefficient	Robust Std. Err	OLS Coefficient	Robust Std. Err
Log (# of violent crimes/ 10K pop)				
Real price of MJ	-0.009	0.006	-0.005	0.003
Real price of Cocaine	0.004	0.003	0.000	0.003
Real beer tax	0.286 ***	0.069	0.172 **	0.070
log(county pop)	-1.123 **	0.497	-1.831 ***	0.443
% of county pop < 18	7.929 **	3.796	4.942	3.190
% of county pop black	4.621	3.537	12.023 ***	2.995
% of county pop other race	20.524 *	12.237	9.770	8.906
% of county pop Hispanic	-3.279	6.029	2.631	3.432
Real per capita income	-2.72E-02 ***	1.03E-02	-2.00E-02 *	1.14E-02
Unemployment rate	0.013	0.016	0.008	0.016
Year	-0.047 ***	0.013	-0.054 ***	0.015
Crime per officer			0.518 ***	0.101
Drug arrests/total crime			-0.578 *	0.326
Constant	108.014 ***	30.087	129.284 ***	34.111
Log (# of property crimes / 10 K pop)				
Real price of MJ	-0.003	0.003	-0.005 *	0.003
Real price of Cocaine	0.003	0.002	0.003	0.002
Real beer tax	0.186 ***	0.045	0.026	0.053
log(county pop)	0.718 *	0.418	0.057	0.299
% of county pop < 18	0.092	3.026	9.524 ***	2.537
% of county pop black	0.151	3.146	-2.015	2.840
% of county pop other race	-6.555	5.029	-5.729	3.816
% of county pop Hispanic	-6.965 **	3.139	-9.127 ***	2.355
Real per capita income	-1.41E-02 **	7.16E-03	4.33E-03	7.54E-03
Unemployment rate	0.013	0.013	0.006	0.009
Year	0.002	0.015	0.026 **	0.013
Crime per officer			0.467 ***	0.064
Drug arrests/total crime			-1.704 ***	0.324
Constant	-8.122	30.964	-48.733	26.608

All models include as additional regressors city fixed effects.
*** Indicates significance at 1% level (two-tailed test), ** indicates significance at 5% level (two-tailed test) and * indicates significance at the 10% level (two-tailed test).

APPENDIX

Table A1. Marginal Effects and Robust Standard Errors from Probit Estimation of Prob(Using Marijuana)[a]

	MJ50		MJ72HR		UNDERMJ	
Price MJ	-0.0011	*	-0.0011	*	-0.0006	**
	(0.001)		(0.001)		(0.000)	
MALE	0.1491	***	0.0863	***	0.0266	***
	(0.003)		(0.003)		(0.001)	
BLACK	0.0294	***	0.0439	***	0.0059	***
	(0.004)		(0.004)		(0.002)	
HISPANIC	-0.0722	***	-0.0592	***	-0.0114	***
	(0.005)		(0.004)		(0.002)	
OTHR RACE	-0.1022	***	-0.0676	***	-0.0108	***
	(0.009)		(0.008)		(0.004)	
AGED 18-24	0.0375	***	0.0280	***	-0.0009	
	(0.005)		(0.005)		(0.002)	
AGED 25-34	-0.1381	***	-0.0699	***	-0.0279	***
	(0.005)		(0.005)		(0.002)	
AGED >34	-0.2601	***	-0.1728	***	-0.0566	***
	(0.004)		(0.004)		(0.002)	
EDU12	-0.0584	***	-0.0569	***	-0.0138	***
	(0.003)		(0.003)		(0.001)	
MEDUC	0.0133	**	0.0196	***	0.0033	
	(0.006)		(0.006)		(0.002)	
LEGAL INCOME	0.0000	***	0.0000	***	0.0000	***
	(0.000)		(0.000)		(0.000)	
ILLEGAL INCOME	0.0000	***	0.0000	***	0.0000	***
	(0.000)		(0.000)		(0.000)	
YEAR	0.0051	**	0.0054	**	0.0032	***
	(0.002)		(0.002)		(0.001)	
PRICE BEER	0.0038		0.0339	**	0.0007	
	(0.016)		(0.015)		(0.007)	
Distance Indicator	0.0418	***	0.0119	*	-0.0054	*
	(0.007)		(0.007)		(0.003)	
PRICE COCAINE	0.0004		0.0006		0.0000	
	(0.001)		(0.001)		(0.000)	
QUARTER	-0.0021		-0.0016		0.0005	
	(0.001)		(0.001)		(0.001)	

Statistical significance is designated as follows: *** indicates significance at the 1% level (2-tailed test), ** indicates significance at the 5% level , and * indicates significance at the 10% level.

Table A2.
ADAM Locations and Fipscodes

Albuquerque	35001	Minneapolis	27053
Anchorage	2020	New Orleans	22071
Atlanta	13121	New York	36061
Birmingham	1073	Oklahoma City	40109
Chicago	17031	Omaha	31055
Cleveland	39035	Philadelphia	42101
Dallas	48113	Phoenix	4013
Denver	8031	Portland	41051
Des Moines	19153	Sacramento	6067
Detroit	26163	Salt Lake City	49035
Ft. Lauderdale	12011	San Antonio	48029
Houston	48201	San Diego	6073
Indianapolis	18097	San Jose	6085
Kansas City	29095	Seattle	53033
Laredo	48479	Spokane	53063
Las Vegas	32003	St. Louis	29189
Los Angeles	6037	Tucson	4019
Miami	12086	Washington	11001

NOTE: Sites included in the county analysis are those listed in Table 1 except Kansas City, which did not report any data for 1995-1999. Quarterly data is averaged (annually) for the county-level analysis.

From the ADAM codebooks: "Prior to 1998, samples of arrestees for the ADAM/DUF program were drawn from booking facilities within each of the sites and thus were limited to the types of arrestees booked at these facilities. In 11 sites (Atlanta, Chicago, Cleveland, Denver, Detroit, Houston, Kansas City, Omaha, Philadelphia, St. Louis, and Washington, DC), the catchment area represented the central city. The data from the city of Denver included Denver County in its entirety, and the St. Louis data also encompassed a county. (Kansas City ceased being a DUF site after 1992.) In ten additional sites (Dallas, Ft. Lauderdale, Indianapolis, Miami, New Orleans, Manhattan [New York City], Phoenix, Portland, San Antonio, and San Jose), the catchment area was the county, parish, or borough." Post-1997, ADAM expanded as well as "enhanced each site's collection to include the entire county" (NIJ, 2000b).

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Pergamon
ADDICTIVE BEHAVIORS
Addictive Behaviors 28 (2003) 1555–1574

Intimate partner violence and substance use: A longitudinal day-to-day examination

William Fals-Stewart*, James Golden, Julie A. Schumacher

Research Institute on Addictions, University at Buffalo, State University of New York, 1021 Main Street, Buffalo, NY 14203 1016, USA

Abstract

The likelihood of male-to-female physical aggression on days of male partners' substance use, during a 15-month period, was examined. Participants were from married or cohabiting partner violent men entering a drug abuse treatment program ($N = 149$). Compared to days of no drug or alcohol use, the likelihood of male-to-female physical aggression was significantly higher on days of substance use, after controlling for male partners' antisocial personality (ASP) disorder and couples' global relationship distress. Of the psychoactive substances examined, the use of alcohol and cocaine was associated with significant increases in the daily likelihood of male-to-female physical aggression; cannabis and opiates were not significantly associated with an increased likelihood of male partner violence.
© 2003 Elsevier Ltd. All rights reserved.

Keywords: Partner violence; Substance use; Physical aggression

1. Introduction

Although once viewed as primarily a private family matter, intimate partner violence (IPV) has become increasingly recognized as a significant public health concern during the last 20 years. Nationally representative surveys of couples in the United States indicate 15–20% of dyads experience an incident of IPV each year (e.g., Schafer,

* Corresponding author. Tel.: +1-716-887-2210; fax: +1-716-887-2543.
E-mail address: wstewart@ria.buffalo.edu (W. Fals-Stewart).

0306-4603/$ – see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.addbeh.2003.08.035

Caetano, & Clark, 1998; Straus & Gelles, 1990). As pervasive as IPV is in the general population, its prevalence is substantially higher among couples in which one or both partners abuse alcohol or other drugs. For example, the prevalence of male-to-female physical aggression among married or cohabiting men seeking treatment for alcoholism is four to six times higher than demographically matched nonsubstance-abusing individuals (e.g., Murphy & O'Farrell, 1994). A similarly high prevalence of male-to-female physical aggression has been found among married or cohabiting men seeking treatment for abuse of drugs other than alcohol (e.g., Fals-Stewart, Kashdan, O'Farrell, & Birchler, 2002).

Although multiple studies have found a fairly strong relationship between the use of alcohol and the occurrence of IPV (for reviews, see Hotaling & Sugarman, 1986; Leonard, 1993; Schumacher, Feldbau-Kohn, Slep, & Heyman, 2001), the functional role of alcohol consumption in episodes of IPV has been the subject of considerable and, at times, heated debate. Some have argued that alcohol intoxication, via its psychopharmacologic effects of ethanol on cognitive processing (e.g., Chermack & Taylor, 1995) or the expectancies associated with intoxication (Critchlow, 1983), facilitates all types of violence, including IPV. This explanation of the link between alcohol use and violence is often referred to as the proximal effects model. However, others have countered that the relationship between alcohol use and violence is spurious (e.g., alcohol use and violence are related to another variable, such as the presence of antisocial personality (ASP), and thus appear directly connected when they, in fact, are not) or is largely indirect (e.g., drinking leads to poor relationship adjustment, which creates an environment conducive to aggression). Although these competing explanations have focused mostly on the relationship between alcohol use and IPV, they also apply more broadly to the relationship between the use of and intoxication from any psychoactive substance and violence (e.g., Wekerle & Wall, 2002).

Implicit in the proximal effects model is that there should be a temporal relationship between substance use and violence, that is, it would be expected that episodes of violence (including IPV) would most likely occur after drinking or drug use and within a comparatively brief time period after consumption (i.e., when the perpetrator is experiencing the intoxicating effects of the ingested substance or suffering from the residual effects of intoxication, such as withdrawal). Unfortunately, because of limitations in data collection and general assessment methods, it has been difficult to ascertain the temporal association between substance use and IPV. Most investigations to date have relied largely on correlational analyses, demonstrating, for example, that individuals who report more frequent drug or alcohol use are more likely to report engaging in IPV compared to individuals who use psychoactive substances less frequently or not at all. Although the information from such studies provides some support for the role of substance use in IPV, the inherent difficulty in drawing more substantive conclusions from these findings is that it is not clear when the substance use and when the episodes of violence occur. From most studies, it cannot be ascertained whether substance use and the episodes of IPV even occurred on the same day; as such, drawing valid inferences about the proximal relationship of intoxication in IPV is not possible.

However, in a study recently completed by our group (Fals-Stewart, 2003), we addressed many of these issues. In this investigation, we collected detailed daily diaries, covering a 15-month period, about the occurrence and timing of daily episodes of drinking and male-to-female physical aggression from male and female partners with histories of IPV in which the male partners were entering an alcoholism or domestic violence treatment program. The diaries contained information about not only the occurrences of male-to-female aggression but also information about (a) the time of day these episodes happened, (b) whether the male partner drank alcohol during the same day when the violence occurred, and (c) what time of day the drinking started and ended. This allowed for a detailed examination of the daily temporal relationship between male-to-female aggression and drinking. Counting alcohol and male-to-female aggression as linked only on days when the drinking occurred before the IPV episode, for men entering the domestic violence treatment program (alcoholism treatment program odds in parentheses), the odds of any male-to-female physical aggression were more than 8 times (11 times) higher on days when men drank than on days of no alcohol consumption. The odds of severe male-to-female physical aggression were more than 11 times (11 times) higher on days of men's drinking than on days of no drinking. Moreover, in both samples, over 60% of all episodes occurred within 2 h of drinking by the male partner. From an assessment and methodological standpoint, this investigation was an important advancement and increased our understanding of the role of alcohol use and intoxication in episodes of male-to-female physical aggression.

However, a major limitation of this investigation was its exclusive focus on alcohol use. In their extensive review of the link between substance use and violence, Miczek et al. (1994) note that the association between alcohol use and aggression is, by far, the most widely researched and most well established. Research on the links between use of other drugs and the occurrence of violence in general, and IPV in particular, is not nearly as evolved as alcohol-violence research. Most of the research exploring the relationship between illicit drug use and IPV has been correlational in nature, with the temporal association between drug use and IPV remaining unexplored. Moreover, the relationship between violence and illicit substance use is obfuscated by the presence of ASP characteristics observed among many individuals who abuse drugs, which can serve to create a spurious relationship between the occurrence of violence (both in general and between intimate partners) and substance use.

Thus, the purpose of the present study is to examine the day-to-day relationship between substance use and IPV among men seeking treatment for drug abuse who reported a history of male-to-female aggression. This present investigation used the same methods of assessment and data collection used in our earlier work focusing on alcohol use, thus, allowing for the day-to-day examination of the relationship between the occurrence of male-to-female physical aggression and the male partners' use of various psychoactive drugs, in addition to alcohol. In these analyses, we controlled for the presence of ASP among male partners', which could have spuriously inflated the relationship between substance use and violence. Because alcohol and other drug use is associated with relationship distress (e.g., Fals-Stewart, Birchler, & O'Farrell, 1999), which may create a context for IPV and thus spuriously inflate

the day-to-day association between substance use and violence, we also controlled for couples' levels of dyadic adjustment.

2. Method

2.1. Participants

2.1.1. Sociodemographic characteristics

Participants were married or cohabiting male and female partners who reported at least one act of male-to-female physical aggression in their relationship during the previous year. Participants were recruited from partner violent male patients entering a 12-week outpatient substance abuse treatment program and their female partners.

Of the 421 married or cohabiting men consecutively admitted to the program, at least one of the partners in 245 (58%) of these dyads reported at least one act of male-to-female aggression during the year before the pretreatment assessment and were asked to participate. Of these, 32 (13%) men refused to be in the investigation. The intimate female partners of 23 men (9%) who initially agreed to be in the study refused to participate when the investigation was described more fully; data from these couples were not included. Men in 20 couples (8%) who agreed to participate left treatment before complete baseline assessment data were collected. For 21 couples (9%), one or both partners dropped out of the study at some point during the follow-up period (i.e., they could not be located or refused to provide required data) and thus did not provide full information about IPV, substance use, or both.[1] Thus, 149 male patients and their partners were included in the investigation.

The demographic and background characteristics of the final sample are located in Table 1. Statistical comparisons of these characteristics of the couples that participated and the 96 dyads that were not included, using analysis of variance and binomial tests, revealed the partners who were not included were significantly (P's $< .05$) younger (M = 30.4 years, S.D. = 7.2) and had shorter lengths of relationship with their partners (M = 3.1 years, S.D. = 5.9).

2.1.2. Description of substance abuse treatment

As noted, the male partners were recruited from a substance abuse treatment program. The program specialized in the treatment of individuals who primarily abused psychoactive substances other than alcohol, although the majority of patients treated in this setting also

[1] The approach of eliminating participants who did not provide complete data (i.e., listwise deletion) can result in biased parameter estimates. Although other alternatives for handling missing data were considered (e.g., multiple imputation, maximum likelihood methods), the problem we faced was not only missing data about whether substance use or violence occurred, but also specifically when these events occurred on a given day. Because we had fairly good participant compliance and did not have many dropouts, it was decided to report the analyses of complete data versus making any estimates, based on some type of imputation, about the occurrence and specific timing of the behaviors under consideration.

Table 1
Baseline characteristics of final sample ($N = 149$)

Characteristics	Statistic
Mean (S.D.)	
Male partners' age	36.1 (8.2)
Female partners' age	34.9 (11.6)
Male partners' education	12.4 (1.1)
Female partners' education	12.5 (1.2)
Years married or cohabiting	8.1 (4.9)
Annual income (in thousands of U.S. dollars)	27.6 (19.0)
Number (%) cohabiting but not legally married	44 (30)
Male partners' (and female partners') race/ethnicity	
White	90 (94)
African American	39 (33)
Hispanic	13 (14)
Other	5 (6)
Mean (S.D.) couple DAS score	90.2 (20.4)
Mean (S.D.) PDA for male participants	28.2 (34.3)
No. (%) of male partners meeting criteria for the following DSM-IV substance use dependence disorders	
Alcohol	91 (61)
Cocaine	77 (52)
Opiates	58 (39)
Cannabis	18 (12)
'Other'	36 (24)
Number (%) of male partners meeting *DSM-IV* criteria for Antisocial Personality Disorder	57 (38)
Mean (S.D.) CTS subscale score for male-to-female	
Verbal aggression	64.6 (17.9)
Overall violence	6.5 (3.2)
Severe violence	1.9 (2.6)
Mean (S.D.) CTS subscale score for female-to-male	
Verbal aggression	34.8 (33.6)
Overall violence	7.9 (5.1)
Severe violence	1.5 (1.9)

DAS = Dyadic Adjustment Scale; PDA = percentage of days abstinent derived from the TLFB; *DSM-IV = Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. (American Psychiatric Association, 1994); CTS = Conflict Tactics Scale. For partners' race/ethnicity, the number of male partners in each category is provided outside the parentheses; the number of female partners in each category is provided within the parentheses.

had alcohol use disorders in addition to other drug use disorders. Participants received weekly individual and group counseling over a 12-week period. The intervention followed a traditional 12-step facilitation model of substance abuse treatment, while also encouraging participants to engage in self-help support meetings. According to treatment providers in this program, partner violence was only discussed if the issue was raised in the context of group or individual treatment. Patients who reported that they engaged in IPV were referred

to a domestic violence treatment program after completion of the drug abuse treatment program.[2]

It is important to emphasize this study was not a treatment outcome study; men were recruited from the treatment program because the setting allowed for convenient access to and recruitment of men who had engaged in partner violence, along with their intimate partners, both of whom could then be trained in the use of the substance use and partner violence diaries. Use of the diaries was a critical component of the investigation, increasing the reliability of daily reports of both substance use and violence.

2.2. Materials and measures

2.2.1. Diaries

Upon admission to the study, male and female partners participated in extensive didactic training on the use of the daily diaries, conducted by a research assistant (RA), during which they were each given a 15-month supply of log books and were instructed how to fill out the daily log sheets. Each logbook contained a 5-month supply of diary sheets to record daily episodes of male partner's drinking and other drug use and male-to-female physical aggression. The daily substance use log included space for four different drinking or other substance use episodes per day. For each day of substance use by the male partners, both partners were asked to record each time a substance use episode (i.e., drinking or other drug use) began and ended (defined as the last use of a substance).

In the diaries, participants recorded the time each episode of IPV happened and the type of partner violence that occurred. Violence type was classified by the categories used in the Conflict Tactics Scale (CTS; Straus, 1990): (a) threw something at partner, (b) pushed, grabbed or shoved, (c) slapped, (d) kicked, bit, or hit, (e) hit, or tried to hit, with something, (f) beat up, (g) threatened with a knife or gun, (h) used a knife or gun, or (i) other types of physical aggression not otherwise specified. It is possible more than one type of violent act could occur as part of any circumscribed violent episode (e.g., within a single conflict, a male partner might shove his partner and also throw something at his partner); all types of partner physical aggression occurring on a given day and during a given episode were recorded in the log. As with the CTS, items d–h are considered types of severe violence. On each day, the log also required respondents to note if they had any face-to-face contact with their identified partner. Partners were considered to have face-to-face contact even in circumstances in which the contact was brief (e.g., picking up children for visitation). Any face-to-face contact represented an opportunity for male-to-female physical aggression to occur between partners. Days in which partners did not have any face-to-face contact were not included in the analytic models because there was no opportunity for IPV to occur.

[2] The information collected from the couples about the occurrence of IPV was not shared with the clinical providers in the treatment program. A review of the clinical charts of the men who participated in the investigation revealed that 14 (9%) were referred to a domestic violence treatment program after treatment. According to data collected as part of the posttreatment data collection, only one of these men attended the domestic violence treatment program to which they were referred.

Each partner was asked to mail his or her diary to investigators each week, using prepaid addressed envelopes. If a weekly diary was not received at or before 4 days after it was supposed to be mailed, the participant who had failed to mail the diary was contacted by telephone by an RA, who then queried the participant about substance use and episodes of violence for the week covered by the missing diary. Participants were paid US$5.00 for each weekly diary that was completed and mailed. The information recorded by the partners on their diaries was transferred to daily calendars, which covered the 15-month period under consideration. Partners also participated in face-to-face interviews with RAs every 3 months, during which the calendars were reviewed, evaluated, and corrected (if necessary). This combination of diaries and timeline calendar interviewing has been shown to be a reliable and valid method of collecting information about the daily occurrence of IPV (Fals-Stewart, Birchler, & Kelley, 2003).

2.2.2. Relationship violence

The CTS was used to assess the frequency of male- and female-perpetrated verbal aggression, overall violence, and severe violence. Respondents rated each CTS item on a seven-point scale (never, once, twice, 3–5 times, 6–10 times, 11–20 times, more than 20 times) for the frequency that they and their intimate partners engaged in the behavior during the last 12 months. Straus (1990) recommended scoring the frequency of violent acts using the middle of yearly frequency range for each CTS response category as follows: never = 0; once = 1; twice = 2; 3–5 times = 4; 6–10 times = 8; 11–20 times = 15; more than 20 times = 25. A combined self- and partner-report was used. For example, if either the male partner or his intimate partner reported the male partner had been violent in the last year, he would be coded as violent. This approach is frequently used to address concerns about underreporting and leads to higher prevalence rates than self-reports alone.

The CTS Verbal Aggression subscale has six items (e.g., yelled and/or insulted, threatened to hit or throw something at the partner). The CTS Violence subscale has eight items: (a) threw something at the partner; (b) pushed, grabbed, or shoved; (c) slapped; (d) kicked, bit, or hit; (e) hit, or tried to hit, with something; (f) beat up; (g) threatened with a knife or gun; and (h) used a knife or gun. Frequency scores based on all eight items are labeled overall violence; scores based on items d–h provide a measure of severe violence (Straus, 1990).

2.2.3. Substance use

The Timeline Followback Interview (TLFB; Fals-Stewart, O'Farrell, Freitas, McFarlin, & Rutigliano, 2000) is a well-validated semistructured interview designed to assess frequency of drug and alcohol use. The TLFB uses a calendar and other memory aids to gather retrospective estimates of an individual's daily drinking and other drug use over a specified time period, up to 12 months from the interview date. The substance use index derived from the TLFB used in the present investigation was percentage of days abstinent (PDA), which was operationally defined as the percentage of days in the measurement interval the patient reported no alcohol or drug use and was not in jail or a hospital for reasons related to drug or alcohol use.

Male partners were interviewed with the psychoactive substance use modules of the Structured Clinical Interview for *DSM-IV* (SCID; First, Spitzer, Gibbon, & Williams, 1995),

administered by one of two master's-level RAs (both of whom were trained by William Fals-Stewart, who has extensive experience administering the SCID). Interrater reliability was assessed using a paired-rater design. Videotaped interviews of 20 patients entering a drug abuse treatment center were independently observed by both primary interviewers and by the author. Kappas between the two primary interviewers for the substance use disorders ranged from .80 to 1.0. Kappas between William Fals-Stewart and the primary interviewers also ranged from .90 to 1.0. These kappa coefficients reflect good-to-excellent observer agreement (Landis & Koch, 1977).

2.2.4. ASP disorder

Male partners were interviewed with the ASP module from the SCID by master's-level RAs. Using the same approach to assess interrater reliability that was used with the substance use disorders (i.e., review of 20 patient interviews rated independently by the RAs and by William Fals-Stewart), the RAs and William Fals-Stewart had perfect agreement on ASP diagnosis for the videotaped cases.

2.2.5. Relationship disharmony and conflict

Partners completed the Dyadic Adjustment Scale (DAS; Spanier, 1976), a widely used inventory of general relationship adjustment and satisfaction. Higher scores indicate higher levels of general relationship satisfaction. Traditionally, scores less than 98 indicate significant relationship dissatisfaction. Previous studies have revealed the DAS to have high reliability, with alpha coefficients typically exceeding .90 and stability coefficients exceeding .85 (e.g., Carey, Spector, Lantigna, & Krauss, 1993). As reported in the original reference, the DAS also reliably discriminates between distressed and nondistressed couples. For this investigation, partners' scores were averaged to get a couple-level measure of relationship distress.

2.3. Procedure

2.3.1. Assessment

Partners were interviewed by master's-level RAs at pretreatment, posttreatment, and quarterly thereafter for 1 year. At pretreatment, partners completed the DAS, CTS, SCID, and TLFB (to assess male partners' frequency of substance use during the previous 12-month period). As noted, they were also trained in the use of the daily diaries. At the scheduled end of treatment (i.e., 3 months after program admission), and quarterly thereafter for 12 months, partners were also interviewed separately in the drug treatment program facility by an RA. During that interview, the partners were provided copies of the calendars on which male-to-female physical aggression and substance use behavior were recorded. At this interview, any time periods for which information was not complete or if there were other additions or corrections the partners wished to make, they could do so during these face-to-face contacts. Although all interviews were to be conducted in a face-to-face format, a small proportion of interviews were conducted by telephone (i.e., less than 10%) when participants were either away from the area or refused to participate in face-to-face interviews. Partners were paid for participation in the baseline, posttreatment, and all follow-up interviews.

Partners demonstrated fairly high compliance with completing and mailing the weekly diaries. On average, participants mailed the weekly diaries on time roughly 65% of the time (i.e., they were received within 4 days of the mailing date by the designated RA). Moreover, in roughly 85% of instances when diaries were not completed on time or otherwise were not received (e.g., lost in the mail), partners were successfully contacted by telephone and the necessary data were gathered on the occurrence and timing of substance use (i.e., drug and alcohol use) and male-to-female physical aggression.

2.4. Statistical analytic method

2.4.1. General analytic approach

To examine the daily conditional relationship between substance use and male partner physical aggression, two-level hierarchical generalized linear model analyses (HGLM; Raudenbush & Bryk, 2002) were conducted using the MLWin program, Version 1.2 (Goldstein et al., 1998). In these logistic regression time series models, the occurrence of male-to-female physical aggression on a given day was the dependent measure and male partners' substance use on the same day was the primary independent measure of interest. The focus of the analysis was on the joint dependency of these two behaviors (i.e., on the extent to which the likelihood of an event or behavior is influenced by the occurrence of another behavior). The change in the odds of male-to-female physical aggression occurring on days of face-to-face contact between partners when the male partner used a psychoactive substance (i.e., alcohol or another drug) before the violent episode compared to days of no substance use or substance use only after the occurrence of violent episodes was examined.[3]

Because the dependent measure can take values of either 0 (i.e., no partner violence) or 1 (i.e., occurrence of partner violence), the HGLMs used a Bernoulli sampling distribution and a logit link function. Use of the different psychoactive substances was treated as a Level 1 time-dependent covariate. Partner violence and substance use were nested within participants (Level 2). A first-order autoregressive structure was used and penalized quasi-likelihood was implemented for parameter estimation.

Partner physical aggression and substance use by the male partners were counted as linked on a given day only if the first episode of substance use preceded the first act of male-to-female violence. For the present study, if multiple types of violence occurred on a given day, the type of violence occurring on the day was considered 'severe' if any of the violent acts were severe.

Although obtained from both partners, data provided by the female partners regarding episodes of male-to-female physical aggression and their reports of face-to-face contact were used in the analyses reported. Female reports of male-to-female physical aggression were used

[3] For six episodes of male-to-female aggression, substance use occurred and ended close to the end of one day (i.e., shortly before midnight) and the episode of violence closely followed but occurred the day after the substance use (i.e., shortly after midnight). Using our criteria for determining if substance use was linked on a given day, these particular episodes of substance use and violence were not classified as linked because they occurred on different days. In the models presented, these episodes of IPV and substance use were not, in fact, counted as linked. This decision was deemed the most conservative in this analysis; however, if these substance use and violence episodes are counted as linked, the results reported do not change substantively.

because some studies suggest, perhaps because of issues related to social desirability, that men report fewer episodes of male-to-female physical aggression than their female counterparts (e.g., Archer, 1999).

Additionally, substance use information provided by the male partners was used in the analytic models. Although men's reports of their own substance use could also be influenced by positive impression management or dissimulation, the male participants were, of course, the only individuals in the dyads who have full knowledge of when they drank or used other drugs, particularly given that much of the male partners' substance use can occur in settings where the female partner is not present. An important advantage of using different partners' reports of violence and substance use, respectively, is that the effect of the perception bias held by any single member of the dyad that violence and substance use are related is largely reduced or eliminated if the reports of the behaviors of interest are given by different respondents.[4]

2.4.2. Control variables

In these models, to control for levels of male partners' ASP characteristics, the SCID diagnostic classification of ASP was entered as a Level 2 predictor. To control for level of couples' relationship distress, partners' mean DAS scores were also included in the models as Level 2 variables. In addition to serving as control variables, including ASP diagnosis and DAS couples score in the model allowed for the examination of these variables' main effects on likelihood of violence on a given day, regardless of substance use.

2.4.3. Model building approach

Among the male participants in the investigation, the following psychoactive substances were used on a sufficient number of days to model their potential impact on the occurrence of male-to-female aggression: (a) alcohol, (b) cocaine, (c) cannabis, and (d) opiates.[5] We used a sequential approach to examine the relationship between the use of these drugs and the occurrence of male-to-female aggression. First, we examined the univariate relationship

[4] We also had reports about occurrences of male-to-female physical aggression from the male partners and reports of male partners' substance use by the female partners. For episodes of violence, male and female partners' reports moderately related, pooled across all couples, the kappa coefficient was .61 ($P < .001$). Using male reports of violence in the models did yield substantively different results than those that are reported. In terms of substance use, however, female partners reported that they were aware of drinking or other drug use by their male partners, but in many instances could not report times or were unable to identify the substances used. In the quarterly interviews, female partners reported that the male partners often drank or used drugs while not in their presence (e.g., with friends after work). Use of female reports about substance use in the models yielded a significant day-to-day relationship between substance use and male-to-female physical aggression (which was also found when using men's reports). However, use of female reports about male partners' use of specific substances and the timing of such use was not practical due to the amount of missing information in those reports.

[5] The participants in this sample did use other drugs other than alcohol, cocaine, opiates, and cannabis. These included LSD, amphetamines, methaqualone, phencyclidine, and anxiolytics. However, the number of days of use of any of these drugs, pooled across the sample, was less than 3% of the total number of days of face-to-face contact with their partners, compared to greater than 15% of the days or more for use of alcohol, cocaine, opiates, and cannabis by the male participants. Thus, the small number of days of use of these other substances precluded a meaningful examination of their effect on IPV.

between the use of any of these drugs and the occurrence of violence. If we found this conditional relationship to be significant, we then planned to examine the effects of each substance individually using model building strategies and methods for logistic regression described by Hosmer and Lemeshow (1989). Specifically, we initially conducted univariate analyses with the use of each substance considered in separate models. All substances in the univariate analyses that had a P value of less than .25 were then retained as candidates for inclusion in the multivariate HGLM (Mickey & Greenland, 1989). All of the univariate and multivariate HGLMs conducted included ASP diagnosis of the male partners and couple DAS scores as control variables.

3. Results

3.1. Male partners' substance use and male-to-female physical aggression during the assessment period

The mean (S.D.) number of days of face-to-face contact between partners was 249.3 (104.6). Among these couples, 52 (35%) of the female partners reported at least one act of male-to-female physical aggression and 102 (68%) of the male partners reported drinking or using another psychoactive substance on one or more of the days of face-to-face contact. Pooled across couples, the number of days of male-to-female physical aggression was 499; of these, 179 (36%) were episodes of severe aggression. On 299 (60%) days of any physical aggression and on 128 (72%) days of severe violence, the male partner drank or used drugs before the violent episode.

3.2. The day-to-day relationship between substance use and the occurrence of male-to-female physical aggression

After controlling for ASP and couple DAS scores, the likelihood of any male-to-female physical aggression was significantly higher on days of substance use compared to days of no substance use, $B = 1.22$, S.E. $= 0.14$, $z = 8.71$, $P < .001$, odds ratio (OR) $= 3.38$. Similarly, the likelihood of severe male-to-female physical aggression on a given day was significantly higher on days of substance use compared to days of no substance use, $B = 1.39$, S.E. $= 0.13$, $z = 10.69$, $P < .001$, OR $= 4.01$.

With ASP and couple DAS scores included in the models as control variables, the day-to-day univariate relationships between each of the psychoactive substances and the occurrence of any male-to-female physical aggression and severe male-to-female physical aggression are located in Table 2. Three of the four drugs (i.e., alcohol, cocaine, and heroin) met the selection criterion for inclusion in the final multivariate model (i.e., all had P's $< .25$) for any male-to-female physical aggression and two of the four drugs (i.e., alcohol and cocaine) met the selection criterion for inclusion in the final multivariate model for severe male-to-female physical aggression. Cannabis did not meet the selection criterion for consideration to be entered into the final multivariate models for any or severe violence.

Table 2
Parameter estimates for univariate hierarchical generalized linear models examining the day-to-day relationship of alcohol, cocaine, opiates, or cannabis and the occurrence of any and severe male-to-female physical aggression

Fixed effects	*B*	S.E.	*z*	OR
Any physical aggression				
Alcohol	1.79	0.09	19.91•••	5.99
Cocaine	1.28	0.13	9.85•••	3.60
Opiates	0.30	0.16	1.87••	1.34
Cannabis	−0.06	0.05	−1.10•	0.94
Severe physical aggression				
Alcohol	1.92	0.08	36.51•••	6.82
Cocaine	1.11	0.14	7.93•••	3.03
Opiates	0.13	0.11	1.08•	1.13
Cannabis	−0.10	0.09	−1.04•	0.90

In these models, the presence of ASP disorder and couple DAS score were entered as control variables. All substances were evaluated in separate models (i.e., they were not entered simultaneously). Use of substances that was related to violence at $P<.25$ were eligible for inclusion in the final multivariate models.

• $P>.25$.
•• $P<.10$.
••• $P<.001$.

The final multivariate models for any male-to-female physical aggression and severe male-to-female aggression are located in Table 3. Alcohol and cocaine were significantly associated with an increased likelihood of any male-to-female physical aggression; opiate use was not significant in this model. Even after controlling for ASP and DAS, the odds of male partner violence increased more than fourfold on days of drinking and nearly threefold on days of cocaine use. Similarly, alcohol and cocaine were significantly associated with an increased likelihood of the occurrence of severe violence. The odds of severe male-to-female physical aggression were over five times higher on days of drinking and nearly three times higher on days of cocaine use.

In the models for any and severe physical aggression, we also explored whether the combination of alcohol and cocaine was significantly associated with an increased likelihood of violence. We explored other substance combinations as well (e.g., opiates and cocaine, alcohol and cannabis, alcohol and opiates). In all of the models for any and severe physical aggression, use of multiple drugs on a given day did not significantly increase the likelihood of male partner violence above the increases in violence attributable to the individual substances (i.e., all *P*'s for the combinations were less than .05). Interactions between each substance and the presence of ASP were also not significant in any models.

3.3. Examination of the trend in the temporal relationship between substance use and IPV

If it is assumed that substance intoxication or withdrawal serves to facilitate acts of partner violence, it would follow that, on days when substance use and violence co-occur, most acts of male partner aggression should occur close in time to episodes of male partners' substance use.

Table 3
Parameter estimates for hierarchical generalized linear models examining the day-to-day relationship of alcohol, cocaine, and opiate use and any and severe male-to-female physical aggression

Fixed effects	B	S.E.	z	OR
Any physical aggression				
Intercept	−4.61	0.14	−34.38***	0.01
ASP	0.09	0.03	2.70**	1.09
DAS	−0.06	0.02	−2.44*	0.94
Alcohol	1.48	0.09	16.44***	4.39
Cocaine	1.06	0.08	13.25***	2.89
Opiates	0.13	0.11	1.18	1.13
Severe physical aggression				
Intercept	−6.13	0.21	29.19***	0.01
ASP	0.14	0.04	3.99***	1.15
DAS	−0.04	0.02	−2.19*	1.04
Alcohol	1.69	0.10	16.25***	5.42
Cocaine	1.03	0.09	10.95***	2.80

ASP = Antisocial personality disorder for male partners (coded "1" if present, "0" if absent); DAS = Dyadic Adjustment Scale (couple score). As noted in Table 2, alcohol, cocaine, and opiates were eligible for inclusion in the model for any physical aggression; only alcohol and cocaine were eligible for inclusion in the model for severe physical aggression.

* $P<.05$.
** $P<.01$.
*** $P<.001$.

To explore this hypothesis, all days on which male partners consumed alcohol or used cocaine and male-to-female physical aggression occurred were isolated. We placed our focus only on alcohol and cocaine use based on the results of the multivariate HGLMs described earlier.

On each of these days, the time of day of the first episode of violence was identified from the female partners' reports. From the male partners' reports, all drinking episodes and cocaine use episodes on that day occurring before the episode of violence were marked; of these, the substance use episode occurring closest in time to the act of violence was identified. The substance use episode was considered to be closest if the male-to-female aggression was bracketed in time by the start and completion of a cocaine use or drinking episode. In instances when the violence did not occur during a substance use period, the episode ending nearest in time to the act of violence was considered closest. The amount of time between the end of the closest episode of male partners' drinking or cocaine use and the act of partner violence was calculated; when substance use was occurring when the violent episode took place, the amount of time between drinking and violence was assumed to be zero. The time between substance use and violence was transformed into an ordered multinominal time variable: (a) 0–1 h 59 min, (b) 2–3 h 59 min, (c) 4–5 h 59 min, (d) 6–7 h 59 min, and (e) eight or more hours.

Violence episodes involving cocaine and episodes involving alcohol were examined separately. On days when both substances were used, the violent episode was considered related to the drug that was used closest in time to the aggressive event. For six episodes

of any violence and three episodes of severe violence, it could not be determined which drug was used closest in time to the violent episode; these days were excluded from the analysis.

The relationships between the ordered multinominal time variable and both any and severe partner violence were examined. The percentage of acts of any male-to-female physical aggression happening in each time period related to alcohol use and related to cocaine use are shown in Panel A of Fig. 1. To test the trend of the relationship between the likelihood of any male-to-female aggression and the time of drinking, an HGLM was performed on these data. Occurrences of violence in each time frame were a count dependent variable; the multinominal time variable was a Level 1 predictor. Participants who engaged in violence represented Level 2. Conceptually, the occurrences of male-to-female physical aggression during the different

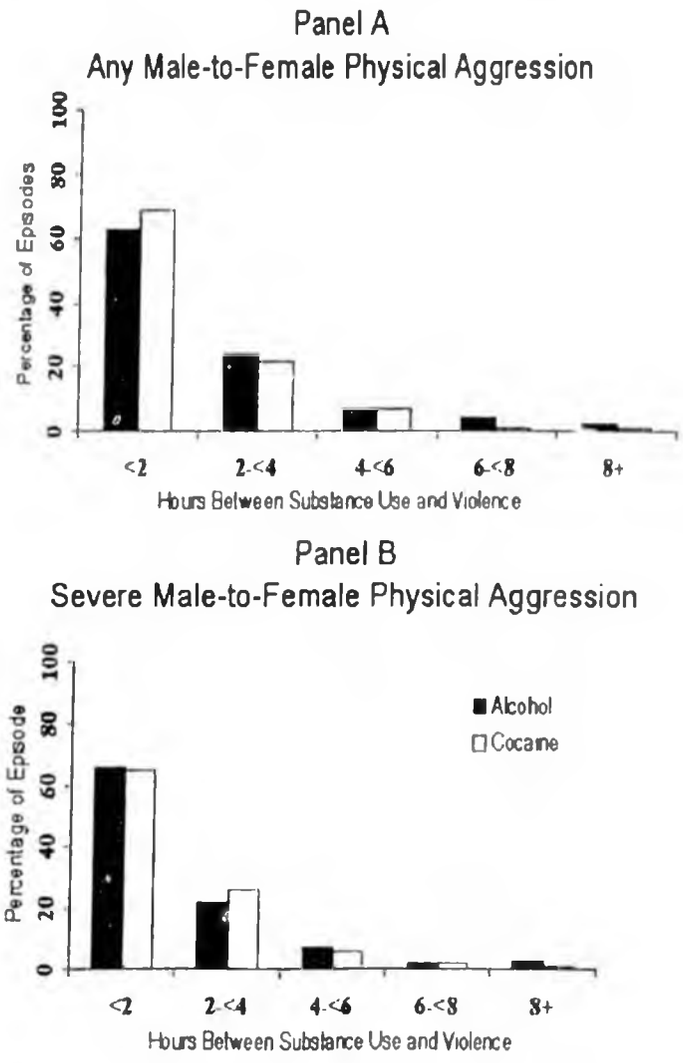


Fig. 1. The percentage of episodes of any male-to-female physical aggression (Panel A) and severe male-to-female physical aggression (Panel B) occurring at different time periods after male partners' use of alcohol or cocaine ended.

abuse often leads to relationship distress, thereby creating a context in which IPV is more likely to occur. However, because both the presence of male partners' ASP and couple DAS scores were controlled in all of the analytic models exploring the IPV–substance use link, these did not account for the significant day-to-day relationships between alcohol use, cocaine use, and male-to-female physical aggression.

The findings of the present investigation provide a replication of our earlier diary study examining the link between alcohol use and IPV (Fals-Stewart, 2003), which also demonstrated significant increases in male-to-female physical aggression on days of alcohol use for partner violent men entering either an alcoholism treatment program or domestic violence treatment program. Moreover, the current study also represents an important extension of that earlier research by exploring the effects of other commonly abused illicit drugs on the occurrence of IPV and demonstrating, for the first time, a significant day-to-day relationship between cocaine use and IPV.

Although our findings provide support for a potential causal role for alcohol and cocaine use in the occurrence of male-to-female physical aggression, it is important to note that the results of the present investigation cannot rule out noncausal explanations. For example, it is possible that, for some occurrences of IPV, men in this study may have decided to aggress against their female partners and subsequently used alcohol or other drugs to overcome any inhibitions about engaging in such behavior.

Because similar assessment and data collection methods were used, this investigation shares many of the strengths of the Fals-Stewart (2003) study. More specifically, both studies obtained prospective, daily reports of substance use and partner violence over an extended time interval, thus allowing for comprehensive analyses of these behaviors' day-to-day conditional relationship. Perhaps because of the regular contact with participants, there were comparatively few participant dropouts from the study during the course of data collection. We also collected information about male-to-female physical aggression and substance use separately from different partners (i.e., IPV information from the female partner, substance use by the male partner); thus, the effects of any preconceptions about the link between these behaviors on our findings were reduced.

In addition, the present study required participants to mail their diaries each week to a designated RA so information about IPV and substance use could be recorded; participants who failed to mail their diaries in a timely manner were contacted by telephone and interviewed to collect the data. This process ensured that data were solicited and collected about a fairly brief assessment interval (i.e., each week of the 15-month period), reducing the effects of decaying memory on report accuracy. In contrast, participants in the Fals-Stewart (2003) investigation were asked to maintain their diaries and were contacted regularly to encourage consistent recording in the diaries, but participants were not asked to mail the diaries. They were asked to bring the diaries to follow-up interviews every 3 months, where they were then used as memory aids to complete timeline interviews. Thus, it could not be discerned when participants completed the diaries and, in fact, if participants filled out the logs in a timely manner. Given our interest in day-to-day events, efforts to gather data each week and monitoring its collection likely enhanced compliance and accuracy of participants' reports compared to our alcohol–IPV diary study.

With these strengths in mind, the present investigation had several significant limitations. The study focused on the conditional relationship of two behaviors: male partners' substance use and male-to-female violence. Although this conditional relationship is important, we also recognize that IPV has multiple determinants and is typically not unidirectional. Information about other daily behaviors likely to influence IPV was not collected as part of the present study. For example, we did not collect information about female partners' drinking or drug use and how that might have influenced the occurrence of violence. Additionally, we did not collect information about female-to-male physical aggression, which appeared to be more frequent in these dyads than male-to-female aggression during the year before these men entered treatment (based on CTS female-to-male physical aggression frequency scores compared to CTS male-to-female physical aggression frequency scores). Comparatively higher frequency of female-to-male physical aggression has also been observed in other IPV investigations (e.g., Fals-Stewart et al., 2003). Thus, future investigations in this area need to explore the dynamic interplay of the occurrence and timing of different behaviors (e.g., both partners' alcohol use, both partners' drug use, female-to-male violence, male-to-female violence) to better understand the antecedence and consequences of IPV. The diary assessment methods used in the current study lend themselves to such an examination; given the willingness of participants to engage in this study and comply with the procedures, despite the labor-intensive nature of the assessment approach, more comprehensive day-to-day studies of IPV are both possible and practical. Other daily data collection methods, such as interactive voice response technology (e.g., Mundt, 1997), which allows respondents to make daily telephone calls and respond to queries about behaviors occurring during the day, may also yield reliable temporal information about the interrelationship of IPV and substance use.

Compared to examination of the effects of a single psychoactive substance, such as alcohol, on IPV, using participants who regularly ingested multiple substances presented certain challenges that make interpretation of the effect of any single substance difficult. For example, many individuals drink alcohol to ameliorate some of the unpleasant post-acute intoxication effects of cocaine (e.g., irritability, paranoia, anxiety; e.g., Gold, 1997). As noted earlier, when examining the temporal relationship between cocaine use, alcohol use, and male-to-female aggression, we counted the violence episode as linked to the substance used closest in time to the male partners' aggressive behavior. For certain specific episodes of male-to-female aggression, based on the calendar reports, male partners had used cocaine extensively during the day, but had begun to drink after the extended cocaine use had ceased. The violence occurred after the drinking had started and thus was counted as linked to alcohol use. Although this is objectively accurate, it may be that these violence episodes were more a consequence of the cocaine use. Moreover, we make reference to the occurrence of male IPV being related to cocaine or alcohol *intoxication*, but the anecdotal reports of many participants suggest that violence occurred during the post-intoxication phase of these substances, which are often marked by increased irritability, fatigue, anxiety, and so forth. Thus, it is perhaps most accurate to consider violence to be related to the psychophysiological effects of these drugs, which includes both intoxication and withdrawal.

We also were only able to focus on four psychoactive substances in these analyses, primarily because participants from these programs used other drugs rather infrequently. Investigations seeking to explore the effects of other drugs on IPV may have to engage in a different recruitment strategy (e.g., oversampling married or cohabiting amphetamine users) to ensure sufficient use of these other substances to explore their influence on partner violence. We also recruited participants from a substance abuse treatment program, which allowed us the opportunity to recruit individuals who admittedly engaged in drug use and to train partners extensively in the use of the diaries. Although the present investigation was not a treatment outcome study, the effects of treatment on the link between male-to-female aggression and substance use are unclear. Additionally, our results may not generalize to those who are not seeking treatment for substance abuse; efforts need to be undertaken to recruit married or cohabiting alcohol- and drug-abusing individuals from the general populations to examine the effects of different psychoactive substances on IPV.

Despite these limitations, the results of the study provide further support for the facilitative role of alcohol and cocaine use in the occurrence of IPV. Understanding factors that contribute to IPV may lead to improvements in the methods of prevention and intervention used to address IPV in clinical samples and in the community.

Acknowledgements

This project was supported, in part, by grants from the National Institute on Drug Abuse (R01DA12189, R01DA14402, and R01DA015937) and the National Institute on Alcohol Abuse and Alcoholism (R21AA013690).

We thank Christopher M. Murphy, Department of Psychology, University of Maryland at Baltimore County, Timothy J. O'Farrell, Department of Psychiatry, Harvard Medical School, and Gary R. Birchler, Department of Psychiatry, University of California San Diego Medical School, for their helpful comments throughout this investigation. Additionally, we wish to thank Katherine Masyn, Graduate School of Education and Information Studies, University of California, Los Angeles, for her assistance with data analysis and Kenneth E. Leonard, Research Institute on Addictions, University at Buffalo, The State University of New York, for his insightful suggestions on earlier drafts of this article.

References

American Psychiatric Association, (1994). *Diagnostic and statistical manual of mental disorders* (4th ed.). Washington, DC: Author.

Archer, J. (1999). Assessment of the reliability of the Conflict Tactics Scales: A meta-analytic review. *Journal of Interpersonal Violence, 14*, 1263–1289.

Carey, M. P., Spector, I. P., Lantigna, L. J., & Krauss, D. J. (1993). Reliability of the Dyadic Adjustment Scale. *Psychological Assessment, 5*, 23–240.

Chermack, S. T., & Taylor, S. P. (1995). Alcohol and human physical aggression: Pharmacological versus expectancy effects. *Journal of Studies on Alcohol, 56*, 449–456.

Critchlow, B. (1983). Blaming the booze: The attribution of responsibility for drunk behavior. *Personality and Social Psychology Bulletin, 9*, 451–473.

Fals-Stewart, W. (2003). The occurrence of partner physical aggression on days of alcohol consumption: A longitudinal diary study. *Journal of Consulting and Clinical Psychology, 71*, 41–52.

Fals-Stewart, W., Birchler, G. R., & Kelley, M. L. (2003). The timeline followback spousal violence interview to assess physical aggression between intimate partners: Reliability and validity. *Journal of Family Violence, 18*, 131–142.

Fals-Stewart, W., Birchler, G. R., & O'Farrell, T. J. (1999). Drug-abusing patients and their intimate partners: Dyadic adjustment, relationship stability, and substance use. *Journal of Abnormal Psychology, 108*, 11–23.

Fals-Stewart, W., Kashdan, T. B., O'Farrell, T. J., & Birchler, G. R. (2002). Behavioral couples therapy for drug-abusing patients: Effects on partner violence. *Journal of Substance Abuse Treatment, 21*, 1–10.

Fals-Stewart, W., O'Farrell, T. J., Freitas, T. T., McFarlin, S. K., & Rutigliano, P. (2000). The timeline followback reports of psychoactive substance use by drug-abusing patients: Psychometric properties. *Journal of Consulting and Clinical Psychology, 68*, 134–144.

First, M., Spitzer, L., Gibbon, M., & Williams, J. (1995). *Structural clinical interview for Axis I DSM-IV disorders (SCID)*. Washington, DC: American Psychiatric Association.

Gold, M. S. (1997). Cocaine (and crack): Clinical aspects. In J. H. Lowinson, P. Ruiz, R. B. Millman, J. G. Langrod (Eds.), *Substance abuse: A comprehensive textbook* (3rd ed.) (pp. 181–206). Baltimore, MD: Williams & Wilkins.

Goldstein, H., Rasbash, J., Plewis, I., Draper, D., Browne, W., Yang, M., Woodhouse, G., & Healy, M. (1998). *A user's guide to MlwiN*. London: Institute of Education, University of London.

Hotaling, G. T., & Sugarman, D. B. (1986). An analysis of risk markers in husband to wife violence: The current state of knowledge. *Violence and Victims, 2*, 101–124.

Hosmer, D. W., & Lemeshow, S. (1989). *Applied logistic regression*. New York: Wiley.

Landis, J. K., & Koch, G. G. (1977). The measurement of observer agreement for categorical data. *Biometrics, 33*, 159–174.

Leonard, K. E. (1993). Drinking patterns and intoxication in marital violence: Review, critique, and future directions for research. *U.S. Department of Health and Human Services, research monograph 24: Alcohol and interpersonal violence: Fostering multidisciplinary perspective* (pp. 253–280). Rockville, MD: National Institutes of Health, NIH Publication No. 93-3496.

Miczek, K. A., DeBold, J. F., Haney, M., Tidey, J., Vivian, J., & Weerts, E. M. (1994). Alcohol, drugs of abuse, and violence. In A. J. Reiss, & J. A. Roth (Eds.), *Understanding and preventing violence* (pp. 377–570). Washington, DC: National Academy Press.

Mickey, J., & Greenland, S. (1989). A study of the impact of confounder selection criteria on effect estimation. *American Journal of Epidemiology, 129*, 125–137.

Mundt, J. C. (1997). Interactive voice response systems in clinical research. *Psychiatric Services, 48*, 611–612.

Murphy, C. M., & O'Farrell, T. J. (1994). Factors associated with marital aggression in male alcoholics. *Journal of Family Psychology, 8*, 321–335.

Raudenbush, S. W., & Bryk, A. S. (2002). *Hierarchical linear models: Applications and data analysis methods*. Thousand Oaks, CA: Sage.

Schafer, J., Caetano, R., & Clark, C. (1998). Rates of intimate partner violence in the United States. *American Journal of Public Health, 88*, 1702–1704.

Schumacher, J. A., Feldbau-Kohn, S., Slep, A. M. S., & Heyman, R. E. (2001). Risk factors for male-to-female partner physical abuse. *Aggression and Violent Behavior, 6*, 281–352.

Spanier, G. (1976). Measuring dyadic adjustment: New scales for assessing the quality of marriage and similar dyads. *Journal of Marriage and the Family, 38*, 15–30.

Straus, M. A. (1990). The Conflict Tactics Scale and its critics: An evaluation and new data on validity and

reliability. In M. A. Straus, & R. J. Gelles (Eds.), *Physical violence in American families* (pp. 49–73). New Brunswick, NJ: Transaction.

Straus, M. A., & Gelles, R. J. (1990). *Physical violence in American families: Risk factors and adaptations to violence in 8145 families*. New Brunswick, NJ: Transaction Publishers.

Wekerle, C., & Wall, A. -M. (2002). *The violence and addiction equation: Theoretical and clinical issues in substance abuse and relationship violence*. Philadelphia, PA: Brunner/Mazel.

Drug and Alcohol Review (December 2003), 22, 401 – 408

Taylor & Francis
Healthsciences

Substance use and the prediction of young offender recidivism

ALDIS L. PUTNIŅŠ

Department of Human Services, South Australia and School of Psychology, University of South Australia, Australia

Abstract

The problem considered is whether self-reported substance use can be used in the estimation of recidivism risk among youths placed in secure care. The Secure Care Psychosocial Screening (SECAPS) and offending records of 447 youths admitted to detention centres in South Australia were examined. The target outcome was any new offending within 6 months of release. Use of a psychoactive substance at the time of committing the most recent offence was not a significant predictor of subsequent offending, nor was acknowledging having a problem with drug or alcohol use. In relation to the recent use of alcohol, marijuana, hallucinogens, sedatives/hypnotics, narcotics, stimulants and inhalants, only the use of alcohol and inhalants appeared to have significant relationships with recidivism. While the relationships were too small to permit using these items on their own to estimate re-offending risk, recent alcohol and inhalant use could be included as part of a broader recidivism risk assessment. [Putniņš AL. Substance use and the prediction of young offender recidivism. *Drug Alcohol Rev* 2003;22:401 – 408]

Key words: juvenile delinquents, prediction, recidivism, risk, substance use, young offenders.

Introduction

A number of studies have indicated that substance use and juvenile offending are often closely associated activities [1]. This link has been confirmed in research investigations of young offenders in both police detention [2] and in youth detention centres in different Australian states [3 – 14]. The largest Australian study of a detention population to date describes patterns of substance use among 900 incarcerated young offenders in South Australia [12]. The major findings were:

- Incidences of any use of various substances by the young offenders during a recent 1-month period ranged from 10% for narcotics (opioids) to 81% for marijuana.
- The young offenders more often reported having used various psychoactive substances (other than alcohol) during a 1-month period than did a large national sample of high school students [15]. The incidences were 2 – 5 times greater, depending on the particular class of substance.
- While any use of alcohol during a 1-month period was similar between the two groups (namely 73% of young offenders and 68% of students), moderate drinking by young offenders was rare, with more than half (53%) consuming 10 or more drinks on a typical drinking occasion.
- Although a wide range of substances was used by many of the offenders, daily use was largely restricted to alcohol and marijuana (10% and 44% of respondents, respectively). No other substance was used daily by more than 3% of the respondents.
- A majority (60%) of the offenders reported having used substances at the time of committing their last offence.
- Among those who used a substance at the time of their last offence, the substances most often used were alcohol (62%) and marijuana (53%).

The above results are based on data gathered from psychosocial screening assessments that are carried out routinely to inform staff about each youth's needs and risks. Among the risks often considered in assessments of young offenders is that of re-offending. To assess this risk it is important to know what relationships various background factors and behaviours have with later offending. This includes knowing whether predictive relationships exist between substance use and recidi-

Aldis L. Putniņš Dip App Psych, MA, Chief Clinical Psychologist, Family and Youth Services, Department of Human Services, and doctoral candidate in the School of Psychology at the University of South Australia. Correspondence to Aldis L. Putniņš, Family and Youth Services, 2 Norton Summit Rd, Magill SA 5072, Australia. Tel. (08) 8333 1920; Fax. (08) 8364 7041; E-mail: putnins.aldis@saugov.sa.gov.au

Received 22 April 2002; accepted for publication 27 June 2003.

ISSN 0959-5236 print/ISSN 1465-3362 online/03/040401-08 © Australian Professional Society on Alcohol and Other Drugs
DOI: 10.1080/09595230310001613912

vism. The causal relationships between the use of various substances and offending by youths are complex and likely to consist of both bi-directional relationships and common causes [16] and might be different for different substances. This clouds the question of to what degree substance use is predictive of, rather than just concurrently associated with, offending.

The aim of this investigation is to examine the longitudinal relationship between substance use and criminal recidivism. Few such studies with young offenders have been undertaken elsewhere [17] and none previously in Australia.

Method

Subjects and procedure

Subjects were youths who: a) were admitted between 1994 and 1996 to either of South Australia's two secure care centres for young offenders, b) underwent a standardised psychosocial screening assessment while in secure care, and; c) were released from secure care at least 6 months before the end of 1997. Youths whose stays are longer than a few days are routinely assessed in relation to various aspects of psychological and social adjustment, including substance use. Assessed youths include both those on remand as well as those serving detention orders. Reassessments are usually undertaken if a youth is readmitted and more than 12 months have elapsed since they were last assessed.

Measure

The assessment items are part of the Secure Care Psychosocial Screening (SECAPS) [18]. This is a standardized individually administered assessment that includes items about how often various substances were used during the last month before being placed in secure care. The assessments are carried out by youth workers, psychologists or social workers and take about 30 minutes to complete. As given on the questionnaire, substances listed are: alcohol (beer, wine, spirits); marijuana (grass, hash); acid, LSD, datura [also known as Angel's Trumpet—a garden plant with hallucinogenic properties], magic mushrooms or other hallucinogens; sedatives or sleeping tablets such as Mogadon, Serepax, Valium, Rohypnol or similar (without doctor's prescription); heroin, morphine or other narcotics; cocaine, speed, pep pills or other stimulants (without doctor's prescription); sniffed (breathed deeply) from spray cans or sniffed items such as glue, petrol, thinner, butane gas or similar. These are summarized (together with their abbreviations) as: alcohol (Alco); marijuana (Marij); hallucinogens (Hallu); sedatives/hypnotics (Sed/Hyp); narcotics (Narc); stimulants (Stim); inhalants (Inhal). Substances under "Sedatives/Hypnotics" included anti-anxiety agents. Frequency of use was indicated on a five-point scale, namely: never; once or twice a month; once or twice a week; several times a week; daily or almost daily. Other items from the SECAPS assessment considered here include what substances, if any, were used at the time of their last offence, whether the respondent felt they had a problem with substance use and whether any natural parents or siblings had had problems with drugs or alcohol.

As the information about substance use derives from self-reports, questions about its accuracy can be raised. Error due to poor recall is minimized here by restricting questions about frequency to use during the last month in the community. Similarly, the item about substances used when they offended was restricted to the most recent offence. Error can also result from deliberate distortion. Youths in justice settings could be expected to under-report rather than over-report their substance use more often. Studies that have used chemical analyses to check the accuracy of self-reports [2,19–21] indicate that under-reporting is more likely in relation to very recent use (previous 2–3 days) of hard drugs such as cocaine and heroin and that reports of use over the last 4 weeks tend to be more accurate. It is the longer period that is inquired about in the SECAPS. There are other factors that reduce the tendency to not reveal the full extent of substance use. First, the SECAPS assessment is introduced to each youth as a routine assessment to help staff become more aware of needs and issues concerning the youth. It is pointed out that it is not a court-ordered assessment. This helps to reduce the anxiety that some youths might have about the assessment. Secondly, the substance use items in the SECAPS assessment come after a number of more general background items and basic skills tests. This allows the assessor to establish rapport with the youth and for the youth to settle in to the assessment. Thirdly, substance use is so widespread among young offenders that it is normative in this group. In a facility for young offenders, fear of condemnation by admitting to substance use is minimal.

An aid to fuller disclosure in the SECAPS is the use (conditional on each youth's literacy level) of a self-administered pencil-and-paper questionnaire to describe substance use. Studies have found greater disclosure using this format compared to face-to-face interviews [22].

Generally it has been the experience of SECAPS assessors that, when other sources of information have been available, on most occasions there has been a reasonably good concordance between the youth's report and other sources.

The examination of the relationship between self-reported substance use and subsequent re-offending used the full court-adjudicated offending histories of all youths who completed SECAPS assessments during

the first 3 years of the assessment program (namely 1994–96). The outcome was each youth's recidivism status (dichotomous outcome) at 6 months from the time of their next release. This was determined by whether any proven (court-adjudicated) offending had occurred within 6 months of the first release after the SECAPS assessment. As previous predictive studies have often examined violent recidivism as a separate outcome [23], note was also taken of whether any of the new offences were violent offences. The follow-up period extended to the end of 1997. Youths not released within 6 months of the end of the follow-up period were excluded from the study. Offence records were obtained from the Office of Crime Statistics in the South Australian Attorney-General's department. Only records of offences dealt with by South Australian courts were available.

Statistical methods

The bivariate associations between the substance use variables (assessed while the young offenders were in secure care) and later recidivism status are examined using product–moment correlations and χ^2 tests. Some of the youths were re-admitted to secure care and were re-assessed a second time. Thus, two sets of substance use and post-release recidivism data are available. As the number of second assessments is smaller than the number of first assessments, greater weight needs to be placed on the first assessment results. From previous prediction studies [17,24] it is known that most single variables have only weak to modest relationships with recidivism and that results often vary between studies. One way of increasing confidence in results is to raise the alpha value so that only highly significant results are accepted. A disadvantage is that relatively weak yet genuine relationships will be dismissed. Another strategy is to set alpha at a modest level and to look for consistency in the results. The latter approach is adopted here. The second assessment data are retained as a means of checking the consistency of the results from the analysis of the first assessment data. It is expected that any significant relationships will, at best, be modest in strength. If a variable has a weak although positive and significant relationship in the analysis of the first assessment data, confidence in the relationship being genuine will be increased if it also observed to have a positive relationship in the analysis of the second assessment data. If, however, the relationship in the second assessment data is zero or negative, then despite the larger subject numbers in the first assessment data, one would be hesitant to accept the first assessment result as genuine. As the second assessment data are based on smaller subject numbers, they have less statistical power. Therefore the levels of statistical significance of the second assessment results are less important than are consistencies in direction and strength compared to the first assessment results.

Regarding scaling, the predicted outcome (recidivism) is dichotomous. Dichotomous variables can be treated as having interval scale properties [25]. The substance use items of greatest interest in this analysis are reports of the frequencies of substances used during the last month before placement in secure care. These are measured on a five-point ascending scale (none; 1–2/month; 1–2/week; several times/week; daily or almost daily). The scale can be treated in one of two ways. The first is as a physical time scale. If, for simplicity, a month is regarded as being 4 weeks (28 days), then the scale values would be as follows: none = 0; 1–2/month = 1.5; 1–2/week = 6; several times/week = 16; daily or almost daily = 26. The values are the midpoints of the frequency ranges. This is an interval scale. The second is to treat the frequencies as a psychological scale of perceived intensity, similar to a psychophysical scale. This is how the measured scale points were selected and how the scale is analysed here. The scale values are 1 to 5 (none = 1 daily = 5), the scale being treated as approximately interval. The two scales are mathematically related ($y \approx x^2 - 1$, where y = time scale values and x = psychological scale values). In practice the results of analyses of the two types of scales yield very similar results, largely because product–moment correlations suffer little error when different scoring systems are compared to any selected "true" scoring system [26].

Results

Patterns of substance use for the offender group from which this sample was drawn are reported in a separate publication [12] and are summarized in the Introduction section of this paper.

Discarding four initial assessments in which no substance use responses were recorded left 454 youths with relevant assessment data. Due to either death or non-release from secure care 6 months or more before the end of the follow-up period, the number of youths whose assessments were included in the recidivism analyses was 447 (first assessment group). Of these, 140 had a subsequent SECAPS assessment within the same assessment period (i.e. 1994–96). One assessment had no substance use responses recorded. Of the remaining youths with a second assessment, 103 were released from secure care 6 months or more before the end of the follow-up period and were included in the recidivism analysis (second assessment group).

Of the first assessment respondents, 92% were males and 27% described themselves as being Aboriginal. Ages for the total group ranged from 11 to 19 years

(mean age = 15.9 years), with most subjects (83%) falling within the 14–17-year age range. Among the second assessment respondents, 95% were males and 31% described themselves as being Aboriginal. Ages for this group ranged from 12 to 18 years (mean age = 16.3 years), with most subjects (89%) falling within the 15–18-year age range. The mean time from release after the second assessment to the end of the follow-up period was 651 days (21 months). All subjects who were 18 years or older were incarcerated for offences committed before they turned 18.

Results are presented in Table 1 for the relationships between the frequencies of substances used during the month before incarceration and subsequent re-offending. None of the relationships are strong. No obvious pattern of use distinguishes recidivism for violent offences from recidivism for non-violent forms of criminal offending. Violent offences here include various threats of harm and offences that can cause a fear of direct harm, but exclude sexual offences. Assaults account for 70.4% of all the offences in the violent offence category, with robbery with violence and robbery with an offensive weapon accounting for a further 14.8% (further details are available on request from the author).

There had been an expectation that greater use of any substance would be related positively to recidivism. While most of the correlations (although not all) were positive, many were too small to be of either practical or statistical significance. The substances related to recidivism most consistently were alcohol and inhalants: nine of the 12 correlations involving these substances were statistically significant, whereas only two of the other 30 correlations were significant.

An examination of the relationship between substances used at the time of the youths' last offences and subsequent recidivism (see Table 2) did not reveal any consistent trends.

The use of particular substances is often transitory or episodic. This is evident from the correlations between substance use frequencies reported at the first and second SECAPS assessments (see Table 3). The [illegible] are from the larger sample of 900 assessed young offenders from which the offender assessments in the recidivism study were drawn. A minimum of 6 months separation between first and second assessments was specified in order to reduce the chances of some subjects not being released between their first and second assessments. (During the initial implementation of the SECAPS program some youths were reassessed in less than 12 months and, in a few cases, without having been released.) It can be seen that the stability coefficients are all quite low, particularly for the less frequently used substances. This can be expected to reduce the strength of the relationship between the use of particular substances and subsequent re-offending. For example, of 12 reassessed youths who in their first assessment reported recent use of narcotics, only two of them reported recent narcotics use in their second assessment. Of the 25 youths who in their second assessment reported recent use of narcotics, only two had reported any use of narcotics earlier.

The relationship between reported problem use of substances by other immediate natural family members and recidivism was examined. Responses were coded as: no = 1, don't know = 2, yes = 3. No significant relationships were found between recidivism status 6 months after release and responses to this item at either the first ($\chi^2 = 0.699$, df = 2, $n = 446$) or second ($\chi^2 = 0.722$, df = 2, $n = 103$) SECAPS assessments.

The use of some substances might be predictive of offending in some demographic groups but not in others. If, however, general predictive measures are sought then these must demonstrate some degree of predictive consistency across different groups. Results are presented in Table 4 that are relevant to this question. Neither self-reported problems with substance use nor the use of a psychoactive substance at the time of the last offence were consistently related to recidivism.

Table 1. *Correlations between frequency of substances used during the last month prior to incarceration and recidivism status 6 months after release*

	Alco	Marij	Hallu	Sedhyp	Narc	Stim	Inhal
1st assess ($n = 445-447$)							
Any offending	0.08*	0.01	0.02	0.04	−0.02	0.05	0.10*
Violent offending	0.13**	−0.01	0.05	0.09*	0.06	0.08	0.16**
Other offending	0.08	0.00	0.03	0.01	−0.03	0.04	0.08*
2nd assess ($n = 103$)							
Any offending	0.23*	−0.02	0.05	0.11	0.10	−0.04	0.21*
Violent offending	0.09	0.05	0.16*	0.04	−0.05	−0.06	0.14
Other offending	0.21*	−0.04	0.02	0.10	0.10	−0.03	0.22*

*$p \leq 0.05$; **$p \leq 0.01$ (one-tailed).

Table 2. *Correlations between the use of various substances at the time of the last offence and recidivism status 6 months after release from secure care*

	Alco	Marij	Hallu	Sedhyp	Narc	Stim	Inhal
1st assess ($n = 444$)							
Any offending	0.04	− 0.01	0.00	− 0.00	− 0.00	0.05	0.03
Violent offending	0.05	− 0.01	− 0.04	0.03	0.10*	0.00	0.17**
Other offending	0.02	− 0.03	0.02	− 0.01	0.01	0.06	0.03
2nd assess ($n = 103$)							
Any offending	0.06	− 0.07	− 0.08	0.01	0.08	0.04	0.14
Violent offending	− 0.06	0.13	0.25**	− 0.01	− 0.04	− 0.02	0.10
Other offending	− 0.08	− 0.06	0.08	0.02	0.08	0.05	0.14

* $p \leqslant 0.05$; ** $p \leqslant 0.01$ (one-tailed).

Table 3. *Correlations between substance use frequencies reported at the first and second SECAPS assessments† where 6 months or more had elapsed between assessments*

	Alco	Marij	Hallu	Sedhyp	Narc	Stim	Inhal
r	0.33**	0.40**	0.14*	0.13*	0.09	0.09	0.12

†Time between assessments ranged between 184 and 1468 days ($M = 554$). $n = 186$ for all substances except inhalants ($n = 185$).
*$p \leqslant 0.05$; **$p \leqslant 0.01$ (one-tailed).

Table 4. *Correlations between self-reported frequencies of substances used during last month before incarceration, any substance use at the time of last offence, self-reported problem use and recidivism status 6 months after release from secure care*

	1st assessments			2nd assessments†	
	Females (all)	Non-Abor. males	Abor. Males	Non-Abor. (m + f)	Abor. (m + f)
Alcohol	0.26	0.04	0.14	0.13	0.37*
Marijuana	− 0.11	0.02	0.06	− 0.14	0.19
Hallucin0.	0.40**	− 0.01	− 0.10	0.04	0.03
Sed/Hyp	0.47**	− 0.06	0.10	0.07	0.21
Narcotics	0.22	− 0.03	− 0.05	− 0.13	0.32*
Stimulants	0.25	0.04	0.01	− 0.09	0.05
Inhalants	0.31*	0.08	0.05	0.22*	0.19
Use offend	0.27	0.04	− 0.02	0.02	− 0.01
Problem	0.28*	− 0.08	0.01	− 0.02	0.31*
ALCIN	0.38**	0.07	0.16	0.22*	0.37*
Other subs	0.35**	− 0.00	0.02	− 0.08	0.24
n	36 − 38	310 − 311	97 − 98	71	32

Use offend = used a substance at the time of the last offence; Problem = youth considers his/her substance use to be a problem; ALCIN = Alcohol use frequency + Inhalant use frequency; Other subs (use frequencies) = Marij + Hallu + Sed/Hyp + Narc + Stim.
†There were too few females ($n = 5$) among those retested to allow separate analysis by gender. *$p \leqslant 0.05$; **$p \leqslant 0.01$ (one-tailed).

Examining the different groups, the results for females stand out. In this group, with the exception of marijuana use, all the substance use variables are either significant or display positive trends in their relationship with recidivism. Some of the relationships are quite strong, such as the correlation of 0.47 between recidivism and the use of sedatives/hypnotics.

Of the individual substances, only alcohol and inhalants had consistently positive correlations across the different groups. The correlations were weakest in

the first assessment non-Aboriginal male subgroup but increased among those who were reassessed. These positive relationships are generally strengthened when alcohol and inhalant use frequencies are summed to form a measure called ALCIN. This combined measure had highly significant correlations with recidivism status after both first ($r = 0.12$, $p = 0.007$, $n = 446$) and second ($r = 0.28$, $p = 0.002$, $n = 103$) assessments. Examining the various subgroups it is seen that all the correlations between ALCIN and recidivism are positive and that three of the five correlations are statistically significant. By contrast, an index of all the other substances used (Other subs) failed to show any relationship with recidivism in the three largest subgroups and was statistically significant only for the female subgroup (Table 4).

The relationship between the ALCIN index and recidivism can be seen clearly in Table 5. A fairly consistent increase in subsequent recidivism is evident as the ALCIN scores increase.

Discussion

Regarding the prediction of recidivism, as no obvious pattern of recent substance use distinguished general offending, violent offending and non-violent offending, further discussion here considers only general offending. Neither the use of a substance in general (*Use offend*) nor the use of any particular substance at the time of the last offence consistently predicted recidivism—nor did self-reported problems with substance use. Although marijuana was the most widely used substance, there was no support for using it as a marker for increased risk of re-offending. That marijuana is often reported to have been used at the time of last offending is not surprising, given that marijuana is the most frequently used of all the psychoactive substances. The close association between offending and marijuana use might be largely coincidental rather than causal, simply because a large proportion of young offenders at any one time are under the influence of marijuana.

Recent alcohol and inhalant use appear to be the substances that are most consistently predictive of recidivism across different offending types and across different demographic subgroups. Both alcohol and inhalants are central nervous system depressants and both have disinhibiting effects. The use of inhalants might also be a marker for less maturity and poorer self-control particularly as, unlike other substances, it tends to be used by younger detainees [12]. The link between alcohol use and offending has been particularly well documented, including among young people [27]. A combined index of recent alcohol and inhalant use might be a useful addition to a broader recidivism risk assessment instrument.

Although the recent use of other substances failed to show any consistent relationship with recidivism in most of the subject subgroups examined, there was a trend among the females for all substances except marijuana to be related to increased recidivism risk. Due to the relatively small number of females here, replication is needed on a larger sample. If confirmed, however, it could indicate that, for the optimal prediction of offending risk, gender differences in the predictive strength of some variables should be taken into account.

Despite much media attention to the link between crime (particularly acquisitive crimes) and narcotic use

Table 5. *Alcohol–inhalant use index (ALCIN)* scores by recidivism status at 6 months follow-up*

ALCIN scores	6 months post-1st			6 months post-2nd		
	SECAPS			SECAPS		
	% not offend	% re-offend	*n*	% not offend	% re-offend	*n*
1.0	37.0	63.0	92	54.2	45.8	24
1.5	35.2	64.8	122	52.6	47.4	19
2.0	36.8	63.2	114	43.5	56.5	23
2.5	16.7	83.3	48	22.2	77.8	18
3.0	26.4	73.6	53	25.0	75.0	16
3.5	20.0	80.0	10	0.0	100.0	2
4.0	20.0	80.0	5	-	-	0
4.5	0.0	100.0	2	-	-	0
5.0	-	-	0	0.0	100.0	1
Total	32.4	67.7	446	39.8	60.2	103

*ALCIN is the sum of the frequencies of alcohol use and inhalant use during the last month before placement in secure care. A score of 1.0 indicates that neither substance was used. A score of 5.0 indicates daily use of both substances.

(predominantly heroin), among the juvenile male subjects studied here recent use of narcotics had no power to predict recidivism. It could be that this is because few youths use narcotics and even fewer are dependent—most of their narcotics use probably still being experimental or recreational. Many youths have not established consistent or regular patterns of use, suggesting that much of their use, particularly of substances other than marijuana and alcohol, is capricious and might often be transitory.

The statistical weakness of recent substance use as a marker for increased offending risk observed here might be due to a number of factors. While there is a close association between substance use and the act of offending, the stability of substance use among youths over time might be too weak for most substances to be reliable predictors. Perhaps the self-reports of recent substance use by youths in secure care are too distorted to be valid. Although there is little evidence to suggest that there is severe distortion in most of the young offenders' self-reports, the use of physical drug testing is one possible way of verifying the accuracy of such assessment items. Dissimulation might be reduced and the stability of patterns of use increased if, rather than very recent substance use, reports of use over a longer period are used. While lifetime use is likely to be difficult to estimate accurately, perhaps the regular use of various substances during the preceding 6 months might be a more stable measure. This possibility is being explored by introducing such an item into the next revision of the SECAPS assessment.

There is also the problem of homogeneity. While there is good concurrent discrimination between young offenders and non-offenders with regard to their substance use, perhaps those who are placed in secure care long enough to be assessed are not all that different from each other. Most markers, including substance use, at least when taken singly, would have no more than weak relationships with recidivism. The situation might be similar to choosing basketball players. While height might be a predictor of who will get into a team, once a team has been established and there has been some attrition among the players, height will probably be a weak predictor of basketball playing ability among existing players.

Substance use in many previous studies has been found to have only a very modest relationship with recidivism. From an analysis of 60 studies involving almost 55 000 subjects, Gendreau, Coggin & Little [24] reported a weighted mean Pearson's r of 0.10 for substance abuse and adult recidivism. Cottle, Lee & Heilbrun [17], in their analysis of studies that examined recidivism among young offenders, obtained weighted mean effect sizes (Z_r) of 0.15 for substance abuse and recidivism (six studies, 1111 subjects) and 0.01 for substance use and recidivism (two studies, 9366 subjects). Overall, substance abuse was very modestly predictive but substance use was not. In the light of these results it is not surprising that stronger relationships were not observed between substance use and recidivism in the present sample.

Conclusions

Despite the prominence given in the media to the issue of "hard drugs", the substances used most frequently by both young offenders and non-offenders are the so-called "soft drugs", namely alcohol and marijuana. Of these, alcohol appears to have a stronger direct association with acts of offending— due most probably to its strong disinhibiting properties. Ways of restricting adolescents' access to alcohol more effectively need to be considered. The other class of substances that showed a degree of predictive consistency across different groups was inhalants. An index of recent alcohol and inhalant use, although predictively too weak to use on its own, might be a useful addition to a broader recidivism risk assessment.

References

[1] Loeber R, Stouthamer-Loeber M. Prediction. In: Quay HC, ed. Handbook of juvenile delinquency. New York: Wiley, 1987:325–82.

[2] Makkai T, McGregor K. Drug use monitoring in Australia: 2001 annual report on drug use among police detainees. Research and Public Policy Series no. 41. Canberra: Australian Institute of Criminology, 2002.

[3] Copeland J, Howard J. Alcohol and other drug issues amongst NSW juvenile detainees. Paper presented at Australia's 1st Forensic Psychology Conference, Sydney, February, 2001.

[4] Crundall I. Survey of drug use among young people in Victorian youth training and reception centres. Melbourne: Victorian Health Department, 1987.

[5] Fasher AM, Dunbar N, Rothenbury, BA, Bebb DK, Young SJW. The health of a group of young Australians in a New South Wales juvenile justice detention centre: a pilot study. J Paediatric Child Health 1997;33:426–9.

[6] Hando J, Howard J, Zibert E. Risky drug practices and treatment needs of youth detained in New South Wales Juvenile Justice Centres. Drug Alcohol Rev 1997;16:137–45.

[7] Howard J, Zibert E. Curious, bored and wanting to feel good: the drug use of detained young offenders. Drug Alcohol Rev 1990;9:225–31.

[8] Howard J, Copeland J, Nicholas J, Karacanta A. Young offenders, substance use, depression and suicidal behaviour. Paper presented at Australia's 1st Forensic Psychology Conference, Sydney, February, 2001.

[9] Lennings C, Pritchard M. Prevalence of drug use prior to detention among residents of youth detention centres in Queensland. Drug Alcohol Rev 1999;18:145–52.

[10] Putniņš AL. The Adolescent Alcohol Involvement Scale: some findings with young offenders. Drug Alcohol Rev 1992;11:253–8.

[11] Putniņš AL. Recent drug use and suicidal behaviour among young offenders. Drug Alcohol Rev 1995;14:151–8.

[12] Putnins AL. Substance use by South Australian young offenders. Information Bulletin, no. 19, Adelaide: Office of Crime Statistics, Attorney-General's Department, 2001. (downloadable at http://www.ocsar.sa.gov.au/docs/information_bulletins/IB19.pdf)
[13] Putnins AL, Harvey SJR. Alcohol abuse among young offenders. Med J Aust 1992;156:753–5.
[14] Watts P. Youth in custody project: a profile of juvenile offenders' drug use patterns. Perth: Department of Community Services, 1992.
[15] Letcher T, White V. Australian secondary students' use of over-the-counter and illicit substances in 1996. Anti-Cancer Council of Victoria: Melbourne, 1998.
[16] Rutter M, Giller H, Hagell A. Antisocial behavior by young people. Cambridge, UK: Cambridge University Press, 1998.
[17] Cottle CC, Lee RJ, Heilbrun K. The prediction of criminal recidivism in juveniles: a meta-analysis. Criminal Justice Behav 2001;28:367–94.
[18] Putnins AL. Secure care psychosocial screening: manual for SECAPS V.4. Adelaide: Department of Human Services, Family and Youth Services, 1998.
[19] Fendrich M, Xu Y. The validity of drug use reports from juvenile arrestees. Int J Addict 1994; 29:971–85.
[20] Feucht TE, Stephens RC, Walker ML. Drug use among juvenile arrestees: a comparison of self-report, urinalysis and hair assay. J Drug Issues 1994;24:99–116.
[21] Mieczkowski T, Newel R, Wraight B. Using hair analysis, urinalysis, and self-reports to estimate drug use in a sample of detained juveniles. Subst Use Misuse 1998;33:1547–67.
[22] Harrison L. The validity of self-reported drug use in survey research: an overview and critique of research methods. In: Harrison L, Hughes A, eds. The validity of self-reported drug use: improving the accuracy of survey estimates. Rockville, MD: National Institute on Drug Abuse, 1997:17–36.
[23] Gendreau P, Goggin C, Smith P. Is the PCL-R really the "unparalleled" measure of offender risk? A lesson in knowledge cumulatio Criminal Justice Behav 2002;29:397–426.
[24] Gendreau P, Goggin C, Little T. Predicting adult offender recidivism: what works! (User Report no. 1996–07). Ottawa: Department of the Solicitor General of Canada, 1996.
[25] Nei NH, Hull CH, Jenkins JG, Steinbrenner K, Bent DH. SPSS: statistical package for the social sciences (2nd edn). New York, NY: McGraw-Hill, 1975.
[26] Labowitz S. The assignment of numbers to rank order categories. Am Soc Rev 1970;35:515–24.
[27] Komro KA, Williams CL, Forster JL, Perry CL, Farbakhsh K, Stigler MH. The relationship between adolescent alcohol use and delinquent and violent behaviors. J Child Adolesc Subst Abuse 1999;9:13–28.

3

Stepping-Stones, Gateways, and the Prevention of Drug Problems

Researchers, theorists, politicians, and parents have all expressed concern about marijuana's potential to lead to the use of drugs with worse negative consequences. Proponents of these stepping-stone and gateway theories suggest that even if the adverse effects of marijuana are minimal, the drug can still cause trouble by ushering users toward the consumption of other illicit substances, including heroin and crack. According to this premise, marijuana should remain a primary concern because these other drugs create so many hardships. Comparable arguments appear against underage drinking and cigarette smoking. The gateway and stepping-stone theories have generated considerable research and debate for many years. The research remains difficult to evaluate without clear definitions of a stepping-stone and gateway. Interpreting this literature requires a good understanding of causality. Many popular reports confuse the causes of drug use with simple precursors. Confusion about the actual causes of drug consumption can impair any effort to prevent substance abuse and related problems. Thus, this chapter defines a stepping-stone and gateway, reviews the requirements for causality, examines the literature relating marijuana consumption to the use of harder drugs, and discusses the prevention of drug problems.

A stepping-stone provides a helpful foothold along a path, which serves as an odd metaphor for drug use. Stepping-stone theories often imply that marijuana produces a biological effect that somehow leads to the uncontrollable consumption of other drugs. This sort of theorizing began over 40 years ago (Nahas, 1990). Descriptions in popular culture create the impression that marijuana intoxication produces an insatiable

urge for more and different drugs, something similar to the way eating salt makes people thirsty. Data do not support these ideas. Marijuana and hard drugs do share some biological effects. For example, THC, the opiates, and cocaine alter the dopamine system in comparable ways (Koob & Le Moal, 1997). The cannabinoids, however, have their own receptor that does not react directly to drugs like heroin and cocaine.

Additional evidence against a biological stepping-stone appears in animal research. If marijuana created physiological changes that increased the desire for other drugs, animals exposed to cannabis would likely ingest other intoxicants when given the opportunity. Yet rodents exposed to THC do not show a sudden willingness to press levers for other drugs. They do not even appear willing to give themselves more THC (Schenk & Partridge, 1999; Wiley 1999). Thus, physiological mechanisms do not explain any link between marijuana and the use of other intoxicants (Institute of Medicine [IOM], 1999; Zimmer & Morgan, 1997).

Gateways and Causality

The lack of evidence for an obvious, biological stepping-stone inspired theorists to formulate ideas about marijuana as a gateway drug. A gateway usually serves as a passage to a region. Proponents of gateway theory show that people who use drugs like heroin and cocaine often used alcohol, tobacco, and marijuana first (Kandel, Yamaguchi, & Chen, 1992; Miller, 1994). Confusion about these theories has led to the idea that gateway drugs cause users to consume other substances. The prominent researchers of gateway theory never state that one drug causes the ingestion of another one. They simply report that cigarette smoking often precedes marijuana consumption, which usually precedes the use of other illicit drugs. Nevertheless, a few other authors misunderstand these data and create the impression that smoking marijuana leads inevitably to the use of other drugs (Nahas, 1990). Avoiding these misunderstandings requires a thorough understanding of causes.

The idea that one drug causes the use of another drug is difficult to prove. Proof of a cause creating an effect requires at least three clear criteria. These criteria were first proposed in the 1700s by the Scottish philosopher David Hume, one of the British empiricists. Hume emphasized that a cause creates an effect only under certain conditions. The conditions are association, temporal antecedence, and isolation. Associ-

ation means that the cause and effect must occur together. Temporal antecedence means that the cause must occur first, before the effect. Isolation means that all alternative causes must be ruled out. That is, the effect could not have occurred because of some other potential cause (Hume, 1739).

The best evidence for causality comes from experiments where the hypothesized cause can be manipulated. The cause should lead to the effect; its absence should create no effect (or a different one). For example, an experiment might reveal that marijuana causes intoxication by comparing people who smoked cannabis to an equivalent group of other people who smoked a placebo. This sort of experiment could provide evidence for all three of Hume's criteria. A large group of people who are not under the influence of any drug might begin by rating their intoxication. Presumably, all would claim their intoxication level was 0. The experimenter would then choose half these people at random to smoke marijuana. The other half would smoke a credible placebo. This random selection of people would help ensure that the two groups are similar. A second assessment of intoxication would likely reveal higher ratings of intoxication for the people who smoked marijuana than those who smoked the placebo.

The data from this experiment would satisfy Hume's criteria. The marijuana group's higher intoxication ratings reveal that the drug and the effect are associated. Because the groups did not differ before smoking, only after, the marijuana apparently preceded the effect. Thus, the temporal antecedence is fulfilled. Finally, all other sources of intoxication are ruled out because the two groups only differ in smoking cannabis or placebo. This condition helps eliminate any alternative explanations or causes. These data support the conclusion that marijuana can be isolated as the cause of this intoxication.

A simple experiment works well for proving cannabis causes intoxication, but researchers cannot use a human experiment to test the gateway theory. Randomly exposing people to marijuana to see who goes on to snort coke, bang junk, or drop acid creates many practical and ethical problems. These problems make isolating marijuana as the cause of other drug use impossible in humans. An obvious alternative approach could employ animal participants. No animal experiments have found that exposure to THC increases the likelihood of using other drugs or of even working for more THC (Schenk & Partridge, 1999; Wiley, 1999). Thus, gateway theory's only support comes from correlational studies.

Correlational investigations often examine users of crack or heroin and ask which drugs they used previously. These studies may establish an association and temporal antecedence, but fail to isolate marijuana as a cause. At first glance, the idea that users of hard drugs used marijuana previously seems compelling evidence for marijuana's contribution to drug problems. Nevertheless, a couple of exaggerated examples may illustrate how treating the data as causal evidence is erroneous.

Errors in Causal Reasoning

Suppose data revealed that the crime rate in a city rises as the number of churches increases. This association might lead some cynic to hypothesize that churches cause crime. Data may suggest that the churches are built prior to the increases in crime, further supporting the theory. Both the association between cause and effect and the precedence of the cause appear. Nevertheless, these two facts alone do not establish that churches cause crime. An alternative explanation remains. As cities grow larger, both crime and the number of churches increase. The size of the population accounts for both of these increases. One need not cause the other. Another example concerns shoe size and vocabulary. Data reveal that people who know more words also have larger shoes. One might hypothesize that memory for words is stored in the feet. Obviously, age can account for this relationship. As children grow older their feet grow and they learn more words.

Although these examples appear absurd, data misinterpreted to support that marijuana causes crack addiction are comparable to those in support of churches causing crime and vocabulary increasing shoe size. In fact, the correlations for these absurd examples are probably larger than those linking marijuana to crack. Most studies cited in support of the gateway theory show that people using heroin or crack used marijuana first. Unfortunately, these data tell little about the magnitude of the association between marijuana and hard drugs. Because only the users of hard drugs serve as participants, the data neglect the many, many people who consumed cannabis but no other illicit drugs. The use of marijuana also does not always precede the use of harder drugs, limiting the support for temporal antecedence. That is, some people try crack or ecstasy before they smoke cannabis. These data also fail to isolate mari-

juana as a cause. The association, temporal antecedence, and isolation criteria are explained in more detail below.

Association

Hume's first criterion for establishing a cause concerns association. Despite popular stereotypes, the association between marijuana and harder drugs is not particularly strong. Many people who abuse hard drugs used marijuana first, but few people who smoke marijuana go on to consume other intoxicants. One study found that 75% of men who used marijuana between 10 and 99 times never used any other illicit drug (Kandel & Davies, 1992). Part of the absence of an association stems from the small number of people who use hard drugs relative to the many who have tried marijuana. Data from the Substance Abuse and Mental Health Services Administration (SAMHSA, 2000) can shed light on this question (see table 3.1).

Most associations are expressed as a correlation coefficient, a number ranging from −1 to +1 that depicts how well two phenomena go together. If everyone who tried marijuana also snorted cocaine, their correlation would be 1.0. Few phenomena go together perfectly, but larger numbers (up to 1.0) mean a stronger relationship. Correlations around .3 frequently receive some attention in the social sciences. For example, Scholastic Aptitude Test math scores correlate approximately .3 with grades in math classes (Gougeon, 1984). Personality measures and alcohol consumption often correlate between .3 and .4 (Earleywine, Finn, & Martin, 1990; Earleywine & Finn, 1991). Correlations smaller than .3 often attract little attention.

Table 3.1. 1999 Drug Use Rates in America (in millions)

	Marijuana	Cocaine	Crack	Heroin
Lifetime	76.4	25.4	5.9	3.0
Past year	19.5	3.7	1.0	0.4
Past month	11.1	1.5	0.4	0.2

Data from Substance Abuse and Mental Health Services Administration (SAMHSA) (2000). Summary of findings from the 1999 National Household Survey on Drug Abuse. Rockville, MD: SAMHSA.

Based on the national survey data, the actual correlation between marijuana and crack cocaine use is .02. This calculation assumes that everyone who used crack cocaine used marijuana first. In addition, this calculation takes into account the many people who use marijuana and never try the harder drug. The correlations between marijuana and heroin are even smaller. (See the final section of this chapter for the computations.) Thus, most correlations that scientists view as important are over 15 times larger than the correlation between marijuana and crack cocaine use.

Standard measures of the correlation between marijuana use and the use of harder drugs are very small. They offer little support for an association between marijuana and other drugs. In an effort to depict the link between marijuana and other drugs in a different way, some authors have turned to another statistical procedure known as conditional probabilities. Conditional probabilities reveal the chances that people will try a harder drug if they have tried marijuana. They are computed by dividing the number of users of the harder drug by the number of marijuana users. If everyone who smoked marijuana tried crack, the conditional probability would be 1.0. If half the marijuana users tried crack, the conditional probability would be .5. If we had 100 people and 30 of them used cannabis, the conditional probability of using cannabis would be .3. If 10 of those 30 went on to try crack, the chance of using cocaine given that cannabis was used first would be one-third.

Again, assume that everyone in the national survey who used a hard drug tried marijuana first. The chance of trying powder cocaine after trying marijuana appears to be relatively high. If all 25 million people who tried cocaine were among the 76 million who had also tried marijuana, 25 million divided by 76 million equals .33. Thus, 1 in 3 people who try marijuana also try cocaine. This number is certainly large enough to warrant concern. Statistics like these motivated drug reformers in the Netherlands to remove criminal penalties for small amounts of marijuana in hope of separating it from the cocaine drug market. They also inspired increased penalties for cannabis in the United States.

The conditional probability linking marijuana to cocaine may be alarming. Nevertheless, the number of marijuana users who continue to use cocaine regularly is markedly smaller. Although 25 million Americans have used cocaine in their lifetimes, fewer than 4 million used it in the past year. Assume that these people use the drug at least once a year, and that they all tried marijuana first. Thus, the chances of marijuana

leading to yearly cocaine use are 4 million (the number of yearly cocaine users) divided by 76 million (the number who tried cannabis), or about .05. This means only 1 in 20 people who try marijuana use cocaine once a year or more. Even fewer people used cocaine in the last month (1.5 million). Comparable computations suggest that the chances of trying marijuana and then using cocaine monthly are .02, or about 1 in 50. Thus, less than 2 in 100 marijuana users go on to use cocaine monthly. The probabilities for using crack cocaine and heroin are even lower (see table 3.2).

Thus, the association between marijuana consumption and problem use of other drugs is very small. In fact, studies of the gateway theory do not assess the problems associated with hard drug use; they simply focus on trying other substances. Some studies consider trying a drug a single time as confirmation of use (e.g., Blaze-Temple & Lo, 1992), an approach that has drawn criticism (Zimmer & Morgan, 1997). Trying marijuana is not sufficient to cause the use of harder drugs. Even if the association were markedly larger, this criterion alone does not establish causality. Causal arguments require temporal antecedence and isolation, too.

Table 3.2. Gateway Associations

Of all Americans who have tried marijuana
Few have used marijuana regularly
approximately 1 in 4 used marijuana in the past year (25.5%)
approximately 1 in 7 used marijuana in the past month (14.7%)
Few people who have tried marijuana have used cocaine
approximately 1 in 3 tried cocaine (33.0%)
approximately 1 in 20 used cocaine in the past year (4.8%)
approximately 1 in 50 used cocaine in the past month (2.0%)
Even fewer people who have tried marijuana have used crack
approximately 1 in 13 tried crack (7.7%)
approximately 1 in 100 used crack in the past year (1.3%)
approximately 1 in 200 used crack in the past month (0.5%)
Even fewer people who have tried marijuana have used heroin
approximately 1 in 26 tried heroin (3.9%)
approximately 1 in 200 used heroin in the past year (0.5%)
approximately 1 in 333 used heroin in the past month (0.3%)

These calculations assume that everyone who ever tried hard drugs used marijuana first. Data from Substance Abuse and Mental Health Services Administration (SAMHSA) (2000). Summary of findings from the 1999 National Household Survey on Drug Abuse, Rockville, MD: SAMHSA.

Temporal Antecedence

If marijuana actually caused the consumption of other intoxicants, cannabis consumption must precede the use of hard drugs. Many studies show that hard drug users smoke marijuana first. The stereotyped progression of the use of drugs probably begins with caffeine, but no data address this drug's potential as a gateway. Most research suggests that adolescents first use alcohol or nicotine. Some authors argue that cigarettes serve as the actual gateway to drug problems (Kandel et al., 1992; Labouvie, Bates, & Pandina, 1997). A subset of the people who drink alcohol and smoke cigarettes subsequently use marijuana. A subset of those who try marijuana then use harder drugs like cocaine, crack, and heroin. Some researchers report that over 90% of people who try hard drugs tried marijuana first, suggesting temporal antecedence. They also ate white sugar, breathed air, and attended grade school. Thus, although hard drug users smoke marijuana before turning to other substances, this fact alone does not prove causality.

In addition, the order of drug use is not always perfectly consistent with the idea that marijuana is the gateway. Many hard drug users do not start with marijuana. Allen Ginsberg, the celebrated "beat" poet, serves as one notable exception. He injected heroin before smoking cannabis (Ginsberg, 1966). Large samples with thousands of respondents show a range of hard drug users who did not try marijuana first. One study found that as few as 1% of people who used hard drugs had not tried marijuana (Donovan & Jessor, 1983). In contrast, 15% of another sample of heavy drug users started with cocaine or intravenous drugs before smoking marijuana (Golub & Johnson, 1994). A study of Australian youth found that 29% of those who had used amphetamine, LSD, cocaine, or heroin had not used marijuana first (Blaze-Temple & Lo, 1992). Other research found 39% of a sample used hard drugs before trying cannabis (Mackesy-Amiti, Fendrich, & Goldstein, 1997). Thus, temporal antecedence applies in some cases of hard drug use, but not all. Even a perfect ordering with marijuana preceding all other drug use does not prove causality without isolation.

Isolation: Independent Processes or Problem Behavior?

Hume's last criterion for causality concerns isolation. If marijuana actually causes the use of hard drugs, other explanations should not account

for any association between them. At least two alternative explanations have some empirical support. One concerns the idea that the initiation of each drug arises from its own individual process. Miller (1994) calls this approach the statistical independence hypothesis. This hypothesis states that using one drug stems from its own availability, expectancies, and motivations that are separate from those related to another drug. Thus, the initiation of caffeine may stem from one process; the initiation of heroin may stem from another. The other idea that may account for stages of drug use focuses on the abuse of any and all substances as part of a cluster of larger problem behaviors. This problem behavior theory views substance abuse, unsafe sex, crime, and delinquency as all part of the same underlying trouble.

The rationale for individual processes follows statistical logic. People who participate in rare events likely engage in popular activities first. For example, more people view television than skydive. Thus, we would expect that most skydivers watched TV before they leaped from a plane. This fact need not mean that television causes skydiving. The two acts probably arise from independent, individual processes. Yet the most common one occurs first simply because it is more common. Comparable logic applies to drug consumption. People who use drugs will likely begin with those that are most common. Thus, individuals may use marijuana before cocaine because marijuana is more prevalent in our culture. Yet this fact need not mean that marijuana caused cocaine consumption. A massive study of four national samples including over 6,000 participants suggests that a large portion of the appearance of stages of drug use can be accounted for by statistically independent processes (Miller, 1994). This model does not account for all the data, but independent processes clearly contribute to the progression of drug use.

An alternative way to test the statistical independence hypothesis might examine neighborhoods where crack cocaine is more available than marijuana. If most drug users in such neighborhoods smoked crack before cannabis, the role of availability might receive some support. Under these circumstances, few could conclude that crack is a gateway leading to cannabis. Instead, people use the most available drug first and less available drugs later or not at all.

Another alternative explanation of drug sequencing concerns problem behavior theory. According to this theory, a small group of adolescents engage in a cluster of actions that all may lead to negative consequences (Jessor & Jessor, 1977). These problem behaviors include drug consump-

tion, poor school performance, unsafe sex, and criminal activities. According to this theory, the association between cannabis use and the consumption of other drugs does not arise because marijuana causes problems with other substances. Instead, both marijuana and the use of other intoxicants arise from the underlying problem orientation in a subset of individuals.

Many studies reveal strong correlations among the use of different drugs (Earleywine & Newcomb, 1997). Several potentially dangerous actions also correlate with drug use (Jessor, 1998). Miller (1994) analyzed data from four national surveys including more than 6,000 participants and found that problem behavior theory may account for the appearance of stage-like progressions in substance use. He found a large subgroup who used many drugs, and another set of people who used no drugs at all. These results are consistent with the idea that an underlying "problem-proneness" may account for links between marijuana and other drugs. Essentially, cannabis does not cause cocaine consumption, but a subset of people who like marijuana also like cocaine.

In addition to statistical independence and problem behavior theory, a third set of findings also supports arguments against marijuana as an isolated cause of hard drug use. Studies that show personality traits correlate with the use of multiple substances may mean that a personality characteristic led to both marijuana use and hard drug use. These data suggest that the same personality traits that can lead to smoking cannabis can also lead to snorting cocaine. Thus, the marijuana may not cause the use of the other drugs; both stem from the same underlying characteristic. Although evidence for an addictive personality is clearly limited (Nathan, 1988), people who report strong desires for thrill, adventures, and sensations often use a greater variety and amount of drugs (Simon, Stacy, Sussman, & Dent, 1994).

These findings support the idea that marijuana cannot be isolated as the cause of the use of hard drugs. Simple exposure to cannabis is not strongly associated with the use of other intoxicants. Hard drug users do not always use marijuana first. Causes other than marijuana also lead to the consumption of heroin or cocaine. Nevertheless, some authors argue that marijuana may still contribute to the use of harder drugs, even if it is not a unitary cause. They assert that even if cannabis does not qualify as the cause of other drug problems, it facilitates the use of more substances, increasing the likelihood of trouble.

Marijuana as Contributor Rather than Cause

Few interesting behaviors, including drug use, arise from a single process. Data do not support the idea that smoking marijuana causes the abuse of other substances. Nevertheless, perhaps marijuana "contributes" to the use of other drugs, even if it does not serve as the sole cause. This contributing process could work in several ways. For example, smoking marijuana may lead people to think of themselves as illicit drug users, making hard drug consumption more likely. Another pathway may arise when purchasing marijuana exposes people to the market for other drugs. In addition, marijuana intoxication may limit a person's ability to refuse harder drugs when they are offered. These factors may interact to contribute to the transition from cannabis consumption to hard drug use. Each of these paths is discussed in the following paragraphs.

One potential path for marijuana's impact on substance abuse concerns an individual's identity as an illicit drug user. Despite rampant consumption of caffeine and nicotine, few of us see ourselves as drug users. Most people who have never consumed an illicit drug would claim that they have no intention of snorting cocaine or smoking crack. Yet people might alter their impressions of themselves after smoking marijuana. With continued consumption of cannabis, people may see themselves as illicit drug users. After establishing this identity, their chances of trying other drugs may increase. Thus, people who may have had no intention of using cocaine or crack before they smoked marijuana may consider consuming these drugs after a period of cannabis use. Researchers have yet to examine this potential path, but studies along these lines may prove fruitful. Longitudinal studies might assess each individual's identity as a drug user over time. Some of those who try marijuana may adopt this identity; others may not. If those who smoke cannabis and subsequently consider themselves illicit drug users make the transition to hard drugs, the data would support this theory.

Another pathway may involve exposure to the illicit drug market. Suppliers of cannabis may also sell harder drugs, exposing marijuana purchasers to cocaine or heroin. A supplier may have a set of marketing strategies for these harder drugs, including strong personal testimony about their quality. Each purchase of marijuana may expose people to sales pitches for more harmful drugs, perhaps increasing the likelihood

of eventually trying them. Few studies address this course, but it has a certain intuitive appeal. This line of reasoning motivated marijuana decriminalization in the Netherlands in an attempt to separate it from the hard drug market. Some studies suggest that this move decreased the consumption of hard drugs (see chapter 10). Other studies might include interviewing hard drug users to see if they first obtained these drugs from the same person who supplied their cannabis.

Finally, perhaps marijuana users would be more likely to try other drugs during intoxication. People often use combinations of different substances (Earleywine & Newcomb, 1997). Yet no data address if people first try cocaine or heroin while experiencing cannabis's effects. The cognitive impairments associated with marijuana intoxication might decrease an individual's ability to resist using other drugs. A couple of experiments might shed light on this phenomenon. Researchers might provide access to cocaine or heroin after injecting THC into rodents to see if they are more likely to consume the new drugs during intoxication. Studies of human reactions might rely on self-reported willingness to try other drugs after smoking marijuana. People may claim to be more likely to ingest a new substance after consuming cannabis than they would after smoking a placebo. These data would support the idea that marijuana intoxication alters the probability of consuming hard drugs.

Preventing Substance Abuse

If marijuana consumption led directly to the abuse of hard drugs, preventing substance abuse would be simpler. In fact, drug problems arise from complex interactions of multiple factors. Preventing addiction and other aspects of substance abuse proves difficult. Many attempts have been relatively unsuccessful, including scare tactics, basic drug education, the Drug Abuse Resistance Education (DARE) program, and enhancing self-esteem. Other programs show more promise, including interactive sessions that teach techniques for combating peer pressure to use drugs. Social influence programs combine multiple strategies and have proven effective at decreasing drug use (Sussman, Dent, Stacy, & Craig, 1998). Unfortunately, no program has consistently eliminated drug abuse in all participants, and the impact of prevention efforts can often dissipate quickly (Shope, Copeland, Kamp, & Lang, 1998). Deterring drug problems remains an ongoing challenge.

standing in front of other participants to declare their intention. These activities have helped alter attitudes about drugs in other interventions. In addition to these activities, social influence programs add unique components to improve outcomes.

The unique components of social influence programs include increasing awareness about the actual number of drug users, developing skills for refusing drugs when offered, and combating indirect social pressures to use drugs. Perceptions of the number of users often lead to a skewed sense of drug consumption. People often hold the faulty idea that drug use is extremely common, and may feel that they should use drugs in order to obey this norm. Drug users often assume that everyone else uses drugs, too. Perceptions of norms for behavior guide actions in many domains. Objective information about drug consumption often surprises participants, who frequently overestimate the incidence of use (Perkins, Meilman, Leichliter, Cashin, & Presley, 1999). Accurate assessments of the number of users may minimize pressures related to the idea that everyone else consumes illicit drugs.

Drug refusal skills focus on resisting peer pressure to consume drugs. These include more than Nancy Reagan's simplistic recommendations to "just say no." Students engage in role plays designed to enhance their ability to decline drugs whenever they are offered. Strategies include keeping their refusals direct, suggesting alternative activities, avoiding situations where drugs are prevalent, and walking away if pressures feel threatening. Increasing awareness of indirect pressures to use drugs often focuses on the inaccuracy of glamorized media portrayals of substance use. Indirect pressures also may arise when social models, including parents, older siblings, and peers use drugs. Increasing awareness about these pressures may help inoculate against drug use (Donaldson et al., 1996). The majority of programs that employ this social influence approach have had positive effects (Hansen, 1992). Implementing them in more settings with detailed follow-up research can help minimize drug problems in ways that simplistic assumptions about marijuana as a gateway cannot.

Conclusions

The idea that marijuana serves as a gateway or stepping-stone to the consumption of harder drugs with worse negative consequences has generated considerable interest. There is no evidence that cannabis creates

physiological changes that increase the desire for drugs. The idea that marijuana causes subsequent drug use also appears unfounded. Causes require association, temporal antecedence, and isolation. Evidence for the association between marijuana and other drugs remains limited. Data do reveal that the majority of cocaine and heroin users consumed cannabis first. Nevertheless, only a minority of marijuana smokers try cocaine, crack, or heroin. Only a few people become regular users of these intoxicants. In addition, marijuana does not precede the use of hard drugs in all cases. Finally, correlations between marijuana smoking, hard drug consumption, and other problem behaviors suggest that one drug may not lead to another so much as all use of illicit substances reflects an underlying deviance or personality characteristic. Thus, prevention of drug problems requires more than staying away from cannabis.

Many programs designed to minimize substance abuse have met with only limited success. The scare tactics of the 1960s and 1970s had little impact on drug use. The DARE program, though popular, does little to prevent the use of illicit substances. The enhancement of self-esteem also does not prevent drug problems. One series of studies suggests that programs designed to minimize the impact of social influences to use drugs holds considerable promise. By providing valid information on the relative infrequency of drug use and valuable coaching on ways to resist pressures to use intoxicants, these programs can help decrease the incidence of abuse and dependence.

Comment on the Computation of Correlations

A few adventurous souls may wish to know the exact correlation between marijuana use and the use of other drugs. A Pearson product-moment correlation can be computed from a 2 × 2 table using the cross products and the marginals, in a manner that is easier done than said. Cross products are computed by multiplying the numbers along the diagonal. Marginals are the totals across each row and column. The correlation (R) equals the difference in the cross products divided by the square root of the product of all four marginals (Rosenthal & Rosnow, 1991). Using the data on drug use from 1999, and an assumption of 221 million adult Americans, we can compute the correlation between marijuana and crack cocaine use. Assume absolutely everyone who tried

The idea that
unfounded. Caus
on. Evidence for the
nains limited. Data do
consumed cannabis
nokers try cocaine,
r users of these intox-
ıse of hard drugs in
king, hard drug con-
ıat one drug may not
es reflects an under-
, prevention of drug
innabis.

buse have met with
s and 1970s had little
popular, does little to
ıt of self-esteem also
s suggests that pro-
ıfluences to use drugs
mation on the rela-
ıng on ways to resist
elp decrease the inci-

xact correlation be-
A Pearson product-
2 table using the cross
sier done than said.
ımbers along the di-
nd column. The cor-
ucts divided by the
osenthal & Rosnow,
an assumption of 221
lation between mar-
everyone who tried

Table 3.3. Millions of Americans Who Have Tried Marijuana, Crack Cocaine, Both, or Neither (1999)

	Tried marijuana		
Tried crack	Yes	No	Total
Yes	6	0	6
No	70	145	215
Total	76	145	

crack tried marijuana previously. The number of people (in millions), who tried marijuana, crack cocaine, both, or neither, appears in table 3.3.

Thus, of 221 million adult Americans, 76 million tried marijuana and 145 million did not. Assume that the 6 million Americans who tried crack cocaine also tried marijuana. Thus, 70 million people who tried marijuana never tried crack. The correlation from this table is computed by starting with the difference in the cross products. Moving from the upper left to lower right on the diagonal, we have 6 million × 145 million = 8.7×10^{13}. The upper right times the lower left is 0 × 70 million = 0. The difference between these two equals 8.7×10^{13}. We divide this number by the square root of the product of the four marginals. SQRT (76 million × 145 million × 6 million × 215 million)= 3.77×10^{15}. We divide 8.7×10^{13} by this number and get a correlation of .02. The numbers for heroin are even smaller because so few people have ever tried it. Thus, the correlation between marijuana consumption and the regular use of these harder drugs is negligible.

FAX NO. : 4155527178 Jan. 13 2004 11:27AM P5

Cancer Causes and Control, 1997, 8, pp. 722-728

Marijuana use and cancer incidence (California, United States)

Stephen Sidney, Charles P. Quesenberry, Jr., Gary D. Friedman, and Irene S. Tekawa

(Received 16 December 1996; accepted in revised form 12 May 1997)

The purpose of this retrospective cohort study was to examine the relationship of marijuana use to cancer incidence. The study population consisted of 64,855 examinees in the Kaiser Permanente multiphasic health checkup in San Francisco and Oakland (California, United States), between 1979-85, aged 15 to 49 years, who completed self-administered questionnaires about smoking habits, including marijuana use. Follow-up for cancer incidence was conducted through 1993 (mean length 8.6 years). Compared with nonusers/experimenters (lifetime use of less than seven times), ever- and current use of marijuana were not associated with increased risk of cancer of all sites (relative risk [RR] = 0.9, 95 percent confidence interval [CI] = 0.7-1.2 for ever-use in men; RR = 1.0, CI = 0.8-1.1 in women) in analyses adjusted for sociodemographic factors, cigarette smoking, and alcohol use. Marijuana use also was not associated with tobacco-related cancers or with cancer of the following sites: colorectal, lung, melanoma, prostate, breast, cervix. Among nonsmokers of tobacco cigarettes, ever having used marijuana was associated with increased risk of prostate cancer (RR = 3.1, CI = 1.0-9.5) and nearly significantly increased risk of cervical cancer (RR = 1.4, CI = 1.0-2.1). We conclude that, in this relatively young study cohort, marijuana use and cancer were not associated in overall analyses, but that associations in nonsmokers of tobacco cigarettes suggested that marijuana use might affect certain site-specific cancer risks. *Cancer Causes and Control* 1997, 8, 722-728

Key words: Cancer incidence, marijuana, retrospective cohort study, United States.

Introduction

Marijuana use is by far more prevalent than the use of any other illegal drug in the United States. It has been estimated that nearly one-third of the US population aged 12 and older has used marijuana.[1] The most common route of administration is smoking. Since marijuana smoke contains many of the same chemicals as tobacco smoke, in addition to containing 60 cannabinoid compounds, it is plausible to hypothesize that it may be carcinogenic.[2] However, marijuana has not been established as a risk factor for any cancer, although it may play a role in the development of lung cancer [3-5] and of head and neck cancers.[6,7] The uncertainty in establishing marijuana as a cancer risk factor may be due, in part, to the difficulty in separating the effects of marijuana from the effects of tobacco cigarettes, since in many instances the marijuana smoker also smokes tobacco cigarettes. Even though a marijuana cigarette may be smoked in a more intense manner (greater puff volume and length of inhalation)[10] than a tobacco cigarette, the total quantity of marijuana smoked by a user during his/her lifetime is

Authors are with the Division of Research, Kaiser Permanente Medical Care Program, Oakland, California, USA. Address correspondence to Dr Sidney, Kaiser Permanente Division of Research, 3505 Broadway, Oakland, California 94611-5714, USA. *This research was supported by Grant no. R01 DA06609 from the US National Institute on Drug Abuse. Dr Friedman is supported in part by Grant no. R[illegible]49761 from the US National Cancer Institute. Data collection regarding alcohol use was supported by a grant from The [illegible]ic Beverage Medical Research Foundation (Baltimore, MD, USA).*

© 1997 Rapid Science Publishers

generally a tiny fraction of the quantity smoked by a tobacco cigarette user.

We report here the findings of a study of the relationship of marijuana use to cancer incidence in a cohort of nearly 65,000 members of a large, prepaid health plan. This study is important because relatively little research has been reported regarding the relationship of marijuana use to human cancer, and we are unaware of any other cohort studies which have examined this issue. We hypothesized that marijuana use would be associated with increased risk of tobacco-related cancers, but that it might be difficult to detect this risk because of the coexistence of tobacco cigarette smoking in marijuana smokers. In previously published work,[11] we did not find an association between marijuana use and cancer mortality.

Materials and methods

Study population

The study cohort is composed of 64,855 Kaiser Permanente Medical Care Program (KPMCP) members, aged 15 to 49 years (mean 33 years), who voluntarily completed self-administered research questionnaires between mid-1979 through 1985 regarding tobacco, marijuana, and alcohol use in the context of a multiphasic health checkup (MHC) conducted in the San Francisco (until 1980) and Oakland Kaiser Permanente facilities in California (US). Written assurance was provided at the beginning of the questionnaires that all answers would be kept confidential, and that the questionnaire would not become part of the medical record or sent to the member's doctor. Follow-up was carried out from the date of the MHC to date of the earliest of the following: cancer diagnosis (n = 1,421); death (n = 495); diagnosis of HIV positivity or AIDS (n = 384); membership termination (n = 34,887); or 31 December 1993 (n = 27,668). The mean length of follow-up was 8.6 years.

Source of follow-up data

Incident cancers through 1993 were determined from computerized databases of confirmed cancer cases maintained by the Northern California Cancer Center (prior to 1988) and from the Kaiser Permanente Northern California Regional Cancer Registry (1988-93). Cancer cases were categorized according to ICD-9 codes.[12] Cancer sites categorized as smoking-related included upper aerodigestive (including esophagus), lung, pancreas, kidney, and bladder, as specified by the International Agency for Research on Cancer (IARC) in 1984.[13] We did not include cervical cancer and acute leukemia in the grouping of smoking-related cancers, although evidence has accumulated linking smoking to cancer of these sites.[14,15] HIV/AIDS cases were ascertained from the Northern California Kaiser Permanente Medical Care Program HIV/AIDS database. We excluded 92 cancer cases that occurred subsequent to or within one year prior to the date of HIV/AIDS diagnosis, distributed as follows: 68 Kaposi's sarcoma; 16 lymphatic cancers; eight other sites.

Mortality was ascertained through 1993 by computer-matching names and other demographic data with the California death file using the California Automated Mortality Linkage and Information System (CAMLIS).[16] In a test subset of 4,695 MHC examinees, this method was found to produce more false-negative results (11 percent *cf* six percent of known dead classified as alive) and fewer false-positive results (0.07 percent *cf* 1.2 percent of known alive classified as dead) compared with utilization of the National Death Index in ascertainment of mortality.[16] Membership status was determined for each year by examination of computerized files maintained by the Northern California Kaiser Permanente Medical Care Program.

Determination of marijuana use

Current marijuana smoking was defined by respondent's admission to smoking currently and more than six times ever. Former marijuana smoking was defined by denial of current smoking but admission to having smoked more than six times ever. Nonsmoking was defined as never having smoked. Experimenters were defined as those admitting to having ever smoked from one to six times. Ever-smokers included current and former users but excluded experimenters. Duration of use (number of years) and frequency of use ('less than once a month,' 'about once or twice a month,' 'about once or twice a week,' and 'almost every day') were assessed in ever-users. Data were not collected in former users regarding the length of time since they last used marijuana.

Determination of tobacco cigarette use and alcohol use

Persons were classified as current, former, or never-smokers of tobacco cigarettes on the basis of their questionnaire responses.[17] Current and former smokers were also questioned about frequency (number of cigarettes per day) and duration (years) of smoking. Alcohol consumption was categorized as current use, former use, and nonuse. Current drinkers were questioned about how many drinks they usually had during the past year: 'nine or more per day,' 'six to eight per day,' 'three to five per day,' 'one or two per day,' 'less than one per day, but more than one per month,' and 'less than one per month (special occasions only).'

Analytic methods

The analyses were planned to compare the risk of cancer associated with ever-use of marijuana and with current use of marijuana relative to never or experimental use.

FROM :. FAX NO. : 4155527170 Jan. 13 2004 09:12PM P1

RECEIVED JAN 1 3 2004

Statistical analyses were performed using SAS programs.[11] Age-adjusted incidence rates were calculated by the direct method using 10-year age groupings with the 1990 US population as the standard. Cox proportional hazards models were used to examine the joint effect of sociodemographic characteristics, marijuana use, tobacco, and alcohol use on the risk of cancer, from which estimates of relative risks (RR) and associated 95 percent confidence intervals (CI) were obtained.[11] Two-way interactions between marijuana and tobacco use and between marijuana and alcohol were tested by including cross-product terms in the proportional hazards models. The interaction terms were statistically significant in a few of the models (tobacco and ever-use of marijuana for colorectal cancer in women and melanoma in men; alcohol and both ever- and current use of marijuana for prostate cancer in men; alcohol and both ever- and current use of marijuana for breast cancer in women). However, the RR estimates associated with tobacco or alcohol use within any given level of marijuana use in these models had wide CIs and lack of dose-response, so that only the main effects are reported in this paper. To obtain estimates of the overall risk associated with marijuana use, adjusted for tobacco cigarette use, tobacco cigarette use was categorized as a three-level variable (*i.e.*, nonuser, former user, current user).

Results

Sociodemographic characteristics (Table 1)

Current users, former users, experimenters, and nonusers, respectively, comprised 22 percent, 20 percent, 20 percent, and 38 percent of the cohort. The percentage of ever-users was highest in the 20 to 29 year age group. Ever-use of marijuana was more common in men than in women, and more common in Whites followed by Blacks, Hispanics, and Asians.

Tobacco cigarette use

The distribution of marijuana use (ever *cf* nonusers/experimenter) and tobacco cigarette smoking (ever *cf* nonsmoker) are shown in Table 2. The prevalence of a history of tobacco-cigarette smoking was 54 percent higher in ever-users of marijuana (59.9 percent) than in nonusers/experimenters (38.8 percent). A substantial proportion of marijuana users were nonsmokers of tobacco cigarettes (40.1 percent of ever-users of marijuana [10,710 of 26,733]).

Distribution of cancer sites

Overall, there were 379 incident cancers in men, and 1,042 incident cancers in women. We performed analyses for cancers of all sites, tobacco-related cancers, and individual

Table 1. Sociodemographic characteristics of a cohort of Kaiser Permanente Medical Care Program members ($n = 64,855$) by marijuana use status, June 1979 through December 1985

Status at multiphasic health checkup	Never	Experimenter	Former	Current
Age (yrs)				
15-19	902	558	508	757
20-29	5,489	3,864	4,734	5,970
30-39	8,929	5,320	5,751	5,759
40-49	9,647	3,413	1,707	1,547
Gender				
Male	9,072	5,271	6,075	7,502
Female	15,895	7,884	6,625	6,531
Race				
White	9,894	7,316	8,372	8,743
Black	7,654	3,770	2,839	3,974
Asian	6,085	1,082	649	399
Hispanic	1,525	615	476	528
Other/unknown	809	392	365	389
Education				
≤ High school	5,837	2,420	1,887	2,518
Technical/business school/ some college	8,706	4,760	4,458	5,435
College graduate/ post graduate	9,941	5,703	6,034	5,850
Unknown	483	272	321	230
Total	24,967	13,155	12,700	14,033

FROM :
FAX NO. : 4155527178
Jan. 13 2004 09:06AM P3

sites with 30 or more gender-specific incident cancers (colorectal, lung, and melanoma for both genders; prostate for men, and breast and cervix for women). The counts for all these groupings and sites by marijuana and tobacco-cigarette use status are shown in Tables 3 and 4.

Table 2. Distribution of study population by gender and by ever-use of marijuana and tobacco cigarettes, Kaiser Permanente Medical Care Program

Marijuana/cigarette smoking history		Men	Women
Marijuana use	Tobacco cigarette use	No.	No.
Never	Never	8,170	15,360
Never	Ever	6,173	8,419
Ever	Never	5,593	5,117
Ever	Ever	7,984	8,039
Total		27,920	36,935

Marijuana and tobacco cigarette use in relation to cancer incidence

As expected, tobacco cigarette use, regardless of marijuana use status, was associated with increased risks of tobacco-related cancer ranging from 2.7 to 3.8 relative to nonuse of marijuana and tobacco cigarettes in models adjusted for age, race/ethnicity, education, and alcohol use (Tables 3 and 4); RRs for lung cancer associated with tobacco cigarette use ranged from 9.2 to 11.2. Ever-use of marijuana by nonsmokers of tobacco cigarettes was associated with increased risk in men of prostate cancer (RR = 3.1, CI = 1.0–9.5) and with a nearly significant increased risk in women of cervical cancer (RR = 1.4, CI = 1.0–2.1) relative to nonuse of marijuana and tobacco cigarettes. Additional adjustment for marital status did not appreciably alter the estimates of RRs for cancer of these sites, nor was it statistically significantly associated with these cancer sites. We also examined the association of marijuana use with invasive cervical cancer, comprising 11 percent (33 of 302) of all cervical cancers. Ever-use of marijuana in nonsmokers of tobacco cigarettes was asso-

Table 3. Counts, age-adjusted rates, and relative risks (RR) of all cancers, tobacco-related cancers, and cancers of specific sites by marijuana and cigarette smoking status in men, Kaiser Permanente Medical Care Program

Site of cancer	Marijuana, cigarette smoking history	Number of cases	Rate[a]	RR[b]	(CI)[c]
All sites	Never, never	109	149	1.0	—
	Never, ever	138	169	1.1	(0.9-1.5)
	Ever, never	38	186	0.8	(0.5-1.2)
	Ever, ever	96	165	1.1	(0.8-1.5)
Tobacco-related	Never, never	12	19	1.0	—
	Never, ever	56	68	3.1	(1.6-5.8)
	Ever, never	3	7	0.8	(0.2-2.9)
	Ever, ever	28	39	2.8	(1.4-5.6)
Colorectal	Never, never	16	16	1.0	—
	Never, ever	15	18	0.8	(0.4-1.6)
	Ever, never	4	7	0.7	(0.2-2.1)
	Ever, ever	10	29	0.9	(0.4-1.9)
Lung	Never, never	2	3	1.0	—
	Never, ever	32	39	10.3	(2.4-43.7)
	Ever, never	0	—	—	—
	Ever, ever	14	28	9.2	(2.0-42.0)
Melanoma	Never, never	23	27	1.0	—
	Never, ever	10	9	0.5	(0.2-1.0)
	Ever, never	6	11	0.5	(0.2-1.3)
	Ever, ever	19	25	1.1	(0.6-2.0)
Prostate	Never, never	9	16	1.0	—
	Never, ever	21	28	2.0	(0.9-4.5)
	Ever, never	5	95	3.1	(1.0-9.5)
	Ever, ever	7	31	1.7	(0.6-4.9)

[a] Per 100,000 person-years, age adjusted to 1990 US population.
[b] Adjusted for age, race, education, and alcohol use.
[c] CI = 95% confidence interval.

FROM :

FAX NO. : 4155527170

Jan. 13 2004 09:13AM P2

Table 4. Counts, age-adjusted rates, and relative risks (RR) of all cancers, tobacco-related cancers, and cancers of specific sites by marijuana and cigarette smoking status in women, Kaiser Permanente Medical Care Program

Site of cancer	Marijuana, cigarette smoking history	Number of cases	Rate[a]	RR[b]	(CI)[c]
All sites	Never, never	408	260	1.0	—
	Never, ever	353	393	1.3	(1.1-1.5)
	Ever, never	93	403	1.1	(0.8-1.3)
	Ever, ever	188	408	1.2	(1.0-1.4)
Tobacco-related	Never, never	18	12	1.0	—
	Never, ever	55	54	3.8	(2.1-6.7)
	Ever, never	0	—	—	—
	Ever, ever	10	47	2.7	(1.2-6.3)
Colorectal	Never, never	27	18	1.0	—
	Never, ever	28	26	1.4	(0.8-2.4)
	Ever, never	1	2	0.3	(0.0-2.5)
	Ever, ever	6	8	0.9	(0.4-2.3)
Lung	Never, never	5	4	1.0	—
	Never, ever	36	35	9.8	(3.6-26.5)
	Ever, never	0	—	—	—
	Ever, ever	8	44	11.2	(3.3-37.7)
Melanoma	Never, never	23	11	1.0	—
	Never, ever	18	18	1.1	(0.6-2.0)
	Ever, never	8	71	1.0	(0.4-2.3)
	Ever, ever	16	19	1.2	(0.6-2.5)
Breast	Never, never	171	101	1.0	—
	Never, ever	113	117	0.9	(0.7-1.2)
	Ever, never	22	115	0.8	(0.5-1.3)
	Ever, ever	54	138	1.0	(0.8-1.5)
Cervix	Never, never	92	62	1.0	—
	Never, ever	80	118	1.7	(1.2-2.3)
	Ever, never	48	119	1.4	(1.0-2.1)
	Ever, ever	82	125	1.6	(1.2-2.2)

[a] Per 100,000 person-years, age adjusted to 1990 US population.
[b] Adjusted for age, race, education, and alcohol use.
[c] CI = 95% confidence interval.

ciated with a nonsignificant increased risk of invasive cervical cancer (RR = 2.4, CI = 0.8-6.7). The overall risks of cancer associated with ever-use of marijuana are shown in Table 5, adjusted for tobacco cigarette smoking status (non-, former, current) as well as the other variables noted earlier. Ever use of marijuana was not associated in men or in women with increased or decreased risk of any cancer grouping or individual site. The results of analyses of cancer incidence excluding the 222 (15.6 percent of total cancers) which developed within the first two years of follow-up was similar to the overall results, suggesting that the overall results were not affected by symptoms caused by cancer prior to its diagnosis that affected the decision to use marijuana.

The findings in regard to current marijuana use were similar to those for ever-use of marijuana. Current marijuana use also was associated with increased risk of prostate cancer (RR = 4.7, CI = 1.4-15.5) and a nearly

Table 5. Risk of cancer in ever-users of marijuana relative to nonusers/experimenters adjusted for cigarette smoking status and other variables,[a] Kaiser Permanente Medical Care Program

Site of cancer	Men		Women	
	RR[b]	(CI)[c]	RR[b]	(CI)[c]
All sites	0.9	(0.7-1.2)	1.0	(0.8-1.1)
Tobacco-related	0.9	(0.6-1.4)	0.7	(0.3-1.4)
Colorectal	0.9	(0.5-1.8)	0.6	(0.2-1.3)
Lung	0.9	(0.5-1.7)	1.1	(0.5-2.6)
Melanoma	1.2	(0.7-2.1)	1.1	(0.6-1.9)
Prostate	1.3	(0.6-2.6)	—	—
Breast	—	—	1.0	(0.8-1.3)
Cervix	—	—	1.1	(0.9-1.5)

[a] Adjusted for age, race, education, alcohol use, and tobacco cigarette smoking.
[b] RR = relative risk.
[c] CI = 95% confidence interval.

FROM : FAX NO. : 4155527170 Jan. 13 2004 09:06AM P4

significant increased risk of cervical cancer (RR = 1.6, CI = 1.0-2.5).

We examined the association of duration (years) and frequency of marijuana use for cancer-site groupings and for individual sites with 10 or more gender-specific incident cancers among ever-users of marijuana. Duration of use was not associated with the risk of any cancer site or grouping of cancers. For prostate cancer, a tendency toward an association of frequency of marijuana use with increased risk was evident, with usage one or more times per week (56.3 percent of male ever-users) associated with a nonsignificant twofold increase in the risk of prostate cancer relative to nonusers/experimenters. However, the addition of frequency of use did not improve the fit of any of the models for prostate cancer or for cancer of any other site or grouping of cancers.

Discussion

The main findings were the lack of association of marijuana use with overall cancer incidence and with the incidence of all tobacco-related cancers combined. Marijuana use was associated with an increased risk of prostate cancer in men who were nonsmokers of tobacco cigarettes, and a nearly significant risk of cervical cancer in women who were current marijuana smokers and nonsmokers of tobacco cigarettes.

The association between marijuana use and prostate cancer found in this study raises the question of potential hormonal mediation. There is a significant body of evidence suggesting that androgens are important in prostate carcinogenesis, including the following: (i) androgens are required for the normal growth and maintenance of the prostate;[30] (ii) testosterone has been shown to induce prostate cancer in laboratory rodents;[31] and (iii) prostate cancer rarely occurs in eunuchs, and antiandrogen therapy or ablation results in regression of prostate cancer.[32] Studies examining the relationship of serum testosterone to prostate cancer in humans have not shown consistent results.[33,34] An early study showing that plasma testosterone levels in men were decreased in chronic marijuana users[35] has not been supported by most of the numerous subsequent studies regarding this issue.[36] Sexual activity measures have been inconsistently associated with prostate cancer,[37] although they are associated with psychoactive drug use.[38] It is notable that the prostate cancer cases represented in this study are relatively young compared with those occurring in the general population, since the maximum age reached by this cohort during follow-up was 63 years.

Cigarette smoking has been shown to be a risk factor for cervical cancer in many studies.[15] The association of marijuana use with cervical cancer in nonsmokers might reflect confounding by sexual activity, since number of sexual partners is a risk factor for cervical cancer[39] and is associated with psychoactive drug use.[38]

The major limitations of this study include reliance on self-report for ascertainment of marijuana-use status; inability to study change in marijuana-use status during follow-up; and lack of lengthy follow-up into the geriatric age range, as noted earlier. We do not believe that underreporting of marijuana use is likely to have been a significant problem because data collection on marijuana use was completed before the acceleration of the 'War on Drugs' in the late 1980s, during a period of time when the environment surrounding marijuana use was more accepting. Additionally, marijuana use rates in the study cohort were similar to those reported during the same time period by the National Household Survey on Drug Abuse, the most authoritative source of statistics on illegal drug use in the US.[39] Lack of longitudinal data regarding an exposure is a common feature of many cohort studies. We believe that it is unlikely that ever-use of marijuana would have increased substantially over time, because a relatively small proportion of the cohort are likely to have initiated marijuana use during follow-up which occurred in a period marked by a significant decline in self-reported marijuana use in the US.[1]

In conclusion, this study did not show any significant associations between marijuana use and cancer in overall analyses, but showed associations suggesting increased risk of prostate and cervical cancer in marijuana users who were nonsmokers of tobacco cigarettes. We do not consider any of the findings to be conclusive, and as with all epidemiologic work, we strongly suggest that marijuana use and cancer be studied in other settings.

Acknowledgements — The authors acknowledge Steve Wilson and Anne Zishka for computer programming, Leo Hurley for consultation regarding the use of the Kaiser Permanente HIV/AIDS database, and Diana Holt for technical assistance in preparing the manuscript.

References

1. Substance Abuse and Mental Health Services Administration. *Preliminary Estimates from the 1994 National Household Survey. Advance Report No. 10.* Rockville, MD (USA): SAMHSA, 1995.
2. Hoffman D, Brunnemann KD, Gori BG, Wynder EL. On the carcinogenicity of marijuana smoke. *Recent Adv Phytochem* 1975; 9: 63-81.
3. Gong H Jr, Fligiel S, Tashkin DP, Barbers RG. Tracheobronchial changes in habitual, heavy smokers of marijuana with and without tobacco. *Am Rev Respir Dis* 1987; 136: 142-9.
4. Taylor FM. Marijuana as a potential respiratory tract carcinogen: A retrospective analysis of a community hospital population. *South Med J* 1988; 81: 1213-6.

5. Tashkin DP. Is frequent marijuana smoking harmful to health [Letter]. *West J Med* 1993; 158: 635-7.
6. Caplan GA, Brigham BA. Marijuana smoking and carcinoma of the tongue. Is there an association? *Cancer* 1989; 66: 1005-6.
7. Donald PJ. Advanced malignancy in the young marijuana smoker. In: Friedman H, Specter S, Klein TW, *et al*, eds. *Drugs of Abuse, Immunity, and Immunodeficiency*. New York, NY (USA): Plenum Press, 1991: 33-46.
8. Donald PJ. Marijuana and upper aerodigestive tract malignancy in young patients. In: Nahas GG, Latour C, eds. *Cannabis Physiopathology, Epidemiology, Detection*. Boca Raton, FL (USA): CRC Press, 1993: 165-83.
9. Nahas G, Latour C. The human toxicity of marijuana. *Med J Aust* 1992; 156: 495-7.
10. Wu TC, Tashkin DP, Djahed B, Rose JE. Pulmonary hazards of smoking marijuana as compared with tobacco. *N Engl J Med* 1988; 318: 347-51.
11. Sidney S, Beck JE, Tekawa IS, Quesenberry CP, Friedman GD. Marijuana use and mortality. *Am J Public Health* 1997; 87: 585-90.
12. World Health Organization. *International Classification of Diseases*, Ninth Revision. Geneva, Switzerland: WHO, 1977.
13. International Agency for Research on Cancer. *Tobacco Smoking*. Lyon, France: IARC, 1986. *IARC Monogr Eval Carcinog Risk Chem Hum*, Vol. 38.
14. Friedman GD. Cigarette smoking, leukemia, and multiple myeloma. *Ann Epidemiol* 1993; 3: 425-8.
15. Winkelstein W Jr. Smoking and cervical cancer – current status: A review. *Am J Epidemiol* 1990; 131: 945-57.
16. Arellano M, Peterson G, Petitti DB, Smith R. The California automated mortality linkage system. *Am J Public Health* 1984; 74: 1324-30.
17. Friedman G, Sidney S, Polen M. Smoking habits among multiphasic examinees, 1979 to 1984. *West J Med* 1986; 145: 651-6.
18. SAS Institute, Inc. *SAS User's Guide*. Cary, NC (USA): SAS Institute, Inc., 1990.
19. Cox DR, Oakes D. *Analysis of Survival Data*. New York, NY (USA): Chapman and Hall, 1984.
20. Henderson BE, Ross RK, Pike MC, Casagrande JT. Endogenous hormones as a major factor in human cancer. *Cancer Res* 1982; 42: 3232-9.
21. Noble RL. The development of prostatic adenocarcinoma in Nb rats following prolonged sex hormone administration. *Cancer Res* 1977; 37: 1929-33.
22. Huggins C, Hodges CV. Studies on prostate cancer: Effect of castration, of estrogen, and of androgen injection on serum phosphatase in metastatic carcinoma of the prostate. *Cancer Res* 1941; 1: 293-7.
23. Gann PH, Hennekens CH, Ma J, Longcope C, Stampfer MJ. Prospective study of sex hormone levels and risk of prostate cancer. *JNCI* 1996; 88: 1118-26.
24. Hsing AW. Hormones and prostate cancer: Where do we go from here? [Editorial] *JNCI* 1996; 88: 1093-5.
25. Kolodny RC, Masters WH, Kolodner RM, Toro G. Depression of plasma testosterone levels after chronic intensive marihuana use. *N Engl J Med* 1974; 290: 872-4.
26. Block RI, Farinpour R, Schlechte JA. Effects of chronic marijuana use on testosterone, luteinizing hormone, follicle stimulating hormone, prolactin and cortisol in men and women. *Drug Alcohol Depend* 1991; 28: 121-8.
27. Nomura AMY, Kolonel LN. Prostate cancer: a current perspective. In: Armenian HK, Gordis L, Levine MM, Thacker SB, eds. *Epidemiol Rev* 1991; 13: 200-27.
28. Newcomb MD, Bentler PM. *Consequences of Adolescent Drug Use*. Newbury Park, CA (USA): Sage Publications, 1988: 21.
29. Brinton LA. Epidemiology of cervical cancer – an overview. In: Muñoz N, Bosch FX, Shah KV, Meheus A, eds. *The Epidemiology of Human Papillomavirus and Cervical Cancer*. Lyon, France: International Agency for Research on Cancer, 1992: 119; 4-6.
30. National Institute on Drug Abuse. *National Household Survey on Drug Abuse, Population Estimates 1985*. Rockville, MD (USA): NIDA, 1987; DHHS Pub. No. (ADM)87-1539.

Short-Term Effects of Cannabinoids on Immune Phenotype and Function in HIV-1-Infected Patients

Barry M. Bredt, Dana Higuera-Alhino, Starley B. Shade, Samuel J. Hebert, Joseph M. McCune, and Donald I. Abrams

Cannabinoids, including smoked marijuana and Δ^9-tetrahydrocannabinol (THC) (dronabinol, Marinol), have been used to treat human immunodeficiency virus-1 (HIV)–associated anorexia and weight loss. Concerns have been raised, however, that these compounds might have adverse effects on the immune system of subjects with HIV infection. To determine whether such effects occur, the authors designed a randomized, prospective, controlled trial comparing the use of marijuana cigarettes (3.95% THC), dronabinol (2.5 mg), and oral placebo in HIV-infected adults taking protease inhibitor-containing highly active antiretroviral therapy (HAART). Assays of immune phenotype (including flow cytometric quantitation of T cell subpopulations, B cells, and natural killer [NK] cells) and immune function (including assays for induced cytokine production, NK cell function, and lymphoproliferation) were performed at baseline and weekly thereafter. On the basis of these measurements and during this short 21-day study period, few statistically significant effects were noted on immune system phenotypes or functions in this patient population.

Journal of Clinical Pharmacology, 2002;42:82S-89S

In the era prior to the introduction of highly active antiretroviral therapy (HAART), and largely in the absence of any supporting data, smoked marijuana became increasingly used for the treatment of human immunodeficiency virus-1 (HIV)–associated anorexia and weight loss.[1] Legislation was passed in California in 1996 that enabled physicians to recommend marijuana for a number of medical conditions, including the AIDS wasting syndrome. Access to smoked marijuana was facilitated in the San Francisco Bay Area by the creation of numerous cannabis "buyers clubs."[2] At one time, it was estimated that such establishments were providing marijuana to more than 10,000 clients with HIV infection.

Despite anecdotal reports of weight gain and improvement in mood and quality of life in their patients who smoked marijuana, medical providers caring for patients with HIV infection have raised concerns about the safety of marijuana smoking by patients with immune deficiency. Studies of the effect of marijuana on immunity have been contradictory and, when viewed in aggregate, difficult to interpret. The major psychoactive component of marijuana, Δ^9-tetrahydrocannabinol (THC), has been reported to suppress immune functions such as cell proliferation, antibody production, natural killer (NK) cell activity, and macrophage function; to dysregulate production of proinflammatory cytokines such as interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α); and to confer altered susceptibility in vivo to infection with intracellular organisms such as *Legionella pneumophilia* and to herpes simplex virus type-1 infected cells.[3-10]

Two cannabinoid receptors, CB1 and CB2, have been identified.[11] The CB1 receptor, which is preferentially expressed in the brain, has been identified as the

From the Department of Medicine, General Clinical Research Center at San Francisco General Hospital (B. M. Bredt); Gladstone Institute of Virology and Immunology, San Francisco (D. Higuera-Alhino, S. J. Hebert, J. M. McCune); Department of Medicine, Positive Health Program at San Francisco General Hospital (S. B. Shade, D. I. Abrams); and Departments of Medicine and Microbiology and Immunology, University of California, San Francisco (J. M. McCune). Supported by R01 DA/MH 11607, NIAID 2P30 AI27763, and NCRR MO1 RR00083. J. M. McCune is an Elizabeth Glaser Pediatric AIDS Foundation Scientist and a recipient of the Burroughs Wellcome Fund Clinical Scientist Award in Translational Research. Address for reprints: Donald I. Abrams, MD, Professor of Clinical Medicine, San Francisco General Hospital, Ward 84, 995 Portero Avenue, San Francisco, CA 94110.
DOI: 10.1177/0091270002238798

...ely cause of cannabis-mediated central nervous system effects. In contrast, the CB2 receptor is preferentially expressed in peripheral tissues such as the marginal zone of the spleen and on the surface of B lymphocytes and NK cells.[17] Accordingly, the potential exists for interactions between THC and the immune system.

To date, there have been no controlled investigations of the impact of marijuana on immune function in patients with HIV infection. Either as a stimulant or suppressant of immune function, marijuana could potentially lead to increased viral burden. This potential effect also has never been investigated in a prospective, controlled fashion. Finally, the potential for a drug-drug interaction between protease inhibitors and marijuana is particularly worrisome because both are metabolized by the cytochrome P450 enzyme system, and many HIV-infected patients continue to smoke marijuana as an appetite stimulant or to decrease nausea associated with their antiretroviral therapy.[12-16]

To more closely evaluate the possibility of these adverse effects, we designed a study to determine the safety/toxicity profile of cannabinoids in people with HIV infection on protease inhibitor-containing regimens. The specific goals of this study were to determine the short-term effects of cannabinoids (smoked and oral) on HIV RNA levels, the immune system, and the pharmacokinetics of two widely used protease inhibitors, indinavir and nelfinavir. Viral load was selected as the primary endpoint because it might be affected by an interaction between cannabinoids and the metabolism of the protease inhibitor and/or between cannabinoids and the immune system. Reported here are the immune endpoints of this study of the short-term effects of cannabinoids in patients with HIV infection. Published data are reported separately on the short-term effects of cannabinoids on viral load and on the pharmacokinetics of the protease inhibitors.[17,18]

METHODS

Study Population

Subjects were required to be at least 18 years old, have documented HIV infection, and be on a stable antiretroviral treatment regimen that included either indinavir (Crixivan, Merck) or nelfinavir (Viracept, Agouron) for at least 6 weeks prior to enrollment. Upon admission to the San Francisco General Hospital General Clinical Research Center (GCRC) for the 25-day inpatient trial, subjects who had been taking the more recently recommended dose of nelfinavir (1250 mg twice daily) were switched to a dose of 750 mg three times daily for consistency of our pharmacokinetic evaluations.[19] No additional protease inhibitors were allowed during the duration of the study. Subjects were also required to have a stable viral load, defined as less than a threefold (< 0.5 $\log_{10}$) change in HIV RNA level for the 16 weeks prior to enrollment. All subjects were required to have prior experience smoking marijuana (defined as six or more times) to ensure that they knew how to inhale and what neuropsychiatric effects to expect. The study was approved by the Committee on Human Research of the University of California, San Francisco, and signed informed consent was obtained from each participant before enrollment.

Exclusion criteria included the following: any active opportunistic infection or malignancy requiring acute treatment, unintentional loss of ≥ 10% of body weight during the prior 6 months, current substance dependence, methadone maintenance, use of tobacco or cannabinoids (smoked or oral) within 30 days of enrollment, history of serious pulmonary disease, pregnancy, and Stage II or higher AIDS dementia complex. Laboratory exclusion criteria were as follows: hematocrit < 25% and hepatic transaminase elevations greater than five times the upper limit of normal. Therapeutic exclusions were concurrent use of megestrol acetate, nandrolone, oxandrolone, oxymetholone, human growth hormone, thalidomide, pentoxifylline, prednisone, interleukin-2, chemotherapy, radiotherapy, or other investigational agents known to alter immune system function within the prior 8 weeks.

Study Medications

The National Institute on Drug Abuse (NIDA) provided prerolled marijuana cigarettes, weighing on average 0.9 gm and containing 3.95% THC. These cigarettes were kept in a locked and alarmed freezer until they were dispensed to a locked freezer in the GCRC where the inpatient study was conducted. The marijuana cigarettes required rehydration overnight in a humidifier. Subjects randomized to the smoked marijuana arm were housed in a room with a fan ventilating to the outside. To maximize standardization of inhaled doses, research staff monitored subjects while they followed the Foltin uniform puff procedure.[20] Research staff weighed the marijuana cigarettes immediately before and after they were administered to subjects and returned all leftover material to the pharmacy for ultimate return to NIDA. Subjects smoked up to three com-

plete marijuana cigarettes daily, as tolerated, 1 hour prior to meals. Roxane Laboratories (Columbus, OH) supplied dronabinol and matching placebo capsules.

Research Design and Procedures

Subjects were randomized in a double-blind manner to the oral regimens and received either dronabinol 2.5 mg or placebo on the same schedule as the subjects randomized to smoked marijuana. The randomized, placebo-controlled trial was composed of two inpatient phases. The first phase was a 4-day lead-in period, during which time subjects were admitted to the GCRC for measurement of baseline parameters. A urine sample obtained on the day of admission (day −4) was required to be negative for THC. The second phase was a 21-day intervention period beginning with random assignment of treatments on day 0. The subjects were stratified by protease inhibitor (indinavir or nelfinavir) and then allocated with equal probability in blocks of 12 to the study agents (marijuana, dronabinol, and placebo). Subjects were not permitted to have visitors or to leave the confines of the GCRC unless accompanied by research personnel during the 25-day study. All clinical laboratory tests and study procedures were obtained or performed in the GCRC.

Absolute Lymphocyte Counts

Automated complete blood counts with differential were performed in the San Francisco General Hospital Clinical Laboratory, using an automated hematology analyzer (Bayer Technicon H3 System, Bayer Corp., Tarrytown, NY) according to the manufacturer's directions.

Immunophenotyping

Baseline samples were collected on day 0, and follow-up specimens were drawn on days 7, 14, and 21. Four-color flow cytometric immunophenotyping was performed according to the manufacturer's directions with the following panels of antibodies: CD3-Cy5/CD4-PE/CD8-ECD/CD45-FITC, CD3-ECD/CD19-FITC/CD56-PE/CD45-Cy5, CD4-ECD/CD8-Cy5/CD38-PE/HLA-DR-FITC, CD4-ECD/CD8-Cy5/CD25-FITC/CD69-PE, CD4-ECD/CD8-Cy5/CD45RA-FITC/CD62L-PE (all from Beckman Coulter, Inc., Fullerton, CA). Data acquisition and analysis were performed using a Beckman Coulter EPICS XL flow cytometer, running System II, version 3.0.

Cytokine Flow Cytometry

A cytokine flow cytometry assay was used to measure the percentage of CD4+ T cells that are activated (express CD69) and that also synthesize specific cytokines (TNF-α, IFN-γ, or IL-2) in response to stimulation with the CMV antigen.[21] As a positive control, stimulation was carried out with the superantigen *Staphylococcal* enterotoxin B (SEB), and unstimulated cultures served as negative controls. Briefly, heparinized blood was incubated with antibody to CD28 (L293, BD Biosystems, San Jose, CA) alone (negative control), with SEB (Sigma, St. Louis, MO), or with sucrose density gradient-purified virus preparations from human CMV strain AD169-infected human foreskin fibroblast cultures (Advanced Biotechnologies, Inc., Columbia, MD) for 5 hours. Brefeldin A (Sigma) was added during the last 3 hours, followed by addition of FACS™ lysing solution (BD Biosystems), centrifugation, and resuspension of cells in FACS™ permeabilizing solution (BD Biosystems). Cells were then stained with monoclonal antibodies specific for CD4, CD69, and either TNF-α, IFN-γ, or IL-2 and analyzed by flow cytometry. The frequency of CD4+ T cells staining positive for CD69 and for the intracellular cytokine of interest after CMV stimulation was adjusted by subtracting the frequency in unstimulated samples. In preliminary experiments, control stimulants included a mock-infected cell lysate–negative control preparation (BioWhittaker), tissue culture medium including 10% human AB serum, and no stimulation. No significant difference was noted among these negative controls.

Natural Killer Cell Function

The cytolytic activity of NK cells was assessed using K562 erythroleukemic target cells.[22] K562 cell suspensions were labeled with ^{51}Cr for 2 hours at 37°C and supplemented with RPMI 1640 and 10% human AB serum. After centrifugation, cells were stained with trypan blue and counted. Peripheral blood mononuclear cells (PBMC) were isolated by density-gradient centrifugation, counted, adjusted to 1×10^7 cells/ml, and plated in K562 cells at effector:target (E:T) ratios of 6.3:1, 12.5:1, 25:1, 50:1, and 100:1. Culture plates were centrifuged and incubated at 37°C with 5% CO_2 for 4 hours before being harvested and counted. Both net NK cell

[redacted]city and per NK cell cytotoxicity were mea- [redacted]d expressed as percent lysis of target cells at 1 E:T ratio.

mphoproliferation

phoproliferation was measured using a standard tiated thymidine uptake assay.[23] Briefly, PBMC were ubated in quadruplicate with phytohemagglutinin A, Sigma), tetanus toxin (Connaught Laboratories, fwater, PA), CMV antigen (BioWhittaker), or a pool inactivated alloreactive human PBMC for 3 to 6 days then pulsed with 1 μCi of tritiated thymidine. nts per minute (cpm) for each antigen were averged and the stimulation index (SI) calculated. At st one HIV-uninfected control was run weekly ughout the course of the study. In all cases in ich donor cell responses were found to be negative, sitive responses were detected either for that donor h another antigen or for other donors assayed on same day.

tatistical Analysis

e effects of cannabinoids on absolute lymphocyte unts, immunophenotyping analyses, and immune ponses as measured by cytokine flow cytometry, NK [redacted]ny, and lymphoproliferation assay were ana- [redacted]y comparison of the baseline (day 0) parameters ith those derived after cannabinoid treatment (day . Median values of these variables for each arm at eline are reported, as are median values for each m based on the change in each variable between day nd day 21. Because many of the baseline and change iables were not normally distributed, nonparametric tistical tests were performed. Kruskal-Wallis tests ere used to identify statistically significant differences between the placebo arm and each of the nabinoid arms at baseline. Kruskal-Wallis tests ere also used to identify statistically significant differences between the placebo arm and each of the nabinoid arms based on the change in each variable ween day 0 and day 21.

SULTS

ubject Characteristics

ty-two patients completed the study. Twenty paits were randomized to smoke marijuana, 22 to take onabinol, and 20 to take placebo. Of the patients, 55 re male, 3 were female, and 4 were male-to-female transgendered. Half ($n = 31$) of the patients were white, 12 were African American, 10 were Latino, and 9 were of mixed or other ethnicity. More than half of the patients ($n = 33$) were between the ages of 40 and 49, 18 were younger than 40, and 11 were age 50 or older.

Absolute Lymphocytes and Immunophenotyping

Figure 1 shows absolute lymphocyte counts and immunophenotyping results for percent CD4+ T cells, percent CD8+ T cells, percent naive CD4+ T cells, percent naive CD8+ T cells, percent memory/effector CD4+ T cells, percent memory/effector CD8+ T cells, percent CD3-CD19+ B cells, and percent CD3-CD56+ NK cells for all three arms over the 21 days of the study. There were no statistically significant differences in baseline values across the three arms for any of these variables. When we looked at change in these variables between day 0 and day 21, we found only one statistically significant difference when we compared patients in the cannabinoid arms with those in the placebo arm. Changes in absolute lymphocyte counts among those in the marijuana arm were significantly greater compared with changes in the placebo arm (median change = 300 vs. 0.00 cells/μl; $p = 0.01$).

Baseline values were significantly higher in the dronabinol arm compared with the placebo arm for four other immunophenotyping variables: %CD4+HLA-DR+ cells (median = 11.8 vs. 4.5; $p = 0.03$), %CD4+CD38+HLA-DR+ cells (median = 9.0 vs. 4.5; $p = 0.04$), %CD8+HLA-DR+ cells (median = 20.0 vs. 9.6; $p = 0.01$), and %CD8+CD38+HLA-DR+ cells (median = 13.2 vs. 5.2; $p = 0.01$). Although baseline values were also higher for each of these variables in the marijuana arm compared with the placebo arm, this difference was statistically significant only for %CD8+HLA-DR+ cells (median = 13.0 vs. 9.3; $p = 0.03$).

When we looked at change between day 0 and day 21, we observed significant negative changes in the dronabinol arm compared to the placebo arm for two variables: %CD8+CD38+HLA-DR+ cells (median change = −3.50 vs. 0.05; $p = 0.001$) and %CD8+CD69+ cells (median change = −0.30 vs. 0.05; $p = 0.04$). An additional negative change, which approached statistical significance, was seen in %CD4+CD38+HLA-DR+ cells (median change = −1.20 vs. −0.25; $p = 0.06$). However, two of these three variables, %CD8+CD38+HLA-DR+ and %CD4+CD38+HLA-DR+, were significantly higher in the dronabinol arm compared with the placebo arm at day 0. Therefore, the potential confounding

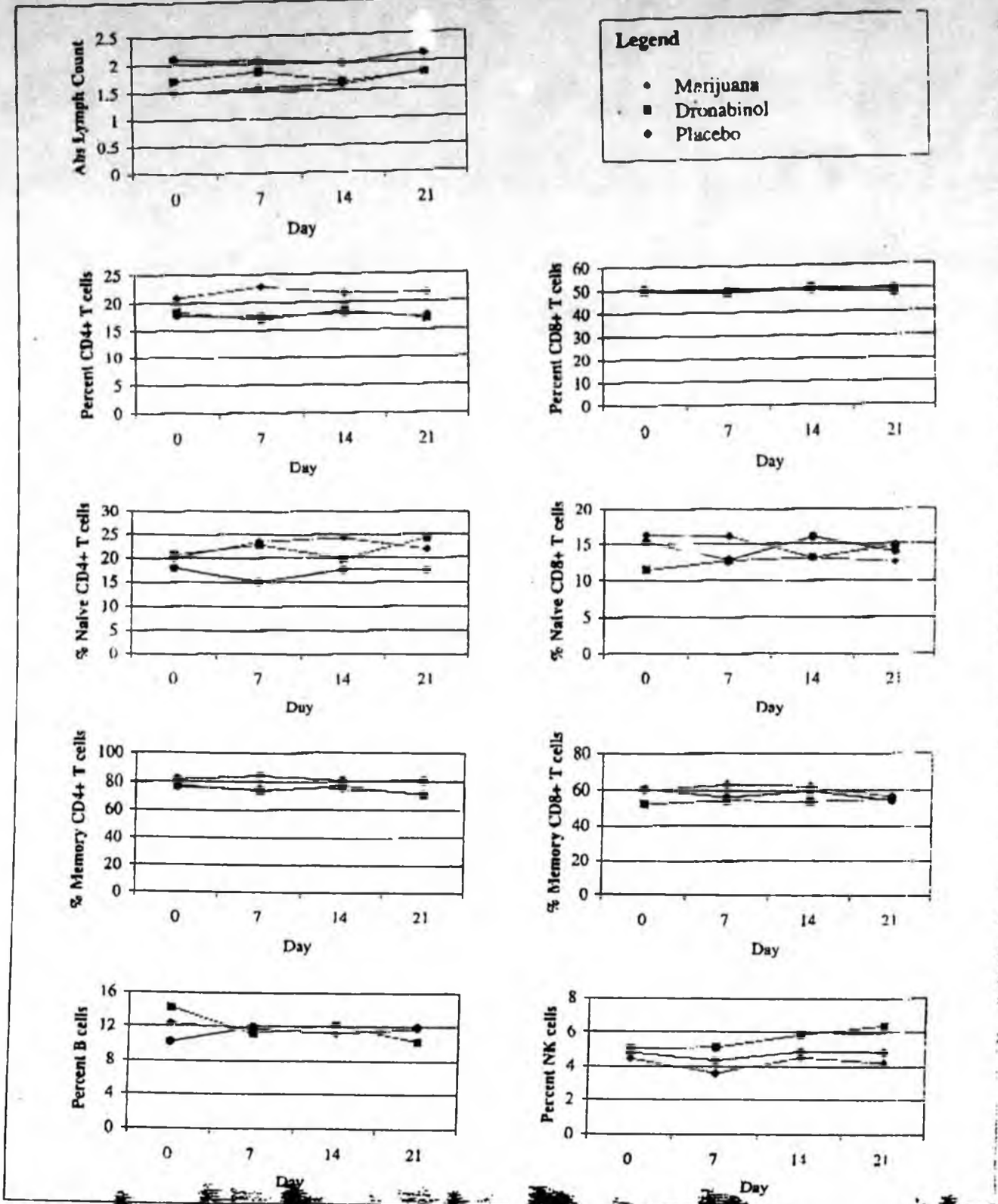


Figure 1. Median absolute and percent lymphocytes for selected variables by arm.

Jan. 13 2004 02:25PM P2

assay) techniques demonstrated decreased interleukin-6 but increased TNF-α levels in a mouse macrophage system.[29]

Many of the reported studies of the immune effects of cannabinoids have been conducted in cell culture systems or animal models. Human studies have evaluated immune function in chronic marijuana smokers. To date, there have been no prospective clinical trials investigating the immune effects of smoked marijuana in patients with HIV infection. Retrospective analyses from the Multicenter AIDS Cohort Study evaluating outcomes in 1662 seropositive users of psychoactive drugs found that none of the drugs used by participants was associated with enhanced clinical or immunologic expression of HIV infection.[30] Of note, use of marijuana in the preceding 2 years was reported by 89% of the seropositive men in the cohort. This was consistent with findings from a previous observation from the San Francisco General Hospital experience.[31] A study of intravenous drug users with HIV infection determined that smoking of drugs such as marijuana was associated with an increased risk of bacterial pneumonia, although there were other confounding associations.[32]

In sum, this study revealed no evidence of detrimental effects of cannabinoids on any of the immune parameters measured. Our conclusions are limited by the short (21-day) duration of this study. In addition, the lack of a blinded control group for the smoked marijuana arm could lead to bias in interpreting some of the results of the main study (e.g., weight changes). However, it is difficult to attribute HIV-1 RNA and lymphocyte subset effects to any such potential bias. We chose not to include a smoked placebo group because we thought it would be impossible to blind marijuana in subjects with prior experience. The disparate results on the effects of THC on the immune system from prior studies may be related to differences in study populations, drug composition, drug concentration, or assay conditions. A key question now will be whether marijuana exerts significant immune effects when administered over longer periods of time.

We are grateful to the research nursing and dietary staff at the SFGH GCRC for the professionalism and compassion with which they conducted the trial. We appreciate the efforts of the SFGH inpatient research pharmacy staff. We are deeply indebted to our committed study participants. Thanks to Roxane Laboratories for the dronabinol and placebo capsules.

REFERENCES

1. Abrams DI: Medical marijuana: tribulations and trials. *J Psychoact Drugs* 1998;30:166-172.

2. Werner CA: Medical marijuana and the AIDS crisis. *J Cannabis Ther* 2001;1(3-4):17-33.

3. Cabral G, Vasquez R: Effects of marijuana on macrophage function. In: Friedman H, Specter S, Klein T (eds.), *Drugs of Abuse, Immunity and Immunodeficiency*. New York: Plenum, 1991.

4. Fischer-Stenger K, Dove Pettit DR, Cabral GA: Delta-9-tetrahydrocannabinol inhibition of tumor necrosis factor-alpha: suppression of post-translational events. *J Pharm Exp Ther* 1993;267:1558-1565.

5. Klein TW, Newton C, Friedman H: Resistance to *Legionella pneumophilia* suppressed by the marijuana component, tetrahydrocannabinol. *J Inf Dis* 1994;169:1177-1179.

6. Klein TW, Newton C, Zhu W, Daaka Y, Friedman H: Delta-9 tetrahydrocannabinol, cytokines and immunity to *Legionella pneumophilin* (43697A). *PSEBM* 1995;209:205-212.

7. Friedman H, Klein TW, Newton C, Daaka Y: Marijuana, receptors and immunomodulation. *Adv Exp Med Biol* 1995;373:103-113.

8. Cabral GA, Pettit D: Drugs and immunity: cannabinoids and their role in decreased resistance to infectious disease. *Journal of Neuroimmunology* 1998;83:116-123.

9. Friedman H, Klein TW: Marijuana and immunity. *Science and Medicine* 1999;6:12-21.

10. Cabral GA: Immune system, in: Grotenhermen F, Russo E (eds.), *Cannabis and Cannabinoids: Pharmacology, Toxicology and Therapeutic Potential*. New York: Haworth, 2002.

11. Pertwee RG: Pharmacology of cannabinoid CB1 and CB2 receptors. *Pharmacol Ther* 1997;74:129-180.

12. Munro S, Thomas KL, Abu-Shaar M: Molecular characterization of a peripheral receptor for cannabinoids. *Nature* 1993;365:61-65.

13. Yamamoto I, Watanabe K, Narimatsu S, Yoshimura H: Recent advances in the metabolism of cannabinoids. *Int J Biochem Cell Biol* 1995;27(8):741-746.

14. Acosta EP, Kakuda TN, Brundage RC, Anderson PL, Fletcher CV: Pharmacodynamics of human immunodeficiency virus type-1 protease inhibitors. *Clin Inf Dis* 2000;30(suppl. 2):S151-S159.

15. Child CC, Mitchell TF, Abrams DI: Patterns of therapeutic marijuana use in two community-based cannabis buyers' cooperatives [abstract 60569]. Paper presented at the 12th World AIDS Conference, Geneva, Switzerland, June-July 1998.

16. Braitstein P, Kendall TR, Chan K, Montaner JSG, O'Shaughnessy MV, Hogg RS: Mary-Jane and her patients: sociodemographic and clinical characteristics of HIV+ individuals using medicinal marijuana and antiretrovirals in British Columbia, Canada [abstract ThPeB5055]. *XIIIth International AIDS Conference* 2000;2:326.

17. Abrams DI, Leiser R, Shade S, Aweeka F, Bredt B, Elbeik T, Hilton J, Schambelan M: Short-term safety of cannabinoids in HIV patients [abstract 744]. Paper presented at the 8th Conference on Retroviruses and Opportunistic Infections, Chicago, February 2001.

18. Kosel BW, Aweeka FT, Benowitz NL, Shade SB, Hilton JF, Lizak PS, Abrams DI: The effects of cannabinoids on the pharmacokinetics of indinavir and nelfinavir. *AIDS* 2002;16:543-550.

19. Johnson M, Peterson A, Winslade J, Glendennin N: Comparison of BID and TID dosing of VIRACEPT® (nelfinavir, NFV) in combination with stavudine (d4T) and lamivudine (3TC) [abstract 373]. Paper presented at the 5th Conference on Retroviruses and Opportunistic Infections, Chicago, February 1998.

Jan. 15 2004 02:27PM P3

...Soltin RW, Fischman MW, Byrne MF: Effects of smoked marijuana on food intake and body weight of humans living in a residential laboratory. *Appetite* 1988;11:1-14.

...Komanduri KV, Viswanathan MN, Wieder ED, Schmidt DK, Brudt ...Jacobson MA, McCune JM: Restoration of cytomegalovirus-specific CD4+ T-lymphocyte responses after ganciclovir and highly active antiretroviral therapy in individuals infected with HIV-1. *Nat Med* 1998;4:953-956.

...Brunner KT, Mauel J, Cerottini JC, Chapius B: Quantitative assay of the lytic interaction of immune lymphoid cells on ^{51}Cr-labeled allogeneic target cells: inhibition by isoantibody and drugs. *Immunology* 1960;4:181.

...Fletcher MA, Morgan R, Klimas NG, Gjerset G: Lymphocyte preparation, In: Rose NR, Conway de Macario E, Fahey JL, Friedman H, Penn GM (eds.). *Manual of Clinical Laboratory Immunology*. 3rd ed. Washington, DC: American Society for Microbiology, 1992,213-219.

...Newton CA, Klein TW, Friedman H: Secondary immunity to *Legionella pneumophilia* are suppressed by Delta-9-tetrahydrocannabinol injection. *Infection and Immunity* 1994;62: 4015-4020.

...Hollister LE: Marijuana and immunity. *J Psychoactive Drugs* 1992;24:159-164.

...Nahas GG, Sutin-Foca N, Armand JP, Morishima A: Inhibition of cellular mediated immunity in marijuana smokers. *Science* 1974: 419-420.

27. White SC, Brin SC, Janicki BW: Mitogen-induced blastogenic responses of lymphocytes from marihuana smokers. *Science* 1975;188: 71-72.

28. Lau RJ, Turbergen DC, Barr M, Domino EF, Benowitz N, Jones RT: Phytohemagglutinin-induced lymphocyte transformation in humans receiving Delta-9-tetrahydrocannabinol. *Science* 1976;192: 805-807.

29. Shivers SC, Newton C, Friedman H, Klein TW: Delta-9-tetrahydrocannabinol (THC) modulates IL-1 bioactivity in human monocyte/macrophage cell lines. *Life Sci* 1994;54: 1281-1289.

30. 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 Multicenter AIDS Cohort Study. *JAMA* 1989;261:3424-3420.

31. Roland A, Felgal DW, Abrams DI, et al: Recreational drug use does not cause AIDS progression: the UCSF AIDS Registry cohort. Paper presented at the Third International Conference on AIDS, Washington, DC, April 1987.

32. Caiaffe WT, Vlahov D, Graham NM, et al: Drug smoking, *Pneumocystis carinii* pneumonia and immunosuppression increase risk of bacterial pneumonia in human immunodeficiency virus-seropositive injection drug users. *Am J Res Crit Care Med* 1994;150: 1493-1498.

Journal of the International Neuropsychological Society (2003), 9, 679–689.
Copyright © 2003 INS. Published by Cambridge University Press. Printed in the USA.
DOI: 10.1017/S1355617703950016

Non-acute (residual) neurocognitive effects of cannabis use: A meta-analytic study

IGOR GRANT,[1,2,3,5] RAUL GONZALEZ,[4,5] CATHERINE L. CAREY,[4,5] LOKI NATARAJAN,[5,6] AND TANYA WOLFSON[5]

[1]Department of Psychiatry, University of California, San Diego
[2]Center for Medicinal Cannabis Research, University of California, San Diego
[3]Veterans Affairs Healthcare System, San Diego, CA
[4]SDSU/UCSD Joint Doctoral Program in Clinical Psychology
[5]HIV Neurobehavioral Research Center, University of California, San Diego
[6]Department of Family and Preventive Medicine, University of California, San Diego

(Received September 12, 2002; Revised December 4, 2002; Accepted December 23, 2002)

Abstract

The possible medicinal use of cannabinoids for chronic diseases emphasizes the need to understand the long-term effects of these compounds on the central nervous system. We provide a quantitative synthesis of empirical research pertaining to the non-acute (residual) effects of cannabis on the neurocognitive performance of adult human subjects. Out of 1,014 studies retrieved using a thorough search strategy, only 11 studies met essential *a priori* inclusion criteria, providing data for a total of 623 cannabis users and 409 non- or minimal users. Neuropsychological results were grouped into 8 ability domains, and effect sizes were calculated by domain for each study individually, and combined for the full set of studies. Using slightly liberalized criteria, an additional four studies were included in a second analysis, bringing the total number of subjects to 1,188 (i.e., 704 cannabis users and 484 non-users). With the exception of both the learning and forgetting domains, effect size confidence intervals for the remaining 6 domains included zero, suggesting a lack of effect. Few studies on the non-acute neurocognitive effects of cannabis meet current research standards; nevertheless, our results indicate that there might be decrements in the ability to learn and remember new information in chronic users, whereas other cognitive abilities are unaffected. However, from a neurocognitive standpoint, the small magnitude of these effect sizes suggests that if cannabis compounds are found to have therapeutic value, they may have an acceptable margin of safety under the more limited conditions of exposure that would likely obtain in a medical setting. (*JINS*, 2003, *9*, 679–689.)

Keywords: Cannabis, Cannabinoids, Marijuana, THC, Cognitive effects, Neuropsychology, Meta-analysis

INTRODUCTION

Recent developments in the scientific and public sectors have reawakened the possibility that cannabis compounds or their synthetic analogues may be proposed as treatments for several medical conditions. At the research level, the discovery of the first cannabinoid receptor (CB1) in 1986, and a second receptor (CB2) in 1992, paved the way to the identification of endocannabinoid-signaling molecules including anandamide and glyceryl-anandamide (Devane et al., 1992; Herkenham, 1992; Herkenham et al., 19[illegible] Howlett et al., 1990; Matsuda et al., 1990; Munro et [illegible], 1993; Pertwee, 1993, 1997).

The CB receptor system is widely distributed in the body, with CB1 primarily localized in the central nervous system. The highest concentrations are found in deep brain structures and the cerebellum (Childers & Breivogel, 1998; Herkenham et al., 1991a, 1991b). Receptors are also found in other organ systems including the uterus, pancreas, and testes (Pertwee, 1997). The CB2 receptor appears to be primarily localized in the spleen and immune cells (Kaminski et al., 1992). Although the biological functions of the endocannabinoid system remain unclear at this time, it is

Dr. Erin D. Bigler served as action editor during the course of this review.

Reprint requests to: Igor Grant, M.D., University of California, Center for Medicinal Cannabis Research, 150 West Washington Street, Second Floor, San Diego, CA 92103. E-mail: igrant@ucsd.edu

FROM : FAX NO. : 4155527170 Jan. 13 2004 02:30PM P5

likely that the CB1 receptor system is important in a number of neurobehavioral events, including dampening of neuro-excitability (Samudo-Pena & Walker, 1997), and perhaps in the initiation and maintenance of complex feeding behaviors, including suckling (Fride et al., 2001; Hao et al., 2000).

From the public health standpoint, there have been increasing anecdotal and limited scientific observations to suggest that cannabinoids may have utility in the management of severe pain, especially neuropathic pain (Noyes et al., 1975), muscular spasticity, tremor in conditions such as multiple sclerosis (Baker et al., 2000, 2001), and improved appetite and weight gain in patients with chronic inanition (Gorter et al., 1992; Nelson et al., 1994; Plasse et al., 1991). The possibility that cannabis might have a benefit in conditions such as AIDS or diabetic neuropathy, muscle spasm in multiple sclerosis, and severe weight loss, nausea, and vomiting related to cancer and its treatments, has been raised and reviewed in some detail by recent expert panels, including the NIH Expert Panel Report (U.S. National Institute of Health, 1997) and by the Institute of Medicine (1999).

These developments have converged with an increasing public sense that cannabis might be beneficial to some patients with severe chronic illnesses, and therefore should be made available to them. Evidence of this now comes from the passing of initiative laws seeking to facilitate access to cannabis by medical patients in nine states in the United States. Therefore, it seems reasonable to expect that the convergence of scientific evidence and public pressure may result in increasing use of cannabis products by patients with certain severe chronic illnesses in the future. If this were to happen, it would naturally raise the concern that cannabis may have certain long-term undesirable effects, particularly with respect to the central nervous system. Although the acute neurobehavioral effects of cannabis intoxication have been characterized and reviewed in some detail (e.g., Solowij, 1998), the very long-term effects of cannabis on brain function are not well understood. In order to assess the state of current knowledge on persisting CNS consequences of cannabis use, we have performed a meta-analysis of the existing literature on neuropsychological evaluation of persons who have been exposed to regular, long-term use of cannabis. Previous reviews have provided excellent summaries of investigations on this topic and their findings (Grant & Mohns, 1975; Pope et al., 1995; Solowij, 1998). In order to avoid duplication of previous efforts and provide new information, we have approached this task with a view of arriving at a quantitative estimate of the potential effects of long-term cannabis consumption on various neurocognitive functions. In this way, we have attempted to estimate effect sizes for each of eight neurocognitive domains, as well as a global indicator of overall neurocognitive functioning as it relates to history of cannabis consumption. Thus, the overall objective of this study was to provide a quantitative synthesis of the research investigating the non-acute (residual) effects of cannabis use on the neurocognitive performance of long-term users. Readers interested in more detailed descriptions of studies on this topic are encouraged to examine the aforementioned reviews. In addition, we have recently published a companion paper (Gonzalez et al., 2002) that qualitatively examines the research methodologies of studies included in this meta-analysis.

METHODS

Literature Search and Study Identification Strategy

Two of the investigators (RG and CC) conducted independent literature searches through several online databases, including Medline/HealthSTAR, PsychInfo, BioSys, Current Contents, Dissertation Abstracts International, Article First, Eric, Science Citation Index Expanded, and Social Science Citation Index. The key words used were (marijuana or marihuana or tetra-hydrocannabinol or THC or cannabis) with the Boolean operator "and" connecting (neuro* or cognitive or assessment or ability or effects or processes or impairment or cognition or drug effects). Boolean operators were slightly modified and tailored to each database, in order to comply with specific database guidelines and to ensure a valid search. The search criteria were liberal, purposely so, in order to avoid missing any potentially relevant citations. The results of the two independent searches are presented in Figure 1. The first investigator identified 824 citations (Data Set A) and the second investigator identified 1,006 citations (Data Set B). After a consensus meeting, both databases were combined, and the investigators agreed that there were 1,014 unique citations.

The two investigators then independently rated each citation by title and abstract (if available) and classified these references into one of four relevance categories: CORE, REVIEW, UNKNOWN, and NOT RELEVANT. An article

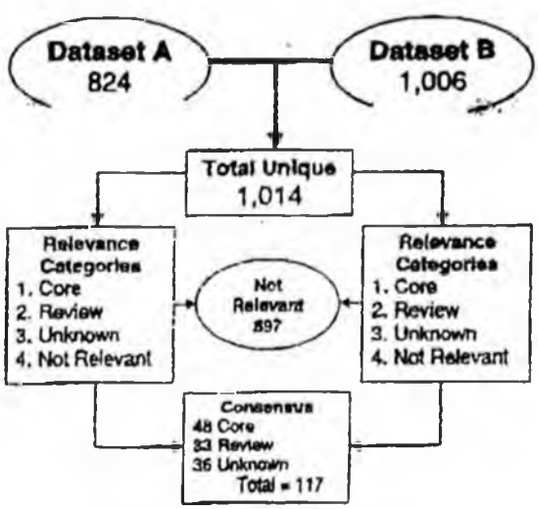


Fig. 1. Literature search process.

was categorized as CORE if, based on title and abstract, the study was highly likely to contain information relevant to the question of persisting, non-acute effects of cannabis exposure on neurocognitive functioning. An article was identified as REVIEW if the title or abstract indicated it was a literature review or an editorial. An UNKNOWN classification was given to an article if there was insufficient information based on an examination of the title or abstract, to confidently place it in one of the other categories. An article was categorized as NOT RELEVANT if it was clear from the title or abstract that it did not address the question of long-term, non-acute effects of cannabis on neurocognitive functioning.

Once these independent classifications were achieved, the two investigators had a second set of meetings to arrive at a consensus classification, resolving the status of the small number of articles upon which their original classification did not agree (seven articles). Figure 1 shows the results of this process. From 1,014 articles, 897 articles were classified as not relevant. Table 1 provides a summary of the major topics represented by articles deemed NOT RELEVANT. The majority of articles were excluded because they either did not deal with human subjects, or they involved studies of children and adolescents who were prenatally exposed or whose exposure to cannabis was not sufficient in duration to explore long-term persisting effects. Another large group of studies concerned psychiatric and other behavioral issues but not neurocognitive functioning *per se*.

After excluding the 33 review articles, the remaining 84 articles originally classified as CORE and UNKNOWN were examined in detail. From these, 38 were ultimately selected for coding as they met the inclusion criteria for this analysis as outlined below. The 38 included 35 of the 48 articles originally classified as CORE. Three additional studies, originally classified as UNKNOWN, were added after being reclassified as CORE upon thorough examination of the complete manuscript.

Before the literature search began, the authors identified a set of criteria that a study should have met in order to adequately answer the principal research question: "Is regular, long-term use of cannabis associated with non-acute (residual) neurocognitive dysfunction, suggestive of brain injury?" The criteria, presented in Table 2, emphasized the necessity of including an appropriate control group (i.e., non-drug using or very lightly drug using), indicating that subjects were drug free (i.e., not acutely intoxicated) at the time of evaluation, addressing potential confounds (e.g., history of heavy use of other substances, presence of other neurological conditions or traumatic brain injury, psychiatric confounds, other neuromedical risks), providing information on cannabis abstinence, and collecting data of sufficient detail to calculate effect sizes for each test administered.

Table 1. Classification of non-relevant studies omitted after initial search (n = 897)

Neurobiology/Pharmacology/Animal	= 314
Psychiatric/Psychological/Prevention	= 231
Prenatal/Infant/Children/Adolescents	= 155
Neurological/Medical/Neuroimaging	= 89
Acute cannabis use or misc. exclusions	= 66
Polydrug/Other drugs	= 24
Completely irrelevant	= 18

Table 2. Original inclusion criteria for studies entering meta-analysis

1. Includes a group of "cannabis only" users
2. Includes an appropriate control group (i.e., non drug-using or very limited cannabis use)
3. Provides sufficient information to calculate effect size
4. Outcome measures include valid neuropsychological tests
5. Cannabis using group is drug-free on day of neuropsychological testing
6. Study addresses other potential substance use in cannabis group
7. Study addresses potential history of neurological or psychiatric problems
8. Study reports length of abstinence from cannabis before testing

We were surprised to discover that only nine studies ultimately met all original inclusion criteria. In a companion review paper (Gonzalez et al., 2002) we provide a more thorough analysis of the methodological limitations that affected many of the studies that we examined. To the nine studies that met all original inclusion criteria, two additional studies were added. One of these studies was brought to the authors' attention during a conference on cannabis organized by the National Institute on Drug Abuse on August 13–14, 2001 in Rockville, Maryland. This article by Pope et al. (2001), in press at the time our analyses were being conducted, met all of the inclusion criteria, and was therefore added to the original meta-analysis of the nine studies. The other manuscript added to our original meta-analysis was authored by Solowij et al. (2002) and was published while this manuscript was under review. Because this study met all of our original inclusion criteria, we felt our analyses would be incomplete without its inclusion. These 11 articles are briefly summarized in Table 3a. The meta-analysis of the 11 studies that met all original inclusion criteria involved data from 1,032 subjects, of whom 623 were regular, moderate, or heavy cannabis users and 409 were either non-users or persons whose exposure to cannabis was extremely limited.

In order to ensure that we were not rejecting potentially informative studies, we reexamined the 38 coded studies with a slightly relaxed set of criteria. We chose to accept a study if it violated no more than one of our *a priori* inclusion criteria (Table 2), as long as neither of two absolutely essential criteria were violated; that is, the study had to have an appropriate non-cannabis using (or extremely limited cannabis using) contrast group, and it had to have enough detail in the presentation of results to permit computation of effect sizes. For example, an often cited investigation by

FROM : FAX NO. : 4155527170 Jan. 13 2004 02:33PM P7

Table 3a. Descriptions of original 11 studies

Study	Users (n)	Control (n)	Frequency or amount of use	Duration of use (yrs)	Length of abstinence (hr)	Cognitive domains assessed[a]
[1]Block & Ghoneim (1993)	144	72	1 to 7+ times/wk	5.8 (*M*) 4.1 (*SD*)	≥24	AE, L, PM, SRT
[2]Carlin & Trupin (1977)	10	10	NR	5 (*M*) range: 2.5–8	≥24	A, AE, L, M, PM, V
[3]Croft et al. (2001)	18	31	lifetime joints: 5309.8 (*M*) 6517.5 (*SD*)	NR	66.5 (*M*) 42.4 (*SD*)	A, AE, F, L, M, V
[4]Ehrenreich et al. (1999)	99	49	use in last 6 mo: 3.5 dys/wk (*M*) 1.9 (*SD*)	4.2 (*M*) 3.4 (*SD*)	29.8 (*M*) 29.5 (*SD*)	A, SRT
[5]Gouzoulis-Mayfrank et al. (2000)	28	28	20.9 dys/mo (*M*) 10.2 (*SD*)	2.9 (*M*) 2.0 (*SD*)	96 (*M*) 372 (*SD*)	A, AE, F, L, PM, SRT, V
[6]Hanil (1996)	19	19	NR	NR	≥336	F, L
[7]Pope & Yurgelun-Todd . (1996)	65	64	≥22 days of the past 30 days	≥2	≥19	A, AE, F, L, V
[8]Pope et al. (2001)	63	72	≥5000 lifetime episodes ≥7 times/week	≥13 years	~672	A, AE, F, L, PM, V
[9]Rodgers (2000)	15	15	4 dys/wk (*M*)	11 (*M*)	≥720	A, F, L, SRT
[10]Solowij (1995)	60	16	15.3 dys/mo (*M*) 10 (*SD*)	7.8 (*M*) 5.1 (*SD*)	≥1008	A, SRT
[11]Solowij et al. (2002)	102	33	median: 2 joints/day 27.9 dys/mo in past 14 wks	17.1 (*M*) 7.9 (*SD*)	17 (median)	A, AE, F, L, PM, V

Note. Numeric superscripts refer to the data presented in Figures 2A and 2B.
[a]A study may have "assessed" a given domain, but their data may not have been included in our analysis if it was presented in a format that was incompatible with our methods for effect size calculations.
A, Attention; AE, Abstraction/Executive; F, Forgetting/Retrieval; L, Learning; M, Motor; PM, Perceptual Motor; SRT, Simple Reaction Time; V, Verbal/Language; NR, not reported.

Fletcher and colleagues (1996), which examined the cognitive correlates of long-term cannabis use in Costa Rican men, did not meet the latter criterion and was therefore excluded. In addition, a study was also included if criterion items #5 and #8 (see Table 2) were the only two criteria not met. This decision was made based on the interdependence of these two items (i.e., studies that did not quantify length of abstinence from cannabis, also did not confirm if subjects were drug-free at time of testing).

As a result of re-inspecting the 38 studies, an additional four studies met the revised criteria necessary for inclusion. These particular studies were initially excluded due to the lack of abstinence information in all but one instance. Nevertheless, based on the totality of the study design, it appeared unlikely that the authors included acutely intoxicated individuals in their analyses. Thus, this expanded meta-analysis based on 15 studies (the 11 original plus the four added) now included 1,188 subjects (i.e., 484 controls and 704 cannabis users). In terms of the meta-analytic methodology, the analysis of the 15 studies was identical in all respects to that of the original 11 studies described above. A brief description of the four additional studies is provided in Table 3b, along with the original inclusion criteria that were not met.

Statistical Methodology

Using the techniques described by Hedges and Olkin (1985) to combine continuous outcome measures, a standardized mean difference (effect size) d, and its variance were calculated for each neuropsychological test that was administered within each of the 11 studies. In particular, $d = (M_e - M_c)/S$, where M_e and M_c were the mean scores on a neuropsychological test for the cannabis using and control groups respectively and S was the standard deviation for the pooled sample. The expression for variance (v), is $v = (n_e + n_c)/(n_e n_c) + d^2/(2(n_e + n_c))$, with n_e and n_c representing the sample sizes for the cannabis users and controls, respectively. Then, within each of the studies, the individual effect sizes were linearly combined by subsets into one of eight neurocognitive ability domains. Thus, if $d_1, d_2, \ldots d_k$ represented the effect sizes for k tests from a particular study all deemed to measure the same neurocognitive ability, a pooled estimate (d'), $d' = \Sigma(w_i d_i)$, was obtained. The decision to group individual tests into domains was necessary due to the lack of overlap between tests across studies. We acknowledge that individual neuropsychological tests assess multiple cognitive abilities; nevertheless, each test was assigned to the cognitive domain it was determined to

FROM : FAX NO. : 4155527170 Jan. 13 2004 02:35PM P8

Table 3b. Study characteristics for four additional studies

Study	Users (*n*)	Control (*n*)	Frequency or amount of use	Duration of use (years)	Cognitive domains assessed*	Cognitive impairment concluded?	Criteria not met†
[12]Dulf et al. (1993)	15	10	1.1 gm/dy (*M*) 0.5 (*SD*)	7.5 (*M*) 2.2 (*SD*)	A	No	5, 8
[13]Grant et al. (1973)	29	29	3 times/mo (median)	4 (median)	A, AE, L, PM	No	5, 8
[14]Rochford et al. (1977)	26	25	NR	3.7 (*M*)	L, PM	No	5, 8
[15]Wig & Varma (1977)	11	11	NR	NR	A, AE, F, L, PM	Yes: memory, concentration	6

Note. Numeric superscripts refer to the data presented in Figures 2A and 2B.
*A study may have "assessed" a given domain, but their data may not have been included in our analysis if it was presented in a format that was incompatible with our methods for effect size calculations.
A, Attention; AE, Abstraction/Executive; F, Forgetting/Retrieval; L, Learning; PM, Perceptual Motor; NR, not reported.
†See Table 2.

best assess. These domains were simple reaction time, attention (e.g., WAIS–R Digit Span, Digit Vigilance), verbal/language (e.g., WAIS–R Vocabulary, Verbal Fluency), abstraction/executive functioning (e.g., Wisconsin Card Sorting Test, Raven's Progressive Matrices), perceptual motor (e.g., WAIS–R Block Design, WAIS-R Object Assembly), simple motor (e.g., Grooved Pegboard, Finger Tapping), learning (e.g., California Verbal Learning Test–Learning Trials, Rey Auditory Verbal Learning Test–Learning Trials), and forgetting/retrieval (e.g., California Verbal Learning Test–Delayed Recall, Rey Auditory Verbal Learning Test–Delayed Recall). As different tests measuring the same neurocognitive domain would be expected to be correlated, the method prescribed by Hedges and Olkin (1985; Chapter 10) was adopted, whereby, the vector of weights $(w_1, \ldots w_k)$ above was chosen to be proportional to the inverse of the covariance matrix of the vector $(d_1, d_2, \ldots d_k)$, thus reflecting the dependence between the tests. We assumed a correlation of .7 between any two tests that were purported to measure the same neurocognitive domain. The assumption of this value had to be made because we did not have individual test results for each subject from each study. However, based on extensive experience in the conduct of neuropsychological studies employing comprehensive neuropsychological test batteries with many thousands of subjects over the years (Grant, et al., 1978, 1979, 1982, 1987; Heaton et al., 1981, 1991, 1995), it has been our experience that tests grouped into a particular domain share about 50% of common variance, with a range of 30% to 70%. Using a correlation of .7 ensures a conservative estimate of the variance of the pooled effect size.

A heterogeneity statistic, Q, was calculated in order to assess whether the effect sizes that were pooled within each study could in fact be said to be measuring the same underlying population effect [illegible] cognitive domain. In a few instances, this exploration indicated a large amount of heterogeneity between tests within a given domain, suggesting that a test may have been incorrectly assigned to a particular domain or would better fit classification under a different cognitive domain. In these cases, the tests within a domain were reexamined, and redistributed to another neurocognitive domain if deemed appropriate based on logical grounds and previous experience (e.g., a computer-assisted test which was assigned to the domain of learning *a priori*, better fit the attention domain).

A fixed effects model was used in our computations. Our choice of using fixed effects rather than random effects, was guided by the judgment that in investigating the potential toxic effects of a substance such as cannabis, it was important to be more "permissive" rather than "conservative" in our modeling of the information due to the likelihood of heterogeneity in data across studies. If a subtle signal were present in a heterogeneous data field, it would be more readily detected using a fixed effects model. Thus, the fixed effects approach was expected to produce somewhat smaller confidence intervals around the effect sizes than would a random effects model, thus increasing the likelihood of detecting a cannabis effect.

The above analysis yielded for each study a vector of effect sizes with variances for each of the neurocognitive domains (with the possibility of missing values if the study in question did not measure a particular neuropsychological domain). Effect sizes were again linearly combined (with weights inversely proportional to the variance) across studies to obtain an overall effect size and a variance for each domain. An across study heterogeneity statistic Q was also computed for each domain. Finally, an overall or global neurocognitive effect size and its variance were computed by pooling the effect sizes across domains. The methodology for this final combination mirrored the methods described above for the within study pooling. As it might be expected that scores on tests corresponding to different neuropsychological domains might be (weakly) correlated, the correlation between [illegible] Again, this estimate was based on the authors' experience of the likely correlation of tests from separate domains. Because the overall determination of the association between cannabis use and neuropsychological impairment was based

FROM : FAX NO. : 4155527170 Jan. 13 2004 02:37PM P9

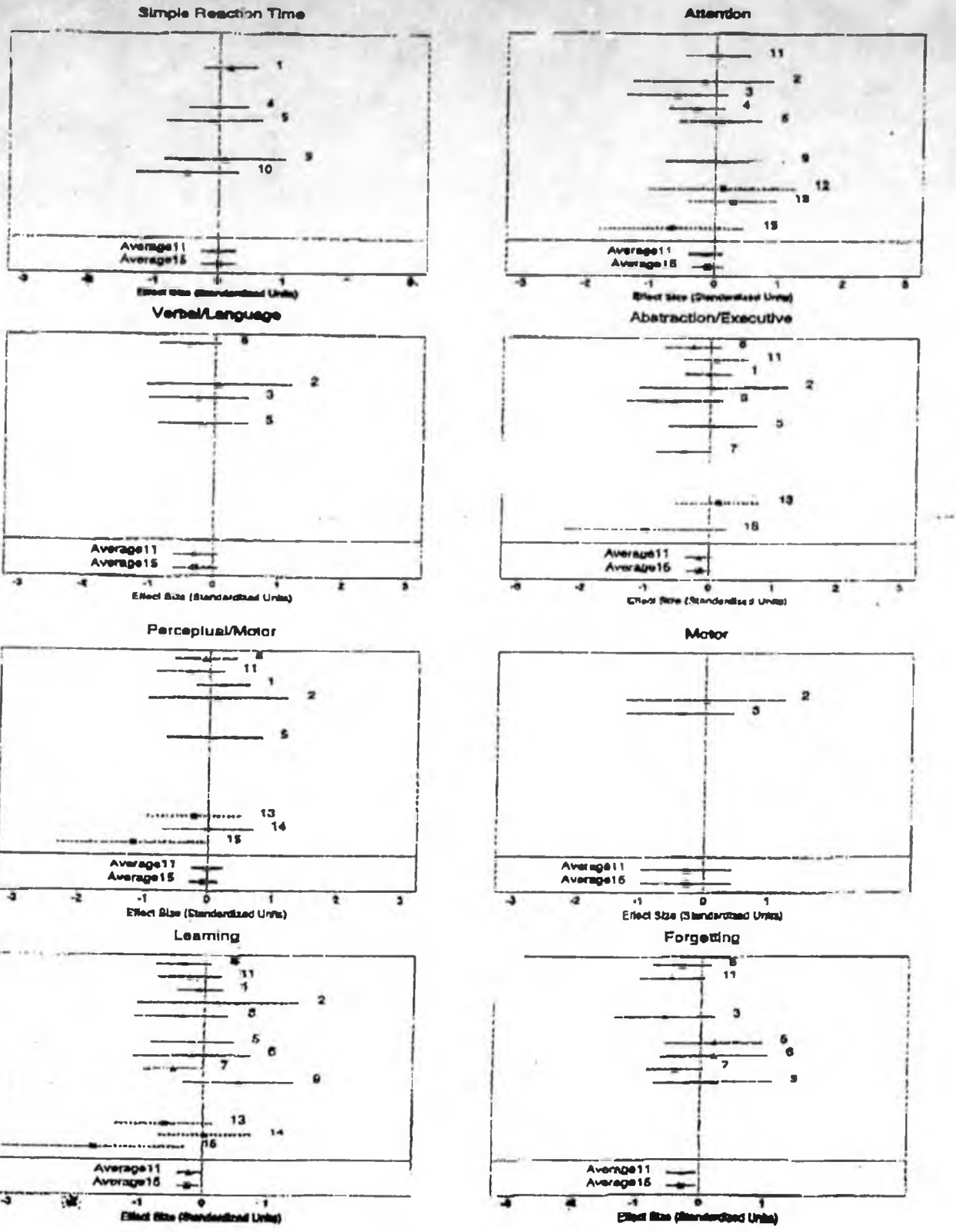


Fig. 2a & 2b.

FROM : FAX NO. : 4155527173 Jan. 13 2004 02:39PM P1

RECEIVED JAN 13 2004

on a large number of test scores measuring eight different neuropsychological domains, 99% confidence intervals were calculated to allow adjustment for multiple comparisons.

RESULTS

The effect sizes for each neurocognitive domain from each study are presented in Figures 2a and 2b. The effect sizes for each domain across the 11 original studies ranged from +.0086 for the perceptual motor domain, to −.28 for the verbal/language domain. In most instances, the 99% confidence interval surrounding the mean effect size for each domain included zero; therefore, the possibility that the effect size observed was indeed zero could not be discounted. However, in the case of the learning [−.21 99%CI (−.39, −.022)] and forgetting [−.27 99%CI (−.49, −.044)] domains the average effect sizes were found to be significant, albeit of small magnitudes. Comparable results were obtained when all 15 studies were considered.

The global measure of neurocognitive performance was determined through a linear combination of effect sizes across all domains. Data from the 11 studies included under the original criteria indicated an average effect size of −.15 99%CI (−.29, −.019) on the global measure of neurocognitive performance. When all 15 studies were considered, the average global neurocognitive effect size was −.16 99% CI (−.29, −.033). Thus, the results of both sets of analyses suggest a small detrimental cannabis effect on overall neurocognitive performance.

Inspecting the effect sizes for neurocognitive domains by study, we noted that one study examining users in India (class-IV caste) of bhang and charas appeared to be a distant outlier. Due to the fact that this study was based on a population very unlike that of other studies in our pool, we repeated the analysis omitting this study from the pool. Eliminating this study had a negligible influence on effect sizes, but did reduce heterogeneity so that none of the domain-specific Q statistics were statistically significant. Table 4 presents the values of Q for each domain across studies, as well as observed effect sizes, both before and after the removal of the outlier study.

Meta-Regression

To determine whether several study and subject characteristics influenced the observed effect sizes, we performed a set of univariate regressions. These analyses were limited to four of the eight domains (attention, abstraction/executive functioning, perceptual motor, and learning) that contained data from a sufficient number of studies. Variables included whether the cannabis-using and control groups were adequately matched with regard to education or intelligence, as well as the extent to which cannabis users and controls were excluded due to other significant drug use. Furthermore, with respect to cannabis using subjects, variables of interest included whether individuals were ascertained to be abstinent from cannabis for at least 24 hr at time of testing, and their duration of cannabis use. Because of the possibility that sex and years of education might moderate neurocognitive performance in the cannabis group, these variables were also examined. For each of the univariate meta-regressions, years of cannabis use, percent female in the cannabis group, and years of education in the cannabis group, were coded as continuous variables. Dichotomous variables were used to represent whether subjects were known to be abstinent from cannabis for 24 hr, were excluded for other significant drug use, and were matched with the control group on education and/or IQ. The meta-regression results indicated that none of the examined covariates significantly moderated the effect size in any of the regressions.

DISCUSSION

The results of our meta-analytic study failed to reveal a substantial, systematic effect of long-term, regular cannabis consumption on the neurocognitive functioning of users who were not acutely intoxicated. For six of the eight neurocognitive ability areas that were surveyed, the confidence intervals for the average effect sizes across studies overlapped zero in each instance, indicating that the effect size could not be distinguished from zero. The two exceptions were in the domains of learning and forgetting. Here when we averaged across the 11 studies that had the most rigorous inclusion/exclusion criteria and the best designs, the effect size for learning was −.21 99%CI (−.39, −.022) indicating a very small but discernible negative effect. This effect was slightly larger when all 15 studies were included [−.24 99%CI (−.41, −.064)]. Similarly, in the domain of forgetting (failure to recall or recognize) the average effect size was −.27 99%CI (−.49, −.044), again suggesting a very small but measurable decrement.

Fig. 2a & 2b. Effect sizes for each neurocognitive domain. Effect sizes derived from the 11 studies included under the original set of criteria are depicted with solid triangles and long-dashed confidence intervals; data for the four studies added under the relaxed criteria are displayed with solid squares and small-dashed confidence intervals. Each effect size and confidence interval is shown with a number that references the study as presented in Table 3a and 3b. The average effect sizes across studies for each domain, are presented at the base of each of the specific domain related figures. A negative effect size represents poorer performance by the cannabis using groups. "Average 11" refers to the average effect size of the studies included under the original criteria; "Average 15" presents effect sizes for the entire set of studies.

Table 4. Effect sizes and estimates of heterogeneity within domains, across studies

Domain	Effect size (99% CI)	Q-statistic	df for Q	p-value for Q
Attention	−.11 (−.34, .12)	11.26	8	.19
	−.083 (−.32, .15)	9.30	7	.23
Abstraction/Executive	−.15 (−.34, .032)	14.24	8	.08
	−.13 (−.32, .052)	10.73	7	.15
Forgetting/Retrieval*	−.27 (−.49, −.044)	10.81	6	.09
Learning*	−.24 (−.41, −.064)	23.09	11	.02
	−.21 (−.39, −.040)	14.60	10	.15
Motor	−.26 (−.96, .43)	.55	1	.46
Perceptual–Motor	−.065 (−.28, .15)	12.80	7	.15
	−.026 (−.25, .20)	5.57	6	.47
Simple Reaction Time	.0086 (−.25, .26)	4.54	4	.34
Verbal/Language	−.28 (−.62, .060)	1.30	3	.73

Note. * denotes a significant effect size; Rows with two sets of numbers contain the values obtained before and after the removal of an outlier study (i.e., Wig & Verma), in the respective order; *df* = degrees of freedom.

These results can be interpreted in several ways. A statistically reliable negative effect was observed in the domain of learning and forgetting, suggesting that chronic long-term cannabis use results in a selective memory defect. While the results are compatible with this conclusion, the effect size for both domains was of a very small magnitude. The "real life" impact of such a small and selective effect is questionable. In addition, it is important to note that most users across studies had histories of heavy long-term cannabis consumption. Therefore, these findings are not likely to generalize to more limited administration of cannabis compounds, as would be seen in a medical setting.

Some of the studies included in our analyses tested cannabis users with less than 24 hr of abstinence, and others reported no information on abstinence at all. As a result, another factor that may have contributed to the small tendency towards worse performance in the cannabis-using group might be attributable to what Pope et al. have called "residual effects." In a recent study by Pope et al. (2001), three groups of subjects were repeatedly examined over a period of 28 days. They included a group of current heavy cannabis users, a group of persons who had heavy histories of past cannabis use but had not used in the recent past, and a group of controls who had very limited experience with cannabis. The active cannabis users were tested on Days zero, 1, 7, and 28 after ceasing active cannabis use. Abstinence was confirmed through regular urinalysis, which detected declining concentrations of THC in the urines of the active users, and demonstrated that all had undetectable THC levels by 28 days. Pope and colleagues noted subtle impairments on several neurocognitive tests in the active cannabis users who had just become abstinent. However, by 28 days, the active cannabis users who had abstained for almost a month were indistinguishable from former heavy users or non-using controls. Pope et al. suggested that the subtle cognitive impairments observed in the active users during the first week of cessation might represent residual effects (i.e., effects of persisting low levels of THC in the system), abstinence phenomena, or both. The Pope et al. data have direct relevance on the interpretation of results obtained in this study. In nearly all instances, heavier cannabis users were asked to abstain for a period of hours or days before testing. Therefore, many of them could have been at risk for "residual effects" or "abstinence phenomena," which might have contributed to slight decrements in their performance. Given this likelihood, it is even more surprising that our meta-analytic study revealed so few effects.

In interpreting the results of this meta-analytic study, several caveats need to be considered. First, many of the studies examined had significant limitations. For example, several studies had small numbers of subjects, reducing our confidence in the individual study's results and creating concerns about generalizability. Second, many studies had insufficient information about potential confounding factors. These factors included recency of last cannabis exposure, extent of exposure to other drugs of abuse, presence of confounding neuropsychiatric factors (e.g., depression, anxiety, personality disorders, etc.), or other neuromedical risks that can independently affect brain function. As an example, the most recent study by Solowij et al. (2002) focused on patients receiving treatment for cannabis dependence, and the controls were non-patients. This study found negative effects on memory. An unanswered question is whether the cannabis users in that study, being persons who sought or were referred to treatment, might consist of a highly selected group that either were experiencing cannabis related cognitive problems, or who had such difficulties as a function of comorbid psychiatric disorders. No data were presented on mood disorders, which can contribute

both to subtle memory difficulties and account for treatment seeking. In this particular study, the long term using group was, on average, 8 years older than the controls. Although the authors attempted to adjust for age in some of their analyses, there is reason to believe that such covariance adjustments often under-correct, and therefore are not an appropriate substitute for proper age matching, especially when interpreting neuropsychological tests which are influenced by age (Adams et al., 1985).

A general issue affecting most studies was that the premorbid neurocognitive abilities of these subjects were largely unknown, as the studies did not document neurocognitive performance before subjects' onset of regular cannabis use. Although methods are available to estimate premorbid intelligence through consideration of performance on tests that are not likely to be impacted by subtle brain injury (e.g., scores on the Vocabulary subtest of the WAIS series), these techniques are often inadequate. For example, we can never be absolutely certain whether the cannabis users might have been brighter than controls to begin with, and then lost some measure of their cognitive function. Nevertheless, many of the confounds discussed would most likely result in poorer scores in the cannabis group, thus increasing the likelihood and magnitude of observed effects. Only studies that begin with the examination of children and young adolescents before they enter the period of risk to cannabis exposure, can sufficiently reduce the influence of confounds, thus answering this question most effectively. An alternative strategy would be to examine monozygotic twins discordant for cannabis and other substance use. In such studies, one can be more confident of controlling for "native endowment." In the absence of such designs, which can be costly to implement, the approach developed by Pope et al. represents the next best alternative. By examining regular active users who were instructed to abstain, and then repeatedly tested during a lengthy supervised abstinence period, studies such as those designed by Pope et al. bring us closer to understanding the persisting effects of cannabis use, while simultaneously tracking the potential confounds of a "residual effect" and "abstinence phenomena."

In addition to the limitations posed by suboptimal study designs, limiting aspects of the statistical methodology necessarily employed when conducting a meta-analysis should also be considered. It is important to recognize that noise and interpretability, inherent in such analyses, present an additional challenge. To compute the average effect size, as discussed in the statistical methodology section, three types of linear combinations were performed. First, within studies, different tests (from study to study) were combined into the eight neuropsychological domains. Then, across studies, domain effect sizes were linearly combined into eight domain effect size estimates. Finally, the eight effect sizes were linearly combined across domains, yielding a highly processed overall effect size that should be subject to caution in interpretation. In regards to the lack of findings when considering the influence of covariates on observed effect sizes, it is important to note that the meta-regressions were performed on data matrices with as many rows as there were studies testing a particular domain (no more than 10). With less than 10 data points per regression, it is necessarily difficult to make any conclusions about the significance of the model.

Finally, it is important not to generalize these findings to special populations. Many of the studies included in our analyses were conducted with better-educated, younger individuals. We do not know if these mostly negative findings would apply to individuals who have other risk factors for neurocognitive impairment and are then exposed to chronic heavy cannabis use. For example, we cannot be certain if individuals with mild head injuries, attention deficit/hyperactivity disorder, or other neuropsychiatric conditions that may affect cognitive capacity, might be equally resistant to the chronic effects of cannabis. In addition, the fact that cannabinoids appear to be well tolerated by healthy adults does not mean that children and adolescents, who are continuing to undergo neurobiological and cognitive development, will be similarly unaffected. Data from several human studies, as well as animal studies examining the effects on the offspring of cannabis-exposed mothers, suggest that neurodevelopmental difficulties can occur. For example, Fried et al. (2001) have noted executive dysfunction in older children and adolescents of mothers who were substantial cannabis users in the Ottawa cohort. Similar findings were noted in the Pittsburgh longitudinal study (Goldschmidt et al., 2000). Thus, it remains entirely possible that exposure of the developing nervous system to cannabinoids may cause alterations that affect cognitive function in the future.

In conclusion, our meta-analysis of studies that have attempted to address the question of longer term neurocognitive disturbance in moderate and heavy cannabis users has failed to demonstrate a substantial, systematic, and detrimental effect of cannabis use on neuropsychological performance. It was surprising to find such few and small effects given that most of the potential biases inherent in our analyses actually increased the likelihood of finding a cannabis effect. Specifically, our use of a fixed effects model resulted in smaller confidence intervals for the effect sizes we computed, thus facilitating the discovery of statistically significant between-group differences. Moreover, many of the confounds inherent in the studies included in our analyses made it more likely for the cannabis using group to demonstrate poorer performance on neuropsychological tests than controls, irrespective of cannabis consumption. Finally, meta-analytic studies are generally criticized for including only investigations that have been published in peer-reviewed journals, because studies that report statistically significant findings are more likely to be published. This "file-drawer" bias can result in an underrepresentation of studies that did not find statistically significant results, therefore also increasing the likelihood of generating statistically significant effect sizes. Nevertheless, when considering all 15 studies (i.e., those that met both strict and more relaxed criteria) we only noted that regular cannabis users per-

formed worse on memory tests, but that the magnitude of the effect was very small. The small magnitude of effect sizes from observations of chronic users of cannabis suggests that cannabis compounds, if found to have therapeutic value, should have a good margin of safety from a neurocognitive standpoint under the more limited conditions of exposure that would likely obtain in a medical setting.

ACKNOWLEDGMENTS

Supported by the University of California Center for Medicinal Cannabis Research. Special thanks to Michelle Pryberger and Kimberly Jones for assistance in formatting graphs and figures.

REFERENCES

Adams, K.M., Brown, G.G., & Grant, I. (1985). Analysis of covariance as a remedy for demographic mismatch of research subject groups: Some sobering simulations. *Journal of Clinical and Experimental Neuropsychology, 7*, 445–462.

Baker, D., Pryce, G., Croxford, J.L., Brown, P., Pertwee, R.G., Huffman, J.W., & Layward, L. (2000). Cannabinoids control spasticity and tremor in a multiple sclerosis model. *Nature, 404*, 84–87.

Baker, D., Pryce, G., Croxford, J.L., Brown, P., Pertwee, R.G., Makriyannis, A., Khanolkar, A., Layward, L., Fezza, F., Bisogno, T., & Di Marzo, V. (2001). Endocannabinoids control spasticity in a multiple sclerosis model. *Faseb Journal, 15*, 300–302.

Block, R.I. & Ghoneim, M.M. (1993). Effects of chronic marijuana use on human cognition. *Psychopharmacology, 110*, 219–228.

Carlin, A.S. & Trupin, E.W. (1977). The effect of long-term chronic marijuana use on neuropsychological functioning. *International Journal of the Addictions, 12*, 617–624.

Childers, S.R. & Breivogel, C.S. (1998). Cannabis and endogenous cannabinoid systems. *Drug and Alcohol Dependence, 51*, 173–187.

Croft, R.J., Mackay, A.J., Mills, A.T.D., & Gruzelier, J.G.H. (2001). The relative contributions of ecstasy and cannabis to cognitive impairment. *Psychopharmacology, 153*, 373–379.

Deif, A., El Sheshai, A., & Fawzy, R.K. (1993). Neurological, psychiatric and C.T. evaluation of chronic cannabis smokers. *Journal of the Medical Research Institute, 14*, 151–160.

Devane, W.A., Hanus, L., Breuer, A., Pertwee, R.G., Stevenson, L.A., Griffin, G., Gibson, D., Mandelbaum, A., Etinger, A., & Mechoulam, R. (1992). Isolation and structure of a brain constituent that binds to the cannabinoid receptor. *Science, 258*, 1946–1949.

Ehrenreich, H., Rinn, T., Kunert, H.J., Moeller, M.R., Poser, W., Schilling, L., Gigerenzer, G., & Hoehe, M.R. (1999). Specific attentional dysfunction in adults following early start of cannabis use. *Psychopharmacology, 142*, 295–301.

Fletcher, J.M., Page, J.B., Francis, D.J., Copeland, K., Naus, M.J., Davis, C.M., Morris, R., Krauskopf, D., & Satz, P. (1996). Cognitive correlates of long-term cannabis use in Costa Rican men. *Archives of General Psychiatry, 53*, 1051–1057.

Fride, E., Ginzburg, Y., Breuer, A., Bisogno, T., Di Marzo, V., & Mechoulam, R. (2001). Critical role of the endogenous cannabinoid system in mouse pup suckling and growth. *European Journal of Pharmacology, 419*, 207–214.

Fried, P.A. & Smith, A.M. (2001). A literature review of the consequences of prenatal marihuana exposure. An emerging theme of a deficiency in aspects of executive function. *Neurotoxicology and Teratology, 23*, 1–11.

Goldschmidt, L., Day, N.L., & Richardson, G.A. (2000). Effects of prenatal marijuana exposure on child behavior problems at age 10. *Neurotoxicology and Teratology, 22*, 325–336.

Gonzalez, R., Carey, C., & Grant, I. (2002). Nonacute (residual) neuropsychological effects of cannabis use: A qualitative analysis and systematic review. *Journal of Clinical Pharmacology, 42*, 48S–57S.

Gorter, R., Seefried, M., & Volberding, P. (1992). Dronabinol effects on weight in patients with HIV infection [Letter to the editor]. *Aids, 6*, p. 127.

Gouzoulis-Mayfrank, E., Daumann, J., Tuchtenhagen, F., Pelz, S., Becker, S., Kunert, H.J., Fimm, B., & Sass, H. (2000). Impaired cognitive performance in drug free users of recreational ecstasy (MDMA). *Journal of Neurology, Neurosurgery and Psychiatry, 68*, 719–725.

Grant, I., Adams, K., & Reed, R. (1979). Normal neuropsychological abilities of alcoholic men in their late thirties. *American Journal of Psychiatry, 136*, 1263–1269.

Grant, I., Adams, K.M., Carlin, A.S., Rennick, P., Judd, L.L., & Schooff, K. (1978). The collaborative neuropsychological study of polydrug abusers. *Archives of General Psychiatry, 35*, 1063–1074.

Grant, I., Atkinson, J.H., Hesselink, J.R., Kennedy, C.I., Richman, D.D., Spector, S.A., & McCutchan, J.A. (1987). Evidence for early central nervous system involvement in the acquired immunodeficiency syndrome (AIDS) and other human immunodeficiency virus (HIV) infections. *Annals of Internal Medicine, 107*, 828–836.

Grant, I., Heaton, R.K., McSweeny, A.J., Adams, K.M., & Timms, R.M. (1982). Neuropsychological findings in hypoxemic chronic obstructive pulmonary disease. *Archives of Internal Medicine, 142*, 1470–1476.

Grant, I. & Mohns, L. (1975). Chronic cerebral effects of alcohol and drug abuse. *International Journal of the Addictions, 10*, 883–920.

Grant, I., Rochford, J., Fleming, T., & Stankard, A. (1973). A neuropsychological assessment of the effects of moderate marihuana use. *Journal of Nervous and Mental Disease, 156*, 278–280.

Hamil, W.L. (1996). Auditory learning and memory performance among veterans with a history of stimulant abuse. *Dissertation Abstracts International: Section B: The Sciences and Engineering, 56*, 4906.

Hao, S., Avraham, Y., Mechoulam, R., & Berry, E.M. (2000). Low dose anandamide affects food intake, cognitive function, neurotransmitter and corticosterone levels in diet-restricted mice. *European Journal of Pharmacology, 392*, 147–156.

Heaton, R.K., Grant, I., Anthony, W.Z., & Lehman, R.A. (1981). A comparison of clinical and automated interpretation of the Halstead-Reitan Battery. *Journal of Clinical Neuropsychology, 3*, 121–141.

Heaton, R.K., Grant, I., Butters, N., White, D.A., Kirson, D., Atkinson, J.H., McCutchan, J.A., Taylor, M.J., Kelly, M.D., Ellis, R.J., Wolfson, T., Velin, R., Marcotte, T.D., Hesselink, J.R., Jernigan, T.L., Chandler, J., Wallace, M., Abramson, I., & the HNRC Group. (1995). The HNRC 500–Neuropsychology of HIV infection at different disease stages. *Journal of the International Neuropsychological Society, 1*, 231–251.

FAX NO. : 4155527170 Jan. 13 2004 02:42PM P5

Heaton, R.K., Grant, I., & Matthews, C.G. (1991). *Comprehensive norms for an expanded Halstead-Reitan Battery: Demographic corrections, research findings, and clinical applications.* Odessa, FL: Psychological Assessment Resources, Inc.

Hedges, L.V. & Olkin, I. (1985). *Statistical methods for meta-analysis.* Orlando, FL: Academic Press.

Herkenham, M. (1992). Cannabinoid receptor localization in brain: Relationship to motor and reward systems. *Annals of the New York Academy of Sciences, 654,* 19–32.

Herkenham, M., Lynn, A.B., de Costa, B.R., & Richfield, E.K. (1991a). Neuronal localization of cannabinoid receptors in the basal ganglia of the rat. *Brain Research, 547,* 267–274.

Herkenham, M., Lynn, A.B., Johnson, M.R., Melvin, L.S., de Costa, B.R., & Rice, K.C. (1991b). Characterization and localization of cannabinoid receptors in rat brain: A quantitative in vitro autoradiographic study. *Journal of Neuroscience, 11,* 563–583.

Herkenham, M., Lynn, A.B., Little, M.D., Johnson, M.R., Melvin, L.S., de Costa, B.R., & Rice, K.C. (1990). Cannabinoid receptor localization in brain. *Proceedings of the National Academy of Sciences of the United States of America, 87,* 1932–1936.

Howlett, A.C., Bidaut-Russell, M., Devane, W.A., Melvin, L.S., Johnson, M.R., & Herkenham, M. (1990). The cannabinoid receptor: Biochemical, anatomical and behavioral characterization. *Trends in Neurosciences, 13,* 420–423.

Institute of Medicine. (1999). *Marijuana and medicine: Assessing the science base.* Washington, DC: Author.

Kaminski, N.E., Abood, M.E., Kessler, F.K., Martin, B.R., & Schatz, A.R. (1992). Identification of a functionally relevant cannabinoid receptor on mouse spleen cells that is involved in cannabinoid-mediated immune modulation. *Molecular Pharmacology, 42,* 736–742.

Matsuda, L.A., Lolait, S.J., Brownstein, M.J., Young, A.C., & Bonner, T.I. (1990). Structure of a cannabinoid receptor and functional expression of the cloned cDNA. *Nature, 346,* 561–564.

Munro, S., Thomas, K.L., & Abu-Shaar, M. (1993). Molecular characterization of a peripheral receptor for cannabinoids. *Nature, 365,* 61–65.

Nelson, K., Walsh, D., Deeter, P., & Sheehan, F. (1994). A phase II study of delta-9-tetrahydrocannabinol for appetite stimulation in cancer-associated anorexia. *Journal of Palliative Care, 10,* 14–18.

Noyes, R., Brunk, S.P., Baram, D.A., & Canter, A. (1975). Analgesic effect of delta-9-tetrahydrocannabinol. *Journal of Clinical Pharmacology, 15,* 139–143.

Pertwee, R. (1993). The evidence for the existence of cannabinoid receptors. *General Pharmacology, 24,* 811–824.

Pertwee, R.G. (1997). Pharmacology of cannabinoid CB1 and CB2 receptors. *Pharmacology and Therapeutics, 74,* 129–180.

Plasse, T.F., Gorter, R.W., Krasnow, S.H., Lane, M., Shepard, K.V., & Wadleigh, R.G. (1991). Recent clinical experience with dronabinol. *Pharmacology, Biochemistry and Behavior, 40,* 695–700.

Pope, H.G., Gruber, A.J., Hudson, J.I., Huestis, M.A., & Yurgelun-Todd, D. (2001). Neuropsychological performance in long-term cannabis users. *Archives of General Psychiatry, 58,* 909–915.

Pope, H.G., Gruber, A.J., & Yurgelun-Todd, D. (1995). The residual neuropsychological effects of cannabis—The current status of research. *Drug and Alcohol Dependence, 38,* 25–34.

Pope, H.G. & Yurgelun-Todd, D. (1996). The residual cognitive effects of heavy marijuana use in college students. *Journal of the American Medical Association, 275,* 521–527.

Rochford, J., Grant, I., & LaVigne, G. (1977). Medical students and drugs: Further neuropsychological and use pattern considerations. *International Journal of the Addictions, 12,* 1057–1065.

Rodgers, J. (2000). Cognitive performance amongst recreational users of "ecstasy." *Psychopharmacology, 151,* 19–24.

Sanudo-Pena, M.C. & Walker, J.M. (1997). Role of the subthalamic nucleus in cannabinoid actions in the substantia nigra of the rat. *Journal of Neurophysiology, 77,* 1635–1638.

Solowij, N. (1995). Do cognitive impairments recover following cessation of cannabis use? *Life Sciences, 56,* 2119–2126.

Solowij, N. (1998). *Cannabis and cognitive functioning.* New York: Cambridge University Press.

Solowij, N., Stephens, R.S., Roffman, R.A., Babor, T., Kadden, R., Miller, M., Christiansen, K., McRee, B., & Vendetti, J. (2002). Cognitive functioning of long-term heavy cannabis users seeking treatment. *Journal of the American Medical Association, 287,* 1123–1131.

US National Institute of Health. (1997). *Report on the medical uses of marijuana.* Bethesda, MD.

Wig, N.N. & Varma, V.K. (1977). Patterns of long-term heavy cannabis use in North India and its effects on cognitive functions: A preliminary report. *Drug and Alcohol Dependence, 2,* 211–219.

Oncologic, Endocrine & Metabolic

Cannabinoid receptor systems: therapeutic targets for tumour intervention

Sarah Jones & John Howl†
†Molecular Pharmacology Group, Biomedical Sciences Division, School of Applied Sciences, University of Wolverhampton, Wulfruna Street, WV1 1SB, UK

The past decade has witnessed a rapid expansion of our understanding of the biological roles of cannabinoids and their cognate receptors. It is now certain that Δ^9-tetrahydrocannabinol, the principle psychoactive component of the *Cannabis sativa* plant, binds and activates membrane receptors of the 7-transmembrane domain, G-protein-coupled superfamily. Several putative endocannabinoids have since been identified, including anandamide, 2-arachidonyl glycerol and noladin ether. Synthesis of numerous cannabinomimetics has also greatly expanded the repertoire of cannabinoid receptor ligands with the pharmacodynamic properties of agonists, antagonists and inverse agonists. Collectively, these ligands have proven to be powerful tools both for the molecular characterisation of cannabinoid receptors and the delineation of their intrinsic signalling pathways. Much of our understanding of the signalling mechanisms activated by cannabinoids is derived from studies of receptors expressed by tumour cells; hence, this review provides a succinct summary of the molecular pharmacology of cannabinoid receptors and their roles in tumour cell biology. Moreover, there is now a genuine expectation that the manipulation of cannabinoid receptor systems may have therapeutic potential for a diverse range of human diseases. Thus, this review also summarises the demonstrated antitumour actions of cannabinoids and indicates possible avenues for the future development of cannabinoids as antitumour agents.

Keywords: cannabinoid, endocannabinoid, signal transduction, tumour

Expert Opin. Ther. Targets (2003) 7(6):749-758

Expert Opinion

1. Introduction
2. Antitumour effects of cannabinoids
3. Expert opinion

For reprint orders, please contact:
reprints@ashley-pub.com

Ashley Publications
www.ashley-pub.com

1. Introduction

1.1 The pharmacology of cannabinoid receptors

For many years, the highly lipophilic nature of cannabinoids proved a barrier to the unequivocal demonstration that the biological effects of Δ^9-tetrahydrocannabinol (Δ^9-THC), and other ligands that demonstrate Δ^9-THC-like pharmacological properties, were receptor-mediated. However, the molecular cloning of a brain receptor that bound these lipid moieties [1] finally proved that the biological actions of cannabinoids were mediated by G-protein-coupled receptors (GPCRs), the quantitatively-dominant class of drug target. To date, only two cannabinoid receptor subtypes have been cloned. The central brain cannabinoid receptor (CB_1) [1] and the peripheral cannabinoid receptor (CB_2) [2] share 44% overall sequence homology that predictably rises to 68% within the seven transmembrane-spanning domains. The use of selective agonists and/or antagonists can discriminate between CB_1- and CB_2-mediated responses. However, both receptors predominantly couple to pertussis toxin-sensitive G proteins of the G_i class. Agonist stimulation of either receptor subtype inhibits adenylyl cyclase, reducing intracellular cAMP, and commonly

2003 © Ashley Publications Ltd ISSN 1472-8222

activates the extracellular signal-regulated kinase (ERK) cascade (see below) [3]. CB_1 receptor activation also inhibits voltage-dependent Ca^{2+} channels and activates inwardly rectifying K^+ channels [4].

1.2 Biological and pathological roles of cannabinoid receptors

The CB_1 receptor is associated with various biological/therapeutic functions, including the inhibition of synaptic transmission, analgesia, reduction in intra-ocular pressure, appetite stimulation, decreased muscle spasms, and various antitumour actions [5]. The known distribution of the CB_1 receptor, expressed by brain and neuronal tissue and particularly enriched in the hippocampus, cerebral cortex, basal ganglia and cerebellum, supports a predominantly central action. In contrast, the peripherally-located CB_2 receptor is predominantly expressed by cells of immune origin, a cellular distribution that supports an immunomodulatory and/or anti-inflammatory role [6-8]. Of particular relevance to this review is an abundance of evidence that the activation of cannabinoid receptor systems can markedly influence cell fate [9,10]. Following brain injury, and in the case of certain neurodegenerative disorders, cannabinoids protect against neuronal insult and promote cell survival [11-14]. Conversely, activation of cannabinoid receptors expressed by tumour cells can inhibit proliferation and induce apoptosis both *in vivo* and *in vitro* [15,16].

1.3 Ligand classification

Cannabinoid receptor ligands may be divided into four distinct groups: i) Classical; ii) non-classical; iii) aminoalkylindoles, and iv) endocannabinoids/eicosanoids. The classical cannabinoids comprise compounds occurring naturally within the *Cannabis sativa* plant, including Δ^9-THC, Δ^8-THC, cannabinol, cannabidiol and their synthetic analogues, including the highly potent HU-210 and desacetyl-L-nantradiol (DALN) [5]. These ABC-tricyclic dibenzopyran derivatives demonstrate equal affinity for CB_1 and CB_2 receptors. Minor modification of these compounds has led to the generation of cannabinoids with either increased affinity (JWH-015 [17]) or selectivity (JWH-133 [18] and HU-308 [19]) for CB_2.

Developed by Pfizer, the non-classical cannabinoids lack the dihydropyran ring of Δ^9-THC [5]. These bicyclic and tricyclic analogues include the highly utilised CP-55940, showing similar affinity for both CB_1 and CB_2 [20].

Aminoalkylindoles with decreased anti-inflammatory properties and derived from analogues of pravadoline [21], were found to possess cannabimimetic activity [22,23]. This group is typified by WIN-55212-2, exhibiting affinity for both CB_1 and CB_2 receptors [5] and the CB_2-selective agonist AM-1241 [24].

In addition to the four main classes of cannabinoids, the diarylether sulfonylester derivative BAY-38-7271 is a new high-affinity CB_1 receptor agonist that is structurally distinct from any cannabinoid receptor ligand known so far [25].

The discovery of putative endogenous ligands, the endocannabinoids, gave further credence to the pharmacological relevance and therapeutic potential of cannabinoids [26,27]. N-arachidonylethanolamine (AEA), more commonly referred to as anandamide, was initially isolated from porcine brain [28], and synthesis of its analogue, arachidonyl-2-chloroethylamide, produced the high-affinity CB_1 agonist ACEA [29]. Shortly afterwards, 2-arachidonyl glycerol (2-AG), isolated from canine gut [30] and rat brain [31], was acknowledged as a potential candidate in the search for further endocannabinoids. Owing to the relatively low affinity displayed by these putative endogenous ligands for cannabinoid receptors, it seems highly probable that further endocannabinoids remain to be isolated. Most recently, a third endocannabinoid candidate, 2-arachidonyl glycerol ether (noladin ether), has gained attention in the quest for further endogenous ligands. Isolated from porcine brain, noladin ether possesses a higher affinity for the central CB_1 receptor than for the peripheral CB_2 receptor, and shows greater metabolic stability than its counterparts, 2-AG and AEA [32]. However, a recent study was unable to detect appreciable amounts of noladin ether in brains from various mammalian species [33].

Synthesis of selective antagonists has greatly assisted our understanding of cannabinoid receptor pharmacology. The most notable CB_1 antagonists include the diarylpyrazole SR-141716 [34], a highly potent CB_1-selective antagonist, and the high-affinity LY-320135 [35]. However, both are reported to demonstrate properties of inverse agonism [36]. CB_2 antagonists comprise the diarylpyrazole, SR-144528 [37], and the aminoalkylindole, AM-630 [38]. Again, both show characteristics of inverse agonism [39], and the latter may exhibit partial agonist activity at the CB_1 receptor [38].

1.4 Biosynthesis and degradation of endocannabinoids

Local production of AEA, and probably other endocannabinoids, is a calcium-dependent process [40]. AEA biosynthesis requires the phospholipase D-mediated hydrolysis of the phospholipid precursor N-arachidonylphosphatidylethanolamine [40,41]. The extracellular signal-regulated activity of phospholipase D could enable many extrinsic factors to regulate AEA biosynthesis. Inactivation of AEA is by a specific membrane transporter [41-43] and subsequent intracellular hydrolysis by the fatty acid amide hydrolase (FAAH) [41,44,45].

2. Antitumour effects of cannabinoids

The antitumour effects of Δ^9-THC and its analogues were first identified in the 1970s. Antineoplastic activities were reported in Lewis lung adenoma cells [46,47], L1210 leukaemia cells [48] and HeLa S3 cells [49]. As detailed below, numerous investigations have since identified antiproliferative, apoptotic, antiangiogenic, and antimetastatic properties of cannabinoids.

2.1 Malignant astrocytomas and gliomas

Attention has recently been focused on the cannabinoid-induced apoptosis of malignant astrocytomas/gliomas both *in vivo* and in cultured cellular systems. Glial cell/astrocyte

malignancies are a relatively rare yet fatal form of brain tumour [10] that can be modelled in rodents by parenchymal inoculation with transformed glioma cell lines. Following inoculation of Wistar rats with C6.9 glioma cells, intratumoural administration of Δ^9-THC and the synthetic cannabinoid WIN-55212-2 reduced tumour growth and promoted regression via apoptotic mechanisms [51]. More recently, an additional mechanism of cannabinoid-mediated glioma/astrocytoma tumour regression has been elucidated by Blazquez and co-workers [52]. Intra-tumoural administration of the non-psychoactive and CB_2-selective ligand, JWH-133, inhibited angiogenesis required for the growth of tumours induced in mice by inoculation with both C6 glioma and human astrocytoma cells.

2.1.1 Signalling

A common second messenger system stimulated by cannabinoid receptor activation is the ERK cascade. The end point of this key signal transduction event is the phosphorylation and activation of ERK1/2, alternatively referred to as p42/44 mitogen-activated protein kinases (MAPKs). Activated ERK1/2, in turn, modulate gene transcription. Although this system is often associated with events leading to cellular proliferation and differentiation, there are paradoxical circumstances during which activation of the ERK cascade leads to cell cycle arrest, apoptosis and necrotic cell death [53,54]. These disparate effects upon cell fate may be a consequence of differences in signal intensity and duration. Cannabinoid receptor stimulation promotes ERK1/2 activation in C6.9 glioma cells, astrocytoma cells and primary astrocytes, and these events are accompanied by the intracellular accumulation of ceramide [55,56]. Ceramide, a sphingosine-based lipid, possesses apoptotic properties. The accumulation of ceramide may be a consequence of the receptor-mediated activation of sphingomyelinase and subsequent hydrolysis of sphingomyelin. More recently, a second pathway leading to ceramide accumulation and apoptosis, that of *de novo* ceramide synthesis [57-59], has also been elucidated. Although the role of cannabinoid-induced sphingomyelin hydrolysis in normal astrocytes is probably the stimulation of glucose metabolism [56,60], evidence strongly indicates that the intracellular accumulation of ceramide contributes to the apoptotic properties of cannabinoids in transformed cells. Moreover, Galve-Roperh and co-workers [51] showed that exposure of C6.9 glioma cells to both Δ^9-THC and synthetic cannabinoid agonists resulted in the generation of two intracellular ceramide peaks that were upstream of ERK activation. The initial peak, a likely response to short-term cannabinoid treatment, probably involved activation of sphingomyelinase by the adaptor protein FAN (factor associated with neutral sphingomyelinase) [61]. This initial rise in ceramide concentration did not play an active role in cannabinoid-mediated apoptosis. A second ceramide peak was observed following 3 days of continued cannabinoid exposure, and this rise was related to C6.9 glioma cell death. Furthermore, following chronic stimulation of cannabinoid receptors on C6.9 gliomas, inhibition of *de novo* ceramide synthesis prevented stimulation of ERK1/2 and also increased the activity of antiapoptotic protein kinase B (PKB) [62] (**Figure 1**).

These observations clearly support a pro-apoptotic role for cannabinoid receptor systems, although there are several caveats to these interpretations. First, other kinase pathways may underlie the effects of cannabinoids on cell fate. Thus, Δ^9-THC-induced cell death, both within C6.9 gliomas and U373MG astrocytoma cells, has also been paralleled to the activation of Jun N-terminal kinase (JNK) [63] and p38 MAPK [51], although selective inhibition would indicate an ERK-mediated apoptotic response [51]. The JNK and p38 MAPK family, in contrast to the ERKs, are considered to be activated by stress signals and contribute to the stress response by altering progression through the cell cycle, DNA repair or apoptosis [64]. Second, the highly potent agonist HU-210 appears to be protective against ceramide-induced apoptosis in the U373MG cell line [65]. CB_1-mediated $\beta\gamma$ subunit dissociation, activation of the Class I_B phosphatidylinositol 3′-kinase isoenzyme, subsequent activation of its target, PKB, and acute ERK activation, appear to constitute pro-survival signals in this cell line [65]. It follows, therefore, that short-term cannabinoid-mediated ERK activation protects against apoptosis, whereas chronic stimulation induces apoptosis. However, as GPCRs, cannabinoid receptors would be expected to desensitise upon stimulation. Thus, it is difficult to understand why cannabinoid receptor-induced apoptosis requires a 3- to 5-day exposure period to cannabinoids.

2.1.2 Functional significance of the CB_2 receptor

CB_2 receptors are largely considered to be peripherally located. However, evidence for CB_2 receptor expression by some gliomas is accumulating and this receptor may also inhibit cell growth. Thus, Δ^9-THC-induced apoptosis of C6.9 glioma cells was only completely inhibited by a combination of both CB_1 and CB_2 antagonists [51]. Moreover, selective activation of the CB_2 receptor induced a regression of glioma cell growth *in vivo* [66].

Of further interest is the finding that CB_2 receptor expression on human astrocytomas appears to be closely correlated with tumour grade and degree of malignancy [66]. Sanchez and co-workers identified both CB_1 and CB_2 receptor expression in 70% of human astrocytomal biopsies [66]. Moreover, Grade IV astrocytomas showed an elevated level of CB_2 receptor expression compared to that of CB_1. The above findings provide a promising therapeutic strategy for cannabinoid treatment of malignant astrocytomas and gliomas, whilst avoiding the unwanted psychotropic affects associated with recruitment of CB_1 receptors.

2.1.3 Cannabinoid-mediated inhibition of angiogenesis and tumour invasiveness

The importance of cannabinoid-based glioma and astrocytoma therapy has increased significantly in the light of recent

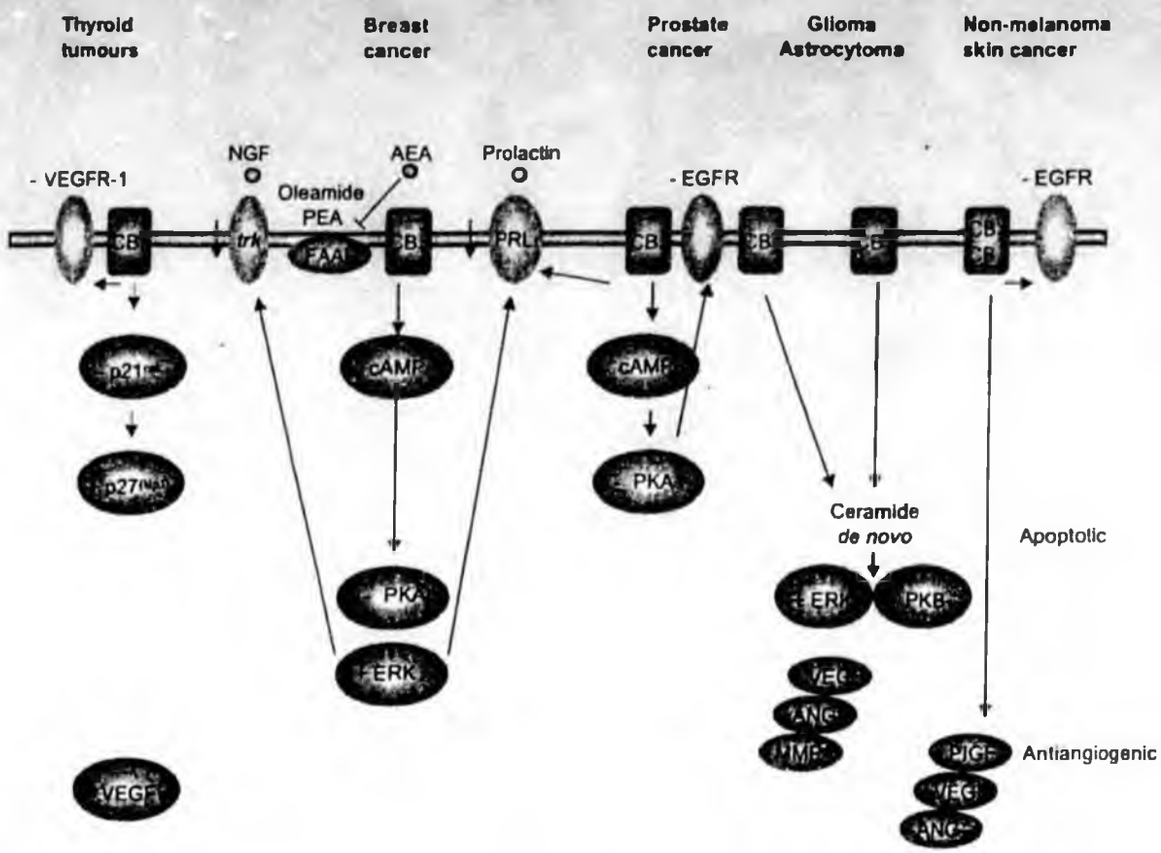


Figure 1. Cannabinoid-mediated antitumour signalling mechanisms. Cannabinoids have been implicated in the tumour suppression of malignant astrocytomas and gliomas, breast and prostate cancer cells, thyroid epithelium, and non-melanoma skin cancer growth. Inhibition of proliferation, induction of apoptosis and impairment of angiogenesis have been attributed to a diversity of intracellular signalling cascades following cannabinoid receptor ligation.

AEA: Anandamide; ANG: Angiopoietin; CB_1: Brain cannabinoid receptor; CB_2: Peripheral cannabinoid receptor; EGFR: Epidermal growth factor receptor; ERK: Extracellular signal-regulated kinase; FAAH: Fatty acid amide hydrolase; MMP: Matrix metalloproteinase; NGF: Nerve growth factor; $p21^{ras}$: Monomeric G protein ras; $p27^{kip1}$: Cyclin-dependent kinase inhibitor; PEA: Palmitoylethanolamide; PlGF: Placental growth factor; PK: Protein kinase; PRLr: Long form of the prolactin receptor; *trk*: High-affinity nerve growth factor receptor; VEGF: Vascular endothelial growth factor, VEGFR: Vascular endothelial growth factor receptor.

findings by Blazquez and co-workers [52]. Administration of the CB_2-selective agonist, JWH-133, proved effective in suppressing the release of pro-angiogenic factors, vascular endothelial growth factor (VEGF) and angiopoietin-2 from C6 glioma and human Grade IV astrocytoma-induced tumours in mice. Furthermore, decreased expression of matrix metalloproteinase (MMP)-2 from tumour biopsies was reported (Figure 1). It has therefore been hypothesised that cannabinoids may target and inhibit endothelial cell survival and migration, thereby restricting tumour blood vessel supply [52]. *In vitro* experiments with primary human umbilical vein endothelial cells (HUVECs) and the cell line ECV304 have indicated that such effects are CB_2-mediated. Furthermore, cannabinoid-induced endothelial cell death and inhibition of endothelial cell migration were abrogated by inhibition of MEK (MAPK kinase) 1/2, thereby implicating the involvement of the ERK signalling cascade. However, caution should be applied when interpreting these findings, as ECV304 cells are derived from the human bladder cancer-derived epithelial cell line T24/83 [67].

In summary, cannabinoid receptors and their associated signalling pathways could prove to be a valuable therapeutic target for the treatment of malignant gliomas and astrocytomas. In these situations, cannabinoids could support apoptosis, suppress the release of pro-angiogenic factors and MMPs and, therefore, prevent tumour growth, angiogenesis and cell invasiveness.

2.2 Human breast cancer cell lines

The therapeutic potential of cannabinoids in the treatment of human breast cancer has been well studied by Di Marzo and co-workers, with particular emphasis placed upon the antiproliferative effects of the endocannabinoids in cellular systems. Rather than inducing apoptosis, the endocannabinoid AEA arrested the proliferation of human breast cancer cells by halting progression through the cell cycle at the G1/S transition

45. UEDA N, YAMAMOTO S: Anandamide amidohydrolase (fatty acid amide hydrolase). *Prostaglandins Other Lipid Mediat.* (2000) 61:19-28.

46. MUNSON AE, HARRIS LS, FRIEDMAN MA, DEWEY WL, CARCHMAN RA: Antineoplastic activity of cannabinoids. *J. Natl. Cancer Inst.* (1975) 55:597-602.

47. WHITE AC, MUNSON JA, MUNSON AE, CARCHMAN RA: Effects of Δ^9-tetrahydrocannabinol in Lewis lung adenocarcinoma cells in tissue culture. *J. Natl. Cancer Inst.* (1976) 56:655-658.

48. CARCHMAN RA, HARRIS LS, MUNSON AE: The inhibition of DNA synthesis by cannabinoids. *Cancer Res.* (1976) 31:95-100.

49. MON MJ, JANSING RL, DOGGETT S, STEIN JL, STEIN GS: Influence of Δ^9-tetrahydrocannabinol on cell proliferation and macromolecular biosynthesis in human cells. *Biochem. Pharmacol.* (1978) 27:1759-1765.

50. MAHER EA, FURNARI FB, BACHOO RM *et al.*: Malignant glioma: genetics and biology of a grave matter. *Genes Dev.* (2001) 15:1311-1333.

51. GALVE-ROPERH I, SANCHEZ C, CORTES ML, DEL PULGAR TG, IZQUIERDO M, GUZMAN M: Anti-tumoral action of cannabinoids: involvement of sustained ceramide accumulation and extracellular signal-regulated kinase activation. *Nat. Med.* (2000) 16:313-319.

•• A seminal report signifying the antitumour effects of cannabinoids *in vivo*.

52. BLAZQUEZ C, CASANOVA ML, PLANAS A *et al.*: Inhibition of tumor angiogenesis by cannabinoids. *FASEB J.* (2003) 17:529-531.

53. PUNIGLIA KM, DECKER SJ: Cell cycle arrest mediated by the MEK/mitogen-activated protein kinase pathway. *Proc. Natl. Acad. Sci. USA* (1997) 94:448-452.

54. YORK RD, YAO H, DILLON T *et al.*: Rap1 mediates sustained MAP kinase activation induced by nerve growth factor. *Nature* (1998) 392:622-626.

55. SANCHEZ C, GALVE-ROPERH I, CANOVA C, BRACHET P, GUZMAN M: Δ^9-tetrahydrocannabinol induces apoptosis in C6.9 glioma cells. *FEBS Lett.* (1998) 436:6-10.

56. SANCHEZ C, GALVE-ROPERH I, RUEDA D, GUZMAN M: Involvement of sphingomyelin hydrolysis and the mitogen-activated protein kinase cascade in the Δ^9-tetrahydrocannabinol-induced stimulation of glucose metabolism in primary astrocytes. *Mol. Pharmacol.* (1998) 54:834-843.

57. PERRY DK, CARTON J, SHAH AK, MEREDITH F, UHLINGER DJ, HANNUN YA: Serine palmitoyltransferase regulates *de novo* ceramide generation during etoposide-induced apoptosis. *J. Biol. Chem.* (2000) 275:9078-9084.

58. HUWILER A, KOLTER T, PFEILSCHIFTER J, SANDHOFF K: Physiology and pathophysiology of sphingolipid metabolism and signaling. *Biochim. Biophys. Acta* (2000) 1485:63-99.

59. GUZMAN M, GALVE-ROPERH I, SANCHEZ C: Ceramide: a new second messenger of cannabinoid action. *Trends Pharmacol. Sci.* (2001) 22:19-22.

60. BLAZQUEZ C, SANCHEZ C, DAZA A, GALVE-ROPERH I, GUZMAN M: The stimulation of ketogenesis by cannabinoids in cultured astrocytes defines carnitine palmitoyl transferase I as a new ceramide activated enzyme. *J. Neurochem.* (1999) 72:1759-1768.

61. SANCHEZ C, RUEDA D, SEGUI D, GALVE-ROPERH I, LEVADE T, GUZMAN M: The cannabinoid receptor of astrocytes is coupled to sphingomyelin hydrolysis through the adaptor protein FAN. *Mol. Pharmacol.* (2001) 59:955-959.

62. GOMEZ DEL PULGAR T, VELASCO G, GUZMAN M: The CB_1 cannabinoid receptor is coupled to the activation of protein kinase B/Akt. *Biochem. J.* (2000) 347:369-373.

63. RUEDA D, GALVE-ROPERH I, HARO A, GUZMAN M: The CB_1 cannabinoid receptor is coupled to the activation of c-Jun-N-terminal kinase. *Mol. Pharmacol.* (2000) 58:814-820.

• These findings prompt an excellent discussion of the diversity of cannabinoid-mediated signal transduction mechanisms in the determination of cell fate.

64. HARPER SJ, LOGRASSO P: Signaling for survival and death in neurons: The role of stress-activated kinases, JNK and p38. *Cell. Signal.* (2001) 13:299-310.

65. GALVE-ROPERH I, RUEDA D, GOMEZ DEL PULGAR T, VELASCO G, GUZMAN M: Mechanism of extracellular signal-regulated kinase activation by the CB_1 cannabinoid receptor. *Mol. Pharmacol.* (2002) 62:1385-1392.

66. SANCHEZ C, DE CEBALLOS ML, GOMEZ DEL PULGAR T *et al.*: Inhibition of glioma growth *in vivo* by selective activation of the CB_2 cannabinoid receptor. *Cancer Res.* (2001) 61:5784-5789.

67. BROWN J, READING SJ, JONES S *et al.*: Critical evaluation of ECV304 as a human endothelial cell model defined by genetic analysis and functional responses: a comparison with the human bladder cancer derived epithelial cell line T24/83. *Lab. Invest.* (2000) 80:37-45.

68. DE PETROCELLIS L, MELCK D, PALMISANO A *et al.*: The endogenous cannabinoid anandamide inhibits human breast cancer cell proliferation. *Proc. Natl. Acad. Sci. USA* (1998) 95:8375-8380.

69. MELCK D, DE PETROCELLIS L, ORLANDO P *et al.*: Suppression of nerve growth factor *trk* receptors and prolactin receptors by endocannabinoids leads to inhibition of human breast and prostate cancer cell proliferation. *Endocrinology* (2000) 141:118-126.

70. MELCK D, RUEDA D, GALVE-ROPERH I, DE PETROCELLIS L, GUZMAN M, DI MARZO V: Involvement of the cAMP–protein kinase A pathway and of mitogen-activated protein kinase in the anti-proliferative effects of anandamide in human breast cancer cells. *FEBS Lett.* (1999) 463:235-240.

71. CRAVATT BF, PROSPER-GARCIA O, SIUZDAK G *et al.*: Chemical characterization of a family of brain lipids that induce sleep. *Science* (1995) 268:1506-1509.

72. BISOGNO T, KATAYAMA K, MELCK D *et al.*: Biosynthesis and degradation of bioactive fatty acid amides in human breast cancer and rat pheochromocytoma cells. *Eur. J. Biochem.* (1998) 254:634-642.

73. MECHOULAM R, FRIDE E, HANUS L *et al.*: Anandamide may mediate sleep induction. *Nature* (1997) 389:25-26.

74. DE PETROCELLIS L, MELCK D, BISOGNO T, DI MARZO V: Endocannabinoids and fatty acid amides in cancer, inflammation and related disorders. *Chem. Phys. Lipids* (2000) 108:191-209.

•• A pioneering review exploring novel therapeutic targets of the endocannabinoid system.

75. BISOGNO T, MAURELLI S, MELCK D, DE PETROCELLIS L, DI MARZO V: Biosynthesis, uptake and degradation of anandamide and palmitoylethanolamide in leukocytes. *J. Biol. Chem.* (1997) 272:3315-3323.

76. LAMBERT DM, DI MARZO V: The palmitoylethanolamide and oleamide enigmas: are these two fatty acid amides cannabimimetic. *Curr. Med. Chem.* (1999) 6:757-773.

77. DI MARZO V, MELCK D, ORLANDO P *et al.*: Palmitoylethanolamide inhibits the expression of fatty acid amide hydrolase and enhances the anti-proliferative effect of anandamide in human breast cancer cells. *Biochem. J.* (2001) 358:249-255.

78. MIMEAULT M, POMMERY N, WATTEZ N, BAILLY C, HENICHART JP: Anti-proliferative and apoptotic effects of anandamide in human prostatic cancer cell lines: implication of epidermal growth factor receptor down-regulation and ceramide production. *Prostate* (2003) 56:1-12.

79. RUIZ L, MIGUEL A, DIAZ-LAVIADA I: Δ^9-Tetrahydrocannabinol induces apoptosis in human prostate PC-3 cells via a receptor-independent mechanism. *FEBS Lett.* (1999) 458:400-404.

80. KAMIYAMA M, FUKUYA Y, TAKIHANA Y *et al.*: Anandamide and capsaicin inhibit proliferation of human prostate cancer cell via cannabinoid receptor and vanilloid receptor respectively. *Eur. Urol. Suppl.* (2003) 2:36.

81. BIFULCO M, LAEZZA C, PORTELLA G *et al.*: Control by the endogenous cannabinoid system of ras oncogene-dependent tumor growth. *FASEB J.* (2001) 15:2745-2747.

82. PORTELLA G, LAEZZA C, LACCETTI P, DE PETROCELLIS L, DI MARZO M, BIFULCO M: Inhibitory effects of cannabinoid CB_1 receptor stimulation on tumor growth and metastatic spreading: actions on signals involved in angiogenesis and metastasis. *FASEB J.* (2003). Epublished ahead of print.

83. CASANOVA ML, BLAZQUEZ C, MARTINEZ-PALACIO J *et al.*: Inhibition of skin tumor growth and angiogenesis *in vivo* by activation of cannabinoid receptors. *J. Clin. Invest.* (2003) 111:43-50.

84. MCKALLIP RJ, LOMBARD C, FISHER M *et al.*: Targeting CB_2 cannabinoid receptors as a novel therapy to treat malignant lymphoblastic disease. *Blood* (2002) 100:627-634.

85. DI MARZO V, DE PETROCELLIS L, FEZZA F, LIGRESTI A, BISOGNO T: Anandamide receptors. *Prostaglandins Leukot. Essent. Fatty Acids* (2002) 66:377-391.

86. SMART D, GUNTHORPE MJ, JERMAN JC *et al.*: The endogenous lipid anandamide is a full agonist at the human vanilloid receptor (hVR1). *Br. J. Pharmacol.* (2000) 129:227-230.

87. ZYGMUNT PM, PETERSSON J, ANDERSSON DA *et al.*: Vanilloid receptors on sensory nerves mediate the vasodilator action of anandamide. *Nature* (1999) 400:452-457.

88. CATERINA MJ, SCHUMACHER MA, TOMINAGA M, ROSEN TA, LEVINE JD, JULIUS D: The capsaicin receptor: a heat-activated ion channel in the pain pathway. *Nature* (1997) 389:816-824.

89. MACCARRONE M, LORENZON T, BARI M, MELINO G, FINAZZI-AGRO A: Anandamide induces apoptosis in human cells via vanilloid receptors. Evidence for a protective role of cannabinoid receptors. *J. Biol. Chem.* (2000) 275:31938-31945.

90. JACOBSSON SO, WALLIN T, FOWLER CJ: Inhibition of rat C6 glioma cell proliferation by endogenous and synthetic cannabinoids. Relative involvement of cannabinoid and vanilloid receptors. *J. Pharmacol. Exp. Ther.* (2001) 299:951-959.

91. SARKER KP, BISWAS KK, TAMAKUCHI M *et al.*: ASK1-p38 MAPK/JNK signaling cascade mediates anandamide-induced PC12 cell death. *J. Neurochem.* (2003) 85:50-61.

92. SARKER KP, OBARA S, NAKATA M, KITAJIMA I, MARUYAMA I: Anandamide induces apoptosis of PC-12 cells: involvement of superoxide and caspase-3. *FEBS Lett.* (2000) 472:39-44.

93. MACCARRONE M, ATTINA M, CARTONI A, BARI M, FINAZZI-AGRO A: Gas chromatography–mass spectrometry analysis of endogenous cannabinoids in healthy and tumoral human brain and human cells in culture. *J. Neurochem.* (2001) 76:594-601.

94. PAGOTTO U, MARSICANO G, FEZZA F *et al.*: Normal human pituitary gland and pituitary adenomas express cannabinoid receptor Type 1 and synthesize endogenous cannabinoids: first evidence for a direct role of cannabinoids on hormone modulation at the human pituitary level. *J. Clin. Endocrinol. Metab.* (2001) 86:2687-2696.

95. LIGRESTI A, BISOGNO T, MATIAS I *et al.*: Possible endocannabinoid control of colorectal cancer growth. *Gastroenterology* (2003) 125:677-687.

96. ZHU LX, SHARMA S, STOLINA M *et al.*: Δ-9-Tetrahydrocannabinol inhibits anti-tumor immunity by a CB_2 receptor-mediated, cytokine-dependent pathway. *J. Immunol.* (2000) 165:373-380.

97. TASHKIN DR, BALDWIN GC, SARAFIAN T, DUBINETT S, ROTH MD: Respiratory and immunologic consequences of marijuana smoking. *J. Clin. Pharmacol.* (2002) 42:S71-S81.

98. JORDA MA, RAYMAN N, VALK P, DE WEE E, DELWEL R: Identification, characterization and function of a novel oncogene: the peripheral cannabinoid receptor CB_2. *Ann. NY Acad. Sci.* (2003) 996:10-16.

99. JOOSTEN M, VALK PJ, JORDA MA *et al.*: Leukemic predisposition of pSca-1/CB_2 transgenic mice. *Exp. Hematol.* (2002) 30:142-149.

100. MELCK D, BISOGNO T, DE PETROCELLIS L *et al.*: Unsaturated long-chain N-acyl-vanillyl-amides (N-AVAMs): vanilloid receptor ligands that inhibit anandamide-facilitated transport and bind to CB_1 receptors. *Biochem. Biophys. Res. Commun.* (1999) 262:275-284.
- Synthesis of novel antitumour agents to target the endocannabinoid system.

101. DI MARZO V, BISOGNO T, MELCK D *et al.*: Interactions between synthetic vanilloids and the endogenous cannabinoid system. *FEBS Lett.* (1998) 436:449-454.

Affiliation

Sarah Jones BSc & John Howl PhD[†]
[†]Author for correspondence
Molecular Pharmacology Group,
Biomedical Sciences Division, School of Applied Sciences, University of Wolverhampton,
Wulfruna Street, WV1 1SB, UK
Tel: +44 (0) 1902 321131;
Fax: +44 (0) 1902 322714;
E-mail: J.Howl@wlv.ac.uk

DOI: 10.1093/brain/awg143 Advanced Access publication April 8, 2003 *Brain* (2003), **126**, 1252–1270

INVITED REVIEW

Cannabis and the brain

Leslie Iversen

Department of Pharmacology, University of Oxford, Oxford, UK

Correspondence to: Leslie Iversen, Department of Pharmacology, University of Oxford, Mansfield Road, Oxford OX1 3QT, UK
E-mail: les.iversen@pharm.ox.ac.uk

Summary

The active compound in herbal cannabis, Δ^9-tetrahydrocannabinol, exerts all of its known central effects through the CB_1 cannabinoid receptor. Research on cannabinoid mechanisms has been facilitated by the availability of selective antagonists acting at CB_1 receptors and the generation of CB_1 receptor knockout mice. Particularly important classes of neurons that express high levels of CB_1 receptors are GABAergic interneurons in hippocampus, amygdala and cerebral cortex, which also contain the neuropeptides cholecystokinin. Activation of CB_1 receptors leads to inhibition of the release of amino acid and monoamine neurotransmitters. The lipid derivatives anandamide and 2-arachidonylglycerol act as endogenous ligands for CB_1 receptors (endocannabinoids). They may act as retrograde synaptic mediators of the phenomena of depolarization-induced suppression of inhibition or excitation in hippocampus and cerebellum. Central effects of cannabinoids include disruption of psychomotor behaviour, short-term memory impairment, intoxication, stimulation of appetite, antinociceptive actions (particularly against pain of neuropathic origin) and anti-emetic effects. Although there are signs of mild cognitive impairment in chronic cannabis users there is little evidence that such impairments are irreversible, or that they are accompanied by drug-induced neuropathology. A proportion of regular users of cannabis develop tolerance and dependence on the drug. Some studies have linked chronic use of cannabis with an increased risk of psychiatric illness, but there is little evidence for any causal link. The potential medical applications of cannabis in the treatment of painful muscle spasms and other symptoms of multiple sclerosis are currently being tested in clinical trials. Medicines based on drugs that enhance the function of endocannabinoids may offer novel therapeutic approaches in the future.

Keywords: cannabinoid CB_1 receptor; Δ^9-tetrahydrocannabinol; rimonabant (SR141716A); anandamide; 2-arachidonylglycerol

Abbreviations: 2-AG = 2-arachidonylglycerol; DSI = depolarization-induced suppression of inhibition; FAAH = fatty acid amide hydrolase; Gi/o = G-proteins negatively linked to adenylate cyclase or to inositol phosphates; LTD = long-term depression; LTP = long-term potentiation; mGlu = metabotropic glutamate; NMDA = *N*-methyl-D-aspartate; THC = Δ^9-tetrahydrocannabinol

Introduction

A large literature exists on the effects of cannabis, with many of the earlier studies conducted in human subjects (Mendelson *et al.*, 1976; Jones, 1978; Hollister, 1986). Unfortunately, much of this research would now be regarded as inadequately controlled and poorly designed. However, research on cannabis has been stimulated in recent years by the recognition that specific receptors exist in the brain that recognize cannabinoids, and by the discovery of a series of endogenous cannabinoids that act as ligands for these receptors. As was the case with opiate research in the 1970s, research on a psychoactive drug of plant origin has revealed a hitherto unknown physiological control mechanism. This review will focus mainly on the more recent literature in this field.

Brain 126 © Guarantors of Brain 2003; all rights reserved

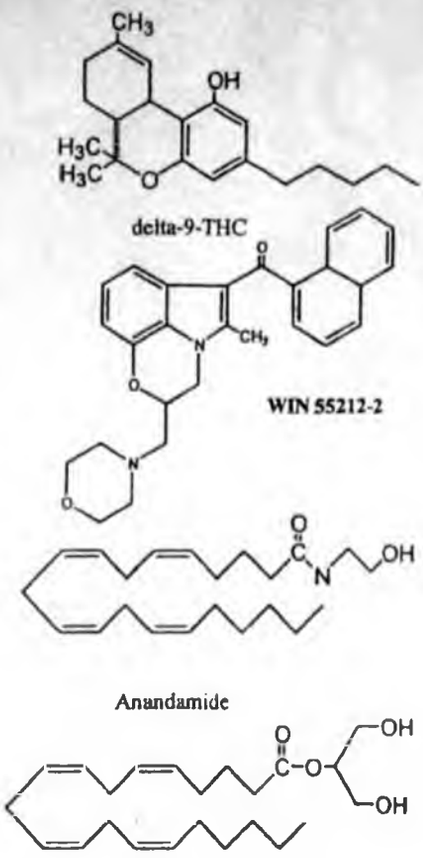
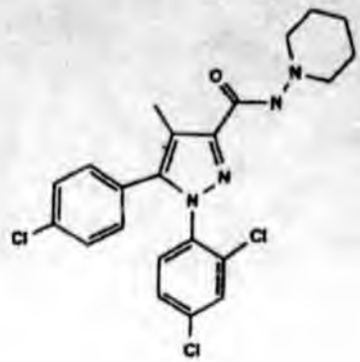


Fig. 1 Chemical structures of THC, the synthetic CB_1 receptor agonist WIN 55,2122 and the endocannabinoids.



SR141716A

Fig. 2 Chemical structure of the CB_1 selective antagonist drug rimonabant (SR141716A).

The cannabinoid system in brain

Exogenous cannabinoids and their receptors

The principal active component in the complex mixture of cannabinoids present in extracts of the plant *Cannabis sativa* is Δ^9-tetrahydrocannabinol (THC) (Mechoulam, 1970) (Fig. 1). THC is a sticky resin that is not soluble in water. Smoking remains the most efficient means of delivering the drug and experienced users can titrate the dose by adjusting the frequency and depth of inhalation (Iversen, 2000). THC or cannabis extracts can also be taken orally in fat-containing foods or dissolved in a suitable pharmaceutical oil, but absorption is delayed and variable (Iversen, 2000). A series of man-made synthetic cannabinoids, some of which are more potent and more water soluble than THC, is also available (Pertwee, 1999) (Fig. 1). All of these compounds act as agonists at the CB_1 cannabinoid receptor (Matsuda *et al.*, 1990), which is the only one known to be expressed in the brain. A second cannabinoid receptor, CB_2, is expressed only in peripheral tissues, principally in the immune system (Munro *et al.*, 1993; Felder and Glass, 1998; Pertwee, 1999). THC and the synthetic cannabinoids also act to some extent as agonists at the CB_2 receptor. Both cannabinoid receptors are members of the G-protein coupled class, and their activation is linked to inhibition of adenylate cyclase activity (Howlett *et al.*, 1988). A series of synthetic drugs is also now available that act as specific antagonists at CB_1 or CB_2 receptors (D'Souza and Kosten, 2001). One of these compounds, rimonabant(SR141716A), which acts selectively to block CB_1 receptors (Rinaldi-Carmona *et al.*, 1994; Compton *et al.*, 1996), has been widely used in studies of the actions of cannabinoids in the CNS (Fig. 2).

Endogenous cannabinoids

Following the discovery of specific cannabinoid receptors, a search was made for naturally occurring ligands of these receptors in mammalian tissues. This led to the discovery of a series of arachidonic acid derivatives with potent actions at cannabinoid receptors. These are: anandamide (*N*-arachidonyl-ethanolamine; Devane *et al.*, 1992), 2-arachidonylglycerol (2-AG; Mechoulam *et al.*, 1995; Sugiura *et al.*, 1995; Stella *et al.*, 1997) and 2-arachidonylglyceryl ether (Hanuš *et al.*, 2001) (Fig. 1). Of these, anandamide is the ligand that has been most extensively studied so far. The endogenous cannabinoids known as 'endocannabinoids' are present only in small amounts in the brain or other tissues. Like other lipid mediators (e.g. prostaglandins) they appear to be synthesized and released locally on demand (see below). Anandamide and the other endogenous cannabinoids are rapidly inactivated by a combination of a transporter mechanism and by the enzyme fatty acid amide hydrolase (FAAH) (Di Marzo *et al.*, 1994; Piomelli *et al.*, 1998; Giuffrida *et al.*, 2001). Genetically engineered mice lacking FAAH displayed elevated levels of anandamide in brain and were supersensitive to the biological actions of anandamide (Cravatt *et al.*, 2001). The discovery of agents that could interfere with the inactivation of endogenous cannabinoids may provide a novel means of pharmaco-



Fig. 3 Distribution of cannabinoid CB_1 receptors in rat brain revealed by an autoradiograph of the binding of radioactively labeled CP-55940 (a high affinity agonist ligand) to a sagittal brain section. The brain regions labelled are: Cb = cerebellum; CbN = deep cerebellar nucleus; cc = corpus callosum; EP = entopeduncular nucleus; fi = fimbria hippocampus; Fr = frontal cortex; FrPaM = frontoparietal cortex motor area; GP = globus pallidus; Hi = hippocampus; IC = inferior colliculus; LP = lateral posterior thalamus; Me = medial amygdaloid nucleus; PO = primary olfactory cortex; PCRt = parvocellular reticular nucleus; SNR = substantia nigra reticulate; Tu = olfactory tubercle; VP = ventroposterior thalamus. Photograph kindly supplied by Dr Miles Herkenham, National Institute of Mental Health, USA.

logically modifying cannabinoid function in the brain (Piomelli *et al.*, 2000).

Neuroanatomical distribution of CB_1 receptors in brain

The distribution of cannabinoid receptors was first mapped in rat brain in autoradiographic studies, using the radioligand [H^3]CP-55,940, which binds with high affinity to CB_1 sites (Herkenham *et al.*, 1991) (Fig. 3). The validity of using this radioligand was confirmed by autoradiographic studies in CB_1 receptor knockout mice, in which no detectable [H^3]CP-55,940 binding sites were observed (Zimmer *et al.*, 1999). More recently, antibodies that target the C- or N-terminal regions of the CB_1 receptor protein have been used for immunohistochemical mapping studies (Egertová *et al.*, 1998; Pettit *et al.*, 1998; Egertová and Elphick, 2000). Immunohistochemistry provides a superior degree of spatial resolution to autoradiography, but the overall pattern of distribution of CB_1 receptors revealed by the two approaches is very similar (Elphick and Egertová, 2001).

The mapping studies in rat brain showed that CB_1 receptors are mainly localized to axons and nerve terminals and are largely absent from the neuronal soma or dendrites. The finding that cannabinoid receptors are predominantly presynaptic rather than postsynaptic is consistent with the postulated role of cannabinoids in modulating neurotransmitter release (see below).

In both animals and man the cerebral cortex, particularly frontal regions, contains high densities of CB_1 receptors. There are also very high densities in the basal ganglia and in the cerebellum (Fig. 3). In the limbic forebrain CB_1 receptors are found particularly in the hypothalamus and in the anterior cingulate cortex. The hippocampus also contains a high density of CB_1 receptors. The relative absence of the cannabinoid receptors from brainstem nuclei may account for the low toxicity of cannabinoids when given in overdose.

The regional distribution of the CB_1 receptor in brain correlates only poorly with the levels of anandamide and other endocannabinoids in different brain regions (Felder *et al.*, 1996; Bisogno *et al.*, 1999). However, measurements of endocannabinoids have yielded variable results, and a strict correlation would not be expected for ligands that are only produced on demand. There is a better correlation between the regional distribution of CB_1 receptors and the enzyme FAAH. FAAH is widely distributed in CNS and other tissues, suggesting that its role is not confined to inactivating endogenous cannabinoids. Nevertheless, particularly high levels of FAAH were found in brain regions that are enriched in CB_1 receptors, and immunohistochemical staining suggested a complementary relationship between FAAH and CB_1 receptors at the synaptic level (Egertová *et al.*, 1998; Elphick and Egertová, 2001). In cerebellum, hippocampus and neocortex FAAH was expressed at high levels in the somato-dendritic regions of neurons that were postsynaptic to CB_1-positive axon terminals. The close and complementary relationship between CB_1 receptors and FAAH led to the hypothesis that FAAH may participate in the inactivation of endogenous cannabinoids released locally at synapses

(Elphick and Egertová, 2001). These authors postulated a retrograde cannabinoid signalling mechanism, whereby endogenous cannabinoids are released in response to synaptic activation, feedback to presynaptic receptors on these axon terminals, and are subsequently inactivated by FAAH after their uptake into the postsynaptic compartment. This hypothesis has been supported independently by neurophysiological findings, as described below.

Effects of cannabinoids on synaptic function

Inhibition of neurotransmitter release

The presynaptic localization of CB_1 receptors suggests a role for cannabinoids in modulating the release of neurotransmitters from axon terminals, and this has been confirmed by a substantial body of experimental data. Early reports (Gill *et al.*, 1970; Roth, 1978) showed that THC inhibited acetylcholine release from electrically stimulated guinea pig ileum. Similar inhibitory effects of THC and other cannabinoids on the release of a variety of neurotransmitters from CNS neurons have been observed in many subsequent studies (Schlicker and Kathmann, 2001). The neurotransmitters involved include L-glutamate, GABA, noradrenaline, dopamine, 5-HT and acetylcholine. The brain regions most often studied *in vitro*, usually in tissue slice preparations, have been cerebellum, hippocampus or neocortex. Neurotransmitter release has been studied directly in superfused preparations, and indirectly by measuring postsynaptic currents. Although most of these studies involved rat or mouse brain, a few studies have shown similar results using human brain tissue (Katona *et al.*, 2000; Schlicker and Kathmann, 2001). Because THC is only poorly water soluble, the more soluble synthetic CB_1 receptor agonists WIN552123, HU210 or CP55-2940 were used in these *in vitro* studies. The specificity of the cannabinoid effects were confirmed by demonstrating that the inhibitory effects of the agonists were completely blocked by the CB_1-selective antagonist rimonabant.

The cellular mechanisms involved in the inhibition of neurotransmitter release by cannabinoids remain unclear. Some have suggested that there is a direct inhibitory effect of CB_1 receptor activation on N-type Ca^{2+} currents (Caulfield and Brown, 1992; MacKie and Hill, 1992). However, the effect appears more likely to involve sites downstream of voltage-dependent Ca^{2+} channels, since a number of studies have shown that cannabinoids reduce the frequencies of miniature excitatory or inhibitory synaptic currents, which are Ca^{2+} independent, rather than altering their amplitude, which is Ca^{2+} sensitive (Schlicker and Kathmann, 2001). Deadwyler *et al.* (1995) suggested that the inhibitory effect of CB_1 receptor activation on adenylate cyclase activity causes a decreased phosphorylation of A-type K^+ channels by the cAMP-dependent enzyme protein kinase A. This, in turn, would activate the A-type K^+ channels and cause a shortening of the duration of presynaptic action potentials as they invade axon terminals.

Biosynthesis of endocannabinoids

Despite their similar chemical structures, the endocannabinoids are produced through distinct biochemical pathways. The formation of anandamide is thought to result from the hydrolysis of the precursor *N*-arachidonoyl phophatidylethanolamine, catalysed by the phosphodiesterase enzyme phospholipase D (Di Marzo *et al.*, 1994; Cadas *et al.*, 1997). 2-AG, on the other hand, is produced by cleavage of an inositol-1,2-diacylglycerol, catalysed by phospholipase C. Although both anandamide and 2-AG can activate CB_1 receptors, it is not clear whether both function as endocannabinoids, and whether their synthesis and release are independently controlled. The levels of 2-AG found in brain (2–10 nmol/g) are 50–1000 times higher than those of anandamide (10–50 pmol/g). There is some evidence for separate control of their biosynthesis. Stimulation of glutamate release from Schaffer collaterals in rat hippocampal slices increased levels of 2-AG, but not anandamide (Stella *et al.*, 1997). On the other hand, another study using *in vivo* microdialysis probes showed that local administration of the dopamine D2 receptor agonist quinpirole caused an increased release of anandamide from rat striatum without affecting levels of 2-AG (Giuffrida *et al.*, 1999). Indeed, despite the much higher tissue levels of 2-AG relative to anandamide and the availability of a very sensitive assay, no 2-AG could be detected at all in the striatal dialysate samples. In cultured rat cortical neurons activation of Ca^{2+} influx by stimulation of glutamate *N*-methyl-D-aspartate (NMDA) receptors caused an increase in 2-AG formation but not anandamide (Stella and Piomelli, 2001). However, if NMDA activation was combined with a cholinergic agonist (carbachol) the formation of both endocannabinoids was increased. In both cases Ca^{2+} influx was required for endocannabinoid synthesis. It is clear that much remains to be learned about the relative roles played by the different endocannabinoids. The biosynthesis of the most recently discovered third endocannabinoid, 2-arachidonylglyceryl ether, remains to be characterized.

Endogenous cannabinoids act as retrograde signal molecules at synapses

Important new insights into the physiological role of cannabinoids has emerged from neurophysiological studies published independently by three different research groups in 2001. A phenomenon known as depolarization-induced suppression of inhibition (DSI) has been known to neurophysiologists for some years (Alger and Pitler, 1995). It is a form of fast retrograde signalling from postsynaptic neurons back to inhibitory cells that innervate them, and is particularly prominent in the hippocampus and cerebellum. Three prop-

erties of DSI suggested to Wilson and Nicoll (2001) that a cannabinoid mechanism might be involved. First DSI, like endocannabinoid synthesis, requires Ca^{2+} influx into the postsynaptic neuron (Lenz *et al.*, 1998). Secondly, DSI is probably presynaptic, since the sensitivity of the postsynaptic cell to GALA is unaffected (Pitler and Alger, 1992). Finally, DSI is blocked by pertussin toxin, which interacts with the Gi-proteins negatively linked adenylate cyclase or to inositol phosphates (Gi/o) protein to which the CB_1 receptor is coupled (Pitler and Alger, 1994). Wilson and Nicoll (2001) used slice preparations of rat hippocampus and induced DSI by brief depolarizing steps in the holding potential of voltage clamped CA1 pyramidal neurons. They found that DSI was completely blocked by the cannabinoid CB_1 receptor antagonists AM251 or rimonabant and could be mimicked by application of the CB_1 receptor agonist WIN55,2122, but the continued presence of the agonist prevented DSI by occlusion. Wilson and Nicoll (2001) were also able to show by recording from pairs of nearby CA1 neurons that depolarizing one of these neurons caused DSI to spread and affect adjacent neurons up to 20 μm away. They suggested that the small, lipid-soluble, freely diffusible endocannabinoids act as retrograde synaptic signals that can affect axon terminals in sphere of influence some 40 μm in diameter.

Ohno-Shosaku *et al.* (2001) came to a similar conclusion using a different experimental paradigm. They recorded from pairs of cultured hippocampal neurons with inhibitory synaptic connections. They found that depolarization of the postsynaptic neurons lead to DSI in approximately two-thirds of the neuron pairs, and showed that this was due to inhibition of GABA release. Those that exhibited DSI, but not the others, proved to be sensitive to the CB_1 receptor agonist WIN55,2122, which mimicked the inhibitory effect of DSI. Both DSI and the cannabinoid effect could be blocked by the CB_1 receptor antagonists AM-281 or rimonabant.

Further support for the conclusion that a cannabinoid-mediated mechanism underlies DSI came from Varma *et al.* (2001), who found that DSI was completely absent in hippocampal slices prepared from CB_1 receptor knockout mice (Ledent *et al.*, 1999). Varma *et al.* (2001) also reported that agonists which stimulate metabotropic glutamate (mGlu) receptors enhanced DSI, whereas the broad-spectrum antagonist of mGlu receptors, LY341495, tended to reduce DSI, suggesting that glutamate may also be involved. Interestingly, Varma *et al.* (2001) found that mGlu agonists failed to have any effect on DSI in the CB_1 knockout animals, suggesting that glutamate acts to enhance the endocannabinoid signal.

Retrograde signalling by endocannabinoids is not restricted to the inhibitory inputs to postsynaptic neurons. Kreitzer and Regehr (2001*a*) showed that depolarization of rat cerebellar Purkinje cells leads to a transient inhibition of excitatory inputs from parallel fibre and climbing fibre inputs, a phenomenon described as depolarization-induced suppression of excitation (DSE). They found that DSE was triggered by Ca^{2+} influx into the Purkinje cells, and could be completely blocked by the CB_1 antagonist AM-251, and mimicked and occluded by the CB_1 receptor agonist WIN55,2122. Kreitzer and Regehr (2001*b*) went on to show that inhibitory inputs to rat cerebellar Purkinje cells from basket cells and stellate cells were subject to DSI, and that this was also blocked by AM-251 and occluded by WIN55,2122. The DSE phenomenon in the cerebellum is also linked to mGlu receptors. Maejima *et al.* (2001) reported that mGlu agonists acting on mouse Purkinje cells mimicked DSE, and the effects could be blocked by CB_1 antagonists.

These findings suggest that endocannabinoids are involved in the rapid modulation of synaptic transmission in CNS by a retrograde signalling system that can influence synapses in a local region of some 40 μm diameter, causing inhibitory effects on both excitatory and inhibitory neurotransmitter release that persist for tens of seconds. This may play an important role in the control of neural circuits, particularly in cerebellum and hippocampus (see below). Exogenously administered Δ^9-THC or other cannabinoids cannot mimic the physiological effects of locally released endocannabinoids. Since they cause long-lasting activation of CB_1 receptors in all brain regions, their overall effect is to cause a persistent inhibition of neurotransmitter release from those nerve terminals that express CB_1 receptors, and as a consequence they temporarily occlude and prevent the phenomena of DSI and DSE.

Effects of cannabinoids on CNS function

Psychomotor control

CB_1 receptors are expressed at particularly high densities in the basal ganglia and cerebellum, so it is not surprising that cannabinoids have complex effects on psychomotor function (reviewed by Rodriguez de Fonseca *et al.*, 1998). One of the earliest reports of the effects of cannabis extracts in experimental animals described the awkward swaying and rolling gait caused by the drug in dogs, with periods of intense activity provoked by tactile or auditory stimuli, and followed eventually by catalepsy and sleep (Dixon, 1899). In rodents cannabinoids tend to have a triphasic effect. Thus in rats low doses of THC (0.2 mg/kg) decreased locomotor activity, while higher doses (1–2 mg/kg) stimulated movements, and catalepsy emerged at doses of 2.5 mg/kg (Sañudo-Peña *et al.*, 2000). Similarly in mice, Adams and Martin (1996) described a 'popcorn effect' in animals treated with THC. Groups of mice are sedated by the drug, but will jump in response to auditory or tactile stimuli, as they fall into other animals these in turn jump, resembling corn popping in a popcorn machine. Interestingly, the CB_1 receptor antagonist rimonabant stimulated locomotor activity in mice, suggesting that there is tonic activity in the endocannabinoid system that contributes to the control of spontaneous levels of activity (Compton *et al.*, 1996).

These effects of cannabinoids may be due, in part, to actions at cerebellar or striatal receptors. Patel and Hillard (2001) used tests of specific cerebellar functions to show that

cannabinoids caused increased gait width and the number of slips on a bar cross test. DeSanty and Dar (2001) observed rotorod impairments in mice after direct injection of synthetic cannabinoids into the cerebellum. These defects were no longer seen in animals pretreated with cerebellar injections of an antisense olgonucleotide directed to a sequence in the CB_1 receptor.

In human subjects it is also possible to demonstrate that cannabis causes impaired performance in test of balance (Greenberg *et al.*, 1994), or in tests that require fine psychomotor control, for example tracking a moving point of light on a screen (Manno *et al.*, 1970). Human cannabis users may also seek isolation and remain immobile for long periods.

A number of authors have attempted to combine what is known of the neuroanatomical distribution of the cannabinoid system and the results of behavioural and electrophysiological studies to speculate on the mechanisms underlying cannabinoid modulation of psychomotor function (Breivogel and Childers, 1998; Sañudo-Peña *et al.*, 1999; Giuffrida *et al.*, 2000; Elphick and Egertová, 2001). The CB_1 receptor is expressed particularly by striatal GABAergic medium-spiny projection neurons, and is abundant in regions containing the axon terminals of these cells (globus pallidus, entopeduncular nucleus and substantia nigra reticulata, and in axon collaterals feeding back to medium-spiny projection neurons in striatum). CB_1 receptors are also abundant on the terminals of glutamatergic projection neurons from the subthalamic nucleus to globus pallidus, entopeduncular nucleus and substantia nigra reticulata. Cannabinoids might thus be expected to inhibit GABA release in striatum and GABA and glutamate release in the other nuclei. Sañudo-Peña *et al.* (1999) suggested that the primary role of the endocannabinoid system may be to inhibit tonic release of glutamate in the substantia nigra, regulating levels of basal motor activity. Exogenous cannabinoids also lead to decreased GABA release in substantia nigra, which could lead to a disinhibition of the inhibitory nigral input to the thalamocortical pathway, resulting in inhibition of movement. To what extent the effects of cannabinoids on motor function are due to actions in the cerebellum remains unclear, although as described above it is likely that effects on posture and balance are mediated in this brain region. As described previously, CB_1 receptors are known to occur abundantly on nearly all of the principal excitatory (glutamatergic) and inhibitory (GABAergic) inputs to cerebellar Purkinje cells.

The results of eliminating the expression of CB_1 receptors in knockout mice have yielded conflicting results. The knockout animals studied by Zimmer *et al.* (1999) displayed reduced levels of basal activity, in support of the hypothesis put forward by Sañudo-Peña *et al.* (1999), suggesting that tonic activation of CB_1 receptors promotes movement. However, the CB_1 knockout animals studied by Ledent *et al.* (1999) showed no change in spontaneous activity, and in some tests they exhibited increased motor activity. This is in line also with the observations of Compton *et al.* (1996) that the CB_1 antagonist SR141716 caused an increase in locomotor activity. The reasons for the discrepant findings in different strains of CB_1 knockout mice are unknown. Clearly, there is as yet only a poor understanding of the actions of cannabinoids in the basal ganglia and cerebellum. Interactions with other chemical signalling systems in the brain are likely to be important. Giuffrida *et al.* (1999) showed, for example, that dopamine D2 receptor agonists caused an increase in anandamide synthesis and release in striatum. Deadwyler *et al.* (1995) described the convergence of multiple presynaptic controls on the terminals of granule cells in cerebellum. In addition to the CB_1 receptor, these terminals also express high densities of kappa opioid, adenosine A_1 and GABA-B receptors, all of which are coupled through a similar Gi/o type G-protein to inhibit adenylate cyclase and are capable of inhibiting glutamate release. Such complexities are likely to prove the norm.

There is anecdotal evidence that cannabis can relieve muscle pain and spasticity in patients suffering from multiple sclerosis (Consroe *et al.*, 1996). Experimental data obtained by Baker *et al.* (2000) in an animal model of multiple sclerosis appears to support such claims. Mice immunized with myelin antigens develop spasticity and tremor. Both symptoms were ameliorated by administration of cannabinoids, and the symptoms were exacerbated by rimonabant, suggesting the involvement of CB_1 receptors and tonic activity in the endocannabinoid system. Controlled clinical trials of cannabis-based medicines for the treatment of multiple sclerosis are currently under way.

Cannabinoid mechanisms in the hippocampus and effects on memory

One of the well established effects of acute intoxication with cannabis in man is an impairment of short-term memory (the extensive literature on human studies is reviewed by Jones, 1978; Miller and Branconnier, 1983; Solowij, 1998; Earleywine, 2002). Many studies have shown significant effects on short-term memory, particularly when tests were used that depend heavily on attention (Abel, 1971; Mendelson *et al.*, 1976). Animal studies have also found that THC, synthetic cannabinoids and anandamide cause deficits in short-term memory in spatial learning tasks (for a review see Hampson and Deadwyler, 1999). These include delayed matching or non-matching tests in rodents (Mallet and Beninger, 1998; Hampson and Deadwyler, 1999), performance in a radial arm maze (Stiglick and Kalant, 1985; Lichtman and Martin, 1996), and a fixed ratio food acquisition task in squirrel monkeys (Nakamura-Palacios *et al.*, 2000). The effects of both cannabinoids (Lichtman and Martin, 1996) and anandamide (Mallet and Beninger, 1998) were reversed by rimonabant, indicating that they are mediated by the CB_1 receptor.

A probable site for these effects is the hippocampus. Hampson and Deadwyler (1999) claimed that the effects of the treatment of rats with cannabinoids on short-term memory in a delayed non-matching to sample test were equivalent to the effects seen after surgical removal of the hippocampus. In each case the animals were unable to segregate information between trials in the task because of disruptions to the processing of sensory information in hippocampal circuits. CB_1 receptors are expressed at high densities in the hippocampus. They are particularly abundant on the terminals of a sub-set of GABAergic basket cell interneurons, which also contain the neuropeptide cholecystokinin (Katona *et al.*, 1999), and this is also the case in human hippocampus (Katona *et al.*, 2000). These are presumably the GABAergic neurons involved in the endocannabinoid-mediated DSI phenomenon described above. The terminals of these cells surround large pyramidal neuron somata in the CA1–CA4 fields. GABAergic neurons in the dentate gyrus also express CB_1 receptors, with terminals concentrated at the boundary of the molecular and granule cell layers (Egertová and Elphick, 2000). In addition CB_1 receptors are expressed, at a lower level, in the glutamatergic pyramidal cells and their terminals. Cannabinoids can thus inhibit both the release of GABA and glutamate in hippocampal circuits.

The mechanisms underlying synaptic plasticity have been studied more intensely in the hippocampus than in any other brain region. In particular, the electrophysiological phenomena of long-term potentiation (LTP) and long-term depression (LTD) are thought to be involved in memory formation at glutamatergic synapses in the hippocampus. A number of studies have shown clearly that cannabinoids inhibit the induction of both LTP and LTD (for review see Elphick and Egertová, 2001). Cannabinoids appear to work by reducing glutamate release below the level needed to activate NMDA receptors, a requirement for LTP and LTD (Shen *et al.*, 1996; Misner and Sullivan, 1999). Although the actions of cannabinoids in reducing GABA release from hippocampal interneurons might have been expected to increase the level of excitability of hippocampal pyramidal cells, it seems that the cannabinoid-induced reduction in glutamate release predominates. The administration of exogenous cannabinoids is, of course, wholly unphysiological and cannot mimic the effects of endocabinnoids that are released in discrete local regions in response to particular patterns of afferent inputs. CB_1 receptors are capable of regulating both inhibitory and excitatory neurotransmitter release in the hippocampus and are thus capable of subtle control of synaptic plasticity. The CB_1-containing GABergic interneurons are thought to control oscillatory electrical activity in the hippocampus in the theta and gamma frequencies, which plays a role in synchronizing pyramidal cell activity (Hoffman and Lupica, 2000). CB_1 agonists decrease the power of such oscillations in hippocampal slices (Hájos *et al.*, 2000) and may thus influence the synchronous activity of pyramidal cells. The physiological importance of cannabinoid-mediated DSI may be to decrease GABAergic inhibition of these cells and thus facilitate learning when hippocampal inputs are active (Wilson and Nicoll, 2001).

One approach to answering the question of what role the tonic release of endocannabinoids may play in hippocampal function has been to examine the effects of CB_1 receptor knockout or of selective CB_1 receptor antagonists. Unfortunately, these studies have so far yielded conflicting results. Bohme *et al.* (2000) reported a significant enhancement of LTP in CB_1 knockout mice, and Reibaud *et al.* (1999) found a significant enhancement of memory in such animals. However, tests with the CB_1 antagonist rimonabant showed no effects on LTP (Terranova *et al.*, 1995) or on learning and memory in a spatial learning task (Mallet and Beninger, 1998), although Terranova *et al.* (1996) reported that rimonabant enhanced memory in a short-term olfactory memory test in rats (social recognition test).

Cannabinoids and the neocortex

Like other intoxicant drugs cannabis causes profound changes in a variety of higher brain functions. The literature on the acute effects of the drug in human subjects is large, and can only be summarized here (for reviews see Jones, 1978; Solowij, 1998; Iversen, 2000; Earleywine, 2002). The distribution of CB_1 receptors in the neocortex has been described in detail (Herkenham *et al.*, 1991; Egertová and Elphick, 2000). As in the hippocampus, the majority of cortical interneurons expressing high levels of CB_1 receptor are GABAergic cells, which also express cholecystokinin (Marsicano and Lutz, 1999). CB_1-positive terminals are concentrated in layers II–III and layers V–VI, with few in layers I or IV. Despite the obvious importance of the abundant CB_1 receptors in the neocortex there have so far been few electrophysiological studies of their effects on neural activity.

The earlier literature, however, contains several reports of the effects of acute and chronic cannabis use on EEG activity, both in man and animals (reviewed by Adams and Martin, 1996; Solowij, 1998). Most studies in man have observed changes consistent with a state of drowsiness, with increases in relative and absolute α power particularly in frontal regions of cortex. In contrast, the CB_1 antagonist rimonabant was shown to induce EEG changes characteristic of arousal in rats, and increased the time spent in wakefulness as opposed to sleep (Santucci *et al.*, 1996). Mechoulam *et al.* (1997) have suggested that anandamide may play a role in the control of the sleep–waking cycle.

Studies of the effects of cannabis on perceptual abilities have yielded a variety of often conflicting results. While users often report a subjective enhancement of visual and auditory perception, sometimes with synesthesia (sounds take on visual colourful qualities), laboratory studies have usually not shown marked changes in visual or auditory perception. One subjective effect that has been confirmed is the sensation that cannabis users experience time as passing more quickly relative to real time. In laboratory tests subjects overestimate

the amount of elapsed time when asked to estimate, or produce shorter than required intervals when asked to signal a period of elapsed time (Hicks *et al.*, 1984; Mathew *et al.*, 1998). This curious effect can also be seen in rats trained to respond for food reward using a fixed interval schedule. When treated with THC or WIN55,2122 the animals shortened their response interval, whereas the antagonist rimonabant lengthened this interval (Han and Robinson, 2001).

There have been many studies of the acute and chronic effects of cannabis on human cognitive function (Jones, 1978; Solowij, 1998; Earleywine, 2002). Performance on a variety of tests of cognitive function is impaired by the drug, but by comparison with alcohol the effects of cannabis are subtle. Whereas even moderate doses of alcohol, for example, impair reaction time, most studies with cannabis have failed to show consistent effects on measures of simple reaction time. Thus the drug's ability to disrupt cognitive function cannot be due to an inability to respond promptly. Among the impairments of cognitive function that have been observed in many, but not all, human studies are: decreased ability to inhibit responses, decreased vigilance, especially for long and boring tasks, decreased ability to perform complex mental arithmetic and impairments in tests of complex reaction times. On the other hand, intoxicated subjects can perform simple arithmetic, learn simple lists of words and recall memories laid down earlier.

Other studies have addressed the question of whether more severe deficits in cognitive function might develop in chronic heavy users of cannabis, or in animals treated for prolonged periods with the drug. The human studies are fraught with difficulties, as described in detail by Earleywine (2002). Among the confounding factors in human studies are that comparisons have to be made between groups of drug users versus non-users, but it is usually impossible to compare the baseline performance of these groups prior to cannabis use to see if they are properly matched. Statistical analysis of such data has often been poor, common errors being the use of so many different tests that the likelihood of finding some significant differences is increased, or the use of inadequate sample sizes. Other drug use can also confound the data. Results have been very variable. Some studies in long-term very heavy users of cannabis (10–20 joints per day for more than 10 years) in Jamaica (Bowman and Pihl, 1973) and Costa Rica (Satz *et al.*, 1976) failed to show any significant difference between users versus non-users using a battery of test assessments of cognitive function, and similar negative results were reported in some studies of US college students (Earleywine, 2002). However, most reports have shown that there are deficits in the performance of complex cognitive tasks in long-term cannabis users, although there is little evidence that these are qualitatively or quantitatively more severe than those seen after acute use of the drug (Earleywine, 2002).

Even more controversial is the question of whether long-term cannabis use can cause irreversible deficits in higher brain function that persists after drug use stops. Many studies have suffered from poor design. It is not sufficient to identify a group of cannabis users and simply to test them after stopping cannabis use. Pope *et al.* (2001), for example, recruited 63 current heavy users, who had smoked cannabis at least 5000 times in their lives, and 72 control subjects. Subjects underwent a 28-day washout from cannabis use, monitored by urine assays. At days 0, 1 and 7 the heavy users scored significantly below control subjects on a battery of neuropsychological tests, particularly in recall of word lists. However, by day 28 there were virtually no differences between the groups on any of the test results, and no significant association between cumulative lifetime cannabis use and test scores. The fact that drug-induced effects on cognitive performance can persist for up to a week after stopping the drug (perhaps because of the persistence of THC in the body, or because of a subtle withdrawal syndrome) means that many earlier studies that did not allow a sufficiently long washout period may be invalid. On the other hand, some well designed studies have shown subtle persistent cognitive deficits in ex-cannabis users. Solowij (1998) recruited a group of people who had used cannabis regularly for at least 5 years but who had stopped on average 2 years before the experiment. The subjects were given a very difficult task. They had to listen to a series of tones, some in the right ear some in the left; the tones were long or short (but differing by only 51 ms) and high or low pitch (but differing very little). Participants had to press a button as fast as possible in response to longer tones of a specified pitch in the correct ear. Previous research using this paradigm showed that current regular cannabis users had difficulty in discriminating between the tones. Measurements of event-related potentials also revealed small but significant abnormalities in the P300 wave (Solowij, 1998). The ex-users continued to make significant errors in the discrimination task, but they showed normal P300 waves. The conclusion of these and many other studies in ex-users seems to be that regular cannabis use can cause small but significant impairments in cognitive function that may persist after drug use stops. Such impairments appear to be associated with long-term heavy use of the drug and are unlikely to affect most recreational users.

Effects of cannabinoids on hypothalamic control of appetite

Many subjective reports suggest that cannabis intoxication is associated with an increased appetite, particularly for sweet foods, even in subjects who were previously satiated. This effect can be confirmed under laboratory conditions (Hollister, 1971; Mattes *et al.*, 1994), although results from studies in human subjects have tended to be variable, perhaps because the increased appetite is focused on certain types of food. Nevertheless, controlled clinical trials showed that THC (dronabinol) had significant beneficial effects in counteracting the loss of appetite and reduction in body weight in patients suffering from the AIDS-related wasting syndrome (Beal *et al.*, 1995), and this is one of the medical indications for which the drug has official approval in the USA.

THC also stimulates food intake in experimental animals, and again the effect is specific for high-fat or sweet high-fat diets, and is not seen in animals offered standard rat chow (Koch, 2001). The endocannabinoid anandamide also stimulates food intake in rats, and the effect is blocked by rimonabant (Williams and Kirkham, 1999). Conversely the CB_1 antagonist rimonabant given on its own suppressed food intake and led to reduced body weight in adult non-obese rats (Colombo *et al.*, 1998). These results suggest that cannabinoids may play a role in the regulation of food intake and body weight (Mechoulam and Fride, 2001). A possible reciprocal link between endocannabinoid mechanisms and the appetite-suppressing hormone leptin was suggested by Di Marzo *et al.* (2001*a*). They found that food-deprived CB_1 receptor knockout mice eat less than their wild-type litter mates, and the CB_1 antagonist rimonabant reduced food intake in the wild-type animals but not in the knockouts. Animals with defective leptin signalling (obese db/db or ob/ob mice and Zucker rats) exhibited elevated hypothalamic levels of anandamide and 2-AG. On the other hand, treatment of normal rats or ob/ob (leptin deficient) mice with leptin caused decreases in hypothalamic levels of the endocannabinoids. These findings suggest that hypothalamic endocannabinoids may play an important role in mediating the appetite-suppressant effects of leptin. At some stages during development these effects of endocannabinoids may be of critical importance. Fride *et al.* (2001) found that administration of the CB_1 antagonist rimonabant to new-born mouse pups had a devastating effect in decreasing milk ingestion and growth, continuing treatment with the antagonist led to death within 4–8 days. The effect of rimonabant could be almost fully reversed by co-administering THC.

Cannabinoids as anti-emetic agents

The ability of THC and the synthetic cannabinoid nabilone to control the nausea and vomiting associated with cancer chemotherapy is one of the few well documented medical applications for these drugs (for reviews of the controlled clinical trials see Vincent *et al.*, 1983; British Medical Association, 1997; Joy *et al.*, 1999; and the meta-analysis reported by Tramèr *et al.*, 2001). THC (dronabinol) and nabilone were approved for medical use in the USA, although neither drug has found much utility. The narrow window between the anti-emetic dose and that causing unwanted psychic effects made these drugs difficult to use. The advent of serotonin 5-HT_3 receptor antagonists as new and more powerful anti-emetic drugs that were free of unwanted psychic effects during the 1980s also made the cannabinoids less attractive.

Studies in experimental animals have confirmed that the anti-emetic effects of cannabinoids are mediated through CB_1 receptors (Darmani, 2002), and in some susceptible species (e.g. the least shrew) the CB_1 antagonist rimonabant is emetic, an effect that can be blocked by THC or WIN55,2122 (Darmani, 2001).

Cannabinoids and pain

Cannabis was widely used in 19th century medicine for pain relief and there is renewed interest in cannabis-based medicines, with pain as one of the key therapeutic targets (British Medical Association, 1997; Joy *et al.*, 1999). Endogenous cannabinoids and cannabinoid receptors exist at various levels in the pain pathways, from peripheral sensory nerve endings to spinal cord and supraspinal centres, in a system that is parallel to but distinct from that involving endorphins and opiate receptors.

Systemically administered THC and synthetic cannabinoids have anti-nociceptive and anti-hyperalgesic effects in a variety of animal models of acute and inflammatory pain (for reviews see Pertwee, 2001; Iversen and Chapman, 2002). Since cannabinoids inhibit motor activity this could prevent animals from exhibiting the normal behavioural reactions in analgesic tests; however, a number of studies have also shown that cannabinoids suppress electrophysiological responses of spinal cord neurons to noxious stimulation, and block spinal c-fos expression in response to such stimulation (Walker *et al.*, 1999; Pertwee, 2001; Iversen and Chapman, 2002). Cannabinoids and anandamide also exert anti-nociceptive effects in animal models of inflammatory pain when injected directly into spinal cord, brain stem or thalamus (Pertwee, 2001). Behavioural studies have shown that cannabinoids reduce thermal and mechanical allodynia in rat models of neuropathic pain (Herzberg *et al.*, 1997; Fox *et al.*, 2001; Iversen and Chapman, 2002). Furthermore, noxious stimulation evoked an increased release of anandamide in the periaqueductal grey region of brainstem, a key site for modulating nociceptive information (Walker *et al.*, 1999). The anti-nociceptive effects of cannabinoids are blocked by the CB_1 antagonist rimonabant, but the antagonist itself does not alter basal pain thresholds, suggesting that these are not controlled by tonic activity in the endocannabinoid system (Compton *et al.*, 1996).

Results obtained with CB_1 receptor knockout mice, however, suggest that not all of the anti-nociceptive effects of THC or anandamide are mediated via CB_1 receptors. Thus, although Di Marzo *et al.* (2000) found that the anti-nociceptive effects of THC were virtually absent in the knockout animals, anandamide continued to show analgesic activity in the hot-plate test. It is possible that the analgesic effects of anandamide are mediated in part through an action at other as yet ill-defined cannabinoid receptors (Breivogel *et al.*, 2001; Hájos *et al.*, 2001). Alternatively, it has been proposed that the effects of anandamide might be mediated through its ability to bind to the vanilloid VR1 receptor, which is present in primary afferent neurons and known to play an important role in nociceptive responses (Di Marzo *et al.*, 2001*b*). To complicate matters further, Zimmer *et al.* (1999), in a different strain of CB_1 receptor knockout mice, found that THC continued to exert some anti-nociceptive actions in hot-plate and formalin tests in the knockout animals. The reasons for the discrepant results obtained

with different strains of CB_1 receptor knockout mice are unknown.

There is evidence for an interaction between cannabinoid and opioid mechanisms. In tests of acute pain (Fuentes *et al.*, 1999) and chronic inflammatory pain (Welch and Stevens, 1992; Smith *et al.*, 1998) THC and morphine acted synergically—one potentiated the anti-nociceptive actions of the other. This potentiation could be blocked by either rimonabant or by naloxone, indicating that both CB_1 and opiate receptors were involved (Fuentes *et al.*, 1999). Meng *et al.* (1998) showed that temporary inactivation of neural activity in the rostral ventromedial medulla (RVM) in rat brainstem prevented the analgesic effects of systemically administered cannabinoids, while leaving their effects on motor activity unaffected. An electrophysiological analysis of the effects of cannabinoids on single cell firing patterns in RVM revealed that the effects of cannabinoids were similar to those elicited by morphine. The authors concluded that cannabinoids may produce analgesia through activation of a brainstem circuit that is also required for opiate analgesia, although the two mechanisms are pharmacologically distinct.

Basic research into the role of cannabinoids and endocannabinoids in pain mechanisms is progressing rapidly. Clinical progress, however, has been slow. A meta-analysis of clinical trials of cannabinoids as analgesics concluded that there was not enough evidence to justify their use in this indication (Campbell *et al.*, 2001). However, this may merely reflect the paucity of data from adequately sized controlled clinical trials, and cannabis-based medicines may yet find genuine medical applications in this field.

Cannabis as an intoxicant and drug of dependence

Cannabis intoxication

Despite being illegal, cannabis is one of the most widely used intoxicants; almost half of all 18 year olds in the USA and in most European countries admit to having tried it at least once, and ~10% of that age group are regular users (Iversen, 2000). There have been many subjective accounts of the cannabis 'high' (see Iversen, 2000; Earleywine, 2002). The experience is highly variable, depending on the dose of drug, the environment and the experience and expectations of the drug user. A typical 'high' is preceded initially by a transient stage of tingling sensations felt in the body and head accompanied by a feeling of dizziness or lightheadedness. The 'high' is a complex experience, characterized by a quickening of mental associations and a sharpened sense of humour, sometimes described as a state of 'fatuous euphoria'. The user feels relaxed and calm, in a dreamlike state disconnected from real world. The intoxicated subject often has difficulty in carrying on a coherent conversation, and may drift into daydreams and fantasies. Drowsiness and sleep may eventually ensue. The feelings of heightened perception, increased appetite and distortion of the sense of time have already been referred to. A survey of 1333 young British cannabis users (Atha and Blanchard, 1997) reported that the most common positive benefits reported were relaxation and relief from stress (25.6%), insight/personal development (8.7%) and euphoria (4.9%); more than half reported some positive benefits. But 21% of the users also attributed some adverse effects to cannabis use, including impaired memory (6.1%), paranoia (5.6%) and amotivation/laziness (4.8%).

As with other intoxicant drugs, little is known about the brain mechanisms that underlie the cannabis 'high'. The intoxicant effects are clearly mediated via CB_1 receptors. Huestis *et al.* (2001) carried out a well controlled study in 63 healthy cannabis users, who received either rimonabant or placebo and smoked either a THC-containing or placebo marijuana cigarette. The CB_1 antagonist blocked the acute psychological effects of the active cigarettes. Interestingly rimonabant itself when given alone (with placebo cigarette) produced no significant psychological effects. Mathew *et al.* (1997) used $H_2{}^{15}O$ and PET to measure changes in regional cerebral blood flow in a double blinded study in 32 volunteers comparing THC with placebo. Self ratings of cannabis intoxication correlated most markedly with increased blood flow in the right frontal region.

Endocannabinoids and CB_1 receptors are present in many regions of the limbic forebrain. For example, Katona *et al.* (2001) reported that CB_1 receptors were expressed in high densities in lateral and basal nuclei in the rat amygdala. As in hippocampus, the CB_1 receptors in these regions were located presynaptically on the terminals of cholecystokinin-containing GABAergic interneurons. Electrophysiological experiments showed that cannabinoids modulated GABAergic synaptic transmission. The authors suggested that such effects might underlie some of the actions of cannabinoids on emotional behaviour. Other experiments have revealed that, in common with other euphoriant drugs, THC selectively activates dopaminergic neurons in the ventral tegmental area. In an electrophysiological study French *et al.* (1997) reported that low doses of THC increased the firing of these cells. Tanda *et al.* (1997) used microdialysis probes to show that low doses of THC (0.15 mg/kg intravenously) caused an increased release of dopamine from the shell region of the nucleus accumbens, an effect that is also seen after administration of heroin, cocaine, d-amphetamine and nicotine. Tanda *et al.* (1997) found that the increased release of dopamine provoked by THC could be blocked by administration of the μ-opiate receptor antagonist naloxonazine, suggesting the involvement of an opioid mechanism.

Tolerance and dependence

Many animal studies have shown that tolerance develops to most of the behavioural and physiological effects of THC (for review see Pertwee, 1991). The earlier clinical literature suggested that tolerance also occurs after repeated administration of THC in man, although many of these studies were poorly controlled (for reviews see Jones, 1978, 1987;

Hollister, 1986). But for many years cannabis was not considered to be a drug of addiction. Withdrawal of the drug did not lead to any obvious physical withdrawal symptoms either in people or in animals, and animals failed to self-administer the drug, a behaviour usually associated with drugs of addiction.

Attitudes have changed markedly in recent years. The DSM-IV (American Psychiatric Association, 1994) defines 'substance dependence' and 'substance abuse' rather than 'addiction'. When the DSM-IV criteria are applied to populations of regular cannabis users surprisingly high proportions appear to be positive by these definitions. Swift *et al.* (2001) undertook a survey of 10 641 Australians aged 18 years and older. They reported that almost one-third of regular cannabis users fell within the definitions of 'substance abuse' (10.7%) or 'substance dependence' (21%). In the USA, Anthony *et al.* (1994) reported the results obtained from a large scale survey which indicated that some 46% of those interviewed had ever used cannabis and 9% of users became dependent. More carefully controlled studies have also shown that a reliable and clinically significant withdrawal syndrome does occur in human cannabis users when the drug is withdrawn. The symptoms include craving for cannabis, decreased appetite, sleep difficulty and weight loss, and may sometimes be accompanied by anger, aggression, increased irritability, restlessness and strange dreams (Budney *et al.*, 2001).

The existence of dependence on cannabinoids in animals is also much more clearly observable because of the availability of CB_1 receptor antagonist drugs that can be used to precipitate withdrawal. Thus, Aceto *et al.* (1996) described a behavioural withdrawal syndrome precipitated by rimonabant in rats treated for only 4 days with doses of THC as low as 0.5–4.0 mg/kg per day. The syndrome included scratching, face rubbing, licking, wet dog shakes, arched back and ptosis—many of the same signs are seen in rats undergoing opiate withdrawal. Similar withdrawal signs could be elicited by rimonabant in rats treated chronically with the synthetic cannabinoids CP-55,940 (Rubino *et al.*, 1998) or WIN55,2122 (Aceto *et al.*, 2001). Rimonabant-induced withdrawal after 2 weeks of treatment of rats with the cannabinoid HU-120 was accompanied by marked elevations of release of the stress-related neuropeptide corticotropin-releasing factor in the amygdala, a result also seen in animals undergoing heroin withdrawal (Rodríguez de Fonseca *et al.*, 1997). An electrophysiological study showed that precipitated withdrawal was also associated with reduced firing of dopamine neurons in the ventral tegmental area of rat brain (Diana *et al.*, 1998). These data indicate clearly that chronic administration of cannabinoids leads to adaptive changes in the brain, some of which are similar to those seen with other drugs of dependence. The ability of THC to cause a selective release of dopamine from the nucleus accumbens (Tanda *et al.*, 1997) also suggests some similarity between THC and other drugs in this category.

Furthermore, although many earlier attempts to obtain reliable self-administration behaviour with THC were unsuccessful (Pertwee, 1991), some success has been achieved recently. Squirrel monkeys were trained to self-administer low doses of THC (2 μg/kg per injection), but only after the animals had first been trained to self-administer cocaine (Tanda *et al.*, 2000). THC is difficult to administer intravenously and these authors succeeded perhaps in part because they succeeded in delivering the drug intravenously in doses comparable to those to which human cannabis users are exposed. The potent synthetic cannabinoids are far more water soluble than THC, which makes intravenous administration easier. Mice could be trained to self-administer intravenous WIN 5,2122, but CB_1 receptor knockout animals failed to exhibit this behaviour (Ledent *et al.*, 1999). Another way of demonstrating the rewarding effects of drugs in animals is the conditioned place preference paradigm, in which an animal learns to approach an environment in which it had previously received a rewarding stimulus. Rats demonstrated a positive THC place preference after doses as low as 1 mg/kg (Lepore *et al.*, 1995).

A number of studies have suggested that there may be links between the development of dependence to cannabinoids and to opiates (Manzanares *et al.*, 1999). Some of the behavioural signs of rimonabant-induced withdrawal in THC treated rats can be mimicked by administration of the opiate antagonist naloxone (Kaymakçalan *et al.*, 1977). Conversely, the withdrawal syndrome precipitated by naloxone in morphine-dependent mice can be partly relieved by administration of THC (Hine *et al.*, 1975) or by endocannabinoids (Yamaguchi *et al.*, 2001). Rats treated chronically with the cannabinoid WIN55,2122 became sensitized to the behavioural effects of heroin (Pontieri *et al.*, 2001). Such interactions can also be demonstrated acutely. A synergy between cannabinoids and opiate analgesics has already been described above. THC also facilitated the anti-nociceptive effects of RB 101, an inhibitor of enkephalin inactivation (Valverde *et al.*, 2001). These authors found that acute administration of THC caused an increased release of Met-enkephalin into microdialysis probes placed into the rat nucleus accumbens.

The availability of receptor knockout animals has also helped to illustrate cannabinoid–opioid interactions. CB_1 receptor knockout mice exhibited greatly reduced morphine self-administration behaviour and less severe naloxone-induced withdrawal signs than in wild-type animals, although the anti-nociceptive actions of morphine were unaffected in the knockout animals (Ledent *et al.*, 1999). The rimonabant-precipitated withdrawal syndrome in THC-treated mice was significantly attenuated in animals with knockout of the pro-enkephalin gene (Valverde *et al.*, 2000). Knockout of the μ-opioid receptor also reduced rimonabant-induced withdrawal signs in THC-treated mice, and there was an attenuated naloxone withdrawal syndrome in morphine dependent CB_1 knockout mice (Lichtman *et al.*, 2001*a*, *b*).

These findings point clearly to interactions between the endogenous cannabinoid and opioid systems in CNS, although the neural circuitry involved remains unknown. Whether this relationship is relevant to the so-called 'gateway' theory is unclear. The US National Household survey of Drug Abuse (US Department of Health and Human Services,

1999) indicated that respondents aged 22 years or older who had started cannabis use before the age of 21 years were 24 times more likely than non-cannabis users to initiate use of hard drugs. But the proportion of cannabis users who progress in this way remains very small (~1% or less), and mathematical modelling using the Monte Carlo method suggested that the association between cannabis use and hard drug use need not be causal but could relate to some common predisposing factor, e.g. 'drug-use propensity' (Morral *et al.*, 2002).

Adverse effects of cannabis on the CNS

Is cannabis neurotoxic?

Although there have been claims that chronic cannabis use may permanently damage the brain, there is little scientific evidence to support these claims (for reviews see Dornbush *et al.*, 1976; Hollister, 1986, 1998; Zimmer and Morgan, 1997). As described above, some studies have revealed a modestly impaired ability to focus attention and filter out irrelevant information in ex-cannabis users (Solowij, 1998), but other studies failed to find any impairments in cognitive function (Pope *et al.*, 2001). There is little evidence that cannabis use impairs work performance or leads to an 'amotivational syndrome' (Dornbush *et al.*, 1976; Hollister, 1986; Abood and Martin, 1992), nor is there any convincing evidence for neuropathological changes in the brains of cannabis users (Hollister, 1986). The earlier studies have been complemented by the application of powerful modern neuroimaging methods. For example, an MRI study compared 18 current, frequent, young adult cannabis users with 13 comparable non-users and found no evidence of cerebral atrophy or regional changes in tissue volumes (Block *et al.*, 2000).

Animal studies have yielded conflicting results. Treatment of rats with high doses of THC given orally for 3 months (Scallet *et al.*, 1987) or subcutaneously for 8 months (Landfield *et al.*, 1988) was reported to lead to neural damage in the hippocampal CA3 zone, with shrunken neurons, reduced synaptic density and loss of cells. However, in another study the potent synthetic cannabinoid WIN55,2122 was administered twice daily (2 mg/kg) to rats and led to an apparent increase in hippocampal granule cell density, and increased dendritic length in the CA3 zone. In perhaps the most severe test of all, rats and mice were treated with THC 5 days each week for 2 years and no histopathological changes were observed in brain, even after 50 mg/kg/day (rats) or 250 mg/kg/day (mice) (Chan *et al.*, 1996). Although claims were made that exposure of a small number of rhesus monkeys to cannabis smoke led to ultrastructural changes in septum and hippocampus (Harper *et al.*, 1977; Heath *et al.*, 1980), subsequent larger scale studies failed to show any cannabis-induced histopathology in monkey brain (Scallet, 1991).

Studies of the effects of cannabinoids on neurons *in vitro* have also yielded inconsistent results. Exposure of rat cortical neurons to THC was reported to decrease their survival, with twice as many cells dead after 2 h exposure to 5 μM THC than in control cultures (Downer *et al.*, 2001). Concentrations of THC as low as 0.1 μM had a significant effect. The effects of THC were accompanied by release of cytochrome *c*, activation of caspase-3 and DNA fragmentation, suggesting an apoptotic mechanism. All of the effects of THC could be blocked by the antagonist AM-251 or by pertussis toxin, suggesting that they were mediated through CB_1 receptors. Toxic effects of THC have also been reported on hippocampal neurons in culture, with 50% cell death after 2 h exposure to 10 μM THC or after 5 days exposure to 1 μM drug (Chan *et al.*, 1998). The antagonist rimonabant blocked these effects, but not pertussis toxin. The authors proposed a toxic mechanism involving arachidonic acid release and formation of free radicals. However, other authors failed to observe any damage in rat cortical neurons exposed for up to 15 days to 1 μM THC, although they found that this concentration of THC killed rat C6 glioma cells, or human astrocytoma U373MG and mouse neuroblastoma N18TG12 cells (Sánchez *et al.*, 1998). In a remarkable study injections of THC into solid tumours of C6 glioma in rodent brain led to increased survival times, and a complete eradication of the tumours was evident in 20–35% of the treated animals (Galve-Roperh *et al.*, 2000). The anti-proliferative effects of cannabinoids has suggested a potential utility for such drugs in cancer treatment (Guzmán *et al.*, 2001).

Some studies have reported neuroprotective actions of cannabinoids. Administration of WIN55,2122 was found to reduce cerebral damage in rat hippocampus or cerebral cortex after global ischaemia or focal ischaemia models *in vivo* (Nagayama *et al.*, 1999). The endocannabinoid 2-AG protected against damage elicited by closed head injury in mouse brain, and the protective effects were blocked by rimonabant (Panikashvili *et al.*, 2001). THC had a similar effect *in vivo* in protecting against damage elicited by ouabain (Van der Stelt *et al.*, 2001). Rat hippocampal neurons in tissue culture were protected against glutamate-mediated damage by low concentrations of WIN55,2122 or CP-55,940 and these effects were mediated through CB_1 receptors (Shen and Thayer, 1998). But not all of these effects seem to require mediation via cannabinoid receptors. Nagayama *et al.* (1999) reported protective effects of WIN55,2122 that did not require either cannabinoid receptor in cortical neurons exposed to hypoxia, and similar findings were reported for the protective actions of anandamide and 2-AG in cortical neuron cultures (Sinor *et al.*, 2000). Both THC and cannabidiol, which is not active on cannabinoid receptors, protected rat cortical neurons against glutamate toxicity (Hampson *et al.*, 1998) and these effects, were also independent of CB_1 receptors. The authors suggested that the protective effects of THC in their studies might be due to the antioxidant properties of these polyphenolic molecules, which have redox potentials higher than those of known antioxidants (e.g. ascorbic acid).

The mixed reports of neurotoxic and neuroprotective effects of cannabinoids are confusing. While it may be possible to demonstrate neurotoxic actions after exposure of neurons to high concentrations of cannabinoids *in vitro*, there is little evidence for any significant neural damage *in vivo* after the administration of pharmacologically relevant doses of these drugs.

Cannabis and psychiatric illness

A temporary form of drug-induced psychosis can occur in some cannabis users. In some of the psychiatric literature this is referred to as 'cannabis psychosis' (or 'marijuana psychosis'). Research psychiatrists, particularly in Britain (Thomas, 1993; Hall and Degenhardt, 2000; Johns, 2001), have studied this condition carefully. It nearly always results from taking large doses of the drug, often in food or drink, and the condition may persist for some time, perhaps as the accumulated body load of THC is washed out. The acute toxic psychosis that is sometimes caused by cannabis can be sufficiently serious to lead to the subject being admitted to hospital, and the initial diagnosis can be confused with schizophrenia, since the patients may display some of the characteristic symptoms of schizophrenic illness. These include delusions of control (being under the control of some outside being or force), grandiose identity, persecution, thought insertion, auditory hallucinations (hearing sounds, usually non-verbal in nature), changed perception and blunting of the emotions. Not all symptoms will be seen in every patient, but there is a considerable similarity to paranoid schizophrenia. This has led some to propose a 'cannabinoid hypothesis of schizophrenia', suggesting that the symptoms of schizophrenic illness might be caused by an abnormal over-activity of endogenous cannabinoid mechanisms in the brain (Emrich *et al.*, 1997).

A number of studies have addressed the more contentious question of whether cannabis use can precipitate long-term psychiatric illness. The strongest evidence seemed to come from a study in Sweden that involved taking detailed medical records and information about the social background and drug-taking habits of 45 570 conscripts on entry to the Swedish army at age 18 years and following up of their subsequent medical history over a 15-year period (Andreasson *et al.*, 1987). A total of 4293 of the conscripts admitted having taken cannabis at least once, but the cannabis users accounted for a disproportionate number of the 246 cases of schizophrenic illness diagnosed in the overall group on follow-up. The relative risk of schizophrenia in those who had used cannabis was 2.4 times greater than in the non-users. In the small number of heavy users (who had taken the drug on more than 50 occasions) the relative risk of schizophrenia increased to 6.0. The authors concluded that cannabis was an independent risk factor for schizophrenia. There have been other similar reports (Mathers and Godse, 1992; Hall and Degenhardt, 2000; Johns, 2001). Hambrecht and Häfner (2000), for example, studied 232 patients in Germany with first-episode schizophrenia. They found that 13% of these had a history of cannabis use, a rate twice that of matched normal controls. At first viewing these findings seem convincing, but they do not prove any cause-and-effect relationship with cannabis. It may simply be that both cannabis use and schizophrenia are related to some common predisposing factor, such as personality. Indeed some psychologists and psychiatrists believe that they can identify psychological traits that are described as 'schizotypy' and which may predict an increased risk of developing clinical psychosis. Some studies in healthy adults have reported that those subjects who used cannabis scored higher on schizotypy scales than non-users (Williams *et al.*, 1996; Skosnik and Spatz, 2001). Half of the cannabis-using subjects in the original Swedish study had used cannabis more than 10 times and subsequently developed schizophrenia had also taken amphetamine, a drug known to be capable of inducing a schizophrenia-like psychosis. The cannabis users also came from deprived social backgrounds, another known risk factor of schizophrenia. More detailed follow-ups of some of the original Swedish cohort, however, claimed to have answered some of these criticisms (Andreasson *et al.*, 1989; Zammit *et al.*, 2002). In addition, further reports from New Zealand (Arseneault *et al.*, 2002; Fergusson *et al.*, 2003), Australia (Patton *et al.*, 2002) and France (Verdoux *et al.*, 2003) add weight to the hypothesis that the development of cannabis dependence in young people is associated with increased rates of psychiatric symptoms, both of psychosis and depression and anxiety (Patton *et al.*, 2002).

Nevertheless, the existence of a causative relationship between cannabis use and long-term psychotic illness remains unproven. If cannabis use did precipitate schizophrenia one might expect to have seen a large increase in the numbers of sufferers from this illness as cannabis use became more common in the West during the past 30 years. However, a detailed review of the epidemiological evidence up to 1990 appeared to show that this has not been the case (Thornicroft, 1990).

On the other hand, it is clear that cannabis can exacerbate the symptoms of existing psychotic illness. While schizophrenic patients seem to use cannabis and other psychoactive drugs as a form of 'self-medication', cannabis can make the key symptoms of delusions and hallucinations worse and it tends to counteract the anti-psychotic effects of the drugs used to treat the illness (Negrete *et al.*, 1986; Linzen *et al.*, 1994). On the other hand, one Swedish study reported that cannabis use made schizophrenic patients less withdrawn and more likely to speak (Peralta and Cuesta, 1992). It would seem prudent, nevertheless, to discourage the use of cannabis in patients with existing psychotic illness.

Conclusion

The discovery of the endocannabinoids and the availability of new pharmacological tools, together with the development of strains of genetically engineered knockout mice that lack

functional cannabinoid receptors, has revitalized the field of cannabis research in the past few years. The effects of administering THC or other cannabinoids can never simulate the highly localized function of the endocannabinoids, which appear to act as a fine control system to regulate neurotransmitter release at the synaptic level. There has been renewed interest in the potential therapeutic applications of cannabis-based medicines (British Medical Association, 1997; Joy *et al.*, 1999; Robson, 2001). THC or other cannabinoid agonists all suffer from the problem of a narrow therapeutic window between the desired clinical benefits and the unwanted psychic side-effects. It is possible that the pharmacological manipulation of the endocannabinoid system, boosting function, for example by drugs that inhibited the inactivation of the endocannabinoids, may offer a safer and more subtle approach to cannabis-based medicines in the future (Piomelli *et al.*, 2000).

References

Abel EL. Marihuana and memory: acquisition or retrieval? Science 1971; 173: 1038–41.

Abood ME, Martin BR. Neurobiology of marijuana abuse. [Review]. Trends Pharmacol Sci 1992; 13: 201–6.

Aceto MD, Scates SM, Lowe JA, et al. Dependence on delta 9-tetrahydrocannabinol: studies on precipitated and abrupt withdrawal. J Pharmacol Exp Ther 1996; 278: 1290–5.

Aceto MD, Scates SM, Martin BR. Spontaneous and precipitated withdrawal with a synthetic cannabinoid, WIN 55212-2. Eur J Pharmacol 2001; 416: 75–81.

Adams IB, Martin BR. Cannabis: pharmacology and toxicology in animals and humans. [Review]. Addiction 1996; 91: 1585–14.

Alger BE, Pitler TA. Retrograde signaling at $GABA_A$-receptor synapses in the mammalian CNS. [Review]. Trends Neurosci 1995; 13: 333–40.

American Psychiatric Association. Diagnostic and statistical manual of mental disorders. DSM-IV. 4th ed. Washington (DC): American Psychiatric Association; 1994.

Andreasson S, Allebeck P, Engstrom A, et al. Cannabis and schizophrenia. A longitudinal study of Swedish conscripts. Lancet 1987; 2: 1483–5.

Andreasson S, Allebeck P, Rydberg U. Schizophrenia in users and nonusers of cannabis. Acta Psychiatr Scand 1989; 79: 505–10.

Anthony JC, Warner LA, Kessler RC. Comparative epidemiology of dependence on tobacco, alcohol, controlled substances and inhalants. Basic findings from the National Comorbidity Survey. Exp Clin Psychopharmacol 1994; 2: 244–68.

Arseneault L, Cannon M, Poulton R, et al. Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study. BMJ 2002; 325: 1212–3.

Atha MJ, Blanchard S. Regular users. Self-reported drug consumption patterns and attitudes towards drugs among 1333 regular cannabis users. Wigan: Independent Drug Monitoring Unit; 1997.

Baker D, Pryce G, Croxford JL, et al. Cannabinoids control spasticity and tremor in a multiple sclerosis model. Nature 2000; 404: 84–7.

Beal JA, Olson R, Laubenstein L, et al. Dronabinol as a treatment for anorexia associated with weight loss in patients with AIDS. J Pain Symptom Manage 1995; 10: 89–97.

Bisogno T, Berrendero F, Ambrosino G, et al. Brain regional distribution of endocannabinoids: implications for their biosynthesis and biological function. Biochem Biophys Res Commun 1999; 256: 377–80.

Block RI, O'Leary DS, Ehrhardt JC, et al. Effects of frequent marijuana use on brain tissue volume and composition. Neuroreport 2000; 11: 491–6.

Bohme GA, Laville M, Ledent C, et al. Enhanced long-term potentiation in mice lacking cannabinoid CB_1 receptors. Neuroscience 2000; 95: 5–7.

Bowman M, Pihl RO. Cannabis: psychological effects of chronic heavy use. A controlled study of intellectual functioning in chronic users of high potency cannabis. Psychopharmacologia 1973; 29: 159–70.

Breivogel CS, Childers SR. The functional neuroanatomy of brain cannabinoid receptors. [Review]. Neurobiol Dis 1998; 5: 417–31.

Breivogel CS, Griffin G, Di Marzo V, et al. Evidence for a new G protein-coupled cannabinoid receptor in mouse brain. Mol Pharmacol 2001; 60: 155–63.

British Medical Association. Therapeutic uses of cannabis. [Review]. Amsterdam: Harwood Academic; 1997.

Budney AJ, Hughes JR, Moore BA, et al. Marijuana abstinence effects in marijuana smokers maintained in their home environment. Arch Gen Psychiatry 2001; 58: 917–24.

Cadas H, di Tomaso E, Piomelli D. Occurrence and biosynthesis of endogenous cannabinoid precursors, N-arachidonoyl phosphatidylethanolamine, in rat brain. J Neurosci 1997; 17: 1226–42.

Campbell FA, Tramer MR, Carroll D, et al. Are cannabinoids an effective and safe treatment option in the management of pain? A qualitative systematic review. [Review]. BMJ 2001; 323: 13–6.

Caulfield MP, Brown DA. Cannabinoid receptor agonists inhibit Ca current in NG108-15 neuroblastoma cells via a pertussis toxin-sensitive mechanism. Br J Pharmacol 1992; 106: 231–2.

Chan PC, Sills RC, Braun AG, et al. Toxicity and carcinogenicity of delta 9-tetrahydrocannabinol in Fischer rats and B6C3F1 mice. Fundam Appl Toxicol 1996; 30: 109–17.

Chan GCK, Hinds TR, Impey S, et al. Hippocampal neurotoxicity of delta 9-tetrahydrocannabinol. J Neurosci 1998; 18: 5322–32.

Colombo G, Agabio R, Diaz G, et al. Appetite suppression and weight loss after the cannabinoid antagonist SR141716. Life Sci 1998; 63: PL113–7.

Compton DR, Aceto MD, Lowe J, et al. In vivo characterization of a specific cannabinoid receptor antagonist (SR141716A): inhibition of delta 9-tetrahydocannabinol-induced responses and

apparent agonist activity. J Pharmacol Exp Ther 1996; 277: 586–94.

Consroe P, Musty R, Rein J, et al. The perceived effects of smoked cannabis on patients with multiple sclerosis. Eur Neurol 1996; 38: 44–8.

Cravatt BF, Demarest K, Patricelli MP, et al. Supersensitivity to anandamide and enhanced endogenous cannabinoid signaling in mice lacking fatty acid amide hydrolase. Proc Natl Acad Sci USA 2001; 98: 9371–6.

Darmani NA. Delta 9-tetrahydocannabinol and synthetic cannabinoids prevent emesis produced by the cannabinoid CB_1 receptor antagonist/inverse agonist SR141716A. Neuropsychopharmacology 2001; 24: 198–203.

Darmani NA. The potent emetogenic effects of the endocannabinoid, 2-AG (2-arachidonylglycerol) are blocked by delta 9-tetrahydrocannabinol and other cannabinoids. J Pharmacol Exp Ther 2002; 300: 34–42.

Deadwyler SA, Hampson RE, Childers SR. Functional significance of cannabinoid receptors in brain. In: Pertwee RG, editor. Cannabinoid receptors. London: Academic Press; 1995. p. 206–31.

DeSanty KP, Dar MS. Cannabinoid-induced motor incoordination through the cerebellar CB_1 receptor in mice. Pharmacol Biochem Behav 2001; 69: 251–9.

Devane WA, Hanus L, Breuer A, et al. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. Science 1992; 258: 1946–9.

Diana M, Melis M, Muntoni AL, et al. Mesolimbic dopaminergic decline after cannabinoid withdrawal. Proc Natl Acad Sci USA 1998; 95: 10269–73.

DiMarzo V, Fontana A, Cadas H, et al. Formation and inactivation of endogenous cannabinoid anandamide in central neurons. Nature 1994; 372: 686–91.

DiMarzo V, Breivogel CS, Tao Q, et al. Levels, metabolism, and pharmacological activity of anandamide in CB_1 cannabinoid receptor knockout mice: evidence for non-CB1, non-CB_2 receptor-mediated actions of anandamide in mouse brain. J Neurochem 2000; 75: 2434–44.

DiMarzo V, Goparaju SK, Wang L, et al. Leptin-regulated endocannabinoids are involved in maintaining food intake. Nature 2001*a*; 410: 822–5.

DiMarzo V, Bisogno T, De Petrocellis L. Anandamide: some like it hot. [Review]. Trends Pharmacol Sci 2001*b*; 22: 346–9.

Dixon WE. The pharmacology of cannabis indica. BMJ 1899; 2: 1354–7.

Dornbush RL, Freedman AM, Fink M, editors. Chronic cannabis use. [Review]. Ann NY Acad Sci 1976; 282: 1–430.

Downer E, Boland B, Fogarty M, et al. Delta 9-tetrahydrocannabinol induces the apoptotic pathway in cultured cortical neurones via activation of the CB_1 receptor. Neuroreport 2001; 12: 3973–8.

D'Souza DC, Kosten TR. Cannabinoid antagonists. [Review]. Arch Gen Psychiatry 2001; 58: 330–1.

Earleywine M. Understanding marijuana. [Review]. Oxford: Oxford University Press; 2002.

Egertová M, Elphick MR. Localisation of cannabinoid receptors in the rat brain using antibodies to the intracellular C-terminal tail of CB_1. J Comp Neurol 2000; 422: 159–71.

Egertová M, Giang DK, Cravatt BF, et al. A new perspective on cannabinoid signalling: complementary localization of fatty acid amide hydrolase and the CB_1 receptor in rat brain. Proc R Soc Lond B Biol Sci 1998; 265: 2081–5.

Elphick MR, Egertová M. The neurobiology and evolution of cannabinoid signalling. [Review]. Philos Trans R Soc Lond B Biol Sci 2001; 356: 381–408.

Emrich HM, Leweke FM, Schneider U. Towards a cannabinoid hypothesis of schizophrenia: cognitive impairments due to dysregulation of the endogenous cannabinoid system. [Review]. Pharmacol Biochem Behav 1997; 56: 803–7.

Felder CC, Glass M. Cannabinoid receptors and their endogenous agonists. [Review]. Annu Rev Pharmacol Toxicol 1998; 38: 179–200.

Felder CC, Nielsen A, Briley EM, et al. Isolation and measurement of the endogenous cannabinoid receptor agonist, anandamide, in brain and peripheral tissues of human and rat. FEBS Lett 1996; 393: 231–5.

Fergusson DM, Horwood LJ, Swain-Campbell NR. Cannabis dependence and psychotic symptoms in young people. Psychol Med 2003; 33: 15–21.

Fox A, Kesingland A, Gentry C, et al. The role of central and peripheral cannabinoid 1 receptors in the antihyperalgesic activity of cannabinoids in a model of neuropathic pain. Pain 2001; 92: 91–100.

French ED, Dillon K, Wu X. Cannabinoids excite dopamine neurons in the ventral tegmentum and substantia nigra. Neuroreport 1997; 8: 649–52.

Fride E, Ginzburg Y, Breuer A, et al. Critical role of the endogenous cannabinoid system in mouse pup suckling and growth. Eur J Pharmacol 2001; 419: 207–14.

Fuentes JA, Ruiz-Gayo M, Manzanares J, et al. Cannabinoids as potential new analgesics. Life Sci 1999; 65: 675–85.

Galve-Roperh I, Sanchez C, Cortés ML, et al. Anti-tumoral action of cannabinoids: involvement of sustained ceramide accumulation and extracellular signal-regulated kinase activation. Nat Med 2000; 6: 313–9.

Gill EW, Paton WDM, Pertwee RG. Preliminary experiments on the chemistry and pharmacology of cannabis. Nature 1970; 229: 134–6.

Giuffrida A, Piomelli D. The endocannabinoid system: a physiological perspective on its role in psychomotor control. [Review]. Chem Phys Lipids 2000; 108: 151–8.

Giuffrida A, Parsons LH, Kerr TM, et al. Dopamine activation of endogenous cannabinoid signaling in dorsal striatum. Nat Neurosci 1999; 2: 358–63.

Giuffrida A, Désarnaud F, Piomelli D. Endogenous cannabinoid signaling and psychomotor disorders. Prostaglandins Other Lipid Mediat 2000; 61: 63–70.

Giuffrida A, Beltramo M, Piomelli D. Mechanisms of endocannabinoid inactivation: biochemistry and pharmacology. [Review]. J Pharmacol Exp Ther 2001; 298: 7–14.

Greenberg HS, Werness SAS, Pugh JE, et al. Short-term effects of smoking marijuana on balance in patients with multiple sclerosis and normal volunteers. Clin Pharmacol Ther 1994; 55: 324–8.

Guzmán M, Sánchez C, Galve-Roperh I. Control of the cell survival/death decision by cannabinoids. [Review]. J Mol Med 2001; 78: 613–25.

Hájos N, Katona I, Naiem SS, et al. Cannabinoids inhibit hippocampal GABAergic transmission and network oscillations. Eur J Neurosci 2000; 12: 3239–49.

Hájos N, Ledent C, Freund TF. Novel cannabinoid-sensitive receptor mediates inhibition of glutamatergic synaptic transmission in the hippocampus. Neuroscience 2001; 106: 1–4.

Hall W, Degenhardt L. Cannabis use and psychosis: a review of clinical and epidemiological evidence. Aust NZ J Psychiatry 2000; 34: 26–34.

Hambrecht M, Hafner H. Cannabis, vulnerability, and the onset of schizophrenia: an epidemiological perspective. Aust NZ J Psychiatry 2000; 34: 468–75.

Hampson RE, Deadwyler SA. Cannabinoids, hippocampal function and memory. [Review]. Life Sci 1999; 65: 715–23.

Hampson RE, Deadwyler SA. Cannabinoids reveal the necessity of hippocampal neural encoding for short-term memory in rats. J Neurosci 2000; 20: 8932–42.

Hampson AJ, Grimaldi M, Axelrod J, et al. Cannabidiol and (-)delta 9-tetrahydrocannabinol are neuroprotective antioxidants. Proc Natl Acad Sci USA 1998; 95: 8268–73.

Han CJ, Robinson JK. Cannabinoid modulation of time estimation in the rat. Behav Neurosci 2001; 115: 243–6.

Hanuš L, Abu-Lafi S, Fride E, et al. 2-arachidonyl glyceryl ether, an endogenous agonist of the cannabinoid CB_1 receptor. Proc Natl Acad Sci USA 2001; 98: 3662–5.

Harper JW, Heath RG, Myers WA. Effects of cannabis sativa on ultrastructure of the synapse in monkey brain. J Neurosci Res 1977; 3: 87–93.

Heath RG, Fitzjarrell AT, Fontana CJ, et al. Cannabis sativa: effects on brain function and ultrastructure in rhesus monkeys. Biol Psychiatry 1980; 15: 657–90.

Herkenham M, Lynn AB, Johnson MR, et al. Characterization and localization of cannabinoid receptors in rat brain: a quantitative in vitro autoradiographic study. J Neurosci 1991; 11: 563–83.

Herzberg U, Eliav E, Bennett GJ, et al. The analgesic effects of R(+)-WIN55,212-2 mesylate, a high affinity cannabinoid agonist, in a rat model of neuropathic pain. Neurosci Lett 1997; 221: 157–60.

Hicks RE, Gualtieri CT, Mayo JP Jr, Perez-Reyes M. Cannabis, atropine, and temporal information processing. Neuropsychobiology 1984; 12: 229–37.

Hine B, Friedman E, Torrelio M, et al. Morphine-dependent rats: blockade of precipitated abstinence by tetrahydrocannabinol. Science 1975; 187: 443–5.

Hoffman AF, Lupica CR. Mechanisms of cannabinoid inhibition of $GABA_A$ synaptic transmission in the hippocampus. J Neurosci 2000; 20: 2470–9.

Hollister LE. Hunger and appetite after single doses of marihuana, alcohol, and dextroamphetamine. Clin Pharmacol Ther 1971; 12: 44–9.

Hollister LE. Health aspects of cannabis. [Review]. Pharmacol Rev 1986; 38: 1–20.

Hollister LE. Health aspects of cannabis: revisited. Int J Neuropsychopharmacol 1998; 1: 71–80.

Howlett AC, Johnson MR, Melvin LS, et al. Nonclassical cannabinoid analgetics inhibit adenylate cyclase: development of a cannabinoid receptor model. Mol Pharmacol 1988; 33: 297–302.

Huestis MA, Gorelick DA, Heishman SJ, et al. Blockade of effects of smoked marijuana by the CB_1-selective cannabinoid receptor antagonist SR141716. Arch Gen Psychiatry 2001; 58: 322–8.

Iversen LL. The science of marijuana. [Review]. Oxford: Oxford University Press, 2000.

Iversen LL, Chapman V. Cannabinoids: a real prospect for pain relief? [Review]. Curr Opin Pharmacol 2002; 2: 50–5.

Johns A. Psychiatric effects of cannabis. [Review]. Br J Psychiatry 2001; 178: 116–22.

Jones RT. Marihuana: human effects. [Review] In: Iversen LL, Iversen SD, Snyder SH, editors. Handbook of psychopharmacology. Vol. 12. New York: Plenum Press; 1978. p. 373–412.

Jones RT. Drug of abuse profile: cannabis. [Review]. Clin Chem 1987; 33 (11 Suppl): 72B–81B.

Joy JE, Watson SJ, Benson JA, editors. Marijuana and medicine, assessing the science base. Washington (DC): National Academy Press; 1999.

Katona I, Sperlagh B, Sik A, et al. Presynaptically located CB_1 cannabinoid receptors regulate GABA release from axon terminals of specific hippocampal interneurons. J Neurosci 1999; 19: 4544–58.

Katona I, Sperlagh B, Maglóczky Z, et al. GABAergic interneurons are the targets of cannabinoid actions in the human hippocampus. Neuroscience 2000; 100: 797–804.

Katona I, Rancz EA, Acsády L, et al. Distribution of CB_1 cannabinoid receptors in the amygdala and their role in the control of GABAergic transmission. J Neurosci 2001; 21: 9506–18.

Kaymakçalan S, Ayhan IH, Tulunay FC. Naloxone-induced or postwithdrawal abstinence signs in delta 9-tetrahydrocannabinol-tolerant rats. Psychopharmacology (Berl) 1977; 55: 243–9.

Koch JE. Delta 9-THC stimulates food intake in Lewis rats. Effects on chow, high-fat and sweet high-fat diets. Pharmacol Biochem Behav 2001; 68: 539–43.

Kreitzer AC, Regehr WG. Retrograde inhibition of presynaptic calcium influx by endogenous cannabinoids at excitatory synapses onto Purkinje cells. Neuron 2001*a*; 29: 717–27.

Kreitzer AC, Regehr WG. Cerebellar depolarization-induced

suppression of inhibition is mediated by endogenous cannabinoids. J Neurosci 2001*b*; 21: RC174–9.

Landfield PW, Cadwallader LB, Vinsant S. Quantitative changes in hippocampal structure following long-term exposure to delta 9-tetrahydrocannabinol: possible mediation by glucocorticoid systems. Brain Res 1988; 443: 47–62.

Lawston J, Borella A, Robinson JK, et al. Changes in hippocampal morphology following chronic treatment with the synthetic cannabinoid WIN 55,212-2. Brain Res 2000; 877: 407–10.

Ledent C, Valverde O, Cossu G, et al. Unresponsiveness to cannabinoids and reduced addictive effects of opiates in CB_1 receptor knockout mice. Science 1999; 283: 401–4.

Lenz RA, Wagner JJ, Alger BE. N- and L-type calcium channel involvement in depolarization-induced suppression of inhibition in rat hippocampal CA1 cells. J Physiol 1998; 512: 61–73.

Lepore M, Vorel SR, Lowinson J, et al. Conditioned place preference induced by delta 9-tetrahydrocannabinol: comparison with cocaine, morphine and food reward. Life Sci 1995; 56: 2073–80.

Lichtman AH, Martin BR. Delta 9-tetrahydrocannabinol impairs spatial memory through a cannabinoid receptor mechanism. Psychopharmacology (Berl) 1996; 126: 125–31.

Lichtman AH, Fisher J, Martin BR. Precipitated cannabinoid withdrawal is reversed by delta 9-tetrahydrocannabinol or clonidine. Pharmacol Biochem Behav 2001*a*; 69: 181–8.

Lichtman AH, Sheikh SM, Loh HH, et al. Opioid and cannabinoid modulation of precipitated withdrawal in delta 9-tetrahydrocannabinol and morphine-dependent mice. J Pharmacol Exp Ther 2001*b*; 298: 1007–14.

Linzen DH, Dingemans PM, Lenior ME. Cannabis abuse and the course of recent-onset schizophrenic disorders. Arch Gen Psychiatry 1994; 51: 273–9.

MacKie K, Hille B. Cannabinoids inhibit N-type calcium channels in neuroblastoma-glioma cells. Proc Natl Acad Sci USA 1992; 89: 3825–9.

Maejima T, Hashimoto K, Yoshida T, et al. Presynaptic inhibition caused by retrograde signal from metabotropic glutamate to cannabinoid receptors. Neuron 2001; 31: 463–75.

Mallet PE, Beninger RJ. The cannabinoid CB_1 receptor antagonist SR141716A attenuates the memory impairment produced by delta 9-tetrahydrocannabinol or anandamide. Psychopharmacology (Berl) 1998; 140: 11–9.

Manno JE, Kiplinger GF, Haine SE, et al. Comparative effects of smoking marihuana or placebo on human motor and mental performance. Clin Pharmacol Ther 1970; 11: 808–15.

Manzanares J, Corchero J, Romero J, et al. Pharmacological and biochemical interactions between opioids and cannabinoids. Trends Pharmacol Sci 1999; 20: 287–94.

Marsicano G, Lutz B. Expression of the cannabinoid receptor CB_1 in distinct neuronal subpopulations in the adult mouse forebrain. Eur J Neurosci 1999; 11: 4213–4225.

Mathers DC, Ghodse AH. Cannabis and psychotic illness. Br J Psychiatry 1992; 161: 648–53.

Mathew RJ, Wilson WH, Coleman RE, et al. Marijuana intoxication and brain activation in marijuana smokers. Life Sci 1997; 60: 2075–89.

Mathew RJ, Wilson WH, Turkington TG, et al. Cerebellar activity and disturbed time sense after THC. Brain Res 1998; 797: 183–9.

Matsuda LA, Lolait SJ, Brownstein MJ, et al. Structure of a cannabinoid receptor and functional expression of the cloned cDNA. Nature 1990; 346: 561–4.

Mattes RD, Engelman K, Shaw LM, et al. Cannabinoids and appetite stimulation. [Review]. Pharmacol Biochem Behav 1994; 49: 187–95.

Mechoulam R. Marihuana chemistry. [Review]. Science 1970; 168: 1159–66.

Mechoulam R, Fride E. Physiology. A hunger for cannabinoids. [Review]. Nature 2001; 410: 763, 765.

Mechoulam R, Ben-Shabat S, Hanuš L, et al. Identification of an endogenous 2-monoglyceride, present in canine gut, that binds to cannabinoid receptors. Biochem Pharmacol 1995; 50: 83–90.

Mechoulam R, Fride E, Hanus L, et al. Anandamide may mediate sleep induction. [Review]. Nature 1997; 389: 25–6.

Mendelson JH, Babor TF, Kuehnle JC, et al. Behavioral and biologic aspects of marijuana use. [Review]. Ann NY Acad Sci 1976; 282: 186–210.

Meng ID, Manning BH, Martin WJ, et al. An analgesia circuit activated by cannabinoids. Nature 1998; 395: 381–3.

Miller LL, Branconnier RJ. Cannabis: effects on memory and the cholinergic limbic system. Psychol Bull 1983; 93: 441–56.

Misner DL, Sullivan JM. Mechanism of cannabinoid effects on long-term potentiation and depression in hippocampal CA1 neurons. J Neurosci 1999; 19: 6795–805.

Morral AR, McCaffrey DF, Paddock SM. Reassessing the marijuana gateway effect. Addiction 2002; 97: 1493–504.

Munro S, Thomas KL, Abu-Shaar M. Molecular characterization of a peripheral receptor for cannabinoids. Nature 1993; 365: 61–5.

Nagayama T, Sinor AD, Simon RP, et al. Cannabinoids and neuroprotection in global and focal cerebral ischemia and in neuronal cultures. J Neurosci 1999; 19: 2987–95.

Nakamura-Palacios EM, Winsauer PJ, Moerschbaecher JM. Effects of the cannabinoid ligand SR141716A alone or in combination with delta-9-tetrahydrocannabinol or scopolamine on learning in squirrel monkeys. Behav Pharmacol 2000; 11: 377–86.

Negrete JC, Knapp WP, Douglas DE, et al. Cannabis affects the severity of schizophrenic symptoms: results of a clinical survey. Psychol Med 1986; 16: 515–20.

Ohno-Shosaku T, Maejima T, Kano M. Endogenous cannabinoids mediate retrograde signals from depolarized postsynaptic neurons to presynaptic terminals. Neuron 2001; 29: 729–38.

Panikashvili D, Simeonidou C, Ben-Shabat S, et al. An endogenous cannabinoid (2-AG) is neuroprotective after brain injury. Nature 2001; 413: 527–31.

Patel S, Hillard CJ. Cannabinoid CB_1 receptor agonists produce cerebellar dysfunction in mice. J Pharmacol Exp Ther 2001; 297: 629–37.

Patton GC, Coffey C, Carlin JB, et al. Cannabis use and mental health in young people: cohort study. BMJ 2002; 325: 1195–8.

Peralta V, Cuesta MJ. Influence of cannabis abuse on schizophrenic psychopathology. Acta Psychiatr Scand 1992; 85: 127–30.

Pertwee RG. Tolerance to and dependence on psychotropic cannabinoids. [Review]. In: Pratt J, editor. The biological basis of drug tolerance and dependence. London: Academic Press; 1991. p. 232–65.

Pertwee RG. Pharmacology of cannabinoid receptor ligands. [Review]. Curr Med Chem 1999; 6: 635–64.

Pertwee RG. Cannabinoid receptors and pain. [Review]. Prog Neurobiol 2001; 63: 569–611.

Pettit DAD, Harrison MP, Olson JM, et al. Immunohistochemical localization of the neural cannabinoid receptor in rat brain. J Neurosci Res 1998; 51: 391–402.

Piomelli D, Beltramo M, Giuffrida A, et al. Endogenous cannabinoid signaling. [Review]. Neurobiol Dis 1998; 5: 462–73.

Piomelli D, Giuffrida A, Calignano A, et al. The endocannabinoid system as a target for therapeutic drugs. [Review]. Trends Pharmacol Sci 2000; 21: 218–24.

Pitler TA, Alger BE. Postsynaptic spike firing reduces synaptic $GABA_A$ responses in hippocampal pyramidal cells. J Neurosci 1992; 12: 4122–32.

Pitler TA, Alger BE. Depolarization-induced suppression of GABAergic inhibition in rat hippocampal pyramidal cells: G protein involvement in a presynaptic mechanism. Neuron 1994; 13: 1447–55.

Pontieri FE, Monnazzi P, Scontrini A, et al. Behavioral sensitization to heroin by cannabinoid pretreatment in the rat. Eur J Pharmacol 2001; 421: R1–3.

Pope HG Jr, Gruber AJ, Hudson JI, et al. Neuropsychological performance in long-term cannabis users. Arch Gen Psychiatry 2001; 58: 909–15.

Reibaud M, Obinu MC, Ledent C, et al. Enhancement of memory in cannabinoid CB_1 receptor knock-out mice. Eur J Pharmacol 1999; 379: R1–2.

Rinaldi-Carmona M, Barth F, Heaulme M, et al. SR141716A, a potent and selective antagonist of the brain cannabinoid receptor. FEBS Lett 1994; 350: 240–4.

Robson P. Therapeutic aspects of cannabis and cannabinoids. [Review]. Br J Psychiatry 2001; 178: 107–15.

RodríguezdeFonseca F, Carrera MR, Navarro M, et al. Activation of corticotropin-releasing factor in the limbic system during cannabinoid withdrawal. Science 1997; 276: 2050–4.

RodríguezdeFonseca F, Del Arco I, Martín-Calderón JL, et al. Role of the endogenous cannabinoid system in the regulation of motor activity. [Review]. Neurobiol Dis 1998; 5: 483–501.

Roth SH. Stereospecific presynaptic inhibitory effect of delta-9-tetrahydrocannabinol on choiinergic transmission in the myenteric plexus of the guinea pig. Can J Physiol Pharmacol 1978; 56: 968–75.

Rubino T, Patrini G, Massi P, et al. Cannabinoid-precipitated withdrawal: a time-course study of the behavioral aspect and its correlation with cannabinoid receptors and G protein expression. J Pharmacol Exp Ther 1998; 285: 813–9.

Sánchez C, Galve-Roperh I, Canova C, et al. Delta 9-tetrahydrocannabinol induces apoptosis in C6 glioma cells. FEBS Lett 1998; 436: 6–10.

Santucci V, Storme JJ, Soubrie P, et al. Arousal-enhancing properties of the CB_1 cannabinoid receptor antagonist SR 141716A in rats as assessed by electroencephalographic spectral and sleep-waking cycle analysis. Life Sci 1996; 58: PL103–10.

Sañudo-Peña MC, Tsou K, Walker JM. Motor actions of cannabinoids in the basal ganglia output nuclei. Life Sci 1999; 65: 703–13.

Sañudo-Peña MC, Romero J, Seale GE, et al. Activational role of cannabinoids on movement. Eur J Pharmacol 2000; 391: 269–74.

Satz P, Fletcher JM, Sutker LS. Neuropsychologic, intellectual, and personality correlates of chronic marijuana use in native Costa Ricans. Ann NY Acad Sci 1976; 282: 266–306.

Scallet AC. Neurotoxicology of cannabis and THC: a review of chronic exposure studies in animals. [Review]. Pharmacol Biochem Behav 1991; 40: 671–6.

Scallet AC, Uemura E, Andrews A, et al. Morphometric studies of the rat hippocampus following chronic delta-9-tetrahydrocannabinol (THC). Brain Res 1987; 436: 193–8.

Schlicker E, Kathmann M. Modulation of transmitter release via presynaptic cannabinoid receptors. [Review]. Trends Pharmacol Sci 2001; 22: 565–72.

Shen M, Thayer SA. Cannabinoid receptor agonists protect cultured rat hippocampal neurons from excitotoxicity. Mol Pharmacol 1998; 54: 459–62.

Shen M, Piser TM, Seybold VS, et al. Cannabinoid receptor agonists inhibit glutamatergic synaptic transmission in rat hippocampal cultures. J Neurosci 1996; 16: 4322–34.

Sinor AD, Irvin SM, Greenberg DA. Endocannabinoids protect cerebral cortical neurons from in vitro ischemia in rats. Neurosci Lett 2000; 278: 157–60.

Skosnik PD, Spatz-Glenn L, Park S. Cannabis use is associated with schizotypy and attentional disinhibition. Schizophr Res 2001; 48: 83–92.

Smith FL, Cichewicz D, Martin ZL, et al. The enhancement of morphine antinociception in mice by delta-9-tetrahydrocannabinol. Pharmacol Biochem Behav 1998; 60: 559–66.

Solowij N. Cannabis and cognitive functioning. [Review]. Cambridge: Cambridge University Press; 1998.

Stella N, Piomelli D. Receptor-dependent formation of endogenous cannabinoids in cortical neurons. Eur J Pharmacol 2001; 425: 189–96.

Stella N, Schweitzer P, Piomelli D. A second endogenous

cannabinoid that modulates long-term potentiation. Nature 1997; 388: 773–8.

Stiglick A, Kalant H. Residual effects of chronic cannabis treatment on behavior in mature rats. Psychopharmacology (Berl) 1985; 85: 436–9.

Sugiura T, Kondo S, Sukagawa A, et al. 2-Arachidonoylglycerol: a possible endogenous cannabinoid receptor ligand in brain. Biochem Biophys Res Commun 1995; 215: 89–97.

Swift W, Hall W, Teesson M. Cannabis use and dependence among Australian adults: results from the National Survey of Mental Health and Wellbeing. Addiction 2001; 96: 737–48.

Tanda G, Pontieri FE, Di Chiara G. Cannabinoid and heroin activation of mesolimbic dopamine transmission by a common μ_1 opioid receptor mechanism. Science 1997; 276: 2048–50.

Tanda G, Munzar P, Goldberg SR. Self-administration behavior is maintained by the psychoactive ingredient of marijuana in squirrel monkeys. Nat Neurosci 2000; 3: 1073–4.

Terranova JP, Michaud JC, Le Fur G, et al. Inhibition of long-term potentiation in rat hippocampal slices by anandamide and WIN55212-2: reversal by SR141716-A, a selective antagonist of CB_1 cannabinoid receptors. Naunyn Schmiedebergs Arch Pharmacol 1995; 352: 576–9.

Terranova JP, Storme JJ, Lafon N, et al. Improvement of memory in rodents by the selective CB_1 cannabinoid receptor antagonist, SR141716. Psychopharmacology (Berl) 1996; 126: 165–72.

Thomas H. Psychiatric symptoms in cannabis users. [Review]. Br J Psychiatry 1993; 163: 141–9.

Thornicroft G. Cannabis and psychosis. Is there epidemiological evidence for an association? Br J Psychiatry 1990; 157: 25–33.

Tramèr MR, Carroll D, Campbell FA, et al. Cannabinoids for control of chemotherapy induced nausea and vomiting: quantitative systematic review. [Review]. BMJ 2001; 323: 16–21.

US Department of Health and Human Services. US National Household Survey of Drug Abuse. 1999. Washington DC.

Valverde O, Maldonado R, Valjent E, et al. Cannabinoid withdrawal syndrome is reduced in pre-proenkephalin knock-out mice. J Neurosci 2000; 15: 9284–9.

Valverde O, Noble F, Beslot F, et al. Delta 9-tetrahydrocannabinol releases and facilitates the effects of endogenous enkephalins: reduction in morphine withdrawal syndrome without change in rewarding effect. Eur J Neurosci 2001; 13: 1816–24.

VanderStelt M, Veldhuis WB, Bär PR, et al. Neuroprotection by delta-9-tetrahydrocannabinol, the main active compound in marijuana, against ouabain-induced in vivo excitotoxicity. J Neurosci 2001; 21: 6475–9.

Varma N, Carlson GC, Ledent C, et al. Metabotropic glutamate receptors drive the endocannabinoid system in hippocampus. J Neurosci 2001; 21: RC188–93.

Verdoux H, Gindre C, Sorbara F, et al. Effects of cannabis and psychosis vulnerability in daily life: an experience sampling test study. Psychol Med 2003; 33: 23–32.

Vincent BJ, McQuiston DJ, Einhorn LH, et al. Review of cannabinoids and their antiemetic effectiveness. [Review]. Drugs 1983; 25 Suppl 1: 52–62.

Walker JM, Hohmann AG, Martin WJ, et al. The neurobiology of cannabinoid analgesia. [Review]. Life Sci 1999; 65: 665–73.

Welch SP, Stevens DL. Antinociceptive activity of intrathecally administered cannabinoids alone, and in combination with morphine, in mice. J Pharmacol Exp Ther 1992; 262: 10–18.

Williams CM, Kirkham TC. Anandamide induces overeating: mediation by central cannabinoid (CB_1) receptors. Psychopharmacology (Berl) 1999; 143: 315–7.

Williams JH, Wellman NA, Rawlins JNP. Cannabis use correlates with schizotypy in healthy people. Addiction 1996; 91: 869–77.

Wilson RI, Nicoll RA. Endogenous cannabinoids mediate retrograde signalling at hippocampal synapses. Nature 2001; 410: 588–92.

Yamaguchi T, Hagiwara Y, Tanaka H, et al. Endogenous cannabinoid, 2-arachidonylglycerol, attenuates naloxone-precipitated withdrawal signs in morphine-dependent mice. Brain Res 2001; 909: 121–6.

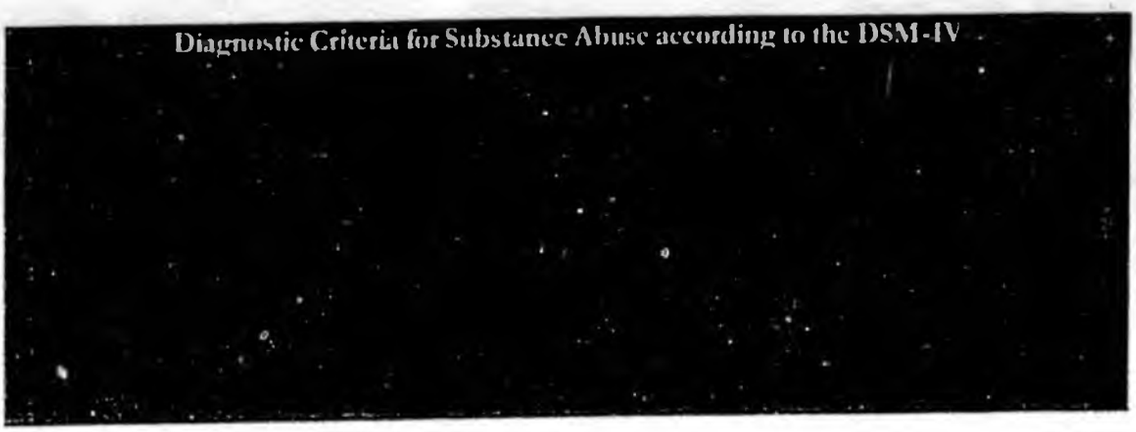
Zammit S, Allebeck P, Andreasson S, et al. Self reported cannabis use as a risk factor for schizophrenia in Swedish conscripts of 1969: historical cohort study. BMJ 2002; 325: 1199.

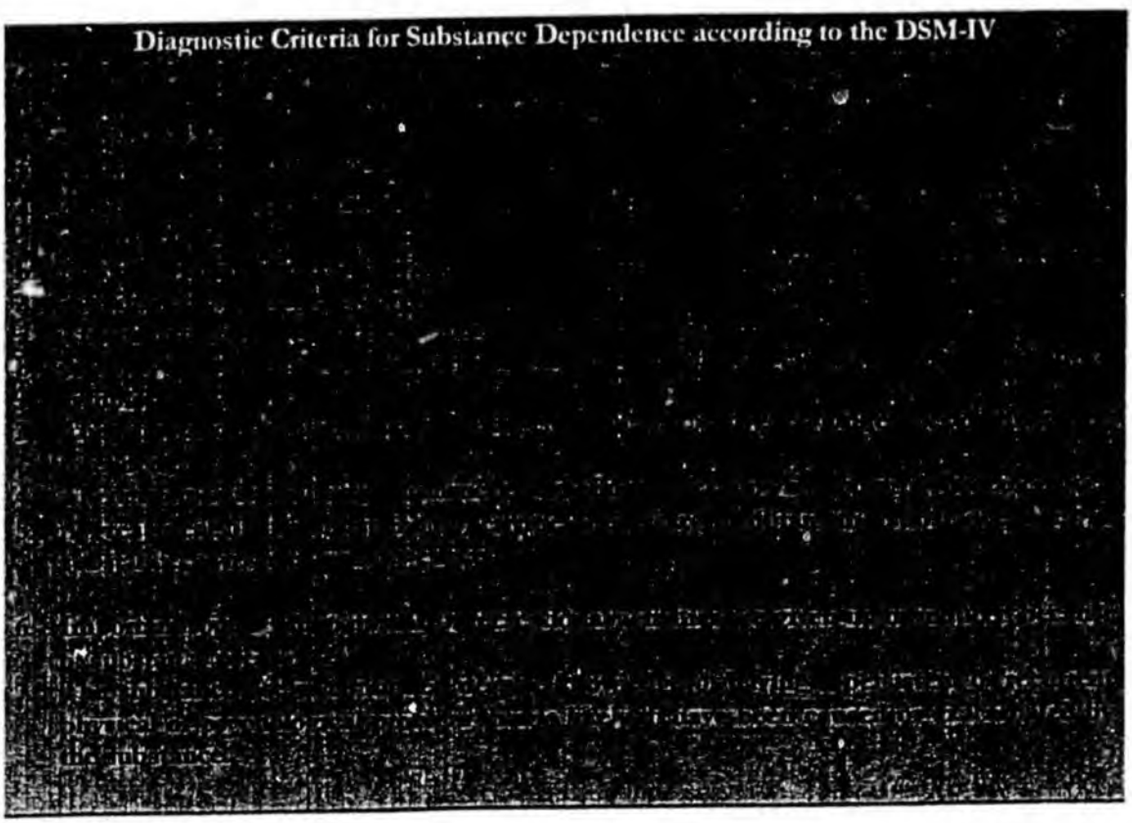
Zimmer L, Morgan JP. Marijuana myths, marijuana facts. [Review]. New York: Lindesmith Center; 1997.

Zimmer A, Zimmer AM, Hohmann AG, et al. Increased mortality, hypoactivity, and hypoalgesia in cannabinoid CB_1 receptor knockout mice. Proc Natl Acad Sci USA 1999; 96: 5780–5.

Received April 15, 2002. Revised January 13, 2003
Accepted January 15, 2003

N


Diagnostic Criteria for Substance Abuse according to the DSM-IV


Diagnostic Criteria for Substance Dependence according to the DSM-IV

6. Trends in Initiation of Substance Use

Estimates of substance use incidence, or initiation, concern the number of new users of illicit drugs, alcohol, or tobacco during a given year. These estimates supplement prevalence estimates as and measures of the Nation's substance use problem. Where prevalence estimates describe the extent of use of substances over some period of time, incidence data describe emerging patterns of use, particularly among young people. In the past, increases and decreases in incidence usually have been followed by corresponding changes in the prevalence of use, particularly among youths.

The incidence estimates in this report are based on the 2002 National Survey on Drug Use and Health (NSDUH). As the 2002 NSDUH constitutes a new baseline year for the survey, these data should not be compared with previously published data from the National Household Survey on Drug Abuse (NHSDA).

The incidence estimates are based on NSDUH 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 date of first use is determined for each substance used by each respondent. By applying sample weights to incidents of first use, estimates of the number of new users of each substance are developed for each year. These estimates include the number of new users at any age (including those younger than age 12) and also are shown for two specific age groups—persons younger than 18 and adults aged 18 or older. In addition, the average age of new users in each year and age-specific rates of first use are estimated.

Although they are not discussed in this chapter, estimates of age-specific incidence rates also are developed. These rates are defined as the number of new users per 1,000 potential new users because they indicate the rate of new use among persons who have not yet used the substance (i.e., potential new users). More precisely, the rates are actually the number of new users per 1,000 person-years of exposure. This measure is widely used in describing the incidence of disease. The method used for computing these rates is described in Section B.4 in **Appendix B**.

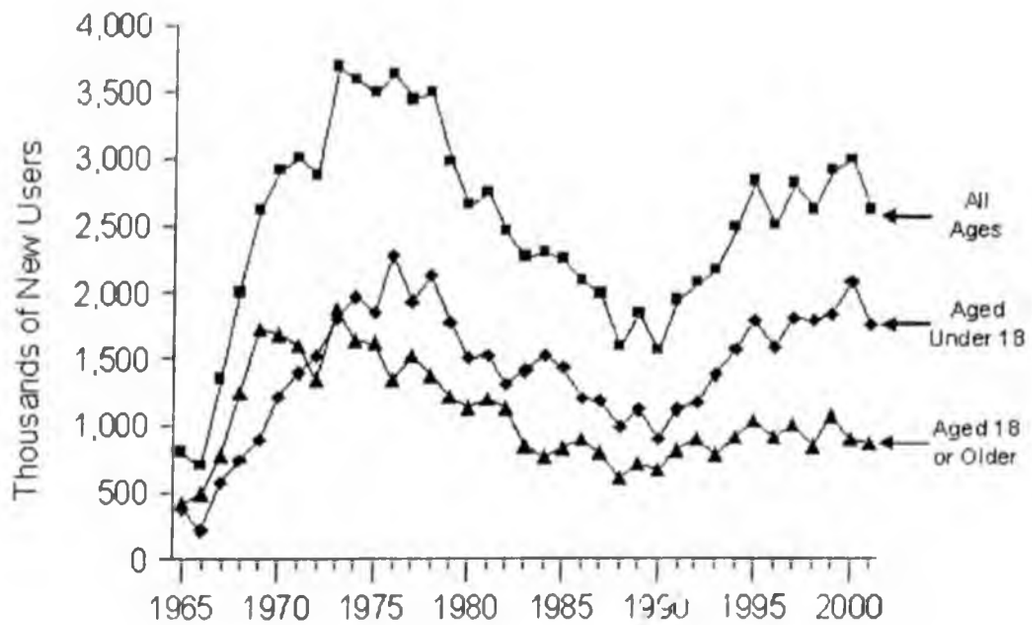
Because the incidence estimates reported herein are based on retrospective reports of age at first substance use by survey respondents interviewed during 2002, they may be subject to several sources of bias. These include bias due to differential mortality of users and nonusers of each substance, bias due to memory errors (recall decay and telescoping), and underreporting bias due to social acceptability and fear of disclosure. See Section B.4 in **Appendix B** for a discussion of these biases. It is possible that some of these biases, particularly telescoping and underreporting because of fear of disclosure, may be affecting estimates for the most recent years more significantly than estimates for earlier years. To account for this bias in the interpretation of the trends, a more stringent standard for determining statistical significance involving estimates from the most recent years (1998 and later) is used in this chapter. Differences are reported to be statistically significant only if they differ at the $\alpha = .01$ level. The usual standard in the rest of the report is the $\alpha = .05$ level. This is an arbitrary standard that provides some protection against incorrect conclusions in the face of potential biases that can fluctuate and even change the direction of estimates from year to year. A more thorough analysis of the problem will be conducted in the future.

Because the incidence estimates are based on retrospective reports of age at first use, the most recent year available for these estimates is 2001, based on the 2002 NSDUH. For two of the measures, first alcohol use and first cigarette use, initiation before age 12 is common. A 2–year lag in reporting for "all ages" estimates is applied for these measures because the NSDUH sample does not cover youths under age 12. The 2–year lag ensures that initiation at ages 10 and 11 is captured in the estimation.

Marijuana

- There were an estimated 2.6 million new marijuana users in 2001. This number is similar to the numbers of new users each year since 1995, but above the number in 1990 (1.6 million).
- In 1965, there were an estimated 0.8 million new users of marijuana. The annual number of marijuana initiates generally increased until about 1973. From 1973 to 1978, the annual number of marijuana initiates remained level at approximately 3.5 million per year. After that, the number of initiates declined to 1.6 million in 1990, then rose to 2.8 million in 1995. From 1995 to 2001, there was no consistent trend, with estimates varying between 2.5 and 3.0 million per year (**Figure 6.1**).

Figure 6.1 Annual Numbers of New Users of Marijuana: 1965–2001



D

- In 2001, about two thirds (67 percent) of new marijuana users were under age 18. This proportion has generally increased since the 1960s, when less than half of initiates were under 18 (**Figure 6.1**). The average age of marijuana initiates was around 19 in the late 1960s and 17.1 in 2001.
- Since 1975, about half of marijuana initiates each year were females (51 percent in 2001). Prior to 1975, females comprised fewer than half of new users, on average. Since 1965, the average age of female initiates has generally been slightly higher than the average age for male initiates.

Cocaine

- Incidence of cocaine use generally rose throughout the 1970s to a peak in 1980 (1.7 million new users) and subsequently declined until 1991 (0.7 million new users). Cocaine initiation steadily increased during the 1990s, reaching 1.2 million in 2001.
- Age-specific incidence rates generally have mirrored the overall incidence trends, with greater initiation among adults than among youths under 18. Approximately 70 percent of cocaine initiates in 2001 were age 18 or older.
- Since 1975, males have generally comprised the majority of cocaine initiates. In 2001, there were 0.7 million new male users and 0.5 million new female users.
- The average age of cocaine initiates rose from 18.6 years in 1968 to 23.8 years in 1990 and subsequently declined to approximately 21 years from 1995 to 2001.

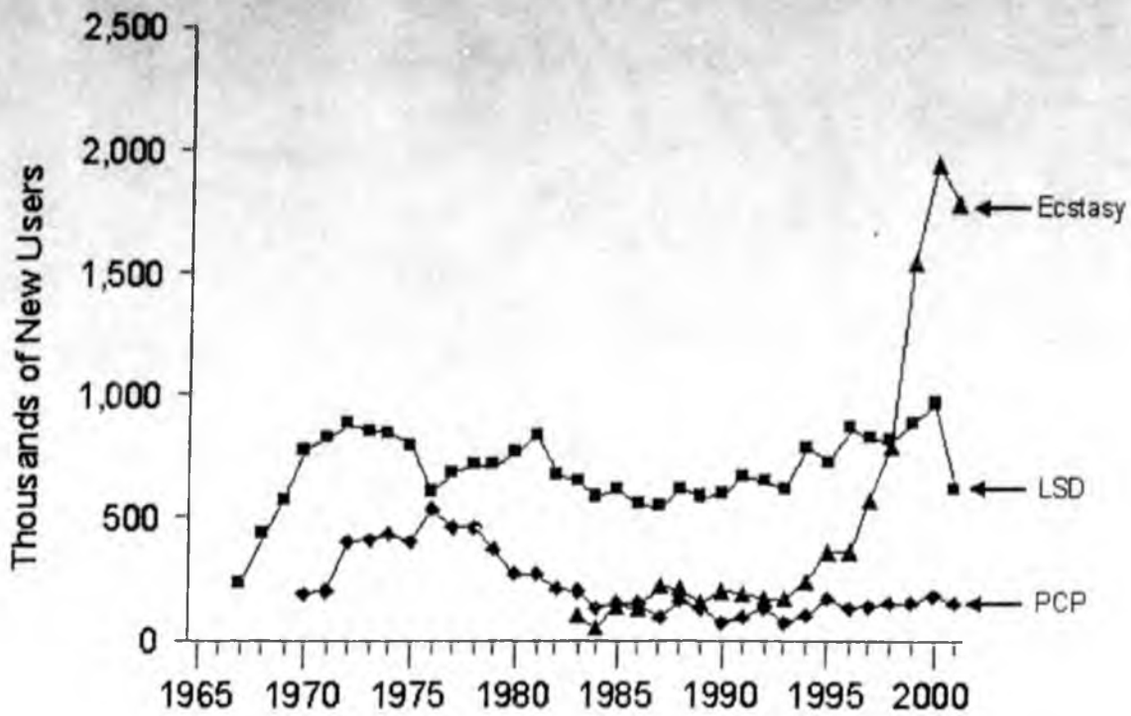
Heroin

- During the latter half of the 1990s, the annual number of heroin initiates rose to a level not reached since the late 1970s. In 1974, there were an estimated 246,000 heroin initiates. Between 1988 and 1994, the annual number of new users ranged from 28,000 to 80,000. Between 1995 and 2001, the number of new heroin users was consistently greater than 100,000.

Hallucinogens

- The incidence of hallucinogen use has exhibited two notable periods of increase. Between 1966 and 1970, the annual number of initiates rose almost sixfold, from 168,000 to 956,000. This increase was driven primarily by use of LSD. The second period of increase in first-time hallucinogen began in 1992 when there were approximately 706,000 new users. By 2000, the number of initiates rose to 1.7 million, which is similar to the number for 2001 (1.6 million). The hallucinogen increase in the 1990s appears to have been driven by increases in use of Ecstasy (i.e., MDMA) (**Figure 6.2**).
- Initiation of Ecstasy use has been rising since 1993, when there were 168,000 new users. There were 1.9 million initiates in 2000 and 1.8 million in 2001 (not a statistically significant decline).

Figure 6.2 Annual Numbers of New Users of Ecstasy, LSD, and PCP: 1965–2001



D

- LSD incidence dropped from 958,000 new users in 2000 to 606,000 in 2001.

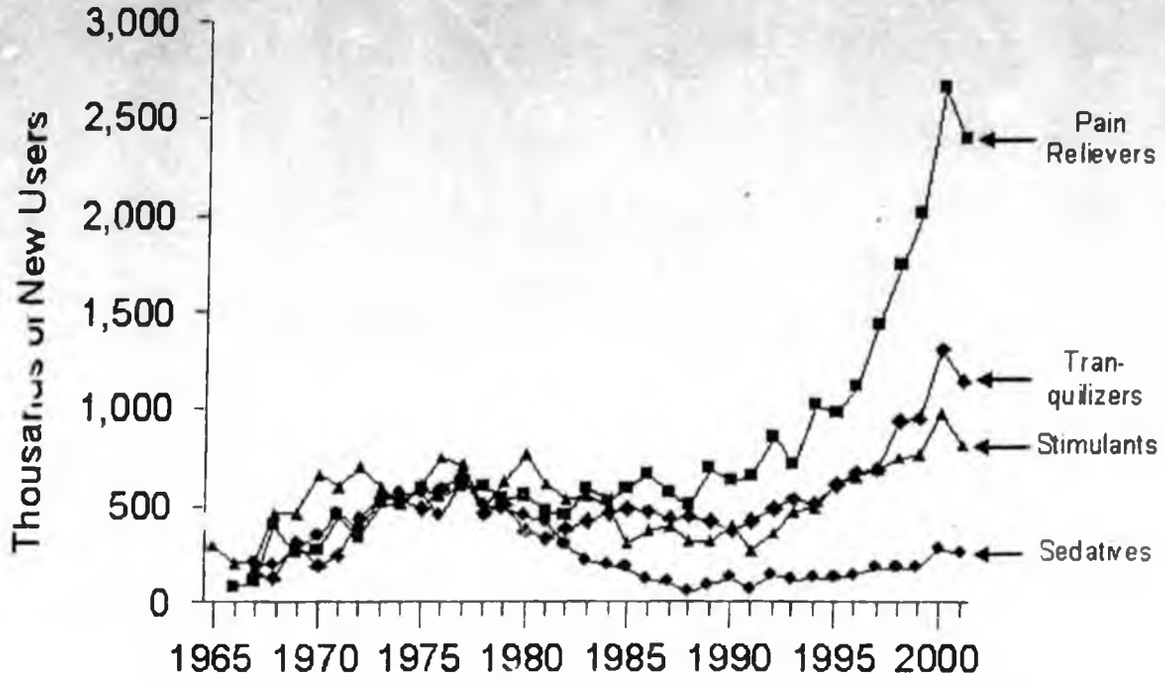
Inhalants

- The number of new inhalant users increased from 627,000 new users in 1994 to 1.2 million in 2000. During this period, more males initiated inhalant use than females. The number of new inhalant users in 2001 was similar to the number in 2000 (1.1 million).
- Inhalant initiates in 2001, as well as in prior years, were predominantly under age 18 (71 percent in 2001).

Psychotherapeutics

- This category includes nonmedical use of any prescription-type pain reliever, tranquilizer, stimulant, or sedative; it also includes methamphetamine. This category does not include over-the-counter substances.
- Pain reliever incidence increased from 1990, when there were 628,000 initiates, to 2000, when there were 2.7 million (**Figure 6.3**). In 2001, the number was 2.4 million, not significantly different from 2000. About half (52 percent) of the new users in 2001 were females.

Figure 6.3 Annual Numbers of New Nonmedical Users of Psychotherapeutics: 1965–2001



D

- First use of stimulants increased during the 1990s from 270,000 in 1991 to 983,000 in 2000 and 808,000 in 2001.
- Incidence of methamphetamine use rose between 1991 (210,000 new users) and 1998 (454,000 new users). Since then, there have been no statistically significant changes. There were an estimated 326,000 methamphetamine initiates in 2001.
- Initiation of tranquilizer use increased steadily during the 1990s, from 372,000 initiates in 1990 to 1.3 million in 2000 and 1.1 million in 2001.
- The number of sedative initiates has remained below 300,000 per year after 1981. During the 1970s, the estimates had risen above 500,000 per year from 1973 to 1975 and peaked at 638,000 in 1977.

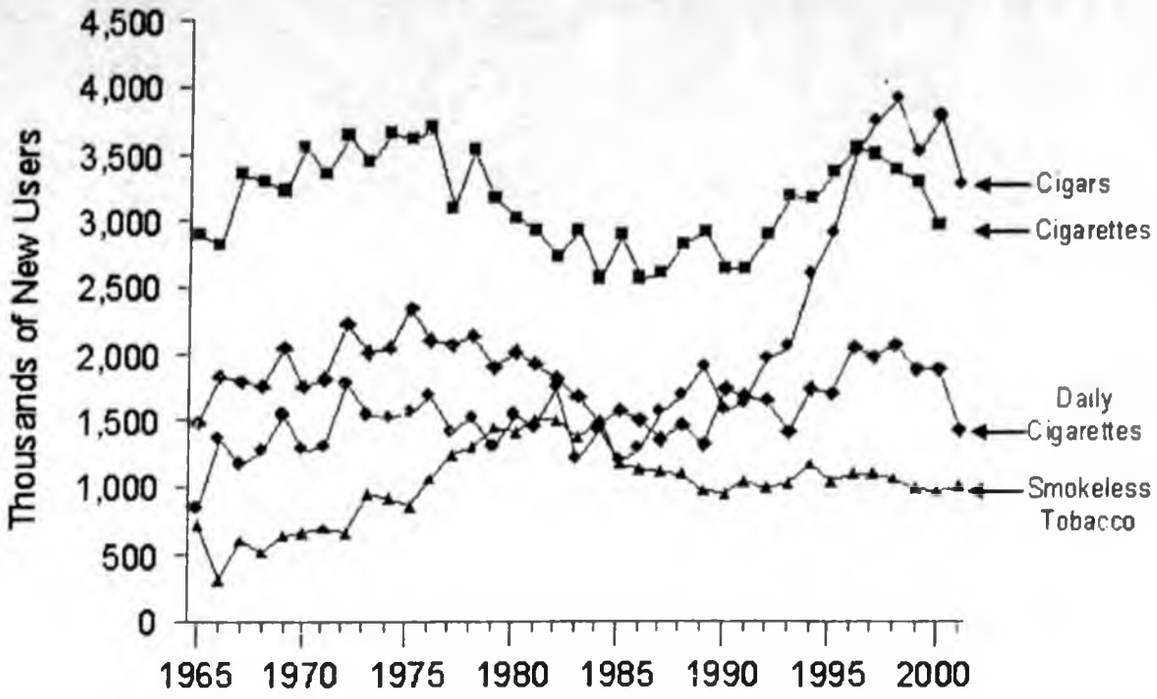
Alcohol

- Alcohol incidence increased steadily during the 1990s, from 3.3 million new users in 1990 to 5.6 million in 2000. Youths under 18 accounted for much of the increase, the number of adolescent initiates nearly doubling from 2.2 million in 1990 to 4.1 million in 2000. During this period, the increase was equally distributed among boys (1.1 million to 2.1 million) and girls (1.1 million to 2.0 million).

Tobacco

- Cigarette initiation increased from 2.6 million initiates in 1990 to 3.6 million in 1996, then decreased to 3.0 million in 2000. Initiation of cigarette use among youths under 18 significantly decreased from 2.8 million new users in 1996 to 2.2 million in 2000 (**Figure 6.4**).

Figure 6.4 Annual Numbers of New Users of Tobacco: 1965–2001



D

- The number of new daily smokers decreased from 2.1 million in 1998 to 1.4 million in 2001. Among youths under 18, the number of new daily smokers decreased from 1.1 million per year between 1997 and 2000 to 757,000 in 2001. This corresponds to a decrease from about 3,000 to about 2,000 new youth smokers per day.
- Approximately three quarters (75 percent) of persons who tried their first cigarette in 2000 were under age 18. Among persons who first began daily smoking in 2001, about half (53 percent) were under age 18. Of the approximately 4,000 new regular smokers per day in 2001, approximately 2,000 per day were under age 18.
- Initiation of cigar smoking more than doubled during the 1990s, from 1.6 million new users in 1990 to 3.9 million in 1998. In 2001, the number of new users dropped to 3.3 million. Since 1990, youths under 18 have constituted an increasingly greater proportion of the number of new cigar smokers, from 21 percent in 1991 to 48 percent in 2001

P

10. Discussion

This report presents findings from the 2002 National Survey on Drug Use and Health (NSDUH). Conducted since 1971 and previously named the National Household Survey on Drug Abuse (NHSDA), the survey underwent several methodological improvements in 2002 that have affected prevalence estimates. As a result, the 2002 estimates are not comparable with estimates from 2001 and earlier surveys. The primary focus of the report is on the numbers of persons and rates for a variety of measures related to substance use and mental health in 2002, including comparisons across sociodemographic and geographic subgroups of the U.S. population. Some of the most important findings for 2002 are presented in the Highlights section of this report.

The prevalence estimates from the 2002 NSDUH are uniformly higher than the corresponding estimates from the 2001 NHSDA. Analyses to date of the effects of the methodological changes in 2002 (see **Appendix C**) indicate that the higher prevalences in 2002 mostly reflect an increase in the reporting of these behaviors by survey respondents due to the $30 incentive payment and other survey improvements, not actual increases in the prevalence of these behaviors and problems. The results of these analyses were presented to a panel of survey methodology experts, who concluded that 2002 estimates should not be compared with 2001 and earlier estimates. The panel also concluded that it would not be possible to develop a method of "adjusting" pre-2002 data to make them comparable for trend assessment.

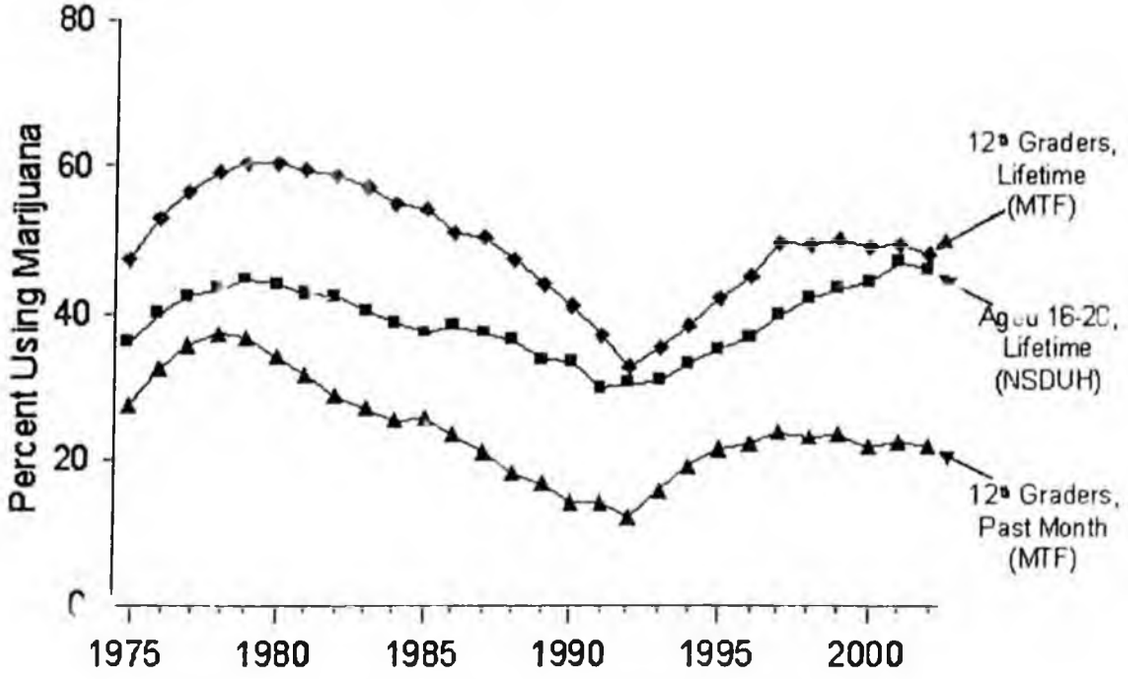
Although traditional comparisons of estimates across years cannot be used to examine recent trends, it is possible to study trends by constructing "retrospective" estimates of lifetime prevalence and incidence produced from the 2002 NSDUH data alone (see **Chapters 5** and **6**). These trends can be compared with the results from Monitoring the Future (MTF), a study sponsored by the National Institute on Drug Abuse (NIDA). **Figure 10.1** shows the trends in lifetime marijuana use based on the 2002 NSDUH retrospective estimates for youths aged 16 to 20, as well as trends in lifetime marijuana use and past month marijuana use among the MTF 12th graders. The two data sources produce similar trends in lifetime prevalence, and the MTF trend in past month use also is similar to the trend for lifetime use. These trends also are consistent with trends for youths aged 12 to 17 and young adults aged 18 to 25 discussed in **Chapter 5**. They show very low rates of illicit drug use in the mid-1960s. In 1965, only 1.8 percent of youths had ever used marijuana. There were dramatic increases in use during the late 1960s and 1970s, and by 1979, 19.6 percent of youths had ever used marijuana. After that, use declined until 1991, when 11.5 percent of youths had ever used marijuana. The trend reversed during the 1990s, reaching 21.9 percent in 2001 before dropping slightly in 2002 to 20.6 percent.

Retrospective estimates based on 2002 NSDUH data are presented in **Table 10.1** for selected substances along with related estimates from the 2002 MTF for youths and young adults. The NSDUH data show decreases from 2001 to 2002 in lifetime use of marijuana, LSD, and cigarettes among youths, but an increase for cocaine among youths. For young adults aged 18 to 25 during this time period, there was a slight increase in lifetime cocaine and Ecstasy use and a decrease in lifetime LSD use. These NSDUH results are generally consistent with MTF trends, with a few exceptions. MTF shows no change in lifetime cocaine use among youths, and it shows decreases in youth Ecstasy and alcohol use not found in

the NSDUH estimates.

Estimates of incidence, or first-time use, also suggest that illicit drug use prevalence had been very low during the early 1960s, but began to increase during the mid-1960s as substantial numbers of young people initiated the use of marijuana. As discussed in **Chapter 6**, annual marijuana incidence increased from about 0.8 million new users in 1965 until it reached a peak of 3.5 million initiates per year during 1973 to 1978, just before the prevalence rates peaked. Interestingly, the annual number of marijuana initiates reached a low point in 1990 (1.6 million), then increased, 2 years before the increase in youth prevalence occurred. This finding demonstrates the value of analyzing the incidence data and using it to forecast future trends in prevalence. Assuming this relationship between incidence and prevalence continues to hold, the continuing high levels (between 2.5 and 3.0 million initiates per year) of marijuana incidence between 1995 and 2001 indicate that substantial declines in youth prevalence may not occur in the near future. However, the NSDUH incidence estimates for youths under age 18 indicate a decline from 2000 to 2001 (from 2.1 million to 1.7 million), which suggests that youth prevalence may decline. The NSDUH youth lifetime prevalence and MTF past month prevalence estimates do show decreases from 2001 to 2002. High rates of marijuana initiation during the 1970s among the cohort identified as the "baby boomers" have resulted in an increase in the numbers needing treatment for substance abuse problems. The increase in marijuana initiation rates during the 1990s may have the same result.

Figure 10.1 Marijuana Use among NSDUH Youths Aged 16 to 20 and MTF 12th Graders: 1975–2002



D

Table 10.1 Comparison of NSDUH and MTF Prevalence Rates

	NSDUH 12–17		MTF 8th and 10th		NSDUH 18–25		MTF 19–24	
	2001	2002	2001	2002	2001	2002	2001	2002
Marijuana								
Lifetime	21.9	20.6	30.3	29.0	53.0	53.8	56.3	56.1
Past Month	--	8.2	14.5	13.1	--	17.3	19.6	19.8
Cocaine								
Lifetime	.3	2.7	5.0	4.9	14.9	15.4	12.4	12.9
Past Month	--	0.6	1.3	1.4	--	2.0	2.5	2.5
Ecstasy								
Lifetime	3.2	3.3	6.6	5.5	13.5	15.1	15.0	16.0
Past Month	--	0.5	2.2	1.6	--	1.1	2.2	1.6
LSD								
Lifetime	3.3	2.7	4.9	3.8	16.6	15.9	15.2	13.9
Past Month	--	0.2	1.3	0.7	--	0.1	1.0	0.4
Alcohol								
Lifetime	43.3	43.4	60.3	57.0	85.5	86.7	88.1	88.4
Past Month	--	17.6	30.3	27.5	--	60.5	67.1	67.7
Cigarettes								
Lifetime	37.3	33.3	44.7	39.4	71.3	71.2	--	--
Past Month	--	13.0	16.8	14.2	--	40.8	32.6	31.4

-- Not available.

Note: NSDUH data in this table are retrospective estimates from the 2002 data. MTF data for 8th and 10th graders are simple averages of estimates for those two grades reported in Johnston, O'Malley, and Bachman (2003b). MTF data for youths aged 19 to 24 are simple averages of estimates for youths aged 19–20, 21–22, and 23–24 reported in Johnston et al. (2003c).

Sources: SAMHSA, Office of Applied Studies, National Survey on Drug Use and Health, 2002.
The Monitoring the Future Study, University of Michigan, 2001 and 2002.

---

[1] RTI International is a trade name of Research Triangle Institute.

Drug and Alcohol Services Information System

The DASIS Report

March 29, 2002

Treatment Referral Sources for Adolescent Marijuana Users

In Brief

- By 1999, more than half of all adolescent marijuana admissions were through the criminal justice system
- Adolescent marijuana admissions through the criminal justice system increased at a higher rate than admissions through other sources

Marijuana was the most common drug of abuse among admissions of adolescents aged 12 to 17 reported to the Treatment Episode Data Set (TEDS) in 1999. The number of adolescent marijuana admissions increased 260 percent between 1992 and 1999. TEDS collects data on nation admissions to primarily publicly f d substance abuse treatment faciliti "Admissions" represent annual treatment episodes rather than the number of individuals entering treatment.

Generally, adolescents entered treatment through the intervention of another person or agency. The Treatment Episode Data Set (TEDS) collects information on the referral source for people entering substance abuse treatment in the public sector. TEDS defines the primary referral sources as follows:

Court/criminal justice referral/DWI/DUI—police official, judge, prosecutor, probation officer or other person affiliated with a Federal, State, or county judicial system; court referral for DWI/DUI; referrals in lieu of or for deferred prosecution, during pretrial release, or before or after adjudication, pre-parole, pre-release, work or home furlough, TASC, or civil commitment

Self- or individual referral—self-referral; family member, friend, or other individual

School—school principal, counselor, or teacher; student assistance program, school system, or educational agency

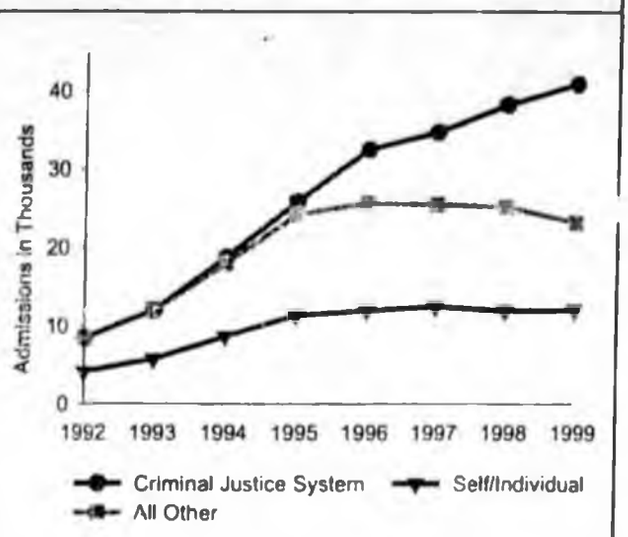
The DASIS Report is published periodically by the Office of Applied Studies, Substance Abuse and Mental Health Services Administration (**SAMHSA**). All material appearing in this report is in the public domain and may be reproduced or copied without permission from **SAMHSA**. Additional copies of this report may be downloaded from http://www.samhsa.gov/oas/facts.cfm. Citation of the source is appreciated. Other reports from the Office of Applied Studies are also available on-line: http://www.DrugAbuseStatistics.samhsa.gov/.

Table 1. Percent Distribution of Adolescent Marijuana Admissions, by Referral Source: 1992-1999*

	1992	1994	1996	1997	1998	1999
No. of Admissions (Thousands)	22	47	73	76	81	79
	Percent Distribution					
Criminal Justice	40.2	41.3	46.2	47.7	50.6	53.6
Self/Individual	19.6	19.0	17.1	17.2	15.9	15.9
School	16.3	16.0	13.2	12.1	11.3	10.5
SA/HC Provider	13.9	14.1	14.0	13.6	12.6	11.7
Other	10.0	9.5	9.4	9.3	9.3	8.3
Total	100.0	100.0	100.0	100.0	100.0	100.0

*1993 and 1995 not shown.
SA=Substance Abuse; HC=Health Care

Figure 1. Number of Adolescent Marijuana Admissions, by Referral Source: 1992-1999



Source: 1999 SAMHSA Treatment Episode Data Set (TEDS)

Other referral sources—substance abuse or health care providers; community, religious, or governmental organizations or agencies providing social services

Trends in Referral Source

In 1999, there were about 79,000 admissions for marijuana/hashish treatment among adolescents aged 12 to 17 (Table 1). This represented an increase from 22,000 admissions in 1992 and 47,000 in 1994. The most common referral source for adolescent marijuana admissions was the criminal justice system. Together with self- or individual referral, these sources account for 60 to 70 percent of all adolescent marijuana admissions in all years.*

In 1999, over half (54 percent) of all adolescent marijuana admissions were through the criminal justice system. This represented a significant increase from the 40 percent referred through the criminal justice system in 1992. The proportions of admissions from other referral sources declined. For example, from 1992 to 1999, self- or individual referrals declined from 20 percent to 16 percent, and referrals through schools declined from 16 percent to 11 percent.

The number of adolescent marijuana admissions increased from 1992 to 1995 for all referral sources (Figure 1). However, while the number of admissions from other referral sources stabilized after 1995, those from the criminal justice system continued to increase.

Referral Source by Sex

There was an overall increase in marijuana admissions for male adolescents from 1994 to 1999 attributable primarily to increased criminal justice referrals (Figure 2). While admissions for marijuana abuse increased by 67 percent from 1994 to 1999 among males, the percentage of those admissions due to criminal justice referrals increased by 108 percent. For females, marijuana admissions between 1994 and 1996 increased 67 percent and criminal justice referrals increased 111 percent. Between 1996 and 1999, however, there was only a 2 percent increase in female marijuana admissions but a 29 percent increase in criminal justice referrals.

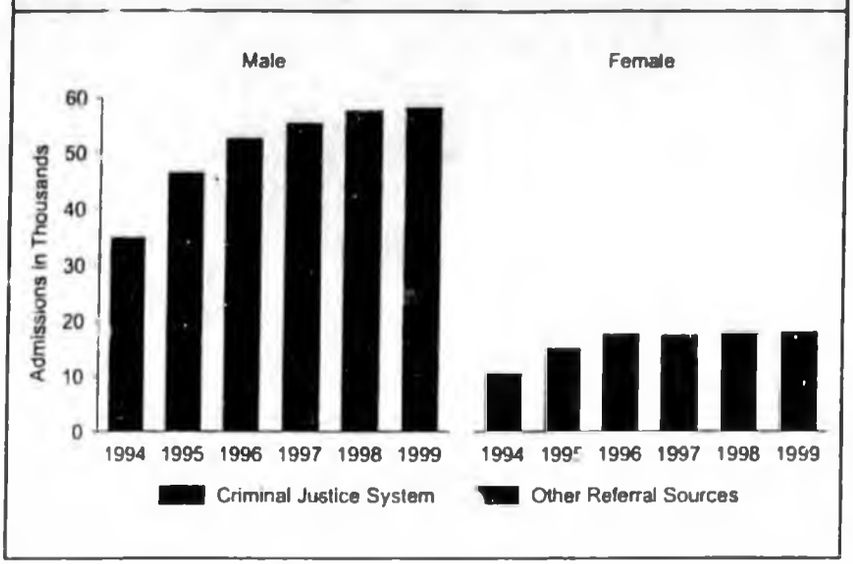
Among all adolescent marijuana admissions, there were three males for every female from 1994 to 1999. Among criminal justice referrals for marijuana abuse, the ratio was six males for every female in 1994. The ratio had declined to 4.5 to 1 by 1999 as more females were referred to treatment for marijuana abuse through the criminal justice system.

Referral Source by Age

Marijuana admissions for 12 to 14 year olds increased 56 percent

*Self-referral is the most common source for adolescent heroin admissions.

Figure 2. Number of Adolescent Marijuana Admissions, by Sex and Referral Source: 1994-1999



The Drug and Alcohol Services Information System (DASIS) is an integrated data system maintained by the Office of Applied Studies, Substance Abuse and Mental Health Services Administration (SAMHSA). One component of DASIS is the Treatment Episode Data Set (TEDS). TEDS is a compilation of data on the demographic characteristics and substance abuse problems of those admitted for substance abuse treatment. The information comes primarily from facilities that receive some public funding. Information on treatment admissions are routinely collected by State administrative systems and then submitted to SAMHSA in a standard format. Approximately 1.6 million records are included in TEDS each year. TEDS records represent admissions rather than individuals, as a person may be admitted to treatment more than once.

The DASIS Report is prepared by the Office of Applied Studies, SAMHSA; Synectics for Management Decisions, Inc., Arlington, Virginia; and RTI, Research Triangle Park, North Carolina.

Information and data for this issue are based on data reported to TEDS through April 16, 2001.

Access the latest TEDS reports at: www.DrugAbuseStatistics.SAMHSA.gov
Access the latest TEDS public use files at: www.icpsr.umich.edu/SAMHDA/teds.html

DEPT. OF HEALTH & HUMAN SERVICES
Substance Abuse & Mental Health Services Admin
Office of Applied Studies — www.samhsa.gov

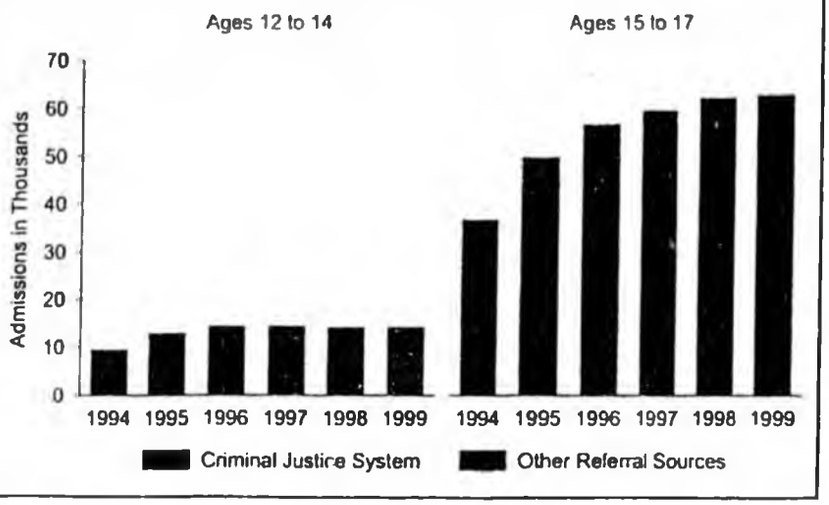
between 1994 and 1996, but decreased slightly (2 percent) from 1996 to 1999 (Figure 3). Marijuana admissions for 15 to 17 year olds increased by 54 percent between 1994 and 1996 but slowed to an 11 percent increase between 1996 and 1999. Criminal justice referrals among marijuana admissions for 12 to 14 year olds and 15 to 17 year olds have increased 21 and 27 percent, respectively, from 1996 to 1999.

Referral Source by Race/Ethnicity

Adolescent marijuana admissions averaged 66 percent White, 21 percent Black, and 13 percent Hispanic between 1994 and 1999 (data not shown). Each racial/ethnic group exhibited the same pattern over that time period—increased numbers of marijuana admissions driven by an increase in treatment referrals through the criminal justice system.

The numbers of Hispanic and Black adolescent marijuana admissions increased by 73 percent each, while the number of White admissions increased by 60 percent. Criminal justice referrals among Hispanic adolescents increased by 129 percent compared with 26 percent for referrals from other sources. Among White adolescents, criminal justice referrals increased by 119 percent compared with 26 percent from other sources. Black adolescents had the lowest percentage increase in criminal justice referrals for marijuana, 91 percent, while referrals from other sources for Black adolescents increased by 50 percent.

Figure 3. Number of Adolescent Marijuana Admissions, by Age Group and Referral Source: 1994-1999



FOR DEBATE

Reassessing the marijuana gateway effect

Andrew R. Morral, Daniel F. McCaffrey & Susan M. Paddock

Drug Policy Research Center, RAND, Arlington, VA, USA

Correspondence to:
Andrew Morral
Senior Behavioral Scientist
Drug Policy Research Center
RAND
1200 South Hayes Street
Arlington, VA 22202-5050
USA
Tel: +1 703 413 1100, ext. 5119
E-mail: morral@rand.org

Submitted 16 October 2001;
initial review completed 12 April 2002;
final version accepted 4 June 2002

ABSTRACT

Aims Strong associations between marijuana use and initiation of hard drugs are cited in support of the claim that marijuana use *per se* increases youths' risk of initiating hard drugs (the 'marijuana gateway' effect). This report examines whether these associations could instead be explained as the result of a common factor—drug use propensity—influencing the probability of both marijuana and other drug use.

Design A model of adolescent drug use initiation in the United States is constructed using parameter estimates derived from US household surveys of drug use conducted between 1982 and 1994. Model assumptions include: (1) individuals have a non-specific random propensity to use drugs that is normally distributed in the population; (2) this propensity is correlated with the risk of having an opportunity to use drugs and with the probability of using them given an opportunity, and (3) neither use nor opportunity to use marijuana is associated with hard drug initiation after conditioning on drug use propensity.

Findings Each of the phenomena used to support claims of a 'marijuana gateway effect' are reproduced by the model, even though marijuana use has no causal influence over hard drug initiation in the model.

Conclusions Marijuana gateway effects may exist. However, our results demonstrate that the phenomena used to motivate belief in such an effect are consistent with an alternative simple, plausible common-factor model. No gateway effect is required to explain them. The common-factor model has implications for evaluating marijuana control policies that differ significantly from those supported by the gateway model.

KEYWORDS Adolescents, drug use, marijuana gateway effect, mathematical model.

INTRODUCTION

Alcohol, tobacco and marijuana are widely regarded as 'gateway' drugs. Although the gateway concept admits a number of definitions, one in particular predominates in drug policy discussions: use of gateway drugs causes youths to have an increased risk of progressing to other, more serious drugs. For instance, in debates on marijuana decriminalization or the medicinal use of marijuana, policy makers frequently suggest that use of marijuana increases youths' risk of initiating more dangerous drugs such as cocaine and heroin (US Congressional Record 1998, 1999). Although marijuana is the least prevalent of the three principal gateway drugs, it is currently the focus of extensive policy reassessment in the United States, Canada, Western Europe and Australia. Using a simulation model, we demonstrate that the primary evidence supporting the marijuana gateway effect can be explained completely by the order in which youths first have the opportunity to use marijuana and other drugs, and by assuming a non-specific liability to use drugs, without any assumption that use of marijuana contributes to the risk of initiating use of hard drugs. We argue that although marijuana gateway effects may truly exist, available evidence does not favor the marijuana gateway effect over the alternative hypothesis that mari-

© 2002 Society for the Study of Addiction to Alcohol and Other Drugs

juana and hard drug initiation are correlated because both are influenced by individuals' heterogenous liabilities to try drugs.

The popular concern that marijuana use increases the risk of progressing to other, more serious drugs is a long-standing one, and has influenced US drug policy since at least the 1950s (Goode 1970; Whitebread & Bonnie 1972; National Research Council 1982). Some social scientists have also suggested that marijuana gateway effects probably account for several phenomena observed in adolescent drug use initiation patterns (e.g. Goode 1970; O'Donnell & Clayton 1982; Yamaguchi & Kandel 1984b). Three such phenomena represent the primary evidence for a marijuana gateway effect. The first concerns the *relative risk* of hard drug initiation for adolescent marijuana users vs. non-users. In general, marijuana users in many countries appear to have a significantly elevated risk for drug use progression (Adler & Kandel 1981; Kandel 1975; Blaze-Temple & Lo 1992; Stenbacka, Allebeck & Romelsjö 1993; Beenstock & Rahav 2002). Indeed, one US study found their risk to be 85 times those of non-users of marijuana (Center on Addiction and Substance Abuse 1994). Another form of relative risk that is occasionally cited in support of the gateway effect is that younger marijuana initiates have a higher risk of initiating hard drug use than older marijuana initiates (O'Donnell & Clayton 1982; Yamaguchi & Kandel 1984b; Kandel & Yamaguchi 1993; Center on Addiction and Substance Abuse 1994). This relative risk differs from the first only insofar as it finds that risk of hard drug initiation is conditioned on a characteristic of the user (age), rather than on marijuana use alone. Therefore, it does not provide strong evidence supporting a gateway effect.

The second observation routinely cited in support of the marijuana gateway effect concerns the remarkably invariant *ordering* in adolescents' initiation of different drug classes. Adolescents rarely initiate hard drug use before marijuana (Ellickson *et al.* 1992; Kandel, Yamaguchi & Chen 1992; O'Donnell & Clayton 1982; Yamaguchi & Kandel 1984a). For instance, in a longitudinal sample of 1265 New Zealand youths between the ages of 15 and 21, Fergusson & Horwood (2000) found only three cases reporting use of hard drugs before marijuana. This figure is dramatically lower than the roughly 124 such cases that would be expected from annual incidence rates if use of marijuana and hard drugs were independent.

The third phenomenon used to support claims of a marijuana gateway effect concerns the strong relationship between the frequency of marijuana consumption and the risk of hard drug initiation: as the frequency of marijuana use increases, so too does the risk of initiating hard drug use (Ellickson *et al.* 1992; Kandel *et al.* 1992; Fergusson & Horwood 2000). Fergusson & Horwood (2000), for instance, developed a proportional hazards model suggesting that youths reporting 50 or more uses of cannabis in the past year had hazards of progression to hard drugs that were more than 140 times greater than those for youths reporting no use of cannabis. Findings like this suggest an even stronger form of the marijuana gateway effect defined earlier: not only does marijuana use increase youths' risk of hard drug initiation, but every instance of marijuana use adds to that risk. For convenience, we refer to this phenomenon as marijuana's apparent *dose–response effect* on hard drug initiation.

The three phenomena of relative risk, ordering in drug use initiation and dose–response are not sufficient to prove that use of marijuana, rather than some associated factor, increases the risk of hard drug initiation (Joy *et al.* 1999). Indeed, a frequently cited alternative explanation is that a common factor, which we might refer to generically as a propensity for drug use, could influence use of both marijuana and hard drugs, thereby causing initiation of these drugs to be correlated (Goode 1972; Huba *et al.* 1981; Donovan & Jessor 1985; Hays *et al.* 1987; MacCoun 1998). For instance, if high drug use propensities elevate individuals' risk for use of both marijuana and hard drugs, this could explain why marijuana users have a higher relative risk of hard drug initiation in comparison with non-users.

This 'common-factor' model does not immediately account for the ordering and dose–response phenomena. To make sense of these observations, proponents of the common-factor approach suggest that ordering in drug use initiation results from the order in which opportunities to use marijuana and hard drugs are presented to young people (Goode 1972; Jessor & Jessor 1980). Those with the highest propensities to use drugs are likely to use the first one offered to them, and that happens to be marijuana in most cases. Moreover, if a high drug use propensity is associated with greater frequencies of drug use, the common-factor theory can also account for the dose–response phenomenon: marijuana use frequency is associated with risk of hard drug initiation because both are controlled by drug use propensity.

The common-factor model is appealing in part because it takes account of what is a substantial scientific literature demonstrating the existence of genetic, familial and environmental characteristics associated with a generalized risk of using both marijuana and hard drugs. For instance, several studies examining drug use among monozygotic and dizygotic twins in the USA demonstrate genetic and family environment contributions to the likelihood of any drug use (van den Bree *et al.* 1998) and any drug use initiation (Tsuang *et al.* 1998; Kendler *et al.* 1999, 2000). Similarly, community drug use or drug

© 2002 Society for the Study of Addiction to Alcohol and Other Drugs

availability may contribute to individuals' risk of using drugs (Lillie-Blanton, Anthony & Schuster 1993).

Although the common-factor model is plausible, previous research has not demonstrated that propensities to use drugs and environmental factors such as drug use opportunities could, in fact, account for the strong relative risk, ordering and dose–response phenomena observed among adolescents. Indeed, two lines of research provide some evidence that the common-factor model cannot account for drug use initiation without assuming a marijuana gateway effect. Firstly, several studies examine the association between marijuana use and the risk of hard drug initiation after controlling for a large number of risk factors, such as delinquency and peer drug use (Yamaguchi & Kandel 1984b; Fergusson & Horwood 2000). By the logic of this approach, any residual marijuana effect on hard drug initiation that remains after controlling for these candidate common factors lends credence to the suggestion that marijuana use *per se* increases the risk of hard drug initiation. However, if the selected covariates are less good proxies for the propensity to use drugs than is marijuana use itself, these findings are perfectly consistent with a strict common-factor model. Because this approach does not observe all or even most individual risk factors, it provides little persuasive evidence against a common-factor explanation. We will illustrate this point with data derived from the model described later on in this paper.

A second approach to contrasting the gateway and common-factor models of drug use initiation uses instrumental variables in an effort to account for both observed and unobserved person-level risk of initiation. Two of these studies (DeSimone 1998; Pacula 1998) suggest that common factors alone cannot explain observed gateway phenomena. The third (Beenstock & Rahav 2002) provides qualified evidence that observed marijuana gateway phenomena are not attributable to a gateway effect, but instead derive from individuals' predispositions to use both marijuana and hard drugs. However, none of these studies take into account the observation that opportunities to use marijuana precede those for hard drugs, and may themselves be associated with propensity to use drugs through, for instance, drug-seeking behavior. This is a critical omission, since proponents of the common-factor model have consistently cited the ordering in drug use opportunities as an essential part of the explanation of ordering in drug use initiation. Indeed, in a series of analyses on US and Panamanian data, Anthony, Van Etten and colleagues have shown that gender, race and neighborhood differences observed in rates of drug use initiation are attributable, to a large extent, to differences in the rates at which groups are exposed to drug use opportunities (Crum, Lillie-Blanton & Anthony 1996; Van Etten, Neumark & Anthony 1997, 1999; Deiva *et al.* 1999; Van Etten & Anthony 1999). Thus, econometric models have not tested the common-factor model adequately.

In this report we describe a Monte Carlo model of drug use initiation with parameters selected to match the drug use experiences of the population of US residents under the age of 22. The model describes the joint distribution of four events: the ages of first opportunity to use marijuana and hard drugs, and the ages of first use of marijuana and hard drugs. Each of these events depends on a common factor—drug use propensity—but conditional on this factor, the ages of first opportunity to use and first use of marijuana are independent of opportunity to use and use of hard drugs. Thus, the model is designed to exclude any causal gateway effect. Random draws from the modeled joint distribution are used to examine the relative risk, ordering and dose–response phenomena that might be expected by chance in the US if model assumptions are accurate.

METHODS

Procedure

We build a common-factor model of adolescent drug use initiation using parameter estimates derived from a representative sample of youths in the US population. With this model, we observe the rates at which phenomena of relative risk, ordering and dose–response can occur when no causal gateway effects are present. We compare these rates to those observed in the sample of US youths to demonstrate that a common-factor model designed to match US rates of drug use initiation and drug use opportunities without a gateway effect can still reproduce all of the gateway phenomena observed in the population. In the remainder of this section we describe the model specification and the statistical methods used to estimate the values for the model parameters and the gateway effects observed among youths in the US.

Model specification

Drug use propensity

Each case is assigned an arbitrary propensity to use drugs, θ, which we conceptualize as the resultant shared risk of reporting use of both marijuana and hard drugs after accounting for all person-level risk factors that remain more or less constant during adolescence. Examples of such invariant predispositions to report drug use could include genetic and family environmental history factors (Kendler *et al.* 1999; Tsuang *et al.* 1998; van den Bree *et al.* 1998; Kendler *et al.* 2000) and community

© 2002 Society for the Study of Addiction to Alcohol and Other Drugs

drug use or drug availability (Lillie-Blanton, Anthony & Schuster 1993). We assume that propensity is correlated not just with the probability of drug use, but also with the probability of having the opportunity to use drugs at any particular age. This assumption is supported by several considerations. Firstly, we define propensity as resulting, in part, from environmental risk factors. Local drug use norms and the availability of drugs are examples of environmental influences likely to affect both individuals' risk of drug use and their risk of having an opportunity to use drugs (Lillie-Blanton *et al.* 1993). Drug use propensity is also likely to be correlated with age of first opportunity to use drugs because individuals with greater propensities are more likely to seek out drug use opportunities, or recognize them when they present themselves. Finally, empirical studies document a strong association between the risk of drug offers (and, by extension, opportunities) and a range of characteristics likely to correlate with drug use propensity, such as smoking, alcohol use and parental substance use (Stenbacka *et al.* 1993). Each of these considerations suggests propensity will be correlated with drug use opportunities as well as drug use.

Although epidemiological studies provide evidence supporting the existence of a drug use propensity (Tsuang *et al.* 1998; van den Bree *et al.* 1998; Kendler *et al.* 1999, 2000), no information exists about its distribution in the population of adolescents. Thus, in the model we draw drug use propensities, θ, at random from a standard normal distribution.

Drug use opportunities

We assume that for any individual, the age of first opportunity to use marijuana, Y_M, and the age of first opportunity to use hard drugs, Y_H, are drawn at random from distributions describing the risk of first marijuana or hard drug use opportunity at each age. These risk distributions are functions of the individual's drug use propensity: higher propensities shift the risk curves so that exposure to a drug use opportunity is more likely at earlier ages. Thus, between the ages 0 and 22, we define the cumulative distribution of age of first opportunity to use marijuana as $1 - S_{YM}(t, \theta)$, where $S_{YM}(t, \theta)$ is the survival function describing the probability that age of first opportunity to use marijuana exceeds t, conditional upon θ. Similarly, the distribution of age of first opportunity to use hard drugs is given by $1 - S_{YH}(t, \theta)$. We use a frailty model to construct these conditional survival functions. Frailty models are a standard approach to describing joint survival functions when risks for each modeled event are presumed to correlate due to heterogeneity across individuals in the population (Hosmer & Lemeshow 1999; Therneau & Grambsch 2000):

$$S_{YM}(t, \theta) = S^{*}_{YM}(t)^{f(\theta)} \text{ for marijuana, and} \quad (1)$$

$$S_{YH}(t, \theta) = S^{*}_{YH}(t)^{f(\theta)} \text{ for hard drugs.} \quad (2)$$

The function f transforms θ to the corresponding value from the Gamma distribution with mean of 1 and variance β_1. Under this parameterization the frailty model produces a correlation between age of first use opportunities Y_M and Y_H that increases as β_1 grows. We estimate β_1 and the functions $S^{*}_{YM}(t)$ and $S^{*}_{YH}(t)$ from US data on adolescent drug use opportunities, as described below. The estimated functions are defined so that marginal survival functions for the model (expected values over θ of $S_{YM}(t, \theta)$ and $S_{YH}(t, \theta)$) equal marginal survival functions fit to our sample of US data.

Drug use initiation

For any individual, first use of marijuana, Z_M, is a random variable drawn from a distribution describing the individual's risk of initiating marijuana at each age. Each individual's risk distribution depends on his or her drug use propensity and age when first presented the opportunity to use marijuana, Y_M. Youths with greater propensities have a greater risk of use at every age, beginning with their age at first opportunity to use a drug.

Specifically, given an individual's drug use propensity and age of first opportunity to use marijuana, the cumulative probability distribution for age of marijuana initiation is given by $1 - S_{ZM}(t, \theta, Y_M)$, where $S_{ZM}(t, \theta, Y_M)$ is the conditional survival function for marijuana initiation. For $t = 8, 9 \ldots 22$,

$$S_{ZM}(t, \theta, Y_M) = \begin{cases} 0, \text{ if } Y_M > t \\ 1 - \pi_M, \text{ if } Y_M \le 8,\ t = 8 \\ F_{\beta_2}(\psi^{*}_{Mt} - \theta)\, S_{ZM}(t-1, \theta, Y_M), \\ \quad \text{if } Y_M \le t,\ t > 8. \end{cases} \quad (3)$$

where F_{β_2} is the cumulative probability function for a normal distribution with mean 0 and variance β_2. Thus, the parameters π_M and ψ^{*}_{Mt}, $t = 9 \ldots 22$ define for the model the marginal probabilities $Pr\{Z_M < 9 \mid Y_M < 9\}$ and the marginal probabilities $Pr\{Z_M = t \mid Y_M \le t,\ Z_M \ge t\} = E[F_{\beta_2}(\psi^{*}_{Mt} - \theta_i)]$, respectively. Age of initiation of hard drugs, Z_H, is drawn independent of Y_M and Z_M from an analogous distribution defined by the parameters β_1, π_H and ψ^{*}_{Ht}, $t = 9 \ldots 22$.

The value of β_2 is the same for both marijuana and hard drugs. This parameter affects the correlation between Z_M and Z_H by controlling the influence of propensity on the probability of initiation. It is chosen so that the model produces a correlation between $L_M = Z_M - Y_M$ and $L_H = Z_H - Y_H$ for youths who used both marijuana and hard drugs by age 22 that matches the same correlation observed in data on adolescents in the US. We set the remaining parameter values so that the marginal

© 2002 Society for the Study of Addiction to Alcohol and Other Drugs

probabilities in the model (i.e. $Pr(Z_M < 9 \mid Y_M < 9)$, $Pr(Z_H < 9 \mid Y_H < 9)$, $Pr(Z_M = t \mid Y_M \leq t,\ Z_M \geq t)$ and $Pr(Z_H = t \mid Y_H \leq t,\ Z_H \geq t)$, $t = 9 \ldots 22$) match the corresponding estimates from our sample of data from the US population.

The joint distribution for Y_M, Z_M, Y_H and Z_H is:

$$\begin{aligned}&Pr\{Y_M = y_M,\ Z_M = z_M,\ Y_H = y_H,\ Z_H = z_H\} = \\ &\int [S_{ZM}(z_M - 1,\ y_M,\ \theta) - [S_{ZM}(z_M,\ y_M,\ \theta)] \times \\ &[S_{YM}(y_M - 1,\ \theta) - S_{YM}(y_M,\ \theta)] \times \\ &[S_{ZH}(z_H - 1,\ y_H,\ \theta) - S_{ZH}(z_H,\ y_H,\ \theta)] \times \\ &[S_{YH}(y_H - 1,\ \theta) - S_{YH}(y_H,\ \theta)]]\ \phi(\theta) d\theta.\end{aligned} \quad (4)$$

where ϕ denotes the density function for a standard normal random variable.

Figure 1 depicts our procedure for drawing random observations from this distribution.

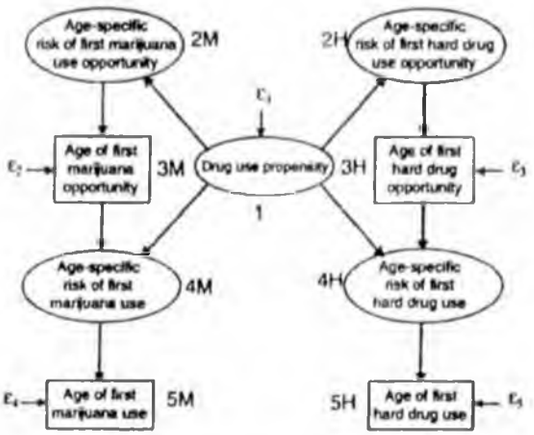


Figure 1 Procedure for generating simulated observations from the model of adolescent drug use initiation. Firstly, a random drug use propensity, θ, is drawn (1), which uniquely determines the risks (or probabilities) of having an opportunity to use marijuana, $S_{YM}(t, \theta)$, and hard drugs, $S_{YH}(t, \theta)$, at every age $t = 0$–22 (2M & 2H; note that epsilons in the figure are used to denote draws of separate, independent random variables from the indicated distributions). A random variable is then drawn from the distribution defined by S_{YM} to determine the age of first opportunity to use marijuana, Y_M, and an independent random variable is drawn to determine the age of the first opportunity to use hard drugs, Y_H (3M & 3H). The values of θ and Y_M then uniquely determine the risk of marijuana initiation at every age greater than Y_M, $S_{ZM}(t, \theta, Y_M)$, and similarly the values of θ and Y_H uniquely determine the risk of hard drug initiation for every age greater than Y_H, $S_{ZH}(t, \theta, Y_H)$ (4M & 4H). Another set of random variables that are independent of each other and all previous random variables are then drawn from the distributions determined by $S_{ZM}(t, \theta, Y_M)$ and $S_{ZH}(t, \theta, Y_H)$ to set age of initiation of marijuana, Z_M, and hard drugs, Z_H (5M & 5H). The additional parameters of the model were all determined to match the marginal distribution of a sample of US youths from the NHSDA

Marijuana use frequency

To examine the dose–response relationship between marijuana use frequency and the risk of hard drug initiation, we categorize each case that initiated use of marijuana into one of five past year use frequencies (no past year use, 1–2 times, 3–11 times, 12–51 times and 52 or more times) at each age, beginning with the age of marijuana initiation. Cases are assigned a marijuana use intensity random effect, ξ_u, which is used to draw a marijuana use frequency from the distribution of use frequencies observed in the US sample with corresponding ages and number of years since marijuana initiation.

We hypothesize that marijuana use frequency is positively correlated with propensity to use drugs. However, because propensity is unobservable, we know of no good data for estimating this correlation. Therefore, we conduct a sensitivity analysis in which the risk of hard drug initiation at each marijuana use frequency is examined as the correlation between ξ_u and θ, ranges from 0 to 1.

Parameter estimation

This section summarizes the statistical methods used to estimate values for each of the model's parameters, β_1, S^*_{YM}, S^*_{YH}, β_2, π_M, π_H and ψ^*_M, and ψ^*_H $t = 9 \ldots 22$. It also describes the methods used to estimate the observed values of the relative risk, ordering and dose–response effects from a sample of data from the US population.

Data source

Estimates for the model parameters and observed values of the relative risk, ordering and dose–response effects were derived from the National Household Survey of Drug Abuse (NHSDA). The NHSDA is an ongoing probability sample survey of the US civilian, non-institutionalized population aged 12 years and older (US Department of Health and Human Services 1999). Data on all 58 846 respondents, 12–25 years of age, from birth cohorts 1964 through 1982, were pooled from the 1982 through 1994-A NHSDA in order to create stable estimates of quite rare events. This pooling was justified by preliminary analyses suggesting that drug use opportunity and initiation survival probabilities were similar across birth cohorts. NHSDA sample weights were applied to make the pooled sample representative of the included birth cohorts. The selected survey years included questions on the ages of initiation and first opportunities to use marijuana, heroin, cocaine and hallucinogens. More recent data on drug use opportunities are not available because these questions were dropped from subsequent administrations of the NHSDA. First opportunity to use and initiation into use of hard drugs were defined as the earliest

© 2002 Society for the Study of Addiction to Alcohol and Other Drugs

reported age of opportunity and use of heroin, cocaine or hallucinogens. Because these data are self-reports of illicit behavior and improper events, they are subject to a variety of well-known biases. Nevertheless, longitudinal investigations indicate that ordering of drug use initiation, a central concern of the present analysis, is reported reliably (Golub *et al.* 2000). Therefore, for our purposes, recall bias is unlikely to significantly affect our principal findings.

Statistical methods

Estimation of β_1 To best match the correlation in ages of first opportunities to use marijuana and hard drugs observed in the NHSDA, we selected $\beta_1 = 3.22$, the maximum likelihood estimate of β_1 for model (1 & 2) fit to a 5% random sample of the NHSDA data, stratified by year of survey administration and birth cohort. The estimate was obtained using the S-Plus Software (MathSoft, Seattle, WA, USA) using the methods described in Therneau & Grambsch (2000).

Estimation of S^*_{YM} and S^*_{YH} The estimates of S^*_{YM} and S^*_{YH} derived directly from the marginal survival functions $S_{YM}(t)$ and $S_{YH}(t)$, which we estimate using data from the NHSDA. We used the actuarial life table method (Miller 1981) to estimate the survival function for first opportunity to use marijuana, $S_{YM}(t)$, defined as the probability that a randomly chosen individual's first opportunity to use marijuana occurs after age t. The actuarial life table method estimates the probability of a first opportunity to use at age t as the ratio of the number of individuals who report the first opportunity at age t to the number of individuals eligible to have a first opportunity at age t. Individuals are ineligible if they had a previous opportunity to use or if they are censored. Respondents are censored if they are interviewed before age t and report no opportunities to use prior to the interview. We used weighted sums in the ratio to account for unequal probability of selection in the NHSDA. The survival function at age t is obtained by multiplying the age-specific probabilities of an opportunity to use. We used analogous procedures to estimate a survival function for the first opportunity to use hard drugs, $S_{YH}(t)$, and survival functions for initiation of marijuana use, $S_{ZM}(t)$, and hard drug use, $S_{ZH}(t)$ (Fig. 2).

Because $f(\theta)$ is distributed as a Gamma random variable with mean one and variance β_1, $E[S^*_{YM}(t)^{f(\theta)}] = 1 - \beta_1 \log S^*_{YM}(t)^{-1/\beta_1}$ (Hogg & Craig 1978). Setting $E[S^*_{YM}(t)^{f(\theta)}]$ equal to the estimated marginal survival function for the NHSDA sample yields, $S^*_{YM}(t) = e^{(1-\hat{S}_{YM}(t)^{-\beta_1})/\beta_1}$. Again, a similar procedure is used to estimate S^*_{YH} from the estimates of β_1 and $S_{YH}(t)$.

Estimation of π_M and π_H Since $\pi_M = Pr\{Z_M < 9 \mid Y_M < 9\}$, we estimate this probability directly from the NHSDA as the sum of the weights from respondents who report marijuana initiation before age nine divided by the sum of the weights from respondents who report an opportunity to

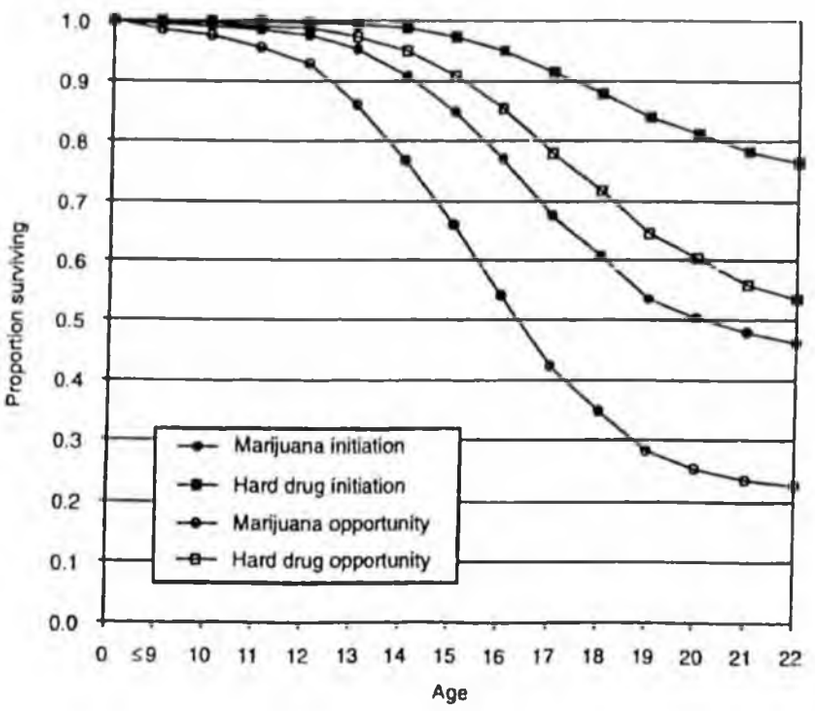


Figure 2 Survival functions estimated from the NHSDA describing the probability of surviving until age t without having the opportunity to use marijuana, the opportunity to use hard drugs, initiating marijuana and initiating hard drugs

© 2002 Society for the Study of Addiction to Alcohol and Other Drugs

use marijuana before age nine. The procedure is repeated for hard drugs.

Estimation of β_2 As noted earlier, we set β_2 so that the model correlation between L_M and L_H matches the NHSDA estimate. For all NHSDA respondents who reported using both marijuana and hard drugs by age 22, we calculated L_M and L_H and their correlation, r. We do not have a closed form for the correlation between L_M and L_H as a function of β_2, $\rho(\beta_2)$ in our simulation model. Therefore, we estimated the function via simulation. For a given value of β_2 we simulated 10 000 observations from the distribution and calculated the correlation between L_M and L_H. We then used the bisection method to search over the values of β_2 to find the value that solved $\rho(\beta_2) - r = 0$.

Estimation of ψ^*_{Mt} and ψ^*_{Ht} To estimate ψ^*_{Mt} we first estimate from the NHSDA $Pr\{Z_M = t \mid Y_M \leq t, Z_M \geq t\}$ as the ratio of the sum of the weights for respondents who initiate use at age t to the sum of the weights of respondents with first opportunity to use marijuana before age $t+1$ who did not initiate use prior to age t. We again did not have a closed form for $E[F_{\beta_2}(\psi^*_{Mt} - \theta_t)] = Pr\{Z_M = t \mid Y_M \leq t, Z_M \geq t\}$ as a function of ψ^*_{Mt} given a value for β_2. Instead we used the bisection method to find a value ψ^*_{Mt} so the $E[F_{\beta_2}(\psi^*_{Mt} - \theta_t)]$ from the simulation model equals our estimate of $Pr\{Z_M = t \mid Y_M \leq t, Z_M \geq t\}$ from the NHSDA. Values for the corresponding hard drug parameter were calculated in a similar manner.

Estimation of the relative risk effect We estimate the risk of hard drug use by 21 using the sample of NHSDA respondents aged 22 or older. We estimate the probability of hard drug use separately for respondents who reported marijuana use by 21 and those who did not. Estimates equal the weighted proportion by stratum. The relative risk is the ratio of the risk for hard drug initiation for marijuana users to the risk for others.

Estimation of ordering effect We used life table methods to estimate the rate at which hard drug initiation precedes marijuana initiation. For each age, t, we summed the weights for respondents who had used neither marijuana nor hard drugs by age t. Call this sum E_t. We subtracted from E_t, C_t the sum of the weights for respondents who were surveyed at age t and had used neither marijuana nor hard drugs—i.e. the weights for censored observations. Let U_t equal the sum of the weights for youth who report initiating hard drugs at age t before initiating marijuana use. We then estimate the probability that hard drug use preceded marijuana use at age t as $P_t = A_t U_t / (E_t - C_t)$, where A_t equals our estimate of the probability that a youth's first use of hard drugs or marijuana is after age t. The survival curve for initiating hard drug use prior to marijuana use equals $S(t) = 1 - \sum_{j=1}^{t} P_j$.

Estimation of the dose–response effect To examine the marginal dose–response effect of the simulated marijuana use frequency on the age of hard drug initiation, a generalized linear model with a complimentary log-log link (Hosmer & Lemeshow 1999) was fitted to the marijuana use frequency and hard drug initiation data from a random sample of 30 000 simulated cases. Whether or not a case initiated hard drug use in a given year was modeled as a function of past year marijuana use intensity (no past year use, 1–2 times, 3–11 times, 12–51 times and 52 or more times) at age t ($t = 12 \ldots 21$). Those who did not initiate hard drug use were censored after age 21.

To compute a corresponding hazard ratio for the NHSDA, we first selected the subset of respondents who reported no hard drug initiation prior to the year preceding the survey. We then stratified these respondents by age at the time of the survey. For each respondent age group we calculated the weighted proportion reporting initiation of hard drug use in the past year by past year marijuana use frequency. For example, we divided 12-year-old respondents into those who did not use marijuana in the past year, those who used marijuana 1–2 times, 3–11 times, 12–51 times or 52 or more times. Within each use group we estimate separately the proportion that initiated hard drugs. We repeat this for all other age groups. The resulting proportions define the hazard of hard drug initiation by age for each level of marijuana use. We assume that the five resulting hazard functions (one for each level of marijuana use) are age-specific, but that a single proportional hazards model describes the relative sizes of the five hazards at all ages. We compute the proportionality constants as the weighted average of the hazard ratios across ages in order to allow ages with less variability to have more weight in the calculation. This procedure for establishing dose–response hazards in the NHSDA is inaccurate, since marijuana use frequency could change after hard drug initiation in the past year. However, we use this NHSDA estimate only for purposes of comparison to analogous hazards observed in our modeled data, not to establish parameters for the model. For this comparison, our NHSDA dose–response estimates are sufficient.

MODEL RESULTS

We drew 1 000 000 observations from the joint distribution, from which three sets of outputs are recorded: simulated marijuana and drug initiation survival functions, $\hat{S}_{2M}(t)$ and $\hat{S}_{2H}(t)$; relative risk of initiating hard drugs by

© 2002 Society for the Study of Addiction to Alcohol and Other Drugs

age 21 for cases with and without prior marijuana initiation, and the percentage of simulated cases for which hard drug use preceded marijuana use by at least 1 year prior to age 22. Because the NHSDA and our simulated cases record age of drug use initiation in whole years, it is not possible to determine if hard drug initiation preceded marijuana initiation if both occurred in the same year. Therefore, we describe hard drug initiation as preceding marijuana initiation only if $Y_H < Y_M$.

Model precision

By design, modeled marijuana and hard drug initiation survival functions, $\hat{S}_{2M}(t)$ and $\hat{S}_{2H}(t)$, closely matched those for the US population shown in Fig. 2. Indeed, actual and modeled survival rates differed by 0.009 or less for each drug at every age.

Gateway effects

Relative risk

In our model, by age 21, users of marijuana were 157 times more likely than non-users to have initiated a hard drug. In comparison, respondents aged 22 or older in our NHSDA sample who initiated marijuana use by age 21 were just 24 times more likely than non-marijuana users to initiate hard drugs. Thus, our model produces a relative risk phenomenon even greater than that observed in the US data, even though the model incorporates no gateway effect. We attribute little significance to the fact that our model produces a relative risk substantially greater than that observed in the NHSDA. The denominator in this ratio is so small that even a slight imprecision in its estimate could more than account for the difference between observed and modeled risk ratios. Thus, for instance, if the true value of $P_r\{Z_H < 22 \mid Z_M > 21\}$ differs from our NHSDA estimate by as little as 0.013, the true relative risk could be greater than 190.

In addition, the elevated relative risk of hard drug initiation among younger marijuana initiates vs. older ones is also reproduced in the model. Among those aged 22 and older in our NHSDA sample, those who initiate marijuana by age 15 have 1.60 times greater risk of becoming a hard drug user by age 22 than those whose marijuana initiation occurs after age 15. Our model produces the larger, but still comparable, relative risk for these groups of 3.44.

Ordering

The proportion of simulated cases for which hard drug initiation preceded marijuana initiation was 0.011. This compares with the corresponding estimate of 0.016 from the NHSDA. Thus, initiation of hard drugs before marijuana was even more rare in our model than in the US household data, suggesting that no gateway effect is required to explain the strong ordering effect observed in youths' drug initiation experiences.

Dose–response

Hazard ratios for hard drug initiation among users of marijuana vs. those who did not use it in the past year are presented in Fig. 3. The figure exhibits a strong dose–response response relationship between marijuana use frequency and the hazard of hard drug initiation at each hypothesized correlation between the marijuana use intensity random effect, ξ, and propensity, θ. Indeed, even assuming zero correlation between these effects, a rising dose–response curve is found, with the heaviest users of marijuana having hazards of hard drug initiation more than 10 times greater than those of non-users.

The corresponding dose–response curve from the NHSDA data is plotted as a series of stars in Fig. 3. This curve bears a striking resemblance to those produced by the model. For the first two levels of marijuana use frequency the US data corresponds closely to the assumption that marijuana use frequency and drug use propensity have a moderate correlation ($r = 0.4$). For the highest marijuana frequencies, US hazard ratios fall between the moderate and high ($r = 0.8$) correlation assumptions.

DISCUSSION

Adolescent drug use initiation

The results reported here demonstrate that a simple common-factor model with population-based parameters can reproduce each of the phenomena previously used to support claims of a marijuana gateway effect. Thus, the strong relative risk, ordering and dose–response relationships observed between marijuana use and hard drug initiation do not require an assumption that marijuana initiation, or even the first opportunity to use it, increases the risk of either hard drug initiation or the opportunity to use hard drugs. While not disproving the existence of a marijuana gateway effect, our findings demonstrate that the primary evidence supporting gateway effects is equally consistent with an alternative model of adolescent drug use initiation in which use, *per se*, of marijuana has no effect on the later use of hard drugs.

Once a general propensity to use drugs is posited, the relative risk of hard drug use among marijuana users vs. non-users can be completely accounted for as a simple consequence of the fact that users of any drug are likely to have higher drug use propensities than non-users. Indeed, our model produced hard drug initiation risk

© 2002 Society for the Study of Addiction to Alcohol and Other Drugs

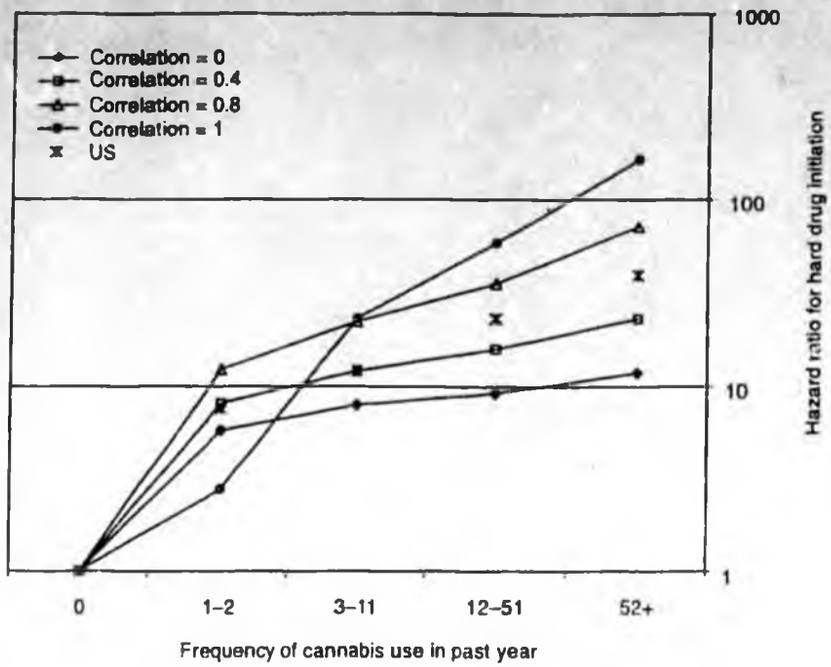


Figure 3 Hard drug initiation hazards, given past-year marijuana use frequency (expressed as a proportion of the hazard given no past year marijuana use) under four assumptions concerning the correlation between the marijuana use intensity random effect and the drug use propensity random effect

ratios greater than those observed in the NHSDA both for users vs. non-users of marijuana and for younger vs. older initiates of marijuana.

With the assumption that use of any drug is conditioned only on an individual's age, drug use propensity and opportunity to use drugs, the observed ordering in drug initiation can be attributed to the fact that opportunities to use marijuana routinely precede opportunities to use hard drugs—often by many years. Using just these assumptions, our model produced rates of hard drug use preceding marijuana use of just 11 per 1000 individuals, reflecting an even more invariant ordering than that found in our NHSDA sample, in which 16 of every 1000 individuals try hard drugs before marijuana.

Finally, even without the reasonable assumption of a correlation between marijuana use intensity and the more general propensity to use drugs, the assumptions of the model suffice to produce a strong dose–response relationship between marijuana use frequency and the risk of hard drug initiation. However, introducing such a correlation strengthens the dose–response relationship considerably. Indeed, as demonstrated by our sensitivity analysis, adjustments to the correlation between marijuana use intensity and drug use propensity suffice to account for the magnitude of the dose–response relationship observed for populations of youths. Again, the observed dose–response relationship between marijuana use frequency and the risk of hard drug initiation requires no marijuana gateway effect for its explanation.

Exhibiting gateway effects by controlling for common factors

Earlier studies have sought to support claims of a gateway effect by showing that marijuana use, *per se*, remains a powerful predictor of hard drug initiation, even after controlling for a wide range of candidate 'common factors' such as individuals' background characteristics, their risk behaviors and the behaviors of their peers (Yamaguchi & Kandel 1984b; Fergusson & Horwood 2000). This approach presumes that the included factors are sufficiently powerful indicators of any unobserved drug use propensity that their inclusion should eliminate any spurious appearance of a relationship between marijuana use and hard drug initiation. Since we know drug use propensities in our simulation model, we can examine the limits of this assumption using a random sample of cases drawn from our model. To do so, we construct variables that are more or less reliable indicators of drug use propensity, where the variances of the normally distributed error terms are used to control the correlation between the drug use propensity and its indicator. These indicators are next included as covariates along with a marijuana use indicator, m, in the following logistic model of hard drug initiation by age 22:

$$P_r\{Z_H < 22\} = \frac{1}{1+e^{-(\alpha+\beta m+\gamma X_1)}} \quad (5)$$

Figure 4 presents the hard drug initiation odds ratios for marijuana users vs. non-users, after controlling for drug use propensity indicators (X) with reliabilities ranging

© 2002 Society for the Study of Addiction to Alcohol and Other Drugs

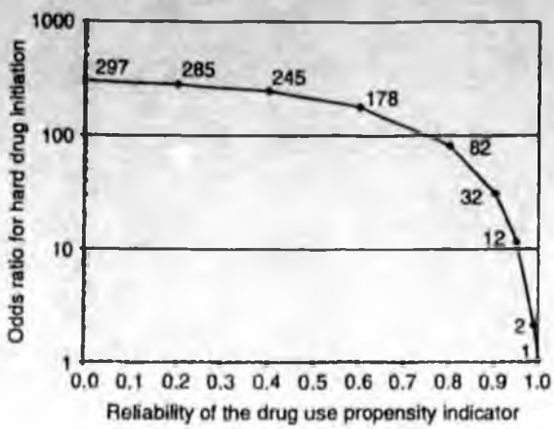


Figure 4 Odds ratios for initiating hard drugs given marijuana use (vs non-use), after controlling for presumptive 'common-factor' variables, as a function of these variables' reliability as indicators of true drug use propensity

between 0 and 1. This figure demonstrates that drug use propensity indicators need to be almost perfectly correlated with true drug use propensity before strong relationships between marijuana use and hard drug use are eliminated. Even when the indicator fails to capture just 2% of the variance in drug use propensity (i.e. its reliability is 0.99), marijuana users appear to have odds of initiating hard drugs that are twice as great as non-users of marijuana. Because it is very unlikely that the covariates included in prior studies have anything like a 0.99 correlation with drug use propensity, it is hardly surprising that controlling for these covariates does not eliminate the association between marijuana and hard drug use.

Model limitations

Several limitations and clarifications on the results are warranted. Firstly, our model relies on a number of untested assumptions and simplifications, such as a normal distribution for propensity and the frailty model for the joint distribution of age of first opportunity to use marijuana or hard drugs. To the extent these assumptions do not approximate corresponding phenomena in the population of youths, the model represents the process of adolescent drug use initiation less well. However, to the extent the model assumptions are plausible, we have demonstrated one possible process of drug use initiation that produces all of the gateway phenomena without requiring a gateway effect. The plausibility of our model is demonstrated through comparisons with estimates from the NHSDA. However, our estimates of the rate at which gateway phenomena occur in the NHSDA also depend on assumptions that may be wrong, like that the hazards of hard drug initiation for different marijuana use frequency groups remain proportional across age groups. If the assumptions are wrong, our NHSDA estimates will be biased and the comparisons provide less good evidence for the plausibility of our simulation model.

Secondly, we have produced a plausible model of adolescent drug use initiation that derives many of its parameter estimates from the NHSDA, a survey of US residents. However, it is quite clear that many of these parameters, like marijuana use prevalence, are specific to the population of youths in the US during the period in which the data used in this study were collected. As such, our estimates of the rate at which gateway effects occur in the NHSDA should not be expected to generalize to other places or times. Similarly, our model is calibrated to correspond to this US data, and might produce quite different results if parameter estimates from a different country or a different time were substituted for those estimates we used.

A third clarification concerns the possible effects of response bias on the appearance of gateway effects in this study, and every other study relying primarily on self-reports of drug use to demonstrate gateway effects. Suppose, for instance, that the likelihood of initiating hard drugs is, in fact, independent of whether or not someone has initiated marijuana or the frequency with which they use it. If there was a systematic under-reporting bias that led some marijuana users to claim to have never used either marijuana or hard drugs, or to under-report their marijuana use frequencies and their use of hard drugs, these biases could lead to the appearance of both the relative risk and dose–response gateway phenomena, although neither truly existed. If response bias accounts for the gateway phenomena, then the propensity factor we include in our model may correspond more to some heterogeneous response bias trait than it does to a true propensity to use drugs. It is for this reason that we have been careful to define propensity in terms of the likelihood of reporting drug use, rather than of engaging in drug use.

Fourthly, we constructed the model in such a way that use of hard drugs is independent of use of marijuana, except insofar as they share a common propensity to use drugs. This feature of the model holds true regardless of the particular values selected for drug use opportunities, use given opportunities or the correlation parameters. Therefore, even though the data set we use to derive these parameters might reflect the operations of a true gateway effect (the NHSDA), we can be certain that model's outputs do not result from any such effects.

The status of the marijuana gateway effect

The model and analyses described above do not disprove the gateway effect. Instead, they demonstrate that each

© 2002 Society for the Study of Addiction to Alcohol and Other Drugs

of the phenomena that appear to support such an effect are, in fact, equally consistent with a plausible alternative that accounts for the known general liability to use drugs and the known differences in when youths receive their first opportunities to use drugs.

Something like a marijuana gateway effect probably does exist, if only because marijuana purchases bring users into contact with a black market that also increases access to hard drugs (Goode 1970). However, this observation does not refute the analysis presented above, since there are at least two ways that gateway effects could exist without undermining a model of drug use initiation that fails to include them. Firstly, it is possible that any true marijuana gateway effects can explain only a tiny fraction of individuals' risk of hard drug use in comparison with the risk attributable to their propensities to use drugs, and is therefore a negligible factor in our model. A second possibility is that marijuana use could increase the risk of hard drug use for some youths, while decreasing the risk for others. As such, true marijuana gateway effects may be counterbalanced in the population by negative marijuana gateway effects, with the net effect of marijuana use on hard drug use being insignificant. Negative gateway effects could occur if, for instance, marijuana sated some youths' desires to experiment with illicit drug use, or if unsatisfying (or penalized) marijuana use experiences discouraged drug use progression among some youths.

The purported marijuana gateway effect is frequently invoked by policy makers as among the primary reasons to resist efforts to relax marijuana policies, such as permitting the medicinal use of marijuana (US Department of Health and Human Services 1999). Whereas social scientists often acknowledge that relative risk, ordering in drug use initiation and dose–response phenomena do not prove the existence of a marijuana gateway effect, they too have frequently drawn policy conclusions that presuppose such an effect. For instance, many have concluded that by postponing youths' marijuana initiation, prevention efforts will reduce the likelihood of hard drug use and abuse (Yamaguchi & Kandel 1984b; Kandel *et al.* 1992; Golub & Johnson 2001). Our model demonstrates how the observed correlations in the use of marijuana and hard drugs may be entirely due to individuals' propensity to use drugs and their opportunities to use them. As such, marijuana policies would have little effect on hard drug use, except insofar as they affected either an individuals' propensity to use any drugs (as might be the case with drug use prevention programs) or they resulted in hard drugs becoming less available or available later in youths' lives.

Because our model provides a straightforward, parsimonious and plausible explanation for each of the phenomena used to support claims of a marijuana gateway effect, we believe the validity of that effect must remain uncertain until new evidence is available directly comparing it with the alternative common-factor model.

ACKNOWLEDGEMENTS

This research was supported by funds from the Center for Substance Abuse Treatment (CSAT) of the Substance Abuse and Mental Health Services Administration, Department of Health and Human Services (grant #TI11433, contract #270-97-7011), by the National Institute on Alcohol Abuse and Alcoholism (grant #R01 AA12457) and by the Drug Policy Research Center at RAND. The opinions expressed herein are those of the authors and do not reflect official positions of the Government. The authors thank Jonathan Caulkins, Mark Kleiman, Robert Macoun, Rosalie Pacula and Peter Reuter for helpful comments on earlier drafts, and Amanda Geller and Mary Watson for administrative assistance.

REFERENCES

Adler, I. & Kandel, D. (1981) Cross-cultural perspectives on developmental stages in adolescent drug use. *Journal of Studies on Alcohol*, 42, 701–715.

Beenstock, M. & Rahav, G. (2002) Testing gateway theory: do cigarette prices affect illicit drug use? *Journal of Health Economics*, 789, 1–20.

Blaze-Temple, D. & Lo, S. K. (1992) Stages of drug use: a community survey of Perth teenagers. *British Journal of Addiction*, 87, 215–225.

van den Bree, M. B., Johnson, E. O., Neale, M. C. & Pickens, R. W. (1998) Genetic and environmental influences on drug use and abuse/dependence in male and female twins. *Drug and Alcohol Dependence*, 52, 231–241.

Center on Addiction and Substance Abuse (1994) *Cigarettes, Alcohol, Marijuana: Gateways to Illicit Drug Use*. White Paper. New York: Columbia University.

Crum, R. M., Lillie-Blanton, M. & Anthony, J. C. (1996) Neighborhood environment and opportunity to use cocaine and other drugs in late childhood and early adolescence. *Drug and Alcohol Dependence*, 43, 155–161.

Delva, J., Van Etten, M. L., Gonzalez, G. B., Cedeno, M. A., Penna, M., Carts, L. H. & Anthony, J. C. (1999) First opportunities to try drugs and the transition to first drug use: evidence from a national school survey in Panama. *Substance Use and Misuse*, 34, 1451–1467.

DeSimone, J. (1998) Is marijuana a gateway drug? *Eastern Economic Journal*, 24, 149–164.

Donovan, J. E. & Jessor, R. (1985) Structure of problem behavior in adolescence and young adulthood. *Journal of Consulting Clinical Psychology*, 53, 890–904.

Ellickson, P. L., Hays, R. D. & Bell, R. M. (1992) Stepping through the drug use sequence: longitudinal scalogram analysis of initiation and regular use. *Journal of Abnormal Psychology*, 101, 441–451.

Fergusson, D. M. & Horwood, L. J. (2000) Does cannabis use

© 2002 Society for the Study of Addiction to Alcohol and Other Drugs

encourage other forms of illicit drug use? *Addiction*, 95, 505–520.

Golub, A. & Johnson, B. D. (2001) Variation in youthful risks of progression from alcohol and tobacco to marijuana and to hard drugs across generations. *American Journal of Public Health*, 91, 225–232.

Golub, A., Labouvie, E. & Johnson, B. D. (2000) Response reliability and the study of adolescent substance use progression. *Journal of Drug Issues*, 30, 103–118.

Goode, E. (1970) *The Marijuana Smokers*. New York: Basic Books.

Goode, E. (1972) Does marijuana lead to dangerous drugs? In: Goode, E., ed. *Drugs in American Society*, 1st edn [Appendix]. New York: Alfred A. Knopf.

Hays, R. D., Widaman, K. F., DiMatteo, M. R. & Stacy, A. W. (1987) Structural equation models of current drug use: are appropriate models so simple(x)? *Journal of Personality and Social Psychology*, 52, 134–144.

Hogg, R. V. & Craig, A. T. (1978) *Introduction to Mathematical Statistics*, 4th edn. New York: Macmillan.

Hosmer, D. S. Jr & Lemeshow, S. (1999) *Applied Survival Analysis*. New York: Wiley.

Huba, G. J., Wingard, J. A. & Bentler, P. M. (1981) A comparison of two latent variable causal models of adolescent drug use. *Journal of Personality and Social Psychology*, 40, 180–193.

Jessor, R. & Jessor, S. (1980) A social-psychological framework for studying drug use. In: Lettieri, D. J., Sayers, M. & Pearson, H. W., eds. *Theories on Drug Abuse: Selected Contemporary Perspectives*, pp. 102–109. Washington, DC: US Government Printing Office.

Joy, J. E., Watson, S. J. Jr & Benson, J. A. Jr (1999) *Marijuana and Medicine: Assessing the Science Base*. Washington, DC: National Academy Press.

Kandel, D. (1975) Stages in adolescent involvement in drug use. *Science*, 190, 912–914.

Kandel, D. B. & Yamaguchi, K. (1993) From beer to crack: developmental patterns of drug involvement. *American Journal of Public Health*, 83, 851–853.

Kandel, D. B., Yamaguchi, K. & Chen, K. (1992) Stages of progression in drug involvement from adolescence to adulthood: further evidence for the gateway theory. *Journal of Studies on Alcohol*, 53, 447–457.

Kendler, K. S., Karkowski, L. M., Corey, L. A., Prescott, C. A. & Neale, M. C. (1999) Genetic and environmental risk factors in the aetiology of illicit drug initiation and subsequent misuse in women. *British Journal of Psychiatry*, 175, 351–356.

Kendler, K. S., Karkowski, L. M., Neale, M. C. & Prescott, C. A. (2000) Illicit psychoactive substance use, heavy use, abuse and dependence in a US population-based sample of male twins. *Archives of General Psychiatry*, 57, 261–269.

Lillie-Blanton, M., Anthony, J. C. & Schuster, C. R. (1993) Probing the meaning of racial/ethnic group comparisons in crack cocaine smoking. *Journal of the American Medical Association*, 269, 993–997.

MacCoun, R. (1998) In what sense (if any) is marijuana a gateway drug? *FAS Drug Policy Analysis Bulletin*, 4, 3–5.

Miller, R. G. Jr (1981) *Survival Analysis*. New York: Wiley.

National Research Council (1982) *An Analysis of Marijuana Policy*. Washington, DC: National Academy Press.

O'Donnell, J. A. & Clayton, R. R. (1982) The stepping-stone hypothesis—marijuana, heroin and causality. *Chemical Dependencies: Behavioral and Biomedical Issues* 4, 229–241.

Paculn, R. L. (1998) *Adolescent Alcohol and Marijuana Consumption: Is There Really a Gateway Effect?* Working Paper 6348. Cambridge, MA: National Bureau of Economic Research, Inc.

Stenbacka, M., Allebeck, P. & Romelsjo, A. (1993) Initiation into drug abuse: the pathway from being offered drugs to trying cannabis and progression to intravenous drug abuse. *Scandinavian Journal of Social Medicine*, 21, 31–39.

Therneau, T. M. & Grambsch, P. M. (2000) *Modeling Survival Data: Extending the Cox Model*. New York: Springer-Verlag.

Tsuang, M. T., Lyons, M. J., Meyer, J. M., Doyle, T., Eisen, S. A., Goldberg, J., True, W., Lin, N., Toomey, R. & Eaves, L. (1998) Co-occurrence of abuse of different drugs in men: the role of drug-specific and shared vulnerabilities. *Archives of General Psychiatry*, 55, 967–972.

United States Congressional Record (1998) *September 15 1998*, pp. H7721–H7723. Washington, DC: US Government Printing Office.

United States Congressional Record (1999) *July 29 1999*, pp. H6640–H6642. Washington, DC: US Government Printing Office.

US Department of Health and Human Services (1999) *National Household Survey on Drug Abuse, 1982–94*. Computer files (ICPSR Version). Town: Inter-University Consortium for Political Social Research.

Van Etten, M. L. & Anthony, J. C. (1999) Comparative epidemiology of initial drug opportunities and transitions to first use: marijuana, cocaine, hallucinogens and heroin. *Drug and Alcohol Dependence*, 54, 117–125.

Van Etten, M. L., Neumark, Y. D. & Anthony, J. C. (1997) Initial opportunity to use marijuana and the transition to first use: United States, 1979–94. *Drug and Alcohol Dependence*, 49, 1–7.

Van Etten, M. L., Neumark, Y. D. & Anthony, J. C. (1999) Male-female differences in the earliest stages of drug involvement. *Addiction*, 94, 1413–1419.

Whitebread, C. H. & Bonnie, R. J. (1972) *The Marijuana Conviction: a History of Marijuana Prohibition in the United States*. Town: University of Virginia Press.

Yamaguchi, K. & Kandel, D. B. (1984a) Patterns of drug use from adolescence to young adulthood: II. Sequences of progression. *American Journal of Public Health*, 74, 668–672.

Yamaguchi, K. & Kandel, D. B. (1984b) Patterns of drug use from adolescence to young adulthood: III. Predictors of progression. *American Journal of Public Health*, 74, 673–681.

© 2002 Society for the Study of Addiction to Alcohol and Other Drugs

STEPPING STONE TO OTHER DRUGS?

The stepping stone theory holds considerable sway in debates on marijuana. In fact, the concern is that cannabis use leads to the use of other drugs, in particular, the so-called hard drugs, such as heroin and cocaine.

> *It logically follows that more people using drugs will increase the number of people being harmed by them. Cannabis is believed to be the foundation upon which most young people begin experimenting with illicit drugs. (...) The "gateway" concept has been around for a long time, and again, although there is no definitive evidence, the National Institute on Drug Abuse has reported that neuro-toxicological research suggests that marijuana "may alter the brain in ways that increase the susceptibility to other drugs." Many believe that cannabis use provides the impetus for those people looking to increase the psychotropic effect a drug has on them.* [51]

We should first define our terms. The "stepping stone" theory holds that cannabis use inevitably leads to use of other drugs. In this theory, cannabis use would lead to neurophysiological changes, affecting in particular the dopaminergic system (also called the reward system), thus creating the need to move on to the use of other drugs. This theory has been completely dismissed by research. We share this conclusion with several international bodies doing drug research, including the British organization *DrugScope*.

> *The Stepping-Stone theory has proved unsustainable and lacking any real evidence base. The "evidence" that most heroin users started with cannabis is hardly surprising and demonstrably fails to account for the overwhelmingly vast majority of cannabis users who do not progress to drugs like crack and heroin. The Stepping-Stone theory (often confused among the general public for the Gateway theory) has been dismissed by scientific inquiry. The notion that cannabis use "causes" further harmful drug use has been, and should be, comprehensively rejected.* [52]

The "gateway" theory suggests that users' trajectories offer them choices as they start their trajectory of use and that one of these choices is to use other drugs. According to this theory, certain factors, such as early initiation and more regular and heavier use, reinforce this possibility. However, these factors themselves, and early initiation to cannabis in particular, are related to earlier factors, arising from the family environment and social living conditions, that predispose the more vulnerable young people to this early initiation and more rapid progress towards regular and heavy use.

---

[51] M. J. Boyd, Chair of the Drug Abuse Committee and Deputy Chief of the Toronto Police Service, Canadian Association of Chiefs of Police, testimony before the Special Senate Committee on Illegal Drugs, Canadian Senate, first session of the thirty-seventh Parliament, Issue 14, page 75.

[52] DrugScope (2001) *Evidence to Home Affairs Committee Inquiry into Drug Policy.* Available on-line at: http://www.drugscope.org.uk/druginfo/evidence-select/evidence.htm

The link between cannabis and other drug use, according to this explanation, is thus a reflection that there are a number of risk factors and life pathways that predispose young people to use cannabis and that they overlap with the life pathways that predispose young people to use other illicit drugs.[53]

In addition to these factors that predispose some young people to heavier use of psychoactive substances – including alcohol and tobacco first of all – the sociological conditions under which users can obtain cannabis are such that they are in contact with an environment that is at least marginal if not criminal. Dealers are often the same people who also sell heroin, crack, amphetamines, cocaine and ecstasy such that the probability that a young cannabis user, already more vulnerable due to the factors of his personal trajectory, would come into contact with these other substances more easily. We would also add that wholesalers and dealers "cut" or even mix their products; we were told at times that ecstasy, for example, could contain many things other than MDNA.

Furthermore, if it is true that use of substances such as heroin and cocaine develops almost necessarily out of prior use of marijuana, then it also develops out of the use of other substances, nicotine and alcohol in particular, which are more gateways to a trajectory of use than cannabis.

If we come back to trends in drug use in the population, while more than 30% have used cannabis, less than 4% have used cocaine and less than 1% heroin.

However, it is true that regular and heavy users are more likely than occasional users to use other substances. The study by Cohen and Kaal[54] discussed in the previous section shows for example that more than 90% of long-term cannabis users have also used tobacco and alcohol during their lifetime. Above all, it also shows that 48% in Amsterdam and 73% in San Francisco have used cocaine at least once in their life, and 37% in Amsterdam, 77% in San Francisco and 47% in Bremen have used hallucinogens at least once. Nevertheless, no regular cannabis users were regular users of other substances. The authors also show that the most common sequence is alcohol (around age 14), tobacco (around age 15), cannabis (around age 17), followed by other drugs in the early 20s.

We feel that the available data show that **it is not cannabis itself that leads to other drug use** but the combination of the following factors:

- Factors related to personal and family history that predispose to early entry on a trajectory of use of psychoactive substances starting with alcohol;
- Early introduction to cannabis, earlier than the average for experimenters, and more rapid progress towards a trajectory of regular use;
- Frequenting of a marginal or deviant environment;
- Availability of various substances from the same dealers.

---

[53] *Ibid.*

[54] Cohen and Kaal, *op. cit.*, page 92-93.

CANNABIS, VIOLENCE AND CRIME

It is clear that there is some association between psychoactive substances and crime. It is just as clear that this link is much more complex than is sometimes thought, as Professor Brochu pointed out during his testimony before the Committee.

> *Just in my office at the Université de Montréal, I have 2,973 studies that attempt to show a link between psycho-active substances and crime. Most of these studies come from the United States or from English-speaking countries, which tends to colour their perspective somewhat, since we know that our neighbours to the south have very clearly opted for a punitive approach to illegal drugs. What comes out of all these studies is that the link between drugs and crime is very complex.*[55]

Since his testimony, Professor Brochu has released the study he mentioned to the Committee.[56]

We can examine the drug-crime relationship from at least three angles: the effects of the substance itself, the effects of the cost of the substance, and the drug's position in the criminal world.

A significant proportion of offenders have psychoactive substance abuse problems, predominantly with alcohol. In fact, the study concludes that alcohol is the substance most frequently associated with violent crime; in the case of crimes against property, illegal drugs predominate. Cannabis ranked third (3% to 6% according to the study), far behind alcohol (24%) and cocaine (8% to 11%).

With respect to the second approach, the authors establish that between 17% and 24% of inmates committed a crime to obtain the money needed to buy their substance of choice, most often cocaine.

Lastly, regarding the third approach, because illegal drugs are marginalized, users are exposed to a deviant environment. In the previous section we noted that, with regard to cannabis, the fact that dealers can offer heroin or crack as well as cannabis could promote a gateway trajectory towards these other drugs. Similarly, the fact that these substances are illegal could contribute to leading people to a trajectory of delinquency. Furthermore, the drug trafficking environment is a relatively violent environment where a whole series of crimes are committed. Lastly, the simple fact of selling cannabis is itself a criminal offence, and we know that a certain number of people are imprisoned for doing so.

All in all, cannabis itself does not lead to a trajectory of delinquency and it is more likely to be the other way around: someone who embarks on a trajectory of delinquency

---

[55] Professor Serge Brochu, Université de Montréal, testimony before the Special Senate Committee on Illegal Drugs, Canadian Senate, First Session of the Thirty-Seventh Parliament, December 10, 2001, Issue 12, page 18.

[56] Brochu, K. et al., (2002) *Proportions of crimes associated with alcohol and other drugs in Canada.* Ottawa: Canadian Centre on Substance Abuse.

when young is exposed to illegal drugs more quickly and can experiment at a younger age and begin a career as a user when younger.

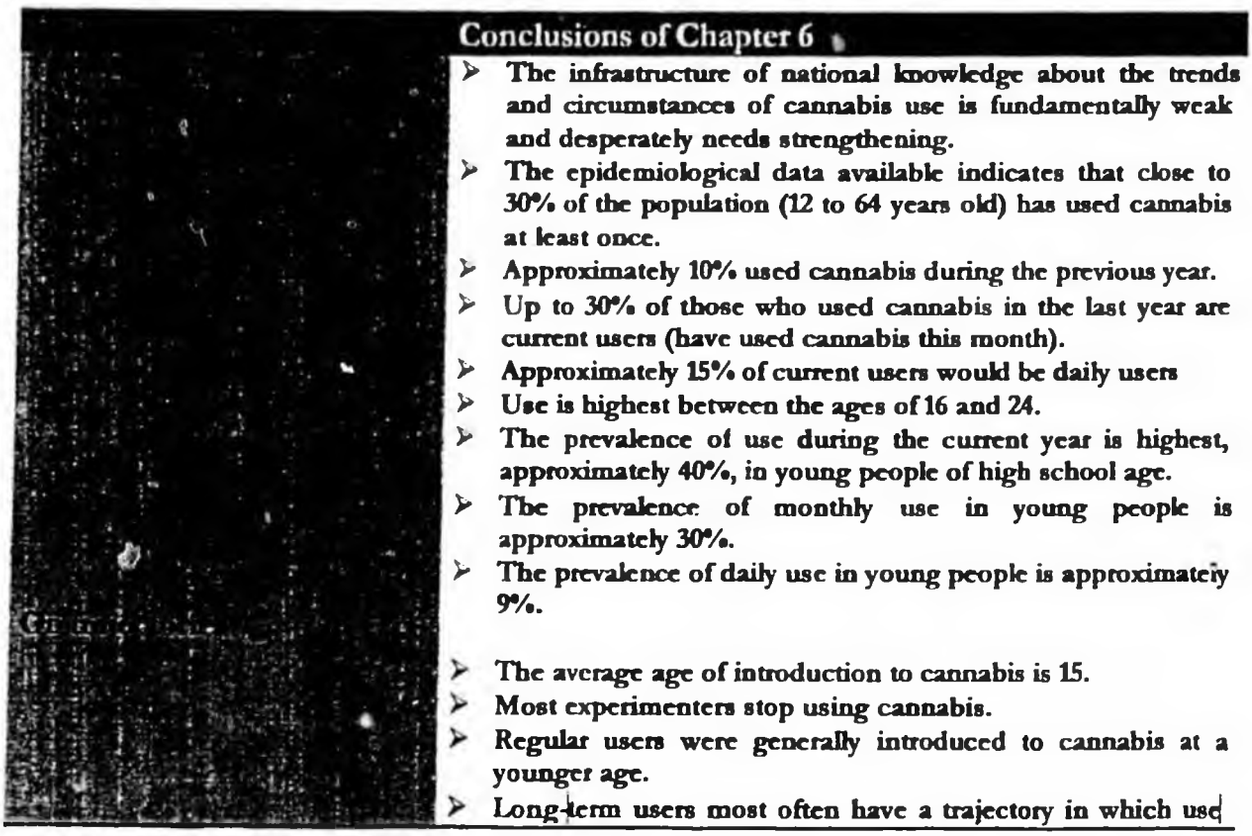
Furthermore, simply because of its relaxing and euphoristic psychoactive effects and its effect of relaxing muscle tone, cannabis is hardly likely to lead to acts of violence.

Data from studies on long-term users confirm this global picture of the relationship between cannabis and crime. Thus, Cohen and Kaal noted that less than 5% of their respondents had committed offences to obtain cannabis (pilfering, shoplifting, theft). The offence committed most frequently in order to obtain cannabis was selling it.

In short, the Committee has learned that cannabis is not a cause of violence or crime except in rare cases, and of course excluding driving while under the influence, which will be dealt with in Chapter 8.

CONCLUSIONS

We have learned the following from all the information on trends, patterns, circumstances, trajectories and social consequences of cannabis use:





rises and falls.

- Long-term regular users experience a period of heavy use in their early 20s.
- Most long-term users integrate their use into their family, social and occupational activities.

- Cannabis itself is not a cause of other drug use.
- Cannabis use can be a gateway because it is illegal, which puts users in contact with other substances.

- Cannabis itself is not a cause of delinquency and crime.
- Young people with a trajectory of regular and heavy use are often already on a deviant if not delinquent trajectory.
- Cannabis is not a cause of violence.

9
Social Problems

The most heated debates about marijuana prohibition often concern the drug's role in social problems. Ideally, drug laws should minimize the negative impact of illicit substances. Arguments for marijuana's illegal status often rely on perceptions of the social problems it might cause, including decreased productivity, dangerous driving, and uncontrollable aggression. If cannabis created such adverse effects, strong penalties for its possession, sale, and use would seem warranted. Popular publications imply that marijuana's role in amotivation, reckless driving, and aggression is a proven fact (e.g., Drug Watch Oregon, 1996; Indiana Prevention Resource Center, 1998; National Institute of Drug Abuse [NIDA], 1998). Yet data reveal that cannabis plays little role in any of these social problems. Details of the relevant studies appear below.

Amotivational Syndrome

Overview

Proponents of marijuana prohibition express concern about the drug's long-term impact on motivation. Despite data to the contrary, stereotypes suggest that regular users of cannabis, particularly adolescents, transform into apathetic slugs uninterested in school, work, or any productive activity (Nahas, 1990). Researchers first identified a subset of lethargic, unmotivated cannabis smokers over 100 years ago (IHDC, 1894). Yet these data did not prove that marijuana actually altered motivation. By the late 1960s, investigators coined the expression "amoti-

vational syndrome" to describe indifferent, listless adolescents who smoked marijuana. Yet the tacit assumption that cannabis drained their motivation was never tested.

Educators and parents grew particularly worried that marijuana destroyed ambition in the young. Case studies suggested that amotivational syndrome included poor hygiene and depressed mood, as well as a loss of energy, productivity, and drive. Authors repeatedly emphasized that the syndrome included an absence of clear goals or focused effort. Researchers suggested that repeated exposure to the drug created this condition, perhaps through a negative effect on the central nervous system (McGlothlin & West, 1968; Smith, 1968). Despite evidence to the contrary, concern about marijuana's influence on motivation continues today (NIDA, 1998). The primary problems with research on amotivational syndrome concern defining its symptoms and proving marijuana actually causes them.

Defining Amotivation

Vague definitions and varied measurements of amotivational syndrome have led to compelling critiques of the idea. Some investigators have examined employment history and educational achievement; others look at performance on laboratory tasks. Yet all claim to measure motivation or amotivational syndrome. Nearly all measurement strategies reflect stereotypically Western values about productivity. Many researchers tacitly assume that motivated people perform well in school, work hard for their employers, and persevere on laboratory tasks. Yet some of the world's most famous achievers failed in these domains. People do not share the same goals or value the pursuit of objectives in the same way. Some cultures emphasize future plans over a focus on the present. Others clearly do not. In fact, the intense pursuit of future goals may minimize enjoyment of the present moment, leading to considerable distress (Burke, 1999).

The notion of amotivational syndrome can inadvertently pathologize behaviors that many people in other cultures find fulfilling (Morningstar, 1985). One culture's amotivational syndrome may be another culture's ideal lifestyle. For example, vacation time varies dramatically from country to country, reflecting different attitudes about leisure and productivity (Robinson, 1994). In addition, motivation and achievement do not

istless adolescents who
...t cannabis drained their

ried that marijuana de-
ggested that amotivational
d mood, as well as a loss
atedly emphasized that
als or focused effort. Re-
the drug created this con-
central nervous system
spite evidence to the con-
tivation continues today
earch on amotivational
roving marijuana actually

motivational syndrome
Some investigators have
ement; others look
measure motivation
rement strategies reflect
. Many researchers tac-
school, work hard for
tasks. Yet some of the
omains. People do not
tives in the same way.
us on the present. Oth-
uture goals may mini-
, to considerable distress

dvertently pathologize
fulfilling (Morningstar,
ay be another culture's
amatically from coun-
leisure and productiv-
nd achievement do not

necessarily lead to happiness or increased satisfaction in life. The idea of amotivational syndrome may present a false promise that accomplishments lead invariably to happiness.

Even within Western culture, the definitions of amotivational syndrome vary considerably. There is no formal diagnosis or established list of symptoms. Most researchers employ their own unique measures of motivation, making comparisons between studies difficult. Reports usually describe amotivation as a subtle shift in priorities. Achievement becomes less important; leisure becomes more important. Sufferers purportedly have few long-term goals or no concrete plans for attaining them. They may lose the ability to concentrate, endure frustration, and participate in life. If a marijuana-induced amotivational syndrome does exist, its symptoms do not sound similar to the obvious problems associated with the abuse of other drugs. Chronic cannabis users rarely report the drastic financial, social, and occupational difficulties typical of addiction to alcohol, opiates, or cocaine. Nevertheless, if marijuana created an absence of drive, it would clearly interfere with the steady achievement stereotypically associated with the American dream.

The purported symptoms of amotivational syndrome are hardly unique to cannabis use. Clinical depression often includes the fatigue, poor concentration, and apathy typical of amotivation. This overlap suggests that a subset of depressed people who use marijuana may account for clinical observations of amotivational syndrome. Sad, unmotivated people may happen to smoke cannabis, giving the impression that the drug has created the symptoms. In fact, the links among depression, amotivation, and marijuana consumption are not particularly straightforward.

Recent data reveal that cannabis consumption has no significant association with depression in adults. A subset of people who use marijuana to cope with problems show more depressive symptoms, but it is not clear that the cannabis caused their depression. People who first tried marijuana before age 16 showed more depression later in life. Yet this relationship disappeared when the use of other drugs was taken into account (Green & Ritter, 2000). A separate study revealed that measures of motivation correlated more with depression than with marijuana consumption, even among heavy users (Musty & Kaback, 1995). Thus, depression, rather than cannabis, may cause amotivational symptoms.

Cannabis as a Cause

The idea that marijuana diminishes motivation requires the same firm evidence of association, temporal antecedence, and isolation discussed in chapter 3 with the gateway effect. Marijuana must precede and correlate with amotivation to cause it. The symptoms also must not stem from some other contributor like personality, depression, or the use of another drug. Ensuring that amotivational syndrome arises from cannabis requires experiments. Researchers can randomly assign people to receive cannabis or placebo. This arrangement ensures that everyone is equally likely to end up in the group that smokes marijuana, assuring that any identified deficits arise from cannabis rather than personality, depression, or other drug use.

In an alternative approach, participants work after smoking a placebo and at other times after smoking cannabis. This strategy, known as a "within-subjects design," ensures that all participants work both intoxicated and sober. Investigators can then compare each person's intoxicated performance to his or her own work in the absence of the drug. Under these circumstances, any identified impairment must stem from cannabis. Thus, laboratory experiments can rule out alternative explanations for marijuana's impact on motivation. This type of research requires extensive time, effort, and funding. Cannabis use over many days should produce the lethargy and lack of ambition typical of the disorder. Only a few laboratory experiments provide enough data from repeated daily exposure to provide any meaningful conclusions.

Laboratory Performance

In one of the first studies of chronic cannabis administration, researchers employed 6 men to build chairs for 70 days. They earned $2 per chair initially, but went on strike twice and raised their fees. They had periods without cannabis, and weeks when they could purchase as much as they wanted, at $.50 per joint. For 28 days, the researchers required that they smoke at least 2 joints containing a total of 17 mg of THC. Generally, the men built fewer chairs and worked fewer hours when required to consume cannabis. They also built fewer chairs immediately after they went on strike and increased their wages. The men showed no other signs of amotivation.

This study clearly supports the idea that intoxication can decrease

productivity (Miles et al., 1974). Yet it is unclear if this would qualify as evidence for amotivational syndrome. Arranging for a strike to increase wages likely required motivation, organization, and drive. Making fewer chairs might reflect lower motivation, but it more likely offers further evidence that intoxication impairs performance.

In another study of chronic administration, researchers paid 30 men to stay in the hospital for 94 days. They ingested no drugs for the first 11 days, smoked cannabis for the next 64, took a break from the drug for a week, used cannabis daily for 9 more days, and then did not smoke the last 3 days. The men smoked an average of 5.2 joints per day when the researchers permitted consumption. They were paid for daily work on two different tasks. One required adding large numbers on a calculator. The other required answering textbook questions. Participants received $.10 for each correct answer on these two tasks. Acute intoxication and chronic exposure had no impact on any measure of performance. The men showed statistically comparable total responses, total correct responses, errors, and time worked throughout the 94-day period (Cohen, 1976). These data offer no support for amotivational syndrome.

These long-term studies offer little support for cannabis-induced losses of productivity. Thus, proponents of marijuana prohibition often cite other research that demonstrates decreased motivation during intoxication. One standard way to manipulate motivation in the laboratory requires offering extra cash for good performance on tasks. In one study of marijuana's effects, researchers attempted to increase motivation and performance on simple tasks by offering financial incentives. On a reaction-time task, intoxicated people did not respond to this incentive as dramatically as the people who had not smoked cannabis. Offering extra money did not motivate people to react more quickly while high, but it did speed reaction times for people who were not intoxicated. The authors emphasize that this result offers little support for amotivational syndrome. Instead, these data mean that intoxicated people do not react to standard techniques for enhancing motivation (Pihl & Sigal, 1978).

Two other studies performed in a residential laboratory revealed that intoxicated men were less likely to perform tasks that they disliked (Foltin et al., 1989, 1990). After smoking marijuana, these men spent less time on work and chores and more time on recreational activities. Popular articles often refer to these studies as evidence for amotivational syndrome. Perhaps intoxication decreases a person's willingness to work

on unappealing projects, but this effect hardly parallels the directionless apathy typical of most definitions of amotivation. If these results qualify as evidence for amotivational syndrome, then most psychoactive drugs could serve as a cause. In fact, anything that might create procrastination, including watching television, could serve as a source of amotivation.

Because laboratory studies of humans offer little evidence for amotivational syndrome, critics point out that the duration of exposure was relatively brief. A couple of months of chronic smoking may not lead to any symptoms, but those who believe in amotivational syndrome charge that the disorder does not appear until later. Few people would participate in a study for a longer period, but animal research has examined the impact of 12 months of drug exposure. In this hallmark study, researchers randomly assigned 62 adolescent male monkeys to inhale cannabis smoke or a placebo. The dosage was similar to 4 or 5 marijuana cigarettes for a human. Some received smoke daily, others only on weekends, for a full year. This arrangement permitted an examination of the impact of long-term exposure to cannabis on motivation and performance.

After the year of exposure, all the monkeys performed two tasks daily for two months. The tasks were typical for primate research. One measure, conditioned position responding, provided the monkeys with a banana-flavored pellet for pressing different buttons in response to different colors. Marijuana had little impact on correct responses. The monkeys who smoked cannabis performed as well as the placebo smokers on the rate of responding and the percentage of correct responses. A subset of monkeys who had smoked every day did not complete as many trials on this task as the placebo smokers, but only during the last month of the experiment. Those who smoked cannabis only on weekends did not differ from the controls on any measure. Thus, conditioned position responding offers little evidence for amotivational syndrome, even after a year of cannabis exposure.

Proponents of marijuana prohibition might argue that conditioned position responding did not require much motivation in the first place. Essentially, the task may have been too easy to show any amotivational effects. Fortunately, the investigators also used a more difficult measure, the progressive ratio (PR) task. In the PR task, the monkeys must press a bar an increasing number of times to receive pellets. If the monkey presses the bar 3 times to get the first pellet, he has to press it 6 times

to get the second pellet, 9 times to get the third pellet, and so on. The number of required presses progresses upward after each reinforcer.

Among a subset of monkeys who practiced the tasks during their year of exposure to smoke, those who received cannabis did not perform as well as those who received placebo. This deficit even appeared for the monkeys who only smoked on weekends. In contrast, the group who did not practice showed the same performance whether they had smoked cannabis or not. That is, those who smoked cannabis but did not practice the task performed equally as well as those who smoked placebo and did not practice the task. Thus, the progressive ratio task showed marijuana-related deficits in monkeys who had practiced the task during the year, but not in the unpracticed monkeys. This result may mean that monkeys who practiced while intoxicated did not learn the task as well as the monkeys who practiced while sober. The responses returned to normal within 3 months of abstinence from cannabis, when all groups performed equally well (Slikker, Paule, Ali, Scallet, & Bailey, 1992).

This study of primates shows decreased performance on a difficult exercise after a year of marijuana use, but only in those who had practiced the task during their exposure to cannabis. The drug had no impact on the easier, conditioned position responding. The investigators did not report changes in hygiene, mood, or other symptoms of amotivational syndrome. This study and some of the human research certainly confirms that intoxication can impair performance on some tasks in some conditions. Nevertheless, this seems like rather slim evidence for full-blown amotivational syndrome. Yet many critics dismiss this laboratory evidence as irrelevant. The term often implies a failure to achieve in life, not simple deficits on laboratory tasks. To further test the role of cannabis in motivation, other investigators have examined marijuana's correlation with educational and work performance. Impairments on these life tasks appear more relevant to the idea of amotivational syndrome.

Correlations with Education and Work

Surveys of associations between drug use and job or school activities lack the experimental control found in the chronic administration studies. Investigators can only assume that marijuana use causes poor performance at work or school. Alternative explanations remain equally tenable. For example, poor adjustment in work or school might lead some

people to use cannabis. A third factor may account for the association, too. Depressed people might perform poorly and choose to use cannabis. People with certain personality characteristics might choose to use marijuana and make school or work a low priority. Thus, a simple association between cannabis consumption and education or work does not prove that amotivational syndrome exists. Nevertheless, the absence of an association between marijuana and achievement might undermine arguments for cannabis-induced amotivation. It is extremely unlikely that the drug causes amotivational syndrome if use and performance do not correlate. Therefore, these studies put the theory behind amotivational syndrome at risk for refutation.

School Performance

Parents and educators express understandable concern about marijuana, amotivational syndrome, and schoolwork. Research has focused on academic achievement in college and high school students. Contrary to popular belief, over half a dozen studies reveal that marijuana smokers and nonsmokers have comparable grades in college. One typical report surveyed 1,400 undergraduates, revealing no differences between users and nonusers on grades, changes in their majors, or number of colleges attended. Chronic users (those who smoked at least 3 times a week for 3 years) took more time off from their schooling but were also more likely to plan to earn a graduate degree (Hochman & Brill, 1973).

Surprisingly, at least two other studies found higher grades in the marijuana smokers than in nonsmokers (Gergen, Gergen, & Morse, 1972; Goode, 1971). Note that, despite these findings, no one has ever proposed that cannabis could help school performance. Users and nonusers also show no differences in their orientations toward achievement, their extracurricular activities, or their participation in sports. Thus, research on college students provides no support for the idea of amotivational syndrome (Zimmer & Morgan, 1997).

Although cannabis consumption in college has no link to school performance, high school students who use marijuana have lower grades and quit school more often. Cannabis smokers in high school also spend less time on their homework and miss more days of school (Kandel & Davies, 1996). At first glance, this association between cannabis and school performance seems consistent with the idea of amotivation. Perhaps cannabis destroys motivation in young teens. Yet data do not support this

restricted form of amotivational syndrome, either. Most heavy users had earned lower grades prior to their marijuana consumption, suggesting cannabis could not have caused the poorer performance (Shedler & Block, 1990). In addition, high school students who smoke cannabis heavily also tend to use alcohol and other illicit substances. Once these factors are taken into account, the link between cannabis and academic performance disappears. These results suggest that drugs other than marijuana might lower grades (Hall, Solowij, & Lennon, 1994).

Marijuana probably does not cause poor school performance. Instead, the regular consumption of cannabis in high school serves as part of a general pattern of deviance. Heavy users appear more unconventional in general. They are more critical of society, less involved in church and school, and more involved in delinquent acts. They often behaved this way before they ever discovered cannabis (Donovan, 1996). Because these young people showed these qualities before using marijuana, the drug seems an unlikely cause of amotivational syndrome in high school students. Thus, depressed, unmotivated, unconventional adolescents may choose to smoke marijuana, but the drug does not appear to create their deviance. Despite this evidence, concerns about drug use in adolescents inspired the National Organization for the Reform of Marijuana Laws to recommend that only adults consume cannabis (NORML, 1996a).

Employment

Two contradictory attitudes have developed about marijuana's impact on job performance. Many people believe the drug destroys motivation and detracts from efficiency, yet others use the drug to enhance their work. Both ideas may be true, depending on the type of job involved. People who perform repetitive, simple tasks may turn to cannabis to relieve the boredom. For example, laborers in India increased their ganja consumption 50% during the harvest season (Chopra & Chopra, 1957). In Jamaica, farm hands who smoked marijuana actually worked harder than those who did not (Comitas, 1976). Perhaps marijuana makes monotonous physical labor more bearable. In contrast, jobs that require complex or rapid decisions likely suffer during intoxication (Chait & Pierri, 1992). Thus, the acute effects of cannabis on performance may vary dramatically with different jobs.

The enduring lack of initiative that defines amotivational syndrome requires more than brief changes in work performance during intoxica-

tion. Wages, hours, and employment history may serve as better indices of motivation on the job. Research performed in countries where workers frequently smoke cannabis has shown little difference between heavy users, occasional users, and abstainers. These groups had comparable forms of employment in Costa Rica and Jamaica (Bowman & Pihl, 1973; Carter, 1980). In Costa Rica, users were unemployed more often than nonusers, probably because of imprisonment for marijuana offenses. Nevertheless, heavy users had better-paying, higher-status jobs than occasional users or abstainers. People with the most stable employment smoked 15.4 joints per day. Those who changed jobs more often smoked less than half that amount, 7.6 joints per day. The unemployed smoked even less- 6.2 joints per day (Page, 1983). Perhaps people with steady employment have enough experience on the job to function properly while intoxicated and enough money to afford marijuana.

In the United States, where cannabis consumption is less prevalent, the impact of the drug on wages, hours, and job turnover still does not support the idea of amotivational syndrome. Data actually suggest some positive links between marijuana consumption and work, but only for adults. One survey of more than 8,000 young adults who held a variety of jobs showed higher wages with increased use (Kaestner, 1994a). People who had smoked more marijuana in their lifetimes earned more money. Note that this correlation does not imply that cannabis consumption actually causes better pay. Perhaps people who earn more money can afford more marijuana. Another report from the same respondents revealed a negative correlation between consumption and work hours for men. Those who smoked more worked fewer hours. Yet given that their wages were higher, they may have become more efficient at work. Hours and consumption did not correlate significantly for women (Kaestner, 1994b).

Other studies of employment histories and drug use reveal that marijuana smokers do not appear to lose their jobs more often than nonsmokers, even though employers are more likely to fire users of other illicit drugs (Normand, Salyards, & Mahoney, 1990; Parish, 1989). One study of over 10,000 military personnel found that cannabis users were discharged more often (McDaniel, 1988). This result may not actually address amotivation because possession of cannabis can serve as a reason for discharge. Some of these recruits may have performed perfectly but lost their jobs because of possession. This effect did not replicate in a survey of navy recruits, which revealed that cannabis users were dis-

charged at the same rate as others (Blank & Fenton, 1991). The respondents in these studies were all over age 18, so these data do not address amotivation in adolescents. Nevertheless, cannabis consumption does not appear to have a dramatic negative impact on wages, hours, or job turnover in adults.

Self-Perceptions of Motivation

A few studies have used the direct and intuitive approach of asking users their perceptions of marijuana's impact on their motivation. This research did not assess the many hypothesized facets of amotivational syndrome, such as lethargy, poor hygiene, and impaired social functioning. Yet these studies do reveal that a percentage of heavy users think that the drug saps their ambition or drive. Interpreting these results requires caution. Many of these participants used illicit drugs besides marijuana. They also could have suffered from unassessed conditions that undermined their energy or motivation. Nevertheless, members of every sample believe that the drug makes them less ambitious or dynamic. In one of the first studies of this kind, researchers interviewed 99 New Yorkers by phone. These people had used marijuana an average of 27 out of the previous 30 days. Eleven of these people (11%) reported reduced energy and motivation. Yet alcohol consumption was not reported, and almost half of the sample used an illicit drug other than marijuana. The report does not reveal if these 11 people who reported less energy also used other illicit drugs, but they clearly attributed their lack of motivation to cannabis (Rainone, Deren, Kleinman, & Wish, 1987).

In another study, investigators interviewed 37 Americans who claimed to have smoked marijuana at least 5,000 times. Three of these heavy users (8%) said that cannabis had a negative impact on their work because it attenuated motivation. In contrast, 7 people (19%) said that the drug enhanced their creativity and improved their work (Gruber, Pope, & Oliva, 1997). The investigators purposely excluded people who used other drugs extensively, which may explain why they found the lowest rate of reported problems with motivation.

Other researchers interviewed 268 Australians who had smoked marijuana at least 3 times per week for the previous 10 years. Over one-fifth of them (21%) felt that cannabis made them tired, unmotivated, or listless. It is unclear if they experienced these symptoms during intoxication

or afterward. The use of other drugs in this sample was quite high, which may have contributed to perceptions of decreased motivation. Almost one-third (30%) of the respondents reported problematic consumption of alcohol, a sedative that lowers motivation and energy. Almost one-fourth (24%) had used an illicit drug besides cannabis in the previous month (Reilly, Didcott, Swift, & Hall, 1998). Thus, despite heavy drinking and the use of other drugs, these heavy cannabis users still reported marijuana altered their motivation. Yet the consumption of these other drugs may have sapped their drive instead.

Note that none of the studies above had a control group that could reveal if people who do not smoke cannabis also struggle with their productivity, enthusiasm, or drive. Many people feel tired, unmotivated, and low in energy without using any drugs at all. Perhaps marijuana smokers misattribute these symptoms to the drug. They may experience the natural ebb and flow of energy that all people feel, but consider this variation a result of marijuana. For example, a study of 237 students found that roughly 5% showed amotivational symptoms whether they used cannabis or not (Duncan, 1987). These results cast doubt on the idea that marijuana attenuates motivation. Instead, a percentage of people at any given time report motivational problems regardless of their drug use. Some of these people smoke cannabis and therefore attribute their lack of motivation to the drug. Yet tenable alternative sources of these problems may get overlooked because of expectancies about marijuana.

In another study, occasional marijuana users served as the control group for a sample of heavy smokers. The 44 occasional users never smoked more than 10 times in a month. The 45 heavy smokers used cannabis daily for at least 2 years. Heavy smokers also consumed more illicit drugs than occasional users, which may account for some differences between the groups. The groups did not differ in mental health, anxiety, depression, emotional control, or happiness. Yet the heavy smokers reported that marijuana was more likely to impair their motivation. The result was statistically significant, but the investigators did not correct for the large number of variables that they examined. Thus, this finding may have appeared by chance. If it did not appear by chance, then heavy users think that marijuana impairs their motivation more than occasional users. Oddly, despite the potential deficit in motivation, heavy users reported a trend toward greater life satisfaction. Again, the investigators did not correct for the large number of comparisons, so this find-

was quite high, which
d motivation. Almost
matic consumption
energy. Almost one-
abis in the previous
despite heavy drink-
bis users still reported
ption of these other

ntrol group that could
uggle with their pro-
d, unmotivated, and
aps marijuana smokers
experience the nat-
onsider this variation
7 students found that
r they used cannabis
the idea that mari-
of people at any given
ug use. Some of
e their lack of moti-
of these problems may
uana.
served as the control
ccasional users never
heavy smokers used
also consumed more
ount for some differ-
fer in mental health,
ness. Yet the heavy
to impair their moti-
the investigators did
they examined. Thus,
not appear by chance,
notivation more than
it in motivation, heavy
on. Again, the inves-
parisons, so this find-

ing may also stem from chance. Nevertheless, these results suggest that heavy users are less motivated but more satisfied with their lives (Kouri, Pope, Yurgelun-Todd, & Gruber, 1995). Perhaps they have rejected the conventional notion that motivation and productivity are essential for fulfillment.

Because the data from all these studies are correlational rather than longitudinal, they do not reveal if the heavy smokers reported poor motivation prior to ever using cannabis. Perhaps people who do not make productivity a priority subsequently choose to use marijuana. It is also unclear if the consumption of other drugs undermined productivity. Users may attribute their decreased ambition to marijuana when other drugs may have created the effect. The fact that the one study that specifically excluded users of other drugs found one of the smallest rates of motivation problems (8%) (Gruber et al., 1997) supports this idea. Mental or physical illnesses may have contributed to these symptoms, too. Nevertheless, it is clear that a percentage of people who use cannabis at high rates feel that the drug impairs their motivation.

Summary

Laboratory studies of humans and primates offer little support for amotivational syndrome. School performance does not vary with cannabis consumption in college students. High school students who smoke marijuana do worse in school. Nevertheless, most performed poorly before they used cannabis, and many used other drugs that probably contributed to their lower grades. Employment data show no links between cannabis use and lower wages, poor work performance, or job turnover. Self-reports in heavy users show that a percentage of people think cannabis impairs their drive, but consumption of other drugs or the presence of physical and emotional problems may serve as the true cause of their lack of motivation.

No studies show the pervasive lethargy, dysphoria, and apathy that initial reports suggested should appear in all heavy users. Thus, the evidence for a cannabis-induced amotivational syndrome is weak. Yet a subset of depressed users may show the symptoms of amotivational syndrome (Musty & Kaback, 1995). These people would likely benefit from cognitive-behavioral treatments for depression, which can improve mood, motivation, and achievement.