Rescheduling Cannabis Under the U.S. Controlled Substances Act Selected Bibliography, Time Line, and Reference Materials

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Notes: Extensive reviews of scientific literature on cannabis by petitioners or the U.S. government will be noted as follows: [review]. Federal Register (FR) filings from 1994 to present are available at GPO Access. The U.S. Code is also available on-line. Court Decisions are available to many university communities by way of Lexus/Nexus Academic Universe; please consult with university librarians, if necessary, to access federal court decisions.

I. Statutory Provisions.

The rescheduling process consists of the following stages:

- Filing of Petition with DEA
- Acceptance of Petition by DEA
- Initial Review by DEA
- Referral to HHS
- Scientific and Medical Evaluation by HHS
- HHS Report to DEA
- Evaluation of Additional Information by DEA
- Publication of DEA Decision
- (Judicial Review by the US Court of Appeals)
- (Public Hearing on Disputed Matters of Fact)

Title 21. Food and Drugs. Chapter 13. Drug Abuse Prevention and Control, Subchapter I, Control and Enforcement. Part B. Authority to Control; Standards and Schedules.

Sec. 811. Authority and criteria for classification of substances [summary]

Under 21 USC 811 the Attorney General has the authority to add to, remove from, or transfer controlled substances between the regulatory schedules established by the Controlled Substances Act. This process is known as a rulemaking procedure and may be initiated by the Attorney General, the Secretary of HHS, or on the petition of any interested party. (21 USC 811 (a))

At the initiation of scheduling proceedings the Attorney General gathers the necessary data and requests from the Secretary of HHS a scientific and medical evaluation of all the available evidence as well as a recommendation on the appropriate scheduling for the drug or substance in question. (21 USC 811 (b))

This evaluation will consider 8 specific factors in making findings to satisfy the criteria for scheduling established in Section 812 regarding accepted medical use, safety for use, abuse potential, and dependence liability. In other words the factors listed in 811(c) are to be used to evaluate the scientific record to assess the criteria established for each respective schedule of the CSA.

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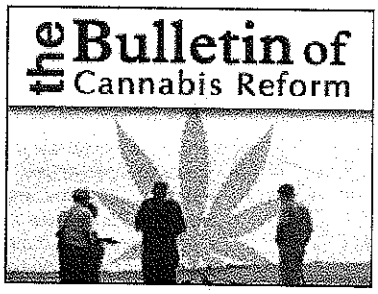

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21 USC 811(c) Factors determinative of control or removal from schedules. [text]

"In making any finding under subsection (a) of section 812 of this title, the Attorney General shall consider the following factors with respect to each drug or other substance proposed to be controlled or removed from the schedules:

(1) Its actual or relative potential for abuse.
(2) Scientific evidence of its pharmacological effect, if known.
(3) The state of current scientific knowledge regarding the drug or other substance.
(4) Its history and current pattern of abuse.
(5) The scope, duration, and significance of abuse.
(6) What, if any, risk there is to the public health.
(7) Its psychic or physiological dependence liability.
(8) Whether the substance is an immediate precursor of a substance already controlled under this subchapter."

Sec. 812. Schedules of controlled substances. [summary]

There are five schedules of controlled substances known as schedules I, II, III, IV, and V. The findings required for each of the schedules involve the following issues: potential for abuse, currently accepted medical use in treatment in the United States, safety for use under medical supervision, and the drug's dependence liability. Schedule I drugs are characterized by a high potential for abuse and a lack of accepted medical use. Schedule II drugs have a high potential for abuse but also have an accepted medical use. The remaining schedules all require an accepted medical use. Schedule III drugs have a lower potential for abuse and dependence liability than Schedule I and II drugs. Schedule IV drugs have a lower potential for abuse and dependence liability than Schedule III drugs, and Schedule V drugs have a lower potential for abuse than Schedule IV drugs. (21 USC 812)

II. Legislative History:

United States Code Congressional and Administrative News. 91st Congress – Second Session. 1970. Comprehensive Drug Abuse Prevention and Control Act of 1970. pgs 4566 – 4657. St. Paul, MN: West Publishing Company.

The legislative history includes a chart indicating fables and facts about marijuana (circa 1970) provided to Congress by the National Institute of Mental Health. (pg 4577-4578) The rescheduling process is reviewed on pages 4599 to 4605. The criteria required for scheduling related findings are defined on pages 4601-4603.

An important letter from Roger Egeberg of the the Department of Health Education and Welfare to Congress regarding the scheduling of cannabis is on pages 4629 – 30. This August 14, 1970 letter states:

" Some question has been raised whether the use of the plant itself produces 'severe psychological or physical dependence" as required by a schedule I or even schedule II criterion. Since there is still a considerable void in our knowledge of the plant and effects of the active drug contained in it, our recommendation is that marihuana be retained in schedule I at least until the completion of certain studies now underway to resolve this issue. If those studies make it appropriate for the Attorney General to change the placement of marihuana to a different schedule, he may do so in accordance with the authority provided under section 201 of the bill."

III. The legal and policy record.

a. Petition # 1, filed by the National Organization for the Reform of Marijuana Laws (NORML) May 18, 1972.

NORML v. Ingersoll 497 F.2d 654 (1974). NORML filed a rescheduling petition under provisions of the CSA. The government declined to initiate proceedings on the basis of their interpretation of U.S. treaty commitments. The Court ruled against the government and ordered them to process the petition.

NORML v. DEA 559 F.2d 735 (1977). The government continued to rely on treaty commitments in their interpretation of scheduling related issues concerning the NORML petition. In this decision the Court makes it clear that the CSA requires a full scientific and medical evaluation and the fulfillment of the rescheduling process before treaty commitments can be evaluated.

NORML v. DEA, Unpublished Disposition, 1980 U.S. App. LEXIS 13100, October 16, 1980. The Court orders the government to start the scientific and medical evaluations required by the NORML petition.

Brandt, Edward N. Asst. Secretary for Health. Scientific and medical findings & recommendations on THC. Letter to Francis M. Mullen, Jr. August 16, 1982. (1027 KB PDF)

Brandt, Edward N. Asst. Secretary for Health. Scientific and medical findings & recommendations on the marijuana plant material. Letter to Francis M. Mullen, Jr. May 13, 1983. [review] (2028 KB PDF)

Macdonald, Donald I. Acting Asst. Secretary for Health. Scientific and medical findings & recommendations on Nabilone. Letter to John Lawn. April 25, 1985. Nabilone is pharmacologically identical to THC. The review of Nabilone is interesting because it relies on different standards than the earlier reviews of THC and marijuana. An FDA advisory panel was utilized, and the panel debated whether Nabilone should be a schedule III or schedule IV drug. The panel recommended schedule III status. The Asst. Sec. of Health recommended schedule II for Nabilone because the panel had not recommended rescheduling for THC, a schedule II drug at that time. (846 KB PDF)

Schedules of Controlled Substances: Rescheduling of Synthetic Dronabinol in Sesame Oil and Encapsulated in Soft Gelatin Capsules from Schedule I to Schedule II. DEA 50 FR 42186-87 October 18, 1985 Notice of Proposed Rulemaking

Schedules of Controlled Substances: Rescheduling of Synthetic Dronabinol in Sesame Oil and Encapsulated in Soft Gelatin Capsules From Schedule I to Schedule II; Statement of Policy. DEA 51 FR 17476-78 July 13, 1986 Final Rule and Statement of Policy

Schedules of Controlled Substances; Proposed Placement of Nabilone into Schedule II. DEA 51 FR 22085-86 June 18, 1986 Notice of Proposed Rulemaking

Schedules of Controlled Substances; Hearing on Petition to Reschedule Marijuana and its Components. DEA 51 FR 22946-47 June 24, 1986 Notice of hearing on petition for rescheduling of marijuana and its components.

Grinspoon v. DEA. 828 F.2d 881 (1987) While this case did not concern marijuana the Court noted that scheduling under the CSA does rely on the relative abuse potential of listed ssubstances.

Schedules of Controlled Substances; Placement of Nabilone into Schedule II. DEA. 52 FR 11042-43. Final Rule. April 7, 1987.

United States Department of Justice, Drug Enforcement Administration. In The Matter Of Marijuana Rescheduling Petition, Docket No. 86-22. Opinion and Recommended Ruling, Findings of Fact, Conclusions of Law and Decision of Administrative Law Judge. Francis L. Young, Administrative Law Judge. Dated: September 6, 1988. [review] . Judge Young recommends that marijuana be placed in schedule II because it has an accepted medical use in the United States.

Marijuana Scheduling Petition; Denial of Petition. DEA 54 FR 53767-53785. December 29, 1989. In this filing the DEA formally rejects Judge Young's recommendations. [review]

Alliance for Cannabis Therapeutics v. DEA. 930 F .2d 936 (1991). The Court ruled that two of the criteria used by DEA in making their findings were unreasonable.

Marijuana Rescheduling Petition; Denial of Petition, Remand. DEA. 57 FR 10499 March 26, 1992. DEA formally rejects Judge Young's findings without using unreasonable criteria. [review]

Alliance for Cannabis Therapeutics v. DEA. 15 F.3d 1131 (1994). The Court upholds DEA's rejection of Judge Young's recommendations.

b. Petition #2 filed by Jon Gettman in 1995.

Petition #2 was an extensive catalog of research and other data specified in 21 USC 812 that emerged after the record was closed in the prior proceedings before Judge Young. Petition #2 focused primarily on challenging whether cannabis has the high potential for abuse required for schedule I status.

- Petition for Rescheduling Cannabis filed July 10, 1995 [review]
- Petition accepted by DEA on July 27, 1995.
- Petition referred to HHS on December 17, 1997.
- Recommendations sent to DEA on January 17, 2001.

Notice of Denial of Petition March 20, 2001.

Notice of Denial of Petition. DEA 66 FR 20037 – 20076 April 18, 2001. This filing contains the complete HHS and DEA scientific reviews of all relevant contemporary literature to the scheduling of cannabis (marijuana), as well as their reasons for declining to reschedule cannabis. [review]

Appeal to the U.S. Court of Appeals. No. 01-1182, United States Court Of Appeals For The District Of Columbia Circuit, March 19, 2002, Argued, May 24, 2002, Decided. After briefs were filed by petitioners and DEA regarding judicial review of the DEA refusal to reschedule cannabis the Court asked for briefs on the issue of the petitioner's standing to seek relief in the federal courts.

Gettman v. Drug Enforcement Administration. 290 F.3d 430 (2002). May 24, 2002. The Court decided that petitioners did not have standing to subject DEA's denial of the petition to review by the Federal Courts because the petitioners were not injured parties. The other issues raised in the legal briefs were not addressed by the Court.

c. Petition #3 filed by the Coalition for Rescheduling Cannabis in 2002.

Petition #3 was filed by coalition of patient advocacy groups and while repeating the argument of Petition #2 it also asserts that marijuana now has accepted medical use in the United States.

- Petition for Rescheduling Cannabis filed on October 9, 2002. [review]
- Petition accepted by DEA on April 3, 2003.
- DEA asks for supplemental information on June 12, 2003.
- DEA receives supplemental information on September 9, 2003.
- DEA refers petition to HHS for scientific and medical review. [July 2004]

d. Other selected rescheduling cases

Buprenorphine. 67 FR 62354. October 7, 2002. Buprenorphine is a semi-synthetic injectable pain killer that was approved for marketing in 1981 and placed in Schedule V in 1985. In December, 2002 HHS instituted proceedings to have the drug rescheduled into Schedule III based on a reevaluation of its abuse potential and consideration of new products about to hit the market.

Marinol. 64 FR 35928. July 2, 1999. Marinol is the synthetic THC pill. The DEA has decided that while THC remains a schedule I substance, THC encapsulated in sesame oil has a lower potential for abuse and in this notice DEA removes Marinol from schedule II and places it in schedule III. The rescheduling was in response to a petition filed by the manufacturer on February 3, 1995. Supplemental information was filed on December 11, 1996. The petition was referred to HHS on August 7, 1997 and HHS provided DEA with its report on September 11, 1998

Fenfluramine. 62 FR 24620. May 6, 1997. Fenfluramine is a weight loss drug. The manufacturer filed a petition to have it removed from the schedules on March 18, 1991. DEA forwarded the petition to HHS for review on December 2, 1991. The drug was eventually removed from the schedules. NOTE: The FDA convened an advisory committee to review the possible removal of fenfluramine from the schedules, and this committee held open public hearings. See 60 FR 44036, which contains notices of several meetings.

Benzodiazepines. 62 FR 33418. June 19, 1997. NOTE: HHS announces public hearings to gather evidence regarding the scheduling of benzodiazepines.

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Petition to Reschedule Cannabis (Marijuana)

per 21 CFR §1308.44(b)

Filed with the
Drug Enforcment Administration

by
The Coalition for Rescheduling Cannabis
www.drugscience.org

October 9, 2002

PETITION TO RESCHEDULE CANNABIS (MARIJUANA)

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Petition to Reschedule Cannabis (Marijuana)

Exhibit A. Statement of the Proposed Rule

The proposed rules for repeal, in the form proposed by the petitioners:

The rule placing marihuana in schedule I [21 CFR 1308.11(d))17)] is repealed because cannabis has an accepted medical use in the United States, is safe for use under medical supervision, has an abuse potential lower than Schedule I or II drugs, and has a dependence liability that is also lower than Schedule I or II drugs.

This is not a petition for the removal of marijuana from scheduling under the Controlled Substances Act (CSA), but a petition to have marijuana removed from Schedule I and rescheduled as "cannabis" in either Schedule III, IV, or V. A consideration of the appropriate scheduling of cannabis should be made on the basis of the scientific and medical evaluation required by the CSA and in accordance with existing law.

Exhibit B. Statement of Grounds

Part I – Introduction of Argument

This petition is based on consideration of research findings not examined in prior proceedings, the emergence of new research findings about marijuana/cannabis since prior rescheduling proceedings, and research findings that cast the record of prior proceedings in a new light.

The Controlled Substances Act specifies eight factors that determine control of a drug or substance or its removal from schedules. The CSA states that these eight factors will be considered when making any finding regarding a drug's accepted medical use, safety for use, abuse potential, or dependence liability; all eight of these factors must be considered in determining the scheduling or rescheduling of cannabis. (21 USC 811(c)) A review of the scientific and medical record for these factors supports recognition of the accepted medical use of cannabis in the United States and requires its rescheduling under the CSA.

(1) Its actual or relative potential for abuse.

The scientific record indicates that cannabis does not have a high potential for abuse; a majority of users do not experience problems which characterize drug abuse. Indications of abuse of cannabis occur at lower rates than for other scheduled drugs such as cocaine and heroin. Neither the actual nor relative potential for abuse of cannabis is sufficiently high to render cannabis unsafe for medical use.

(2) Scientific evidence of its pharmacological effect, if known.

The pharmacological effects of cannabinoid drugs are well-established through both basic and clinical research and are widely documented in the scientific record. The pharmacological effects of cannabis are sufficiently well-known by the scientific and medical communities to have resulted in the accepted medical use of cannabis by doctors and health care professionals.

(3) The state of current scientific knowledge regarding the drug or other substance.

Contemporary scientific knowledge has confirmed the accuracy of patient accounts of the therapeutic effects of cannabis. The side effects of acute use are also well-known and the safety of long-term medical use has also been established.

(4) Its history and current pattern of abuse.

The use and abuse of cannabis has been widespread in the United States since national drug use surveys began in the 1970s. A considerable number of cannabis users suffer from problems that meet the criteria for abuse. However, the large majority of cannabis users do not experience any relevant problems related to their use.

(5) The scope, duration, and significance of abuse.

When compared to legal drugs, abuse problems with cannabis are generally less severe.

6) What, if any, risk there is to the public health.

There is no demonstrable risk to public health posed by medical cannabis use. The denial of therapeutic access to cannabis creates a far greater risk to public health than the minor acute effects of the drug and/or its long-term use under medical use under medical supervision.

(7) Its psychic or physiological dependence liability.

There is a general consensus in the scientific community that cannabis has a relatively low dependence liability compared to other scheduled drugs and substances.

(8) Whether the substance is an immediate precursor of a substance already controlled under this subchapter.

Cannabis is a natural source of dronabinol (THC), the ingredient of Marinol™, a Schedule III drug. There are no grounds to schedule cannabis in a more restrictive schedule than Marinol™.

There have been two prior cannabis rescheduling petitions that have resulted in formal review under the provisions of the Controlled Substances Act. The first of these was filed by NORML in 1972, was subject to numerous court battles, and was finally resolved in 1994. (Alliance for Cannabis Therapeutics v. Drug Enforcement Administration, 15 F.3d 1131 (D.C. Cir. 1994)) By the time it was the subject of administrative hearings and final judicial review the NORML petition solely concerned marijuana's accepted medical use and safety for use under medical supervision. The second petition was filed by Jon Gettman and High Times in 1995, and was formally rejected by the Drug Enforcement Administration in 2001. Judicial review was denied by the Court of Appeals because the petitoners had insufficient standing to involve the federal courts. (Jon Gettman and High Times Magazine v. Drug Enforcement Administration, D.C. Cir. 2001. No. 01-1182, decided March 24, 2002.) The Gettman petition argued that marijuana did not have the high potential for abuse required for Schedule I or Schedule II status.

In their review of the Gettman petition neither DEA nor HHS gave any consideration to marijuana's medical use, its safety for use, its relative abuse potential or its relative dependence liability, as called for by the Controlled Substances Act (CSA). This petition addresses all of these relevant issues.

This petition is being filed by a coalition of interested parties including non-profit organizations and individual citizens. The membership of these organizations and these individual citizens have various interests in the appropriate scheduling of cannabis under federal law, including but not limited to an interest in legal access to cannabis for therapeutic use based on existing medical conditions.

In the following, the terms "marijuana" and "cannabis" will be used synonymously. The latter is often preferred in the scientific community with regard to medicinal uses of the plant Cannabis sativa L. and its derivatives.

Key developments in the assessment of marijuana's medical use include: acceptance of marijuana's medical use by health care professionals; recognition of marijuana as a medicine of last resort by the Institute of Medicine of the National Academy of Sciences; recognition of the therapeutic properties of cannabinoids by the scientific community and health care providers; the emergence of basic research explaining the mode of action of cannabis-based medicines; the emergence of clinical research on the medical use of cannabis; and acceptance of marijuana's medical use by eight states. These developments contradict the CSA's classification of marijuana as having no accepted medical use in the United States.

There is also a growing consensus among scientists and health care providers that in lieu of alternatives marijuana is an adequate delivery system for cannabinoid drugs, and more specifically a consensus that data on the medical efficacy of THC and other cannabinoids drugs is sufficient to recognize marijuana's accepted medical use in the United States.

Because of the nature of the statute "accepted medical use in the United States" exists in society prior to recognition by DEA by way of the fact finding process outlined in 21 USC 811(c), which establishes factors determinative of control. Marijuana does not have to be the best medicine for various conditions, nor does it have to be the best delivery form for cannabinoid drugs, in order to have an accepted medical use. All drugs have side-effects and most conditions have alternate therapies. These are criteria relevant to the drug approval process under the Federal Food Drug and Cosmetic Act (FFDCA), however the CSA's different regulatory purpose provides for simple consideration as to whether or not there is a legitimate need for a regulatory regimen under the CSA. Nor does recognition of accepted medical use under the CSA imply that a substance is recommended for use, this is not even implied by FDA approval.

Marijuana's low dependence liability and low toxicity compared to other drugs of abuse are inconsistent with the drug having the high potential for abuse implied by Schedule I of the CSA. Many individuals use marijuana recreationally or medicinally without becoming dependent or otherwise developing drug abuse problems. Recent evidence shows that far fewer regular users of marijuana have dependency problems than of other drugs such as nicotine or cocaine. Recent evidence indicates that marijuana has an effect on dopamine production in the brain, which is somewhat similar to other legal and illegal drugs (nicotine, caffeine, cocaine, heroin, etc.) and that animals self-administer cannabinoid-1-receptor agonists under certain conditions. However, the actual abuse potential and dependence liability in humans cannot be derived from this basic research, which only helps to explain observations of human behavior.

Marijuana's relative abuse potential has never been assessed as part of rescheduling proceedings. Rather than considering relative toxicity, physical dependence, and pharmacological or neurotoxic effects, in their review of the 1995 petition to reschedule marijuana, the DEA relied, instead, upon social survey data regarding the relative number of users, emergency room visits, and drug treatment admissions for marijuana versus cocaine and heroin. Such crude measures of abuse cannot substitute for the scientific evaluations required by the CSA and performed by the DEA for MDMA, butorphanol and other controlled substances.

Along with assessments of marijuana's low dependence liability and low potential for abuse, recent research findings give new credence to the claims of patients that marijuana has

therapeutic value for them. This scientific evidence casts testimony in original NORML marijuana rescheduling proceedings in a new light.

The legislative history of the Controlled Substances Act requires that the impact of proposed regulations on those most affected by them should be considered as part of the rescheduling process. Two impacts must be considered. With respect to the research, manufacture, and distribution related to marijuana's possible sale as a medicinal drug in accordance with U.S. FDA regulations, the rescheduling of marijuana would lower the development costs associated with securing FDA approval. Second, the impact of rescheduling on individuals who require marijuana for medical purposes must be considered with respect to assessing marijuana's accepted medical use and safety. Continued prohibition of marijuana's medicinal use has a costly effect on individuals who require it for therapeutic use; rescheduling would expedite its legal availability to these individuals both with respect to entry into suitable research programs and to development of a legal production and delivery system.

When considering the criteria specified by the CSA for making findings determinative of scheduling, it is apparent in light of the above that marijuana has at most a similar potential for abuse and dependence liability to Schedule III substances with accepted medical uses in the United States, such as dronabinol (THC) and codeine. This is particularly true in comparison with dronabinol (Marinol™), as it has recently been demonstrated that the medicinal effects of dronabinol and marijuana are largely identical. Consequently, this petition requests proceedings to have marijuana removed from Schedule I and rescheduled in either of Schedules III, IV or V of the Controlled Substances Act based on a formal assessment of its relative abuse potential and dependence liability.

The reclassification of cannabis under state and national law is a well-established trend based on an ongoing recognition by government's, legislative bodies, and electorates that the scientific record does not justify prohibition of cannabis or its classification in the same legal category as narcotic and other dangerous drugs. For example the governments of Canada and Great Britain have recently recognized the need to change the legal status of cannabis in order to facilitate medical access. Furthermore, differences with the U.S. regulatory position have already been established in most U.S. states. Rescheduling of cannabis to distinguish it under the law from more dangerous drugs is wide-spread at the state level (see summary below). Only 6 states have scheduled marijuana in conformity with its federal Schedule I status. Marijuana has its own distinct schedule in 39 states while 5 others have placed it in either a Schedule V or Schedule VI.

For all of these reasons the scientific record provides a compelling case for the removal of mariuana from Schedule I and the rescheduling of cannabis in Schedule III or a less restrictive schedule. This rescheduling would not only exedite the availability of legal cannabis to patients in need, but it would also bring the goverment into compliance with the Controlled Substances Act which, subject to appropriate regulatory restrictions, mandates public access to therapeutic drugs and substances, including cannabis.

Summary of Marijuana and State-level Scheduling Structures

States (6) with marijuana scheduling that conforms to federal status:

Delaware - distinguishes between narcotics and non-narcotics in schedules I and II

Idaho - distinguishes between narcotics and non-narcotics in schedule I

Kansas - schedules conform to federal schedules, but for penalty purposes narcotics and methamphetamine are distinguished from non-narcotic drugs

Nevada - schedules conform to federal schedules, with automatic adjustments based on changes in federal scheduling.

West Virginia - schedules conform to federal schedules, with automatic adjustments based on changes in federal scheduling, distinguishes between narcotic and non-narcotics for sale offenses involving schedule I and II drugs.

Wisconsin - distinguishes between narcotics and non-narcotics in schedules I and II

States (2) with flat penalties that distinguish marijuana from federal schedule I and II substances:

Alabama - distinguishes between a flat penalty and marijuana on posssession offenses, and has harsher penalties for sale of opiates and cocaine than other drugs.

Montana - distinguishes between a flat penalty and marijuana on posssession offenses, and has harsher penalties for sale of opiates and cocaine than other drugs.

State-like jurisdictions (5) that schedule marijuana in Schedule V or VI

Alaska - marijuana is placed in schedule VIa

Arkansas - Arkansas has created a sixth schedule for marijuana and tetrahydocannibinol (THC). [Schedule VI]

District of Columbia - the District has placed hashish and tetrahydocannibinol (THC) in schedule II and has placed marijuana in schedule V.

North Carolina - Schedule VI marijuana

Tennessee - the state CSA also includes a sixth schedule that covers marijuana and tetrahydocannibinols. [schedule VI]

States (39) that have a separate schedule labeled "marijuana":

Arizona, California, Colorado, Connecticut, Florida, Georgia, Hawaii, Illinois, Indiana, Iowa, Kentucky, Louisiana, Maine, Maryland, Massachusetts, Michigan, Minnesota, Mississippi, Missouri, Nebraska, New Hampshire, New Jersey, New Mexico, New York, North Carolina, North Dakota, Ohio, Oklahoma, Oregon, Pennsylvania, Rhode Island, South Carolina, South Dakota, Texas, Utah, Vermont, Virginia, Washington and Wyoming. (Holden, 1991)

Reference

Holden, Gwen A. A Guide to State Controlled Substances Acts. National Criminal Justice Association, January, 1991. Prepared in cooperation with the U.S. Department of Justice, Bureau of Justice Assistance and the National District Attorney's Association, American Prosecutors Research Institute. National Institute of Justice Call Number: 132321

Part II -- Description of new relevant information

According to the National Library of Medicine over 3,900 scientific and medical articles about marijuana, cannabis, cannabinoids, and THC have been published since the last rescheduling petition was submitted in 1995. A considerable part of this new research is relevant to the discussion of the classification or re-classification of marijuana/cannabis. The following arguments, grouped into four main categories, support this petition for the removal of marijuana from Schedule I and its rescheduling to Schedule III or a less restrictive schedule. The primary arguments are presented in detail in Exhibit C, which summarizes the key findings of recent research from over 200 articles reviewed for this petition..

I. Accepted Medical Use in the United States

State laws
The acceptance of cannabis's medical use by eight states since 1996 and the experiences of patients, doctors, and state officials in these states establish marijuana's accepted medical use in the United States

Medical professionals
Cannabis's accepted medical use in the United States is increasingly recognized by health care professionals and the medical community, including the Institute of Medicine. Several medical organizations support legal access to cannabis for medicinal purposes. A new medical journal released in 2001 focuses on the medicinal use of cannabis and cannabinoids. National clinical conferences on the medicinal use of cannabis have been held in the United States in 2000 and 2002 and are scheduled to continue on a bi-annual basis.. Most importantly, data on the number of physicians currently recommending therapeutic marijuana use to their patients demonstrate its acceptance by the medical community in the United States

Patients' experience and their confirmation by early studies
Following state laws that allow for the medical use of cannabis, an increasing number of patients have collected experience with cannabis. Many reported benefits from its use. Some of this experience has been confirmed in reports and clinical investigations or stimulated clinical research that confirmed these patients' experience on other patients suffering from the same disease.

Reviews of earlier clinical studies
Several scientific publications have reviewed evidence from research on the medicinal uses of cannabis indicating that cannabis in fact may offer benefits in the treatment of certain illnesses.

Basic research
The scientific understanding of the endogenous cannabinoid system consisting of specific cannabinoid receptors and their endogenous ligands (endocannabinoids) has considerably increased since 1995. It largely supports and helps explain many of the therapeutic benefits of cannabis and cannabinoids in humans.

Clinical research
Results from clinical research demonstrate that both dronabinol and whole plant cannabis can offer a safe and effective treatment for the following illnesses: muscle spasms in multiple sclerosis, Tourette syndrome, chronic pain, nausea and vomiting in HIV/AIDS and cancer chemotherapy, loss of appetite from cancer, hyperactivity of the bladder in patients with multiple sclerosis and spinal cord injury, and dyskinesia caused by levodopa in Parkinson's disease.

Route of administration.
Progress has been made in recent years in reducing the disadvantages of certain routes of cannabis administration, notably the slow onset of action with oral use and harm associated with the inhalation of combustion products when smoking cannabis.

Pharmaceutical industry.
The pharmaceutical industry is showing not only increasing interest in synthetic modulators of the endogenous cannabinoid system, but also industry members are funding several clinical studies with cannabis whole plant extracts in Europe and Canada with the intention to develop approved cannabis based medicines. This indicates that therapeutic exploitation of natural cannabis will be economically sound. However the present Schedule I classification of cannabis and THC is an impediment to the pharmaceutical development of cannabinoid drugs becaused of the costly restrictions it places on research.

II. Safety of use

Acute side effects
It is now generally accepted that "...except for the harms associated with smoking, the adverse effects of marijuana use are within the range of effects tolerated for other medications" (Institute of Medicine Report of 1999). This opinion is supported by recent clinical research. Besides abuse and dependency, the main side effects of concern are those on the cardiovascular, immune, and hormonal systems, and on cognitive functions.

Documented safety of long-term cannabis use
Studies have shown the long-term use of cannabis to be safe. In contrast to many other medicinal drugs, the long-term use of cannabis does not harm stomach, liver, kidneys and heart.

Side effects of the legal situation
The illegal status of cannabis under most jurisdictions causes negative consequences for many with regard to their career, personal and professional relationsships, suspension of driving privilege, and health.

Cannabis as gateway drug
Recent research suggests that recreationally used cannabis does not act as a gateway drug to harder drugs such as alcohol, cocaine and heroine. The same will apply to users of medicinal cannabis.

III. Dependence liabilty

Basic research on rewarding, tolerance and withdrawal
In recent years, scientists were able to show that animals do self-administer THC under certain conditions. Basic animal research also shows that cannabis produces tolerance and withdrawal. This research helps explain abuse of cannabis and dependency in humans. However, basic research cannot predict how pronounced these effects will be in humans and whether they are stronger or less strong compared to other drugs such as caffeine, nicotine and heroin.

Dependency compared to other drugs
Compared to other widely used drugs (alcohol, tobacco, opiates) a smaller percentage of cannabis users become dependent. Dependency is also less severe compared to many other legal and illegal drugs. The relatively low dependence liability of cannabis is widely recognized.

IV. Abuse potential

Use and Abuse
The government's review of the 1995 marijuana rescheduling petition did not distinguish between use and abuse according to professional standards, such as those in use by the medical and scientific community. Widespread use of cannabis is not an indication of its abuse potential, and widespread use of marijuana without dependency supports the argument that marijuana is safe for use under medical supervision.

Abuse of cannabis
Several studies demonstrate that abuse rates for cannabis are lower than rates for other common drugs. Cannabis use is usually not problematic use and cannabis users usually have no social problems which can be attributed to cannabis. The abuse potential of cannabis is insufficient to justify prohibition of medical use.

Emergency room admissions
Data on both drug treatment and emergency room admissions also distinguish the abuse potential of marijuana from that of other drugs, and establishes its relative abuse potential as lower than Schedule I drugs such as heroin and Schedule II drugs such as cocaine.

Cannabis and dronabinol
There is growing evidence that there is no relevant difference in subjective effects between (Schedule III) dronabinol and cannabis. Thus, it can be expected that the abuse liability is similar for both agents.

Exhibit C. Summary of Evidence

I. Accepted Medical Use in the United States

1) State laws.

The acceptance of cannabis's medical use by eight states since 1996 and the experiences of patients, doctors, and state officials in these states establish marijuana's accepted medical use in the United States

Alaska, California, Colorado, Hawaii, Maine, Nevada, Oregon, and Washington all have enacted legislation accepting marijuana's medical use by its citizens. See Alaska Stat. §§ 17.37.010-17.37.080 & 11.71.090 (1999); Cal. Health & Safety Code § 11362.5(b)(1)(A) and (d) (1996); Colo. Const., Art. XVIII, § 14; Haw. S.B. 862, 20th Legis. (1999) (signed into law on July 12, 2000); Me. Rev. Stat. Ann., Tit. 22, § 2383-B(5) (2000); Nev. Const., Art. 4, § 38; Ore. Rev. Stat. §§ 475.300-475.346 (1999); Wash. Rev. Code §§ 69.51.010-69.51.080 (1997).

For example, the California Health and Safety Code §11362.5(A) indicates that the purpose of the state's medical marijuana statute is:

> "to ensure that seriously ill Californians have the right to obtain and use marijuana for medical purposes where that medical use is deemed appropriate and has been recommended by a physician who has determined that the person's health would benefit from the use of marijuana in the treatment of cancer, anorexia, AIDS, chronic pain, spasticity, glaucoma, arthritis, migraine, or any other illness for which marijuana provides relief"

Another indication of acceptance of marijuana's medical use is Oregon's program of providing identification cards for patients. One requirement is:

> "Valid, written documentation from the person's attending physician stating that the person has been diagnosed with a debilitating medical condition and that the medical use of marijuana may mitigate the symptoms or effects of the person's debilitating medical condition" (Section 4, chapter 4, Oregon Laws 1999; 2a)

The right of doctors to recommend marijuana for medical use under state law has been upheld in federal court. (Conant v. McCaffrey, No. C 97-00139 WHA, 2000 U.S. Dist. LEXIS 13024 , 2000 WL 1281174 (N.D. Cal. Sept. 7, 2000)). In this case the Court recognized that physicians had a right to recommend or otherwise discuss medical marijuana use with their patients, and such actions could not be used by the federal government as a basis to revoke physician's licenses to dispense controlled substances.

The California medical marijuana law was also recently clarified by the state's Supreme Court, explicitly underscoring the state's acceptance of marijuana's medical use:

"As stated, the purpose of the statute is: (1) "[t]o ensure that seriously ill Californians have the right to obtain and use marijuana for medical purposes where that medical use is deemed appropriate and has been recommended by a physician who has determined that the person's health would benefit from the use of marijuana in the treatment of . . . any . . . illness for which marijuana provides relief" (§ 11362.5, subd. (b)(1)(A)); and (2) "[t]o ensure that patients and their primary caregivers who obtain and use marijuana for medical purposes upon the recommendation of a physician are not subject to criminal prosecution or sanction" (§ 11362.5, subd. (b)(1)(B)). Under section 11362.5(d), qualified patients and primary caregivers "who obtain and use marijuana for medical purposes upon the recommendation of a physician" are exempted not only from "criminal . . . sanction" for possession and cultivation of marijuana, but even from "criminal prosecution" (§ 11362.5, subd. (b)(1)(B)), because their conduct is noncriminal, involving as it does the treatment of "seriously ill" persons who "obtain and use marijuana for medical purposes where that medical use is deemed appropriate and has been recommended by a physician who has determined that the person's health would benefit" therefrom (§ 11362.5, subd. (b)(1)(A)).

As a result of the enactment of section 11362.5(d), the possession and cultivation of marijuana is no more criminal — so long as its conditions are satisfied — than the possession and acquisition of any prescription drug with a physician's prescription. Inasmuch as this statute provides that sections 11357 and 11358, which criminalize the possession and cultivation of marijuana, "shall not apply to a patient, or to a patient's primary caregiver, who possesses or cultivates marijuana for the personal medical purposes of the patient upon the written or oral recommendation or approval of a physician" (§ 11362.5(d)), the provision renders possession and cultivation of marijuana noncriminal under the conditions specified." Pg 27-28. (People v. Mower, California Supreme Court Case S094490, July 18, 2002; Ct. App. 5 No Fo30690; County of Tuolumne Super. Ct. No. CR1995.)

2) Medical professionals.

Cannabis's accepted medical use in the United States is increasingly recognized by health care professionals and the medical community, including the Institute of Medicine. Several medical organizations support legal access to cannabis for medicinal purposes. A new medical journal released in 2001 focuses on the medicinal use of cannabis and cannabinoids. National clinical conferences on the medicinal use of cannabis have been held in the United States in 2000 and 2002 and are scheduled to continue on a bi-annual basis.. Most importantly, data on the number of physicians currently recommending therapeutic marijuana use to their patients demonstrate its acceptance by the medical community in the United States.

The most significant evidence of marijuana's acceptance by the medical community in the United States consists of data on the number of physicians currently recommending marijuana medical use by their patients:

> "By any reasonable definition, marijuana has "currently accepted medical use in treatment in the United States." Eight states have officially legalized its medical use. A minimum of 35,000 patients are currently using medical marijuana legally in these states. Over 2,500 different physicians have recommended it for use by their patients. As many as 5% of all registered physicians have recommended marijuana in Oregon and Northern California. Usage rates vary greatly among different regions. The average usage rate in the general population ranges from 80 to 90 per 100,000 in California and Oregon, where there are numerous patient support groups, to fewer than 10 per 100,000 in Colorado and Nevada, where cannabis medicine is still underdeveloped. As many as 1% of the population in Mendocino County, California, are legal medical marijuana users, while Canadian surveys suggest illegal medical usage as high as 2% - 4% in the general population. The widespread and growing popularity of medical marijuana and its potential for treating a wide range of conditions indicate a growing role in American medicine. These facts refute marijuana's current Schedule One misclassification as a drug lacking "currently accepted medical use"" (Gieringer 2002).

A considerable number of organizations representing health care professionals, the medical community, and the general public support granting greater access to medical cannabis for patients in need and recognizing explicitly marijuana's medical use both in the United States and in the international community.

Organizations Supporting Access to Therapeutic Cannabis

1) AIDS Action Council - 1996
2) Alaska Nurses Association - 1998
3) Alaska Voters - 1998
4) Alliance for Cannabis Therapeutics – 1981
5) +American Academy of Family Physicians – 1989, 1995
6) American Civil Liberties Union (ACLU)
7) American Medical Students Association - 1993
8) American Preventive Medical Association – 1997
9) +American Public Health Association (APHA) - 1995
10) Arizona Voters - 1996 & 1998
11) Berkeley, CA - 1979
12) Breckenridge, CO - 1994
13) Burlington, VT - 1994
14) California Academy of Family Physicians - 1996
15) California Democratic Party - 1993
16) California Legislative Council for Older Americans - 1993
17) +California Medical Association - 1994
18) California Nurses Association - 1995
19) California-Pacific Annual Conference of the United Methodist Church - 1996
20) California Pharmacists Association - 1997
21) California Society of Addiction Medicine - 1997
22) California Voters - 1996
23) Cannabis Freedom Fund – 1996
24) Colorado Voters - 2000
25) Colorado Nurses Association - 1995
26) Contigo-Conmigo - 1997
27) Consumer Reports Magazine - 1997
28) Crescent Alliance Self Help for Sickle Cell - 1999
29) Cure AIDS now - 1991
30) District of Columbia Voters - 1999
31) +Episcopal Church of the U.S. - 1982
32) Farmacy - 1999
33) Federation of American Scientists - 1994
34) Florida Governor's Red Ribbon Panel on AIDS - 1993
35) Florida Medical Association - 1997
36) Frisco, CO - 1994
37) Hawaii Kokua Council of Senior Citizens - 2000
38) Hawaii Legislature - 2000
39) Hawaii Nurses Association - 1999
40) Institute of Medicine - 1982 & 1999
41) International Cannabis Alliance of Researchers and Educators (I-CARE) - 1992
42) Iowa Civil Liberties Union
43) Iowa Democratic Party - 1994 & 2000
44) Kaiser Permanente - 1997

45) Life Extension Foundation - 1997
46) Libertarian Party – 1999
47) Los Angeles County AIDS Commission - 1996
48) Lymphoma Foundation of America - 1997
49) Madison, WI – 1993
50) Maine AIDS Alliance - 1997
51) Maine Voters - 1999
52) Marin County, CA - 1993
53) Minnesota Democratic Farm-Labor Party - 1992
54) Mississippi Nurses Association - 1995
55) Mothers Against Misuse and Abuse (MAMA) -1992
56) Multiple Sclerosis California Action Network (MS-CAN) - 1996
57) National Association for Public Health Policy - 1998
58) National Association of Attorneys General - 1983
59) National Association of Criminal Defense Lawyers (NACDL)
60) National Association of People with AIDS - 1992
61) National Nurses Society on Addictions (NNSA) - 1995
62) Nevada Voters - 1998
63) New England Journal of Medicine - 1997
64) New Mexico Nurses Association - 1997
65) New York State Nurses Association - 1995
66) North Carolina Nurses Association - 1996
67) Oakland, California - 1998
68) Oregon Voters – 1998
69) Oregon Green Party - 2001
70) Oregon Democratic Party - 1998
71) Patients Out of Time - 1995
72) Physicians Association for AIDS Care
73) Physicians for Social Responsibility (Oregon) - 1998
74) Republican Liberty Caucus National Committee - 1999
75) San Diego, CA - 1994
76) San Francisco, CA - 1992
77) San Francisco Medical Society - 1996
78) Santa Cruz County, CA - 1993
79) Virginia Nurses Association - 1994
80) Virginia Nurses Society on Addictions - 1993
81) Washington Hemp Education Network - 1999
82) Washington Democratic Party - 1998 & 2000
83) Washington Voters - 1998
84) Wisconsin Democratic Party - 1997
85) Wisconsin Public Health Association - 1999
86) Wisconsin Nurses Association - 1999
87) Women of Reform Judaism - 2000

Organizations Supporting Research on the Therapeutic Use of Cannabis

1) American Academy of Addiction Psychiatry - 2000
2) +American Academy of Family Physicians - 1977

3) American Cancer Society – 1997
4) American Nurses Association, Congress of Nursing Practice - 1996
5) +American Society of Addiction Medicine – 2000
6) +California Medical Association - 1997
7) +Council of Health Organizations - 1971
8) Federation of American Scientists – 1995
9) National Institute of Health Workshop on the Medical Utility of Marijuana - 1997
10) +Northern New England Psychiatric Society
11) Wisconsin State Medical Society – 1998

No Criminal Penalty

1) Alaska Medical Association - 1972
2) +American Academy of Family Physicians - 1977
3) American Bar Association - 1977
4) American Medical Association – 1977
5) +American Public Health Association - 1971
6) American Social Health Association - 1974
7) +Berkeley, CA - 1972
8) B'nai B'rith Women - 1974
9) Central Conference of American Rabbis - 1973
10) +Council of Health Organizations - 1971
11) District of Columbia Medical Society - 1973
12) +Episcopal Church of the U.S. - 1973
13) Episcopal Diocese of New York - 1975
14) Gray Panthers - 1975
15) Illinois Bar Association - 1974
16) Lutheran Student Movement - 1975
17) Massachusetts Bar Association - 1974
18) National Association for Mental Health - 1972
19) National Association of Social Workers - 1975
20) National Council of Churches - 1973
21) National Education Association - 1978
22) New York Bar Association - 1974
23) +Northern New England Psychiatric Society
24) Southern California Psychiatric Society - 1979
25) United Methodists - 1976
26) Unitarian Universalist Association - 1970
27) Vermont Bar Association - 1974
28) +Washington Democratic Party - 2000

Non-U.S. Organizations Supporting Access to Therapeutic Cannabis

1) Australian National Task Force on Cannabis – 1994
2) Australian Medical Association (New South Wales) Limited - 1999
3) British Medical Association - 1997
4) Bundesverband Poliomyelitis (Federal Union for Polio),

5) Germany – 1998
6) Canadian Association of Chiefs of Police - 2001
7) Canadian Medical Association – 2001
8) Canadian Medical Journal - 2001
9) Deutsche AIDS-Hilfe (German AIDS Support Organization)-1998
10) Deutsche Epilepsievereinigung (German Association for Epilepsy) - 1998
11) Deutsche Gesellschaft für Algesiologie (German Society for Algesiology) -1998
12) Deutsche Gesellschaft für Drogen-und Suchtmedizin (German Society for Drug and Addiction Medicine) -1998
13) Deutsche Gesellschaft niedergelassener Ärzte zur Versorgung HIV – Infizierter (German Working Group for Therapists of the HIV infected) - 1998
14) French Ministry of Health - 1997
15) German Bundestag (German Federal Parliament) - 2000
16) Health Canada - 1997
17) House of Lords (UK) Select Committee on Science and Technology - 1999
18) Legalise Cannabis Alliance - 2000
19) New South Wales (Australia) Parliamentary Working Party on the Use of Cannabis for Medical Purposes - 2000
20) Lancet (UK) – 1995, 1998
21) Medical Cannabis Research Foundation (UK) - 2000
22) Preventive Medical Center, Netherlands - 1993
23) Schmerztherapeutisches Kolloquium (Society for Pain Therapists) Germany - 1998
24) Stichting Institute of Medical Marijuana, Netherlands - 1993
25) United Church of Jamaica and Cayman Islands – 2000

+ denotes listing in multiple categories
Source: Patients Out of Time,
http://www.medicalcannabis.com/Grouplist23.pdf

In addition national medical organizations in the United States and Canada are beginning to attend to issues related to medical cannabis use. In a resolution on 19 June 2001 the 547 delegates of the American Medical Association reasserted its opposition to criminalizing patients or doctors who use cannabis (Reuters of June 19, 2001). "Our plea again is that no criminal sanctions be applied to marijuana use, and to encourage our patients to discuss this freely with their doctors," Dr. Herman Abromowitz said.

On May 15, 2001 the Canadian Medical Association Journal (CMAJ) called on the government to decriminalize the possession of marijuana for personal use. Editor John Hoey argues the social and legal consequences of being arrested for marijuana possession far outweighs the minimal health affects of moderate use of the drug (Hoey 2001). The founding president of the International Society for Addiction Medicine, Dr. Nady el Guebaly, backs the federal governments move to legalize the medical use of cannabis (Calgary Herald of 20 July 1999). The medical director of Foothills Hospital's addiction centre supports the limited use

of marijuana for treating nausea associated with chemotherapy and as an appetite stimulant for people suffering from AIDS. But el Guebaly stressed marijuana should only be used on a short-term basis under medically controlled conditions where other therapies have failed and under the supervision of a review board.

Research shows that not only in patients but also in health care professionals the attitude towards the medical value of cannabis depends much on personal experience. Those with some experience regarding the medical use of cannabis are more likely to support having the option of prescribing the drug to patients. This is a strong argument in favor of making the drug available for medical use, since the experience of these professionals must have been overall positive. Otherwise they would not recommend it.

The results of a U.S. survey presented at the annual meeting of the American Society of Addiction Medicine indicate that physicians are divided on the medical use of cannabis (Reuters of 23 April 2001). Researchers at Rhode Island Hospital in Providence asked 960 doctors about their attitude towards the statement, "Doctors should be able to legally prescribe marijuana as medical therapy." 36% of the responders agreed, 38% disagreed and 26% were neutral. Residence in a state that had approved research into the medical use of cannabis as well as a physician's "permissiveness" were associated with supporting the medical use of cannabis. The researchers surveyed physicians in five specialties: addiction medicine, general psychiatry, gynecology, family practice and internal medicine. They found gynecologists and internists more likely to support the medical use of the drug than other surveyed specialists. Because doctors in those two specialties are more likely to see cancer patients, they may be more sensitive to marijuana's potential for managing the side effects of chemotherapy and of pain, the Rhode Island team proposed. They noted that the other specialists surveyed are more likely to see active substance abusers and may be more concerned about the drug's negative effects.

For example, Schwartz (2002) described his personal experience with cannabis, when his son became dependent on the drug, obviously a very difficult period:

> "In 1984, I published in this journal a review entitled "Marijuana: A Crude Drug with a Spectrum of Underappreciated Toxicity." In the introduction to that article, I disclosed that our son Keith, who was 15 years old at the time, was in a long-term, modified outpatient adolescent drug and alcohol rehabilitation program because he had become dependent on marijuana with its associated behavioral, interpersonal, scholastic, and antisocial problems. Keith and most of his friends had experimented several times with LSD, beer, and several other drugs but never used injection drugs. Marijuana was clearly Keith's drug of choice and the only drug he used with regularity. Approximately 1 year later, Keith graduated from the treatment program. He completed the early aftercare component, relapsed several times, and completed a 4-month refresher drug rehabilitation program in another state. Nine years after admission to the first rehabilitation program, Keith finally attained some adult goals. Now 34 years old, he has been drug-free for 10 years. He is the president and owner

> of a successful discount cellular phone business that he started. More important, a decade ago, he reestablished an excellent and close relationship with his parents. As far as I can tell, Keith remains drug-free except for an occasional beer."

Schwartz became a strong opponent of the medical use of the drug, fighting against legal use in several articles (Voth and Schwartz 1997). From his personal background it might be impossible for him to concede that other people find relief with cannabis.

A peer-reviewed journal and national clinical conferences are evidence of acceptance of cannabis' medical use in the continuing education of doctors and other health professionals. *The Journal of Cannabis Therapeutics*, edited by Ethan Russo and published by the Haworth Press, began publication in 2001. This peer-reviewed journal addresses doctors, researchers, and other health professionals who require current information on the use of cannabis in treatment for neurological and other diseases as well as the latest research on endogenous and synthetic cannabinoids. This journal covers the history of cannabis, its clinical applications and components, and the biochemical and pharmacological functions of cannabinoids in man and animals as well as related legislative/legal issues. In addition to reporting on current research, the *Journal of Cannabis Therapeutics* has the goal of facilitating advances in education concerning the history, pharmacology, biochemistry, toxicology, as well as behavioral, psychological, and social effects, of cannabis and the cannabinoids.

National clinical conferences on marijuana's medical use have been held in Iowa (2000) and Oregon (2002), both organized by Patients Out of Time, an educational group dedicated to advancing public understanding of medical cannabis research and the impact of public policies on medical cannabis patients. The conference in 2002 was co-sponsored by the Portland Community College Institute of Health Professionals, the Oregon Health Division, Mothers Against Misuse and Abuse, and the Oregon Nurses Association. The conference proceedings are evidence both of acceptance of marijuana's medical use by the scientific and research communities and of the scope of medical applications of cannabis. Attendees of each conference qualified for continuing medical education credits, evidence of acceptance of the conference curriculum by state health professional associations. The conferences are scheduled to continue on a bi-annual basis.

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3) Patients' experiences and their confirmation.

Following state laws that allow for the medical use of cannabis, an increasing number of patients have collected experience with cannabis. Many reported benefits from its use. Some of this experience has been confirmed in reports and clinical investigations or stimulated clinical research that confirmed these patients' experience on other patients suffering from the same disease

Several examples show that the attitude of people towards the medical use of cannabis is based on such personal experience. Lynn Nofziger, the former White House director of communication and chief speech writer of President Ronald Reagan, stated in a foreword to a book on the medical use of marijuana:

> "Strange as it may seem, here is one right-wing Republican who supports carefully controlled, medical access to marijuana. When our grown daughter was undergoing chemotherapy for lymph cancer, she was sick and vomiting constantly as a result of her treatments. No legal drugs, including the synthetic "marijuana" pill Marinol™, helped her situation. As a result we finally turned to marijuana which, of course, we were forced to obtain illegally. With it, she kept her food down, was comfortable, and even gained weight. (...) A doctor should have every possible medication -- including marijuana -- in his armentarium. (...)" (Nofziger 1999).

In several investigations, patients' experiences were collected by health care professionals and scientists. Among these investigations is the report "*Cannabis. The scientific and medical evidence*" by the British House of Lords Select Committee on Science and Technology (1998) and " *Marijuana and medicine: Assessing the science base*" by the U.S. Institute of Medicine (Joy et al. 1999)

The IOM report, "Marijuana and Medicine: Assessing the Science Base," was ordered by the White House Office of National Drug Control Policy in January 1997 (Joy et al. 1999). Review of available information began in August 1997, including several public hearings, site visits to cannabis buyers' clubs and HIV/AIDS clinics, and months of examining the existing scientific database. The report urges politicians to soften their hard line against the therapeutic use of cannabis and states that marijuana is potentially effective for some symptoms. It recommends rigorous clinical trials and development of a delivery system that eliminates the harmful effects of smoking. Beyond the harms of smoking, the range of problems associated with medical marijuana were within the acceptable range of problems associated with other medications.

Under the headline "Who Uses Medical Marijuana?" the IOM Report of 1999 says:

> "There have been no comprehensive surveys of the demographics and medical conditions of medical marijuana users, but a few reports provide some indication. In each case, survey results should be understood to reflect the situation in

> which they were conducted and are not necessarily characteristic of medical marijuana users as a whole. ... The membership profile of the San Francisco club was similar to that of the Los Angeles Cannabis Resource Center (LACRC), where 83% of the 739 patients were men, 45% were 36-45 years old, and 71% were HIV-positive.... Among the 42 people who spoke at the public workshops or wrote to the study team, only six identified themselves as members of marijuana buyers' clubs. Nonetheless, they presented a similar profile: HIV - AIDS was the predominant disorder, followed by chronic pain (table 1.3) [not included here]. All HIV-AIDS patients reported that marijuana relieved nausea and vomiting and improved their appetite. About half the patients who reported using marijuana for chronic pain also reported that it reduced nausea and vomiting" (Joy et al. 1999).

With regard to the therapeutic potential the report states:

> "The accumulated data indicate a potential therapeutic value for cannabinoid drugs, particularly for symptoms such as pain relief, control of nausea and vomiting, and appetite stimulation. (...)
>
> The effects of cannabinoids on the symptoms studied are generally modest, and in most cases, there are more effective medications. However, people vary in their responses to medications and there will likely always be a subpopulation of patients who do not respond well to other medications" (Joy et al. 1999).

Gieringer (2002) noted that the indications for the medcial use of cannabis in medical cannabis clubs changed in recent years, shifting from predominantly HIV/AIDS to chronic pain, due to three reasons, (1) a heightened appreciation among physicians of cannabis's utility for other conditions; (2) an exodus of former cannabis clubs members to new clubs, and (3) a decline in the number of HIV/AIDS patients with wasting syndrome due to the advent of protease inhibitors.

> "Surveys of C.B.C. members show that cannabis is used for a wide variety of indications. Initial reports from the S.F. C.B.C. showed a high concentration of people with AIDS. A 1993-5 survey of 351 randomly-selected members of the S.F.C.B.C found that 87% (N=305) had a medically verified illness, of whom fully 84.5% (N=258) were HIV positive, a majority being diagnosed with AIDS.[1] Approximately 2% each were diagnosed with multiple sclerosis (N=6) or severe musculoskeletal disorders (N=7); another 11% (N=34) were diagnosed with conditions such as cancer, glaucoma or other diseases. The sample closely reflected the gender and age

> distribution of San Francisco's AIDS population (90% male and a median age of 36).
>
> More recent surveys from other clubs reveal a far more diverse population. Table 12.1 [not included here] summarizes two surveys by Mandel of members of the Oakland Cannabis Buyers' Cooperative (J. Mandel, 1997 and 1998, unpublished). Mandel's first survey, in 1997, found a preponderance of AIDS patients. This is not surprising, since the O.C.B.C. absorbed a heavy influx of patients from San Francisco when the S.F. C.B.C. was first (temporarily) closed in 1996-7. More recently, Mandel's data show that the population of people with AIDS has declined to 29% and is now smaller than those with chronic pain and related disorders (40%, by Mikuriya's classification . . .)" (Gieringer 2002).

In several surveys conducted with patients with several diseases, cannabis preparations have been reported to be helpful.

471 persons with spinal cord injuries were asked about their experience with different pain treatments. The treatments rated as most helpful were opioid medications, physical therapy, and diazepam therapy (Warms et al 2002). Those rated as least helpful were spinal cord stimulation, counseling or psychotherapy, administration of acetaminophen, and administration of amitriptyline. Alternative treatments reported as most helpful were massage therapy and use of cannabis.

In a survey by Consroe et al. (1997), 53 UK and 59 U.S.A people with multiple sclerosis (MS) answered anonymously the first questionnaire on cannabis use and MS:

> "From 9 to 30% of the subjects reported cannabis improved (in descending rank order): spasticity, chronic pain of extremities, acute paroxysmal phenomenon, tremor, emotional dysfunction, anorexia/weight loss, fatigue states, double vision, sexual dysfunction, bowel and bladder dysfunctions, vision dimness, dysfunctions of walking and balance, and memory loss. The MS subjects surveyed have specific therapeutic reasons for smoking cannabis. The survey findings will aid in the design of a clinical trial of cannabis or cannabinoid administration to MS patients or to other patients with similar signs or symptoms" (Consroe et al. 1997).

A similar investigation was conducted with patients suffering from spinal cord injury and presented at the 1998 Symposium of the International Cannabinoid Research Society (Consroe et al. 1998). A questionnaire was mailed out via an intermediate bulk mailing to the Alliance for Cannabis Therapeutics (ACT) of the U.S. Of the 190 mailed questionnaires 106 were returned as valid. 87% of the respondents were male and 13% were female with a mean age of 40 years (range: 18 to 61 years). Patients smoked marijuana for an average of 12 years, a mean of 4 marijuana cigarettes per day, mostly to relieve symptoms. Over 70% of patients

took marijuana together with their other spasmolytic and analgesic medications. 82% reported that symptoms worsened when stopping their use of cannabis. Improvement with marijuana was reported from 99% to 70% of patients (in descending order) for spasms of legs, arms and bladder, muscle and phantom pains, headache, urinary urgency, and paralysis. In less than 70%, improvement was noticed for other bladder dysfunctions, bowel dysfunctions, weakness, and paresthesias. "The results indicate that SCI patients have specific therapeutic reasons for smoking marijuana," the meeting abstract says.

There are several surveys conducted in other countries, among them Australia, The Netherlands and Germany, describing medicinal benefits from cannabis use in several diseases (Barsch 1996, Schnelle et al. 1999, Helliwell 1999, Mueller-Vahl et al. 1997, TNO Preventie en Gezondheid 1998)

The medical use of cannabis not only increased in the U.S., but also in other countries. 1.9 percent of Canadians reported using marijuana for a medical reason in the year preceding a survey of the Centre for Addiction and Mental Health. Interviews were completed with 2508 Ontario adults aged 18 years or more. 49 respondents (1.9%) reported using marijuana for a medical reason in the year preceding the survey. Eighty-five percent of the surveyed medical marijuana users reported using it to help relieve pain or nausea (Ogborne et al. 2000).

Cannabis preparations are used in the treatment of numerous diseases, with marked differences in the available supporting data. For applications such as nausea and vomiting associated with cancer chemotherapy; anorexia and cachexia in HIV/AIDS, and spasticity in multiple sclerosis and spinal cord injury, there is strong evidence for medical benefits. For indications such as epilepsy, movement disorders and depression there is much less available data. However, the history of clinical use of cannabis and cannabinoids has demonstrated that the scientific evidence for a specific indication does not implicitly reflect the actual therapeutic potential for a given disease.

Clinical studies with single cannabinoids or, less often, with whole plant preparations (smoked marijuana, encapsulated cannabis extract) have often been inspired by positive anecdotal experiences of patients employing crude cannabis products (usually without legal sanction). The most often mentioned benefits are the anti-emetic (Dansak 1997), the appetite enhancing (Plasse et al. 1991), the relaxing (Clifford 1983), and the analgesic effects (Noyes & Baram 1974).

Research in recent years added to this pattern. Mueller-Vahl et al. (1997) noted that several patients reported therapeutic benefits from cannabis in Tourette syndrome (Gilles de la Tourette syndrome). This observation resulted in a structured interview which questioned 47 patients with Tourette syndrome at the Medical School of Hannover/Germany on their use of alcohol, nicotine and marijuana and the effects of these substances on their symptoms. Cannabis was reported to have a positive influence on the symptomatology.

> "Using a structured interview, we questioned a larger group of patients with Tourette syndrome (n=47) about the use of nicotine, alcohol, and marijuana and their subjective experiences. Of 28 smoking patients only 2 (7%) reported a tic reduction when smoking [cigarettes]. Of 35 patients drinking

> alcohol 24 (69%) noted an improvement. Thirteen patients reported the use of marijuana, of whom 11 (85%) noted a marked improvement. Our results provided strong evidence that alcohol and, even more than that, marijuana cause much more improvement in TS than nicotine smoking". (...)
>
> With respect to the considerable side effects of those therapy forms presently in use that apply neuroleptics, and considering the limited alternatives, cannabinoids could be used for therapy in the future, when further clinical research by way of controlled studies will have been conducted" (Mueller-Vahl et al. 1997).

These results stimulated research on the efficacy of dronabinol in Tourette syndrome, a study with one patient (Mueller-Vahl et al. 1999a), followed by a randomized double-blind placebo-controlled crossover trial of delta-9-THC in 12 adults (Mueller-Vahl et al. 1999b). Both confirmed the patients' experience described in the interviews.

In several studies, patients' experiences have been further investigated usually leading to a confirmation of their subjective experience. A patient with multiple sclerosis reported a reduction of spasticity and tremor with smoking a cannabis cigarette. This was confirmed in a single case study with smoked cannabis (Meinck et al. 1989). A patient with spinal cord injury reported a reduction of spasticity and pain with smoking cannabis. This experience was confirmed in an extended double-blind controlled study of several weeks with dronabinol (Maurer et al. 1990). A patient with multiple sclerosis who had experienced relief from cannabis smoking received the synthetic THC derivative nabilone in a double blind manner (Martyn et al. 1995). Spasticity was reduced and bladder function was improved with the verum. A patient with a ten-year history of acute and chronic abdominal pain from Familial Mediterranean Fever who required daily morphine (30mg) for analgesia had experienced relief from smoked cannabis (Holdcroft et al. 1997). This subjective experience was confirmed in a double-blind study with a capsulated cannabis extract. The authors stated:

> "This is the first United Kingdom report of the controlled use of a standardised pharmaceutical preparation of cannabinoids in capsular form. The therapy was assessed in a patient with familial Mediterranean fever, who presented with chronic relapsing pain and inflammation of gastrointestinal origin. After determining a suitable analgesic dosage, a double-blind placebo-controlled cross-over trial was conducted using 50 mg tetrahydrocannabinol daily in five doses in the active weeks and measuring effects on parameters of inflammation and pain. Although no anti-inflammatory effects of tetrahydrocannabinol were detected during the trial, a highly significant reduction ($p < 0.001$) in additional analgesic requirements was achieved" (Holdcroft et al. 1997).

In an extended study, patients who receive cannabis through a Compassionate Investigational New Drug Program (IND) of the Food and Drug Administration (FDA) and obtain it from the

National Institute on Drug Abuse (NIDA) were examined with regard to medicinal benefits from smoked cannabis and long-term side effects. Therapeutic effects on several conditions could be confirmed (Russo et al. 2002).

These patients' reports and supporting clinical research confirm that the subjective benefits from cannabis experienced by many patients, suffering from a range of illnesses and symptoms, have a rationale basis.

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4) Reviews of earlier clinical studies

Several scientific publications have reviewed evidence from research on the medicinal uses of cannabis indicating that cannabis in fact may offer benefits in the treatment of certain illnesses

Key quotes from five independent summaries of the medical benefits of the cannabinoid substances in marijuana are presented below. All of them refer to either "cannabis" or to "marijuana" specifically, and they all utilize the conceptual approach implied by Hollister in 2001 (Hollister 2001): clinical evidence on cannabinoids provides an understanding of the medical use of marijuana. The first article is by Grotenhermen, to be published in *Clinical Pharmacokinetics* in October 2002, the second by Williamson and Evans was published in the December 2000 issue of *Drugs,* the third is a review on "Therapeutic aspects of cannabis and cannabinoids" in 2001 by Robson that was commissioned by the British Government, the fourth review is an article by Glass, published in May 2001 in *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, and the fifth is a review article by Porter and Felder in *Pharmacological Therapeutics* in April 2001.

Grotenhermen:

> "Cannabis preparations have been employed in the treatment of numerous diseases, with marked differences in the available supporting data (BMA 1997, Grotenhermen and Russo 2002a, House of Lords 1998, Joy et al. 1999). Besides phytocannabinoids, several synthetic cannabinoid derivatives are under clinical investigation that are devoid of psychotropic effects, and modulators of the endocannabinoid system (re-uptake inhibitors, antagonists at the CB receptor, etc.) will presumably follow.
>
> Hierarchy of Therapeutic Effects
>
> Possible indications for cannabis preparations have been extensively reviewed (BMA 1997, Grinspoon and Bakalar, Grotenhermen 2002b, House of Lords 1999, Joy et al. 1999, Mathre 1997, Mechoulam 1986). To do justice to the scientific evidence with regard to different indications, a hierarchy of therapeutic effects can be devised, with established effects, relatively well-confirmed effects, less confirmed effects and a basic research stage. However the history of research into the therapeutic benefits of cannabis and cannabinoids has demonstrated that the scientific evidence for a specific indication does not necessarily reflect the actual therapeutic potential for a given disease, but sometimes obstacles to clinical research.
>
> Established Effects

Marinol™ (dronabinol) is approved for the medical use in refractory nausea and vomiting caused by antineoplastic drugs in cancer (Abrahamov et al. 1995, Dansak 1997, Lane et al. 1991, Sallan et al. 1980) and for appetite loss in anorexia and cachexia of HIV/AIDS patients (Beal et al. 1997, Plasse et al. 1991). These effects can be regarded as established effects for THC and cannabis. Cesamet™ (nabilone) is approved for nausea and vomiting associated with cancer chemotherapy.

Relatively Well-Confirmed Effects

Spasticity due to spinal cord injury (Brenneisen et al. 1996, Maurer et al. 1990, Petro 1980) and multiple sclerosis (Brenneisen et al. 1996, Meinck et al. 1989, Petro 1980, Petro and Elleberger 1981, Ungerleider et al. 1987), chronic painful conditions especially neurogenic pain (Elsner et al. 2001, Maurer et al. 1990, Notcutt et al. 2001a, Notcutt et al. 2001b, Noyes et al. 1975a, Noyes et al. 1975b), movement disorders (Clifford 1983, Hemming and Yellowlees 1993, Mueller-Vahl et al. 1999, Mueller-Vahl et al. 2002, Sandyk and Awerbuch 1998, Sieradzan et al. 2001), asthma (Hartley et al. 1978, Tashkin et al. 1974, Williams et al. 1976), and glaucoma (Crawford and Merritt 1979, Hepler and Frank 1971, Hepler and Petrus 1976, Merritt et al. 1980, Merritt et al. 1981) can be regarded as relatively well-confirmed effects with small placebo controlled trials demonstrating benefits. However, results were sometimes conflicting.

Less Confirmed Effects

There are several indications in which mainly only case reports suggest benefits. These are allergies (Schnelle et al. 1999), inflammation (Joy et al. 1999), epilepsy (Gordon and Devinsky 2001), intractable hiccups (Gilson and Busalacchi 1998), depression (Beal et al. 1995), bipolar disorders (Grinspoon and Bakalar 1998), anxiety disorders (Joy et al. 1999), dependency to opiates and alcohol (Mikuriya 1970, Schnelle et al. 1999), withdrawal symptoms ((Mikuriya 1970), and disturbed behaviour in Alzheimer's disease (Volicer et al. 1997).

Basic Research Stage

Basic research shows promising possible future therapeutic indications, among them neuroprotection in hypoxia and ischemia due to traumatic head injury, nerve gas damage and stroke (Hampson 2002, Mechoulam and Shohami 2002). Some immunological mechanisms of THC hint to possible benefits in basic mechanisms of T-helper 1 dominated autoimmune diseases, such as multiple sclerosis, arthritis, and Crohn's

disease (Melamede 2002). Other fields of research are disorders of blood pressure (Ralevic and Kendall 2001, Wagner et al. 2001) and anti-neoplastic activity of cannabinoids (Jacobsson et al. 2001, Sanchez et al. 2001). Cannabinoids seem to be able to control the cell survival/death decision (Guzman et al. 2001). Thus cannabinoids may induce proliferation, growth arrest, or apoptosis in a number of cells depending on dose ((Guzman et al. 2001). Several effects observed in animal studies provide the basis for further research, among them effects against diarrhoea in mice (Izzo et al. 2000) and inhibition of bronchospasms provoked by chemical irritants in rats (Calignano et al. 2000).

Williamson:

"Cannabis has a potential for clinical use often obscured by unreliable and purely anecdotal reports. The most important natural cannabinoid is the psychoactive tetrahydrocannabinol (delta9-THC); others include cannabidiol (CBD) and cannabigerol (CBG). Not all the observed effects can be ascribed to THC, and the other constituents may also modulate its action; for example CBD reduces anxiety induced by THC. A standardised extract of the herb may be therefore be more beneficial in practice and clinical trial protocols have been drawn up to assess this. The mechanism of action is still not fully understood, although cannabinoid receptors have been cloned and natural ligands identified. Cannabis is frequently used by patients with multiple sclerosis (MS) for muscle spasm and pain, and in an experimental model of MS low doses of cannabinoids alleviated tremor. Most of the controlled studies have been carried out with THC rather than cannabis herb and so do not mimic the usual clinical situation. Small clinical studies have confirmed the usefulness of THC as an analgesic; CBD and CBG also have analgesic and anti-inflammatory effects, indicating that there is scope for developing drugs which do not have the psychoactive properties of THC. Patients taking the synthetic derivative nabilone for neurogenic pain actually preferred cannabis herb and reported that it relieved not only pain but the associated depression and anxiety. Cannabinoids are effective in chemotherapy-induced emesis and nabilone has been licensed for this use for several years. Currently, the synthetic cannabinoid HU211 is undergoing trials as a protective agent after brain trauma. Anecdotal reports of cannabis use include case studies in migraine and Tourette's syndrome, and as a treatment for asthma and glaucoma. Apart from the smoking aspect, the safety profile of cannabis is fairly good. However, adverse reactions include panic or anxiety attacks, which are worse in the elderly and in women, and less likely in children. Although psychosis has been cited as a

consequence of cannabis use, an examination of psychiatric hospital admissions found no evidence of this, however, it may exacerbate existing symptoms. The relatively slow elimination from the body of the cannabinoids has safety implications for cognitive tasks, especially driving and operating machinery; although driving impairment with cannabis is only moderate, there is a significant interaction with alcohol. Natural materials are highly variable and multiple components need to be standardized to ensure reproducible effects. Pure natural and synthetic compounds do not have these disadvantages but may not have the overall therapeutic effect of the herb" (Williamson, 2000)

Robson:

"[This review [was] commissioned in 1996 by the Department of Health [of Great Britain] (DOH) [In order to] assess therapeutic profile of cannabis and cannabinoids. . . Cannabis and some cannabinoids are effective anti-emetics and analgesics and reduce intra-ocular pressure. There is evidence of symptom relief and improved well-being in selected neurological conditions, AIDS and certain cancers. Cannabinoids may reduce anxiety and improve sleep. Anticonvulsant activity requires clarification. Other properties identified by basic research await evaluation. Standard treatments for many relevant disorders are unsatisfactory. Cannabis is safe in overdose but often produces unwanted effects, typically sedation, intoxication, clumsiness, dizziness, dry mouth, lowered blood pressure or increased heart rate. The discovery of specific receptors and natural ligands may lead to drug developments. Research is needed to optimise dose and route of administration, quantify therapeutic and adverse effects, and examine interactions." (Robson, 2001)

Glass:

"An understanding of the actions of Cannabis (Marijuana) has evolved from folklore to science over the previous hundred years. This progression was spurred by the discovery of an endogenous cannabinoid system consisting of two receptors and two endogenous ligands. This system appears to be intricately involved in normal physiology, specifically in the control of movement, formation of memories and appetite control. As we are developing an increased understanding of the physiological role of endocannabinoids it is becoming clear that they may be involved in the pathology of several neurological diseases. Furthermore an array of potential therapeutic targets is being determined--including specific cannabinoid agonists and antagonists as well as compounds that

interrupt the synthesis, uptake or metabolism of the endocannabinoids. This article reviews the recent progress in understanding the contribution of endocannabinoids to the pathology and therapy of Huntington's disease. Parkinson's disease, schizophrenia and tremor." (Glass, 2001)

Porter:

"The active principle in marijuana, Delta(9)-tetrahydrocannabinol (THC), has been shown to have wide therapeutic application for a number of important medical conditions, including pain, anxiety, glaucoma, nausea, emesis, muscle spasms, and wasting diseases. Delta(9)-THC binds to and activates two known cannabinoid receptors found in mammalian tissue, CB1 and CB2. The development of cannabinoid-based therapeutics has focused predominantly on the CB1 receptor, based on its predominant and abundant localization in the CNS. Like most of the known cannabinoid agonists, Delta(9)-THC is lipophilic and relatively nonselective for both receptor subtypes. Clinical studies show that nonselective cannabinoid agonists are relatively safe and provide therapeutic efficacy, but that they also induce psychotropic side effects. Recent studies of the biosynthesis, release, transport, and disposition of anandamide are beginning to provide an understanding of the role of lipid transmitters in the CNS. This review attempts to link current understanding of the basic biology of the endocannabinoid nervous system to novel opportunities for therapeutic intervention. This new knowledge may facilitate the development of cannabinoid receptor-targeted therapeutics with improved safety and efficacy profiles." (Porter, 2001)

The above summaries provide overwhelming acceptance by the scientific and medical community that cannabis and single cannabinoids can offer therapeutic benefits in many conditions, at least for some of the patients. Recent research on the mechanisms of action of THC and other ligands of the cannabinoid receptor improves the understanding of these benefits and lends further support to this finding.

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5) Basic research.

The scientific understanding of the endogenous cannabinoid system consisting of specific cannabinoid receptors and their endogenous ligands (endocannabinoids) has considerably increased since 1995. It largely supports and helps explain many of the therapeutic benefits of cannabis and cannabinoids in humans.

In recent years, the results of numerous basic research studies have been published. Their findings on the mode of action of cannabinoids provide scientific explanations for the testimony of patients submitted to the first marijuana rescheduling proceedings, which adds considerable weight to their testimony and renders it and other so-called anecdotal evidence relevant to the existing proceedings.

In 1989, the Administrator of DEA rejected the recommendation of an Administrative Law Judge that marijuana be placed in schedule II (54 FR 53,767 - 53,785). In those proceedings, petitioners presented numerous affidavits and testimony regarding individuals' therapeutic use of marijuana. According to DEA, this information has no value.

> "The evidence presented by the pro-marijuana parties regarding use of marijuana to treat various other ailments such as pain, decreased appetite, alcohol and drug addiction, epilepsy, atopic neuroderatitis, sclerodermia and asthma was limited to testimony of individuals who had used marijuana for those conditions and the testimony of the psychiatrists or general practice physicians mentioned earlier. There is not a shred of credible evidence to support any of their claims."(54 Fed. Reg. 53,772 (1989))

Petitioners presented testimony of patients with multiple sclerosis whose use of marijuana allowed them to get up out of their wheelchairs and walk, when without the drug, they could not. According to DEA, these patients are suffering from drug-induced delusions.

> "Why do scientists consider stories from patients and their doctors to be unreliable? First, sick people are not objective scientific observers, especially when it comes to their own health. We have all heard of the placebo effect. . . Second, most of the stories come from people who took marijuana at the same time they took prescription drugs for their symptoms . . . Third, any mind-altering drug that produces euphoria can make a sick person think he feels better. . . Fourth, long-time abusers of marijuana are not immune to illness. Many eventually get cancer, glaucoma, MS and other diseases. People who become dependent on mind-altering drugs tend to rationalize their behavior. They invent excuses, which they can come to believe, to justify their drug dependence." (57 Fed. Reg. 10,499 (1992))

The discovery of the cannabinoid receptor system and subsequent basic research on the therapeutic effects of cannabanoids provides substantial credible evidence to corroborate these and countless other patient reports. All of this research provides a sophisticated and widely recognized understanding on the part of the scientific and medical communities of the veracity and reliability of the existing record of patient accounts. In fact, many research studies on the medical uses of marijuana cite such evidence as part of their scientific foundation.

In recent years, it has been established that most cannabinoid effects are mediated through actions at specific receptor sites. Cannabinoid receptors and their endogenous ligands together constitute the "endogenous cannabinoid system," or the "endocannabinoid system," teleologically millions of years old (De Petrocellis et al. 1999). Thus, it has played a physiological role in man and many other species for a long time.

Some non-receptor mediated effects of phytocannabinoids and synthetic derivatives have also been described, e.g. some effects on the immune system (Bueb et al. 2001) and neuroprotective effects in ischemia and hypoxia (Hampson et al 2002). The anti-emetic effects of THC are in part non-receptor mediated, which is the rationale for the clinical use of THC as an anti-emetic in children receiving cancer chemotherapy (Abramamov et al. 1995). Due to the lower CB1 receptor density in the brain of children compared to adults, they tolerated relatively high doses of Delta-8-THC in a clinical study without significant side effects (Abramamov et al. 1995).

To date, two cannabinoid receptors have been identified, CB1 receptors (cloned in 1990), and CB2 receptors (cloned in 1993). CB1 receptors are found mainly on neurons in the brain, spinal cord and peripheral nervous system, but are also present in certain peripheral organs and tissues, among them endocrine glands, leukocytes, spleen, heart and parts of the reproductive, urinary and gastrointestinal tracts. CB2 receptors occur principally in immune cells, among them leukocytes, spleen and tonsils. There is some evidence for the existence of one or more additional cannabinoid receptor subtypes (Breivogel et al. 2001, Di Marzo et al. 2000, Pertwee 1999). Activation of the CB1 receptor produces cannabis-like effects on psyche and circulation, while activation of the CB2 receptor does not.

The identification of cannabinoid receptors was followed by the detection of endogenous ligands for these receptors, or endogenous cannabinoids or endocannabinoids, a family of endogenous lipids. The most important of these endocannabinoids are arachidonylethanolamide (anandamide) and 2-arachidonylglycerol, both of which are thought to serve as neurotransmitters or neuromodulators (De Petrocellis et al. 2000, Pertwee 2002). Endocannabinoids are released from cells in a stimulus-dependent manner by cleavage of membrane lipid precursors (Giuffrida et al 2001). After release, they are rapidly deactivated by uptake into cells via a carrier-mediated mechanism and enzymatic hydrolysis by fatty acid amide hydrolase (FAAH) (Giuffrida et al 2001).

The endogenous cannabinoid system has been demonstrated to be tonically active in several conditions. Endocannabinoid levels have been demonstrated to be increased in a pain circuit of the brain (periaqueductal gray) following painful stimuli (Walker et al. 1999). Tonic control of spasticity by the endocannabinoid system has been observed in chronic relapsing experimental autoimmune encephalomyelitis (CREAE) in mice, an animal model of multiple

sclerosis (Baker et al. 2001). An increase of cannabinoid receptors following nerve damage was demonstrated in a rat model of chronic neuropathic pain (Siegling et al. 2001) and in a mice model of intestinal inflammation (Izzo et al. 2001). This may increase the potency of cannabinoid agonists used for the treatment of these conditions. Tonic activity has also been demonstrated with regard to appetite control (Di Marzo et al. 2001) and with regard to vomiting in emetic circuits of the brain (Darmani 2001).

Tonic activity of endocannabinoids following damage (pain, spasticity) and increase of cannabinoid receptor density provide a strong rationale basis for several therapeutic effects of cannabis preparations and single cannabinoid receptor agonists.

Many animal studies help to understand observations made in humans, support these observations, or even open the way for new indications. Some of them published in 2001 and 2002 will be shortly summarized here.

Researchers at the Center for Sleep and Ventilatory Disorders at the University of Illinois in Chicago investigated the effects of THC and the endocannabinoid oleamide on sleep, respiratory pattern and sleep apnoea in rats. Carley et al. found that THC and oleamide each stabilized respiration during all sleep stages and decreased apnea (Carley et al. 2002). Authors derive from their findings an important role for endocannabinoids in maintaining autonomic stability during sleep. They further demonstrate potent suppression of sleep apnea by both THC and endocannabinoids, and that this effect may be relevant to the medicinal treatment of sleep-related breathing disorders in humans.

Researchers at the University of Nottingham Medical School (UK) are studying the effects of endocannabinoids on circulation (PA News of 29 December 1998). Anandamide (N-arachidonylethanolamide) has been shown to be a vasorelaxant, particularly in the resistance vasculature (arteries), which can reduce blood pressure. The effects seem to be in part cannabinoid receptor dependent (Randall et al. 1997) and in part cannabinoid receptor independent (Plane et al. 1997). The study is being funded with a £120,000 grant from the British Heart Foundation.

The Endocannabinoid system may be involved in the cardioprotection triggered by lipopolysaccharide (LPS) (Lagneux & Lamontagne 2001). The cardioprotective effects of LPS treatment, in terms of infarction and functional recovery after ischemia in rat hearts, were abolished by a CB(2) receptor antagonist. A CB(1) receptor antagonist had no effect. "Our results suggest an involvement of endocannabinoids, acting through the CB(2) receptors, in the cardioprotection triggered by LPS against myocardial ischemia," researchers write in the *European Journal of Pharmacology*.

In an animal model of Huntington's disease, the administration of an endocannabinoid uptake inhibitor (AM404) reduced motor hyperactivity (Lastres-Becker et al. 2002). The application of an uptake inhibitor results in higher endocannabinoid level acting at CB1 recpetors.

THC and the endocannabinoid anandamide reduced the time until rats started to eat (Williams & Kirkham 2002). Apart from its rapid onset, cannabinoid-induced eating retained the normal, species-typical characteristics. Data suggest that cannabinoids promote eating by increasing the incentive value of food. Research also suggests that endocannabinoids are part

of the brain's complex system for controlling when and how much to eat (Di Marzo et al. 2001). It has been known for some time that leptin is the key hormone for the regulation of the circuit in the hypothalamus responsible for appetite control. Leptin reduces food intake by upregulating appetite-reducing factors and downregulating appetite-stimulating factors. The finding that endocannabinoids (anandamide and 2-arachidonyl glycerol) are involved in this process helps explain why people get hungry after using cannabis or THC and why it helps patients with loss of appetite and weight. In the study published in the journal *Nature*, researchers found that mice lacking CB1 cannabinoid receptors ate less than normal mice did. Also, when ordinary mice were given the cannabinoid receptor antagonist SR141716A that blocks endocannabinoids from acting at these receptors, they ate less than normal as well. Furthermore, reduced levels of leptin were associated with elevated levels of endocannabinoids in the hypothalamus, and application of leptin reduced endocannabinoid levels. These findings indicate that endocannabinoids in the hypothalamus may activate CB1 receptors to maintain food intake, and that they can act independently of the level of certain other appetite-triggering substances.

Cannabinoids decrease secretion in the small intestine. Thus, "they may have therapeutic potential for diarrhoea unresponsive to available therapies," researchers of the Oklahoma Foundation for Digestive Research in Oklahoma City/U.S.A suggest in an article in the *European Journal of Pharmacology* (Tyler et al. 2000). Findings show that cannabinoids inhibit neurally mediated secretion via cannabinoid CB1-receptors and may be useful for treating some forms of diarrhoea.

An international research group has discovered why marijuana causes coughing in some situations but may inhibit bronchospasm and cough in others. This finding could lead to better treatments of respiratory diseases. In a report in the journal *Nature*, scientists from the Institute of Experimental Medicine in Budapest (Hungary), the University of Naples (Italy) and the University of Washington (U.S.A) showed how the endocannabinoid anandamide influences the airways in the lungs. In animal studies with guinea pigs and rats, anandamide exerted a dual effect on bronchial responsiveness. If the muscles in the lungs were constricted by an irritant (capsaicin), the endocannabinoid relaxed the smooth muscles and strongly inhibited coughing. But if the airways were relaxed (by removing the constricting effect of the vagus nerve) anandamide caused a coughing spasm. "We think that by targeting cannabinoid receptors in the upper airways we can control coughs in a number of conditions," Dr. Daniele Piomelli, one of the researchers of the team and pharmacologist at the University of California, said in an interview (Reuters, November 1, 2000). "That's important because most treatments currently available basically act on the brain cough centre, a small region of the brain that is the target for codeine and similar drugs." The group hopes to begin tests in humans soon.

Researchers of the Virginia Commonwealth University in Richmond examined the effect of short-term exposure to THC, morphine, or both drugs in combination on receptor density in a mouse model (Cichewicz et al. 1999). They demonstrated that all three types of opioid receptors were significantly decreased in morphine-tolerant mice, while this reduction was not seen in combination-treated animals. The scientists concluded that a combination of THC and morphine retains high pain mitigating properties without causing changes in receptors that may contribute to tolerance.

Research has shown that endocannabinoids play an important role in emetic circuits of the brain (Darmani 2001). Canadian researchers of Wilfrid Lauier University, Waterloo, Ontario, demonstrated in an animal model of anticipatory nausea and vomiting that THC is able to prevent this form of nausea (Parker et al. 2001). Their study based on the emetic reactions of the musk shrew is published in *Neuroreport*. Retching caused by an injection of lithium chloride was completely suppressed by pre-treatment with a moderate dose of THC. This provides the first experimental evidence in support of reports that THC suppresses anticipatory vomiting. Opiates often cause nausea and vomiting. Cannabinoids were able to reduce opioid-induced vomiting in an animal study with ferrets (Simoneau et al. 2001). A CB1 receptor antagonist but not a CB2 receptor antagonist blocked this antiemetic action, suggesting that antiemetic effects of cannabinoids appear to be mediated by the central nervous system. Other research with animals added to the evidence that cannabinoid receptor agonists are effective against nausea and vomiting (Darmani 2002, Van Sickle et al. 2001).

Several recent studies demonstrated that cannabinoids act, under certain conditions, as anti-cancer agents. In one study, THC and a synthetic cannabinoid induced a remarkable regression of a usually fatal type of brain tumor when tested on laboratory rats (Galve-Roperph et al. 2000). Malignant gliomas, a quick-killing cancer for which there is currently no effective treatment, were induced in 45 rats. One third was treated with THC, another third with the cannabinoid agonist WIN-55,212-2, while the remaining animals were left untreated. Within 18 days, the untreated rats died. In comparison, the two cannabinoids had a dramatic effect, destroying the tumors in a third of the treated rats over a period of seven days, and prolonging the life of another third by up to six weeks. 12 days after cell injection, THC or WIN-55,212-2 were continually injected directly at the site of tumor inoculation over a period of 7 days. THC administration was ineffective in 3 animals and increased the survival of 9 rats up to 19-35 days. The tumor was completely eradicated in 3 of the treated animals. Likewise, the synthetic cannabinoid was ineffective in 6 rats, increased the survival of 4 rats up to 19-43 days and completely eradicated the tumor in 5 animals. The team led by Dr Manuel Guzman from the Complutense University in Madrid said: "These results may provide the basis for a new therapeutic approach for the treatment of malignant gliomas" (UPI of 28 February 2000). He stated that the current experiment tested THC at very low doses and at a late stage, when untreated rats were already starting to die. He predicts that THC should work better if given earlier. But cancer treatments that work in animals may be too toxic or not effective in humans. Cannabinoids are thought to kill tumor cells by inducing programmed cell death, or apoptosis, via an intracellular signaling mechanism. Experiments carried out with two subclones of glioma cells in culture demonstrated that cannabinoids signal apoptosis by a pathway involving cannabinoid receptors, sustained accumulation of the lipid ceramide, and Raf-1/ERK (extracellular signal-regulated kinase activation), inducing a cascade of reactions that leads to cell death.

THC was neuroprotective in rats given the toxic agent ouabain (van der Stelt et al. 2001). THC treated animals showed reduced volume of oedema by 22% in the acute phase and 36% less nerve damage after 7 days. The effect was not CB1 receptor mediated.

The effects of an extract of cannabis in animal tests of depression, spasticity and analgesia were examined (Musty & Deyo 2001). The cannabis extract did not produce an anti-depressive effect in mice. However, the extract produced a decrease in spastic behaviours and

showed analgesic properties. These data suggest that THC extracts will be useful for spastic conditions and for pain.

Research in rats shows that CB receptor agonists exert an inhibitory influence on bladder motility but an excitatory influence on uterus motility (Berkley & Dmitrieva 2001). This inhibitory effect was greater in rats with inflamed bladders than in rats with uninflamed bladders, suggesting that inflammation increases effectiveness of cannabinoids in the bladder. The effect on the uterus was reduced in rats with inflamed bladders. This research supports the positive effects on the hyperactive bladder in patients with multiple sclerosis and spinal cord injury. Other research in rats showed that hyperalgesia associated with inflammation of the urinary bladder was attenuated by the endocannabinoids anandamide (via CB1 receptors) and palmitylethanolamide (putatively via CB2 receptors) in a dose-dependent fashion (Farquhar-Smith & Rice 2001).

Cannabinoids (WIN 55,212-2, HU-210) decreased the acid secretion induced by pentagastrin in the rat (Adami et al. 2002). This effect was blocked by a CB1 receptor antagonist but not by a CB2 receptor antagonist. Thus, the inhibition of acid secretion of the stomach by cannabinoids is mediated by CB1 receptors. This observation confirms the experience of patients with gastric hypersecretion that natural cannabis preparations are effective in relieving their symptoms. This effect has already been described in the 19th century (See 1890).

The synthetic cannabinoid nabilone was effective in reducing inflammation in a rat model of inflammation (Conti et al. 2002). The effects were assumed to be mediated by an uncharacterised CB2-like cannabinoid receptor. In mice, bowel inflammation increased the potency of cannabinoid agonists possibly by 'up-regulating' CB1 receptors (Izzo et al. 2001). In addition, endocannabinoids, whose turnover is increased in intestinal inflammation, might tonically inhibit bowel motility. (Izzo et al. 2001).

Researchers of Novartis in London (UK) examined the effects of cannabinoid agonists on hyperalgesia in a model of neuropathic pain in the rat (Fox et al. 2001). The results show that cannabinoids are highly potent and efficacious antihyperalgesic agents. This activity is likely to be mediated via action in both the central nervous system and in the periphery. Cannabinoids that bind to the CB1 cannabinoid receptor act on a part in the brain (called nucleus reticularis gigantocellularis pars alpha, GiA), which plays an important role in the mitigation of neuropathic pain (Monhemius et al. 2001). Cannabinoids attenuated hyperalgesia evoked by intraplantar injection of capsaicin in rats through spinal and peripheral mechanisms (Johanek et al. 2001). The study shows that cannabinoids possess antihyperalgesic properties at doses that alone do not produce analgesia.

THC lowers intraocular pressure in the rabbit. This effect was substantially attenuated by local pre-treatment with indomethacin, suggesting that THC may influence intraocular pressure at least in part by a prostaglandin-mediated process (Green et al. 2001). Indomethacin is a non-steroidal anti-inflammatory drug and is already known to reduce psychological effects and tachycardia caused by THC. Cannabinoid receptors (CB1) have been found in the trabecular meshwork and ciliary processes of the human eye, and the endocannabinoid anandamide was detected in the trabecular meshwork (Stamer et al. 2001).

Authors assume that the intraocular pressure-lowering effects of cannabinoids result from activation of CB1 receptors in the trabecular meshwork, increasing aqueous outflow.

Further research added to these results on the antineoplastic effects of cannabinoids. One group found that cannabinoid receptors exist in the skin and that their activation inhibits the growth of skin cancer cells (Casanova et al. 2001). CB1 and CB2 type receptors were found in several layers of the skin. In cell experiments, a synthetic cannabinoid receptor agonist induced programmed cell death in skin cancer cells of mice. Another group found that palmitylethanolamide (PEA) enhanced the anti-cancer effect of the endocannabinoid anandamide in human breast cancer cells, in part by inhibiting the expression of fatty acid amide hydrolase (FAAH) (Di Marzo et al. 2001). The FAAH is responsible for the degradation of anandamide. PEA also enhanced the anti-cancer effect of the cannabinoid receptor agonist HU-210.

An international research team demonstrated that endocannabinoid levels are increased in spasticity (Baker et al. 2001). In a multiple sclerosis model, CREAE in mice, spasticity was tonically controlled by the endocannabinoid system. While the endocannabinoid levels were normal in healthy mice and in non-spastic CREAE mice, there was a marked increase of endocannabinoids in spastic CREAE mice. Thus, spastic disorders might be treated by modulating the endocannabinoid system. Other researchers found changes in cannabinoid receptor binding in certain brain regions (striatum, cortex) of rats with experimental allergic encephalomyelitis (EAE) (Berrendero et al. 2001). The EAE is another animal model of multiple sclerosis. These changes might be related to the alleviation of some motor signs observed after the treatment with cannabinoids in multiple sclerosis.

In conclusion, basic research on the functioning of the endogenous cannabinoid system as well as research with animal models for several conditions (multiple sclerosis, neuropathic pain, nausea, cancer and others) provide insight into the effects of exogenous cannabinoids and whole cannabis plant preparations and help to explain therapeutic effects observed in humans.

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6) Clinical research.

Results from clinical research demonstrate that both dronabinol and whole plant cannabis can offer a safe and effective treatment for the following illnesses: muscle spasms in multiple sclerosis, Tourette syndrome, chronic pain, nausea and vomiting in HIV/AIDS and cancer chemotherapy, loss of appetite from cancer, hyperactivity of the bladder in patients with multiple sclerosis and spinal cord injury, and dyskinesia caused by levodopa in Parkinson's disease.

During the 1970's and 1980's, several states conducted research programs comparing smoked marijuana to oral forms of THC. Musty and Rossi reviewed the data from research programs in 6 states. The results from only one of these research programs had been published in peer-reviewed journals before 1995 (Vinciguerra et al. 1988). In their 2001 review, Musty and Rossi wrote:

> "Data were available on 748 patients who smoked marijuana prior to and/or after cancer chemotherapy and 345 patients who used the oral THC capsule.. . . Patients who smoked marijuana experienced 70-100% relief from nausea and vomiting, while those who used the THC capsule experienced 76-88% relief. . . . On the basis of these studies, it appears that smoked marijuana can be a very successful treatment for nausea and vomiting following cancer chemotherapy.. . .The development of smokeless inhalation devices could certainly reduce the potential harm from smoking marijuana." (Musti & Rossi 2001)

In an experimental study with 13 healthy volunteers, smoked cannabis was effective in reducing nausea and vomiting, but the 5-HT3 (serotonin) antagonist ondansetron was significantly more effective (Soderpalm et al. 2001). The study at the Department of Psychiatry of the University of Chicago examined the antiemetic effect of smoked marijuana cigarettes containing 8.4 and 16.9 mg THC compared to 8 mg ondansetron. Nausea and emesis were induced by syrup of ipecac. Marijuana significantly reduced ratings of nausea and slightly reduced the incidence of vomiting compared to placebo. Ondansetron completely eliminated the emetic effects of ipecac. These findings support and extend previous results, indicating that smoked marijuana reduces nausea and emesis. However, its effects were evaluated to be modest relative to the highly potent antiemetic drug ondansetron.

Delta-8-tetrahydrocannabinol (delta-8-THC), a cannabinoid with lower psychotropic potency than the main Cannabis constituent delta-9-THC, was administered at doses of 18 mg per square meter of body surface in edible oil, p.o., to eight children aged 3-13, undergoing cancer chemotherapy (Abrahamov et al. 1995). The children suffered from various hematologic cancers and were treated with different antineoplastic drugs for up to 8 months. The total number of treatments with delta-8-THC was 480. The THC treatment started two hours before each antineoplastic treatment and was continued every 6 hrs for 24 hours. Vomiting was completely prevented. Observed side effects from delta-8-THC observed were negligible.

THC (dronabinol) was not superior to megestrol acetate in improving appetite in cancer patients, according to a study published in January 2002 in the *Journal of Clinical Oncology* (Jatoi et al. 2002). U.S. and Canadian researchers found that 49 percent of those taking THC reported improved appetite, compared with 75 percent on megestrol acetate. Only 3 percent of the dronabinol group gained weight of more than 10 percent over baseline weight, compared with 11 percent following standard treatment with megestrol. A combination of both drugs did not improve the results received by megestrol acetate alone. Patients received either 800 mg megestrol acetate, 2 x 2.5 mg dronabinol, or both drugs. Overall, 469 cancer patients with weight loss had been enrolled in the study between December 1996 and December 1999. The study was conducted as a collaborative trial of the North Central Cancer Treatment Group and the Mayo Clinic.

Several new indications for cannabinoids have been and are under study, including neuroprotection in head trauma, antineoplastic effects for the treatment of cancers, effects against disturbed behavior in patients suffering from Alzheimer's disease, Tourette syndrom, and nausea and vomiting associated with HIV therapy.

Recent research showed that THC was not only effective in reducing nausea and vomiting associated with antineoplastic medication in cancer, but also reduced nausea and vomiting associated with HIV therapy (PRNewswire of 23 October 2000). This research by Roger Anderson and colleagues of Anderson Clinical Research in Pittsburgh was presented in October 2000 at the Fifth Congress on Drug Therapy in HIV Infection in Glasgow (Scotland). 85% (23/27) of HIV/AIDS patients who added dronabinol (THC), the most active cannabinoid, to their current antiretroviral therapy had a 50% improvement in symptoms of nausea and vomiting. The study enrolled patients who were on stable antiretroviral therapy. Twenty-seven patients were randomized to receive dronabinol 2.5 mg twice-daily within one hour of taking their antiretroviral medication (14 patients) or dronabinol 5.0 mg at bedtime (13 patients) for six weeks. At study start and at six weeks, patients were assessed by questionnaire for the number of minutes they did not feel well in the previous 48 hours, the number of episodes of vomiting, and the severity of nausea during the same period. Ninety-three percent (13/14) of patients in the group taking THC twice a day had a greater than 50% improvement in symptoms of nausea and vomiting, and 77% (10/13) of patients taking THC at bedtime had a greater than 50% improvement. The severity of nausea improved by at least one grade in 96% (26/27) of patients and no severe or very severe nausea was experienced in either group after six weeks.

Clinical research in patients with Tourette syndrome was stimulated by reports of patients that they had obtained relief from smoking cannabis. Research on the efficacy of dronabinol in Tourette syndrome included a study with one patient (Mueller-Vahl et al. 1999a), followed by a randomized double-blind placebo-controlled crossover trial of delta-9-THC in 12 adults (Mueller-Vahl et al. 1999b). In the larger study, patients received single doses of 5, 7.5, or 10.0 mg THC. Using both self and examiner rating scales, there was a significant improvement in motor and vocal tics after treatment with THC compared with placebo. In addition, a self-rating scale demonstrated a significant improvement in obsessive compulsive behaviour. No serious adverse reactions occurred. Five patients experienced transient mild side effects such as headache, nausea, dizziness, anxiety, cheerfulness, tremble, dry mouth, and hot flush. All these side effects did not last longer than 6 hours. There were no significant differences after treatment with THC compared with placebo in verbal and visual memory,

reaction time, intelligence, sustained and divided attention, vigilance, and mood. These studies have already been followed by a successful six-week study (unpublished, personal communication Kirsten Mueller-Vahl, 2002). 17 patients completed the entire six-week program. In some participants, THC caused a considerable decrease of symptoms, thus confirming results of the earlier study. Side effects usually were mild even with a dosage of 10 mg THC.

Available preliminary data from research currently conducted in the UK with a cannabis extract that is taken sublingualy supports the analgesic effects of natural cannabis preparations in chronic pain from various causes (Notcutt et al. 2001a-c). A double blind "N of 1" study also showed that a cannabis extract containing equal amounts of THC and CBD was superior to THC with regard to side effects (Notcutt et al. 2001d). The main pain problems of a patient with multiple sclerosis were severe urethral pain and a pain deep within her pelvis. She achieved almost total pain control with the cannabis extract. Psychological side effects were predominantly seen during the periods when she used THC alone. During the periods when she used a 1:1 mixture of THC and CBD, the incidence of side-effects fell dramatically, compared to the same THC dose taken without CBD.

Preliminary results of clinical research conducted in the UK and in Switzerland show that cannabis and THC are able to reduce hyperactivity of the bladder in patients with multiple sclerosis and spinal cord injury (Hagenbach et al. 2001, Brady et al. 2001). The Swiss study conducted at the REHAB in Basel under the guidance of Ulrike Hagenbach includes 15 patients with spastic spinal cord injury who received oral or rectal THC (Hagenbach et al. 2001). Compared to placebo there was an improvement of some parameters of bladder activity, e.g. maximum capacity of the bladder (MCC, maximum cystometric capacity). The British study conducted at the National Hospital for Neurology and Neurosurgery in London under the guidance of Ciaran Brady and Clare Fowler included patients with advanced multiple sclerosis and problems with bladder function who received a sublingual cannabis spray. Maximum bladder capacity increased and frequency of need to urinate decreased both during day and night (Brady et al. 2001).

The therapy of Parkinson's disease using levodopa may cause dyskinesia, a movement disorder. In a pilot study with seven patients, a research group at the University of Manchester, Scotland, showed that nabilone, a synthetic THC derivative, significantly reduced levodopa-induced dyskinesia in patients with Parkinson's disease (Sieradzan et al. 2001).

In eight glaucoma patients resistant to conventional therapies, administering the synthetic cannabinoid-1-receptor agonist WIN55212-2 decreased the intraocular pressure by between 20 and 30% (Porcella et al. 2001). These data confirm that CB1 receptors that have been found in the ciliary body of the eye have direct involvement in the regulation of human intraocular pressure. THC binds to the CB1 receptor which explains the intraocular pressure lowering effects of cannabis.

In a Swiss study at the Clinic Montana under the guidance of Claude Vaney, the effects of capsulated cannabis extract in 57 patients with multiple sclerosis were investigated (Fortissimo 2002). In a crossover design, one half of the patients received a placebo first and then the extract, while the other half received cannabis first. The dose was adjusted according

to individual tolerance. The maximal daily doses ranged from 7.5 to 30 mg THC. Muscle tone assessed with the Ashworth Scale was not significantly influenced by cannabis compared to placebo. However, subjectively the number of muscle spasms and the intensity of spasticity were reduced. Mobility as measured with the Rivermead-Mobility-Index (RMI) was improved with cannabis. Sleep was not significantly influenced. In general, the medication was tolerated well. Neither cognitive nor motor performance were significantly influenced by the cannabis medication.

Another study by a Dutch team using both a cannabis extract and THC in patients suffering from multiple sclerosis (MS) demonstrated that THC is not effective in MS when given in low oral doses of 2.5 or 5 mg oral twice daily (Killestein et al. 2002). In this double-blind, placebo-controlled study in 16 patients with MS who presented with severe spasticity, the safety, tolerability, and efficacy of oral THC and oral cannabis were investiagted. Compared with placebo, neither THC nor cannabis reduced spasticity at the doses applied (2.5 or 5 mg administered orally twice daily). Ungerleider et al. (1987) of the University of California in Los Angeles already noted in their 1987 study that "the 7.5 mg dose is required to achieve significant spasticity reduction" and in 1999 Pertwee recommended "a degree of flexibility with respect to dose level" in studies on THC in multiple sclerosis and to start with 2.5 or 5 mg twice daily.

All six neurosurgical intensive care units in Israel were involved in a double-blind, placebo-controlled study to evaluate the safety of intravenous dexanabinol in treating severe head injury (Knoller et al. 2002). 67 patients aged 16-65 years received a single administration of dexanabinol (48 or 150 mg) or only the vehicle. A highly significant reduction in the percentage of time during which pressure in the head of more than 25 mmHg occurred; perfusion pressure within the brain of below 50 mmHg and systolic blood pressure of below 90 mm Hg were observed in the drug-treated group. A trend toward faster and better neurological effect on the Glasgow outcome scale was also observed after 3 and 6 months. Dexanabinol is a non-psychotropic THC-derivative with neuroprotective properties. The neuroprotective properties of the natural plant cannabinoids THC and cannabidiol (CBD) are similar to those of dexanabinol (Hampson 2002).

Researchers at the Clinic for Anaesthesiology of the University of Cologne (Germany) reported their first experience with THC in pain management (Elsner et al. 2001). All patients treated with THC from February 1998 to January 2000 were evaluated. In six individuals suffering from chronic pain, THC was used in daily doses of 5-20 mg. Sufficient pain relief was achieved in three patients. The remaining three suffered from intolerable side effects such as nausea, dizziness and sedation without a reduction of pain intensity.

Overall recent clinical research shows that cannabis, THC and other agonists of the CB1 receptor are effective in a wide range of symptoms. Effectiveness may also vary widely among patients. THC or cannabis are often not the best medication available for one symptom but the combination of several of its effects may be very useful in a range of chronic illnesses that often present with several symptoms. This was clearly stated by the Institute of Medicine:

> "In cases where symptoms are multifaced, the combination of THC effects might provide a form of adjunctive therapy; for

> example, AIDS wasting patients would likely benefit from a medication that simultaneously reduces anxiety, pain, and nausea while stimulating appetite" (Joy et al. 1999).

Thus, cannabis has been proposed for treatment of several diseases, among them amyotrophic lateral sclerosis and cystic fibrosis. Carter & Rosen (2001) of the University of Washington School of Medicine stated:

> "Marijuana is a substance with many properties that may be applicable to the management of amyotrophic lateral sclerosis (ALS). These include analgesia, muscle relaxation, bronchodilation, saliva reduction, appetite stimulation, and sleep induction. In addition, marijuana has now been shown to have strong antioxidative and neuroprotective effects, which may prolong neuronal cell survival. In areas where it is legal to do so, marijuana should be considered in the pharmacological management of ALS. Further investigation into the usefulness of marijuana in this setting is warranted" (Carter & Rosen 2001).

Ester Fride (2002) analyzed the possible application of cannabis prepartions in the treatment of cystic fibrosis:

> "Cannabis stimulates appetite and food intake. This property has been exploited to benefit AIDS and cancer patients suffering from wasting disease, by administering the whole plant or its active ingredient [delta-9]-tetrahydrocannabinol (THC). (...)
>
> Lack of appetite resulting in malnutrition is a contributing factor to mortality in many Cystic Fibrosis patients. It is proposed here for the first time to administer THC to CF patients. It is hoped that the cannabinoid will alleviate malnutrition and thus help prevent wasting in CF patients. (...)
>
> Recent findings suggest that a lipid imbalance (high arachidonic acid/low DHA) is a primary factor in the etiology of CF and that defective CFTR (CF transmembrane conductor regulator) that characterized the CF condition is responsible for the dysregulation. Endocannbinoids are all fatty acid derivatives. Therefore, it is further proposed here that the CFTR gene product also modulates endocannabinoids and by elevating these levels, symptoms may improve. Indeed, a number of physiological mechanisms of cannabinoids and endocannabinoids coincide with the pathology of CF. Thus it is suggested that potential benefits from THC treatment, in addition to appetite stimulation, will include antiemetic,

> bronchodilating, anti-inflammatory, anti-diarrheal and hypoalgesic effects" (Fride 2002).

Ethan Russo has examined marijuana's potential in the treatment of migraines. His investigations show that modern neurological research lends new credibility to historical and anecdotal reports on the efficacy of cannabis in this area:

> "Cannabis, or 'marijuana,' has been employed in various forms throughout the millennia for both symptomatic and prophylactic treatment of migraine.
>
> In modern times, ethnobotanical and anecdotal references continue to support the efficacy of cannabis for headache treatment, while biochemical studies of THC and anandamide have provided scientific justification for its use via anti-inflammatory, serotonergic and dopaminergic mechanisms, as well as by interaction with NMDA and endogenous opioid systems. These are examined in detail.
>
> The author feels that this collective evidence supports the proposition that experimental protocols of cannabis usage in migraine treatment should go forward employing modern controlled clinical trials" (Russo 2001).

A considerable number of clinical studies are under way to further study the effects of natural cannabis preparations. (Source: Online Bulletins of the International Association for Cannabis as Medicine 1999-2002, www.cannabis-med.org)

Some of these studies are being conducted by GW Pharmaceuticals in the UK. By 2004, the company intends to obtain approval for a cannabis extract to be sprayed under the tongue. The main focus of this research is on chronic pain in patients with spinal cord injury, multiple sclerosis, nerve damage and cancer. GW Pharmaceuticals has expanded its studies to Canada. Under the guidance of the Institute for Oncological and Immunological Research in Berlin (Germany), a multicenter trial with several hundreds of patients is under way in Germany, Switzerland and Austria to test the effectiveness of an oral capsulated cannabis extract in comparison with THC in anorexia and cachexia of cancer patients. The same capsuled extract is used in a study with multiple sclerosis patients in the UK under the guidance of John Zajicek of Derriford Hospital, Plymouth. In total, 660 people will participate in the three-year program, which will involve 38 hospitals across Britain and is funded with £1.2 million pounds (U.S.$1.8 million) by the Medical Research Council (MRC). The study protocol was developed by the Royal Pharmaceutical Society of Great Britain.

A Center for Medicinal Cannabis Research has been set up at the University of California funded with several millions of dollars by the state, focusing on the use of marijuana in cancer and AIDS patients, but also for relieving spasticity and tremors in patients with multiple sclerosis. A study with smoked cannabis in neuropathy (nerve pain) associated with AIDS started under the guidance of Donald Abrams in San Fransisco. Initially, this pilot study, which began in March 2002, involves 16 volunteers. Each participant will stay in the

hospital for nine days, smoking marijuana three times a day on seven of those days. If results of the pilot stady are encouraging, a larger study involving up to 100 subjects will follow. The study is double-blinded and uses THC free cannabis cigarettes as placebos. In San Diego, another researcher wants to examine how repeated treatment with cannabis affects driving ability of patients with HIV-related neuropathy or multiple sclerosis. The patients will be tested using a driving simulator. Another San Diego scientist will study how smoking marijuana might ease the uncontrollable muscle spasms and pain in multiple sclerosis.

In March 2002, a group of Spanish researchers started the first clinical study of cannabinoids in the treatment of cancer at the Hospital of La Laguna (Tenerife). The objective of the phase I-II trial is to evaluate the effects of THC on glioblastoma multiforme, a malignant brain tumor, for which there is currently no effective treatment. The study will be also the first study to investigate intracranial application of THC, an application directly into the brain. It will start with five patients. If the treatment is tolerated well, nine more patients will be added, divided into three groups, each receiving a different dose. THC will be administered for two to eight weeks and doses will depend on tolerance. Those patients will be selected whose tumors are accessible by means of surgery. The study is scheduled to last three years.

In 2002, the Office for Medicinal Cannabis of the Dutch Ministry of Health announced that it will conduct a clinical study on smoked cannabis in 16 multiple sclerosis patients. Results are expected to be available in the second half of 2003.

Health Minister Allan Rock, and Dr. Alan Bernstein, President of the Canadian Institutes of Health Research, announced on 26 July 2001 a Government of Canada contribution of $235,000 to fund a clinical study that will examine the therapeutic uses of cannabis. This is the first clinical trial related to the medical use of marijuana to be funded by Health Canada. Researchers at the Pain Centre of McGill University will conduct a one-year pilot study of smoked cannabis for chronic neuropathic pain at the General Hospital of Montreal. The study will also be the world's first peer-reviewed clinical trial examining the effects of smoked cannabis in a non-HIV or multiple sclerosis population. While other studies have tested the effects of cannabis constituents on pain, this will be the first trial in which participants will smoke the substance as outpatients.

This clinical research provides further evidence of that cannabis provides safe and effective treatment for several illnesses. Cannabis also has tremendous potential for the treatment of a wide variety of conditions as well.

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7) Route of administration.

Progress has been made in recent years in reducing the disadvantages of certain routes of cannabis administration, notably the slow onset of action with oral use and harm associated with the inhalation of combustion products when smoking cannabis.

Unimed Pharmaceuticals announced on February 26, 2002 its intent to develop a metered dose inhaler for cannabis (Business Wire of 26 February 2002). This announcement further indicates that inhalation may have pharmacokinetic advantages over the oral route in some applications. With regard to whole plant preparations, the use of vaporizers and sublingual use (in the studies by GW Pharmaceuticals) has been proposed to avoid concerns over harms associated with smoking.

Grotenhermen examines the issues associated with inhalation of marijuana smoke and the methods availabe to reduce such harm:

> "Inhalation of carcinogenic combustion products associated with smoking is generally regarded as the major health hazard in connection with the medical use of cannabis products. Strategies to reduce respiratory and other adverse events resulting from this common practice include relinquishment of inhalation and replacement by other routes of administration, the use of plants with a high THC content allowing reduction of the amount of smoked plant material, usage of inhalation devices that improve the ratio of THC and tar, and avoidance of the Valsalva maneuver that may cause spontaneous pneumothorax. The major risk associated with oral cannabis use is accidental overdosage, especially in inexperienced users that can be avoided by appropriate dosing procedures. A combination of oral use and inhalation may be meaningful in several indications, decreasing the specific risks of both routes. Preliminary studies using rectal, sublingual and transdermal routes indicate that these alternatives to the two most common forms of ingestion may be utilized medicinally in the future, further reducing the possible risks associated with the administration of cannabis or single cannabinoids" (Grotenhermen 2001).

Gieringer describes vaporization and explains why this is likely the most effective delivery method for the cannabinoids in marijuana.

> "The primary health hazard of medical cannabis is respiratory damage from marijuana smoke. Aside from oral ingestion and other non-smoked delivery systems not yet commercially available, strategies for reducing the harm of smoking include: (1) use of higher potency cannabis and (2) smoking devices aimed at eliminating toxins from the smoke. Studies have found

> that waterpipes and solid filters are ineffectual at improving the THC/tar ratio in cannabis smoke. The most promising alternative appears to be "vaporization," in which cannabis is heated to a point where cannabinoids are emitted without combustion. A feasibility study by NORML and MAPS has demonstrated that an electric vaporizer can successfully generate THC at 185°C while completely suppressing benzene, toluene, and naphthalene formation. Further studies are needed to evaluate how effectively vaporizers suppress other toxins, and how their performance varies using different samples, temperatures, and device designs" (Gieringer 2001).

Albany College of Pharmacy researcher Audra Stinchcomb was awarded a $361,000 three-year grant on 21 January 2000 by the American Cancer Society to study whether cannabinoids can be absorbed effectively through the skin (UPI of 21 January 2000, AP of 21 January 2000). The research could lead to the development of a cannabinoid patch for therapeutic use. It could ease the pain, nausea and vomiting that chemotherapy patients can suffer, according to Gail Tyner-Taylor of the American Cancer Society of New York and New Jersey. The patch could give a continuous, steady dose over a period of days. "Smoking can provide a high immediate dose and make some patients high," said Stinchcomb. "However, a marijuana patch could work better than a pill because people suffering from the effects of chemotherapy have trouble keeping pills down." The grant for the marijuana patch is the first the American Cancer Society has awarded for marijuana research. "Some people may not approve," said Don Distasio of the American Cancer Society, "but we are going to stick to our guns because we see this as an issue of helping patients suffering from unnecessary pain." First results of the research were presented at the *2001 Symposium on the Cannabinoids of the International Cannabinoid Research Society (*Stinchcomb et al. 2001).

One must recall that harms caused by a certain route of administration, particularly smoking, are not caused by the pharmacologically active constituents of marijuana itsself. The Institute of Medicine Report states:

> "The chronic effects of marijuana (...) fall into two categories: the effects of chronic smoking, and the effects of THC" (Joy et al. 1999).

The smoking of other herbs and plants, particularly of tobacco, is not prohibited in the United States, even if harms are well established. One must also note that many medical cannabis users currently avoid smoking-induced harms by taking their cannabis in baked goods. For these reasons, these harms should not be used as an argument to preclude a legitimate medical use of cannabis.

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8) Pharmaceutical industry.

The pharmaceutical industry is showing not only increasing interest in synthetic modulators of the endogenous cannabinoid system, but also industry members are funding several clinical studies with cannabis whole plant extracts in Europe and Canada with the intention to develop approved cannabis based medicines. This indicates that therapeutic exploitation of natural cannabis will be economically sound. However the present Schedule I classification of cannabis and THC is an impediment to the pharmaceutical development of cannabinoid drugs becaused of the costly restrictions it places on research..

Large pharmaceutical companies such as Pfizer, GlaxoSmithKline and Novartis are demonstrating increasing interest in the therapeutic use of cannabinoids and their derivatives, according to a report of the *Wall Street Journal* on 28 February 2001. Other firms are already conducting research, such as the researchers at the Bayer AG who found that cannabinoid CB(1) receptors were upregulated in a rat model of chronic neuropathic pain (Siegling et al. 2001). Today, the only available cannabinoids are THC (dronabinol, Marinol) and the dronabinol derivative nabilone. Individual scientists, academic labs and small drug firms are currently the main promoters of pharmaceutical research, because large drug companies have traditionally been reserved with regard to the cost and the political problems associated with marketing marijuana as medicine. This situation appears to be changing. "We see them -- Pfizer, GlaxoSmithKline, Novartis -- all the time at the meetings of the society now," says Roger Pertwee, professor at the University of Aberdeen in the U.K. and secretary of the International Cannabinoid Research Society (ICRS). "They never came in the past."

Firms that are engaged in natural cannabis preparations are GW Pharmaceuticals in the UK and the phytopharmaceutical company Bionorica in Germany. Research and development costs of GW Pharmaceuticals increased to 5.1 million British Pounds in 2001 (PA News, June 13, 2001). Bionorica just started to manufacture dronabinol, and according to personal communication, intends to manufacture a cannabis extract and to start with clinical research shortly (Grotenhermen 2002). The Institute for Oncological and Immunological Research in Berlin (Germany) intends to licence their capsulated cannabis extract to a pharmaceuticals manufacturer, once research has demonstrated the extract's effectiveness for treatment of severeal illnesses. Several million Euros have already been invested in research.

These activities demonstrate that the cannabinoid system is an increasingly interesting target for the devlopment of drugs by the pharmaceutical industry and that firms are investing millions of dollars into the research with natural cannabis. They appear to be confident that these investments are justified by the medicinal potential of the plant. However, according to the Institute of Medicine development of cannabinoid drugs is greately complicated by the Schedule I classification of both cannabis and tetrahydrocannabinols:

> Under the CSA, marijuana and THC are in Schedule I, the most restrictive schedule. The scheduling of any other cannabinoid under this act first hinges on whether it is found *in the plant.* All cannabinoids in the plant are automatically in Schedule I because they fall under the act's definition of marijuana (21 U.S.C. § 802 (16)). In addition,

under DEA's regulations, synthetic equivalents of the substances contained in the plant and "synthetic substances, derivatives, and their isomers" whose "chemical structure and pharmacological activity" are "similar" to THC also are automatically in Schedule I (21 CFR § 1308.11(d)(27). Based on the examples listed in the regulations, the word *similar* probably limits the applicability of the regulation to isomers of THC, but DEA's interpretation of its own regulations would carry significant weight in any specific situation.

. . . . For the reasons noted above, any changes in scheduling of marijuana and THC would also affect other plant cannabinoids. For the present, however, any cannabinoid found in the plant is automatically controlled in Schedule I.

Investigators are affected by Schedule I requirements even if their research is being conducted *in vitro* or on animals. For example, researchers studying cannabinoids found in the plant are required under the CSA to submit their research protocol to DEA, which issues a registration that is contingent on FDA's evaluation and approval of the protocol (21 CFR § 1301.18). DEA also inspects the researcher's security arrangements. However, the regulatory implications are quite different for cannabinoids *not found in the plant.* Such cannabinoids appear to be unscheduled unless the FDA or DEA decides that they are sufficiently similar to THC to be placed automatically into Schedule I under the regulatory definition outlined above or the FDA or the manufacturer deems them to have potential for abuse, thereby triggering *de novo* the scheduling process noted above. Thus far, the cannabinoids most commonly used in preclinical research (Table 5.1) [not included here] appear to be sufficiently distinct from THC that they are not currently considered controlled substances by definition (F. Sapienza, DEA, personal communication, 1998). No new cannabinoids other than THC have yet been clinically tested in the United States, so scheduling experience is limited. The unscheduled status of some cannabinoids might change as research progresses. Results of early clinical research could lead a manufacturer to proceed with or lead the FDA to require abuse liability testing. Depending on the results of such studies, DHHS might or might not recommend scheduling *de novo* to DEA, which makes the final decision case by case.

Will newly discovered cannabinoids be subject to scheduling? That is a complex question that has no simple answer. The answer depends entirely on each new

cannabinoid—whether it is found in the plant, its chemical and pharmacological relationship to THC, and its potential for abuse. Novel cannabinoids with strong similarity to THC are likely to be scheduled at some point before marketing, whereas those with weak similarity might not be. The manufacturer's submission to FDA, which contains its own studies and its request for a particular schedule, can also shape the outcome. Cannabinoids found in the plant are automatically in Schedule I until the manufacturer requests and provides justification for rescheduling. The CSA does permit DEA to reschedule a substance (move it to a different schedule) and to deschedule a substance (remove it from control under the CSA) according to the scheduling criteria . . . and the process outlined above. (Joy JE, et al, 1999).

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II. Safety of use

9) Acute side effects.

It is now generally accepted that "...except for the harms associated with smoking, the adverse effects of marijuana use are within the range of effects tolerated for other medications" (Institute of Medicine Report of 1999). This opinion is supported by recent clinical research. Besides abuse and dependency, the main side effects of concern are those on the cardiovascular, immune, and hormonal systems, and on cognitive functions.

Research has shown that cannabis produces acute side effects that are within the range of side effects tolerated for other medicinal drugs. Acute side effects relate mainly to psychological effects (cognitive impairment, altered perception) and circulation (decrease of blood pressure). New research adds to the evidence of cannabis's interaction with other medicinal drugs, effects on cognitive function, and increased risk of heart attack.

In an anonymous survey of 128 patients in Germany, Switzerland, and Austria on the medical use of dronabinol and natural cannabis products, 71% reported no side effects (Schnelle et al. 1999). 26% reported moderate and 3% severe effects. The overall judgment of "no side effects" was also given in some cases where certain side effects (e.g. dry mouth or anxiety) were experienced but apparently regarded as minor by the subjects.

The first U.S. study using marijuana for people with HIV has found that smoking the plant does not disrupt the effect of antiretroviral drugs that keep the virus in check (Ksel et al. 2002). Kosel and colleagues of San Francisco General Hospital were limited to focusing on marijuana's safety rather than its effectiveness. The 67 people who participated in the study were kept in the hospital during the 21-day study period. Researchers were especially interested in studying people on drug regimes that contain protease inhibitors, because THC is metabolised by the same system in the liver as those drugs. Subjects on stable regimens involving taking Indinavir 800 mg every 8 h (n = 28) or Nelfinavir 750 mg three time a day (n = 34) were randomized to one of three treatment arms: 3.95% THC marijuana cigarettes, dronabinol 2.5 mg capsules, or placebo capsules administered three times daily. Serial blood sampling was performed at baseline and on day 14 of treatment. In all groups the level of virus in the blood dropped or remained undetectable by current tests. There was no statistically significant difference among the three groups, with those taking THC or marijuana having slightly lower levels. With regard to the pharmacokientic data, the authors stated:

> "Despite a statistically significant decrease in C(max) of IDV in the marijuana arm, the magnitude of changes in IDV and NFV pharmacokinetic parameters in the marijuana arm are likely to have no short-term clinical consequence. The use of marijuana or dronabinol is unlikely to impact antiretroviral efficacy" (Kosel et al. 2002)

Lead researcher Donald Abrahms concluded:

> "Controlled clinical trials investigating smoked marijuana can be safely conducted. Neither smoked nor oral cannabinoids have an adverse effect on HIV RNA levels, immune parameters or protease inhibitor kinetics over a 21 day treatment period in patients with HIV infection on a stable antiretroviral therapy regimen. Use of both smoked marijuana and dronabinol lead to increased weight gain compared to placebo. Further studies to investigate the therapeutic potential of smoked marijuana and other cannabinoids are warranted." (Abrahms et al, 2002)

Although the ability to perform complex cognitive operations is assumed to be impaired following acute marijuana smoking, complex cognitive performance after acute marijuana use has not been adequately assessed under experimental conditions. In a study by Hart et al. (2001) an inter-participant double-blind design was used to evaluate the effects of acute marijuana smoking on complex cognitive performance in experienced marijuana smokers. Acute marijuana smoking produced only minimal effects on complex cognitive task performance:

> "Eighteen healthy research volunteers (8 females, 10 males), averaging 24 marijuana cigarettes per week, completed this three-session outpatient study; sessions were separated by at least 72-hrs. During sessions, participants completed baseline computerized cognitive tasks, smoked a single marijuana cigarette (0%, 1.8%, or 3.9% Delta(9)-THC w/w), and completed additional cognitive tasks. Blood pressure, heart rate, and subjective effects were also assessed throughout sessions. Marijuana cigarettes were administered in a double-blind fashion and the sequence of Delta(9)-THC concentration order was balanced across participants. Although marijuana significantly increased the number of premature responses and the time participants required to complete several tasks, it had no effect on accuracy on measures of cognitive flexibility, mental calculation, and reasoning. Additionally, heart rate and several subjective-effect ratings (e.g., "Good Drug Effect," "High," "Mellow") were significantly increased in a Delta(9)-THC concentration-dependent manner. These data demonstrate that acute marijuana smoking produced minimal effects on complex cognitive task performance in experienced marijuana users" (Hart et al. 2001).

Moderate smoking of cannabis increases the risk of a heart attack for middle-aged and elderly users during the first hour after using the drug, a study published in 2001 says (Mittleman et al. 2001). A small portion (0.2%) of patients suffering from a heart attack had smoked cannabis shortly before symptoms began. Cannabis has an influence on blood pressure and heart rate. This may be of relevance for people with coronary heart disease, as are several other drugs that influence circulation. Of the 3882 patients suffering a heart attack, 124 reported smoking marijuana in the previous year, among them 9 within 1 hour of heart attack symptoms. The risk of heart attack onset was significantly elevated 4.8 times over baseline

(95% confidence interval: 2.4-9.5) in the first hour after cannabis use. In the second hour it was 1.7 times greater, and returned to baseline afterwards. Murray Mittleman, a professor at Harvard Medical School and director of cardiovascular epidemiology at Beth Israel-Deaconess Medical Centre, and his colleagues wrote in their publication that smoking marijuana is "a rare trigger of acute myocardial infarction". He noted that cannabis was about as risky as taking a walk for an active person with heart disease, or as sex for a patient with sedentary life style.

Much research has been conducted to address the question of driving ability under the influence of the drug. For example, a major recent study by the UK Transport Research Laboratory found that one single glass of wine impairs driving ability more than smoking a cannabis cigarette (New Scientist of 19 March 2002). The study also found that drivers on cannabis tended to be aware of their intoxicated state, and drove more cautiously to compensate their impairment. This is in good agreement with earlier research of recent years (reviews: Smiley 1999, Chesher & Longo 2002). Another study investigated the effects of chronic exposure to cannabis on the effects of alcohol on driving-related psychomotor skills. Chronic cannabis use (in the absence of acute administration) did not potentiate the effects of alcohol. In fact, the regular users showed lower scores for dizziness and a superior tracking accuracy compared to infrequent users after they consumed alcohol (Wright & Terry 2002).

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10) Documented safety of long-term cannabis use.

Studies have shown the long-term use of cannabis to be safe. In contrast to many other medicinal drugs, the long-term use of cannabis does not harm stomach, liver, kidneys and heart.

The Missoula Chronic Clinical Cannabis Use Study examined the effects of long-term and legal medical marijuana use. Russo et al. (2002) demonstrated that regular use of cannabis for more than ten years does not cause major harm to patients:

> "The Missoula Chronic Clinical Cannabis Use Study was proposed to investigate the therapeutic benefits and adverse effects of prolonged use of "medical marijuana" in a cohort of seriously ill patients. Use of cannabis was approved through the Compassionate Investigational New Drug Program (IND) of the Food and Drug Administration (FDA). Cannabis is obtained from the National Institute on Drug Abuse (NIDA), and is utilized under the supervision of a study physician. The aim of this study is to examine the overall health status of 4 of the 7 surviving patients in the program. This project provides the first opportunity to scrutinize the long-term effects of cannabis on patients who have used a known dosage of a standardized, heat-sterilized quality-controlled supply of low-grade marijuana for 11 to 27 years. (...)
>
> Results demonstrate clinical effectiveness in these patients in treating glaucoma, chronic musculoskeletal pain, spasm and nausea, and spasticity of multiple sclerosis. All 4 patients are stable with respect to their chronic conditions, and are taking many fewer standard pharmaceuticals than previously. (...) Mild changes in pulmonary function were observed in 2 patients, while no functionally significant attributable sequelae were noted in any other physiological system examined in the study, which included: MRI scans of the brain, pulmonary function tests, chest X-ray, neuropsychological tests, hormone and immunological assays, electroencephalography, P300 testing, history, and neurological clinical examination. (...) These results would support the provision of clinical cannabis to a greater number of patients in need. We believe that cannabis can be a safe and effective medicine with various suggested improvements in the existing Compassionate IND program" (Russo et al. 2002).

The Missoula Chronic Clinical Cannabis Use Study resulted in several important conclusions and recommendations:

1) "Cannabis smoking, even of a crude, low-grade product, provides effective symptomatic relief of pain, muscle spasms, and intraocular pressure elevations in selected patients failing other modes of treatment."
2) "These clinical cannabis patients are able to reduce or eliminate other prescription medicines and their accompanying side effects."
3) "Clinical cannabis provides an improved quality of life in these patients."
4) "The side effect profile of NIDA cannabis in chronic usage suggests some mild pulmonary risk."
5) "No malignant deterioration has been observed.
6) "No consistent or attributable neuropsychological or neurological deterioration has been observed."
7) "No endocrine, hematological or immunological sequelae have been observed."
8) "Improvements in a clinical cannabis program would include a ready and consistent supply of sterilized, potent, organically grown unfertilized female flowering top material, thoroughly cleaned of extraneous inert fibrous matter."
9) "It is the authors' opinion that the Compassionate IND should be reopened and extended to other patients in need of clinical cannabis."
10) "Failing that, local, state and federal laws might be amended to provide regulated and monitored clinical cannabis to suitable candidates" (Russo et al. 2002).

Research on prenatal marijuana exposure found that cognitive functions of children at school age may be impaired. However, these effects seem to be mild and were considerable less compared to alcohol and tobacco. A report from a longitudinal study of the effects of prenatal alcohol and marijuana exposure investigated whether these drugs affect neuropsychological development at 10 years of age (Richardson et al. 2002). 593 children completed a neuropsychological battery. Prenatal alcohol use was found to have a significant negative impact on learning and memory skills. Prenatal marijuana exposure also had a minor effect on learning and memory. Another study assessed cognitive performance in new-borns of 354 mothers at age 6.5, 12, and 13 months (Jacobson et al. 2002). Alcohol use during pregnancy was associated with poorer cognitive performance. The use of cocaine and tobacco was associated with a smaller size at birth. No effects were detected in relation to cannabis use. Low density of cannabinoid receptors in the fetal brain may explain the low prenatal toxicity of cannabis (Biegon and Kerman 2001). Researchers found that low numbers of cannabinoid receptors could be observed as early as the 14th week of gestation. Receptor density increased slowly but did not reach adult levels by the end of the 24th week. The distribution pattern in the fetal brains was markedly different from the adult pattern. Authors conclude:

"The relatively low and regionally selective appearance of cannabinoid receptors in the fetal human brain may explain the relatively mild and selective nature of postnatal

neurobehavioral deficits observed in infants exposed to cannabinoids in utero" (Biegon and Kerman 2001).

The long-term consequences on cognitive function are also a major topic of discussion with regard to adult cannabis use. The first longitudinal study examining the development of cogntive functioning conducted in the U.S. did not find any influence of cannabis use (Lyketsos et al. 1999). This was confirmed by a later Canadian study (Fried et al. 2002)

According to the large-scale study by Lyketsos et al. (1999), the age-related decline of cognitive functioning "...does not appear to be associated with cannabis use." Constantine Lyketsos and colleagues of John Hopkins Hospital in Baltimore conducted a follow-up study of 1,318 people, divided into heavy users, light users, and nonusers of cannabis. All participants had completed a special test, the Mini Mental State Examination (MMSE), in 1981, 1982, and 1993-1996. The individual score differences between 1982 and 1993-1996 were calculated for each study participant. Within these 12 years, the mean score decline for all groups was 1.2 points. The Mini Mental State Examination (MMSE) is a brief and widely used standardized method for assessing cognitive mental status. It assesses orientation, attention, immediate and short-term recall, language, and the ability to follow simple verbal and written commands. The maximum achievable score is 30. Researchers found a decline in all age groups. There was "no significant differences in cognitive decline between heavy users, light users, and nonusers of cannabis." There were also no differences attributable to sex in these subgroups.

Former studies have been hampered by the fact that they are based on retrospective studies with single measurements. In a commentary by Martha Clare Morris and colleagues of the Rush Institute for Healthy Aging in Chicago, the difficulties encountered with the use of single measurements of cognition and the importance of measuring changes are stressed (Morris et al. 1999).

In the second longitudinal study ever conducted, Canadian researchers did not find any long-term effect of heavy cannabis use on overall intelligence (Fried et al. 2002). They compared the intelligence quotient (IQ) of 15 current heavy users of cannabis, 9 current light users, 9 former regular users and 37 non-users in a group of 70 young people. Participants had been followed since birth and now were 17-20 years of age. Current marijuana use was significantly correlated in a dose-related fashion with a decline in IQ when compared to the IQ measured at age 9-12. In current heavy users, the IQ showed a decrease of 4.1 points, compared to gains in IQ points for light current users (5.8), former users (3.5) and non-users (2.6). The authors concluded that current cannabis use "had a negative effect on global IQ score only in subjects who smoked 5 or more joints per week" and that "marijuana does not have a long-term negative impact on global intelligence."

U.S. research at Harvard Medical School showed that cognitive impairment after regular heavy use is reversible (Pope et al. 2001). Three groups of individuals aged 30 to 55 years were compared with regard to their cognitive abilities: (1) 63 current heavy users who had smoked cannabis at least 5000 times in their lives and who were smoking daily at study entry; (2) 45 former heavy users who had also smoked at least 5000 times but fewer than 12 times in the last 3 months; and (3) 72 control subjects who had smoked no more than 50 times in their lives. Results showed that some cognitive deficits appear detectable at least 7 days after

discontinuation of heavy cannabis use. By day 28, however, there were virtually no significant differences among the groups on any of the test results. Authors concluded

> "Some cognitive deficits appear detectable at least 7 days after heavy cannabis use but appear reversible and related to recent cannabis exposure rather than irreversible and related to cumulative lifetime use" (Pope et al. 2001).

However, the discussion on whether regular cannabis use causes a decline in cognitive function continues, as can be seen from a discussion in the *Journal of the American Medical Association* in March and May 2002 (Solowij et al. 2002, Nyquist 2002, Watson 2002, Gunderson et al. 2002, Pope 2002).

Govermental and expert committees in several industrialized countries have also concluded that the side effects of cannabis are relatively benign, supporting its safety even for prolonged use. The Institute of Medicine Report of 1999 states:

> "Marijuana is not a completely benign substance. It is a powerful drug with a variety of effects. However, except for the harms associated with smoking, the adverse effects of marijuana use are within the range of effects tolerated for other medications. (...)

The Canadian Senate's Special Committee on Illegal Drugs has studied the effects of cannabis use for 14 months. The committee states in a premilinary report issued in May 2002 that scientific evidence suggests that marijuana "may have some negative effects on the health of individuals," but that these effects would be "relatively benign" and that marijuana is no gateway drug to the use of hard drugs. Only approximately 10 percent of the users would become chronic users and 5 to 10 percent would become addicted. The preliminary report is available at the web site of the parliament at http://www.parl.gc.ca/illegal-drugs.asp.

A select committee of Britain's House of Lords recommended that cannabis should be rescheduled from a schedule 1 to a schedule 2 drug under the Misuse of Drugs Regulations Act of 1985, since it was not a dangerous drug and in order to facilitate medical research with cannabis (House of Lords 1998). The committee accused the Medicines Control Agency of not dealing with cannabis-based medicines in the same impartial manner as with other medicines (Hause of Lords 2001). In the second report released on 22 March 2001, the select committee on science and technology also called for an end to the prosecution of therapeutic cannabis users who possess or grow cannabis for their own use.

After eight months of deliberation, a health select committee of the parliament of New Zealand tabled its report on research into the mental health effects of cannabis on December 17, 1998, finding that the drug has probably been unduly criticised (New Zealand Herald from 18 December 1998). "Based on the evidence we have heard in the course of this inquiry," the committee concluded, "the negative mental health impact of cannabis appears to have been overstated, particularly in relation to occasional adult users of the drug." "Evidence received in the course of this inquiry has raised serious doubts about commonly held beliefs about cannabis," wrote the committee. "Evidence received during the inquiry supports the

view that there can be subtle cognitive impairment in cannabis users," the report says. In this respect, the committee drew to a large extent on the work of Prof. Wayne Hall of the Australian National Drug and Alcohol Research Centre, who was commissioned to report on scientific research in this area. He found that long-term use of cannabis may cause subtle impairment in the higher cognitive functions of memory, attention and the organisation and integration of complex information. The committee said the evidence also suggested that cannabis did not cause behavioral difficulties, but rather that cannabis was frequently used by youths who misbehaved; neither was it a cause of suicide.

On 22 November 2001, the French National Health and Medical Research Institute (Inserm, Institut National de la Santé et de la Recherche Médicale) presented a 58-page literature review with the title "Cannabis - which effects on behaviour and health?" (Inserm 2001). The report was ordered by a governmental working group on the fight against drugs and drug addiction. Main topics of the report are factors that influence use, acute and chronic effects, and groups of special interest (pregnant women, individuals with mental disorders). It did not deal with the medical use of cannabis. The report stated that about 10 percent of those who ever used cannabis have a risk to become dependent, compared to 30 percent with tobacco, and that cannabis effects on the nervous system are functional and reversible, and do not cause long-term damage.

In response to these findings on the long-term safety of cannabis use, many countries are now relaxing their cannabis laws or are discussing legal access to medical cannabis, among them several European countries, Australia, New Zealand, and Canada.

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11) Side effects of the legal situation.

The illegal status of cannabis under most jurisdictions causes negative consequences for many with regard to their career, personal and professional relationships, suspension of driving privilege, and health.

In a book chapter on side effects of the medical use of cannabis, Grotenhermen states:

> "Natural cannabis products are illegal in most countries. For the most part, no legal distinction is made between recreational and medical use.
>
> If single cannabinoids (dronabinol, nabilone) that may be legally prescribed in some countries are not available, too expensive, or ineffective, therapeutic use of cannabis may provoke various repercussions for the patient who employs it. These include: criminal prosecution or fear thereof, paying a high price for an illegal drug, exposure to possible contamination, use of an unknown concentration of THC with possible variability in dosing, limited forms of administration, and even fear of discussion with the patient's family doctor. The illegality of cannabis presents various obstacles to clinical research" (Grotenhermen 2002).

Australian researchers at the National Centre for Research into the Prevention of Drug Abuse investigated the consequences of the kind of penalty on use and effects (Australian Associated Press of 3 August 1999).

The study compared 68 cannabis users in South Australia (SA) who received expiation notices for minor cannabis offenses to 68 West Australian (WA) users who received criminal convictions for minor offences. Researcher Simon Lenton said a key finding of the survey was that about 90 per cent from both groups said they had not reduced their use of the drug, despite the different penalties. Comparisons of the South Australian and West Australian users showed that WA's criminal convictions system had a far greater negative impact on the lives of cannabis offenders. A third of the WA group, compared to two per cent of the SA group, said they had been dismissed from a job, could not find a new one, or stopped applying for jobs because of their conviction. One fifth of the WA group, compared to one twentieth of the SA group, said they had suffered a relationship problem, and 16 percent of the WA group said that they had been forced to move house or lost accommodation because of their conviction. In an interview, Lenton said while most attention focused on health problems associated with cannabis, "we also need to look at what the effects are of the legal system which we set-up to deal with cannabis use" (Australian Associated Press, August 3, 1999).

At this time, U.S. law on the federal level and in most states treats the medicinal and recreational uses of marijuana and related acquisition alike. Thus, the legal situation of

medical cannabis users is subject to the same negative implications of law enforcement and penalization.

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12) Cannabis as gateway drug.

Recent research suggests that recreationally used cannabis does not act as a gateway drug to harder drugs such as alcohol, cocaine and heroine. The same will apply to users of medicinal cannabis.

Several research studies addressed the question whether cannabis leads to the use of harder drugs such as alcohol, cocaine and heroin.

According to a study to be published by the Centre for Economic Policy Research, London, cannabis does not lead to the use of hard drugs (Sunday Times of 16 December 2001). Findings are based on a survey of drug users in Amsterdam over a 10-year period. The study by Jan van Ours of Tilburg University in the Netherlands shows that cannabis users typically start using the drug between the ages of 18 and 20, while cocaine use usually starts between 20 and 25. But it concludes that cannabis is not a stepping stone to using cocaine or heroin. Four surveys, covering nearly 17,000 people, were carried out in Amsterdam in 1987, 1990, 1994 and 1997. The study found that there was little difference in the probability of an individual taking up cocaine as to whether or not he or she had used cannabis. Although significant numbers of people in the survey did use soft and hard drugs, this was linked with personal characteristics and a predilection to experimentation.

The Institute of Medicine study characterized marijuana's role as a "gateway drug" as follows:

> "Patterns in progression of drug use from adolescence to adulthood are strikingly regular. Because it is the most widely used illicit drug, marijuana is predictably the first illicit drug most people encounter. Not surprisingly, most users of other illicit drugs have used marijuana first. In fact, most drug users begin with alcohol and nicotine before marijuana—usually before they are of legal age.
>
> In the sense that marijuana use typically precedes rather than follows initiation of other illicit drug use, it is indeed a "gateway" drug. But because underage smoking and alcohol use typically precede marijuana use, marijuana is not the most common, and is rarely the first, "gateway" to illicit drug use. There is no conclusive evidence that the drug effects of marijuana are causally linked to the subsequent abuse of other illicit drugs. An important caution is that data on drug use progression cannot be assumed to apply to the use of drugs for medical purposes. It does not follow from those data that if marijuana were available by prescription for medical use, the pattern of drug use would remain the same as seen in illicit use" (Joy et al. 1999)

A more recent study based on national survey data also does not support the hypothesis that increases in marijuana use lead to increased use of more dangerous drugs among the general public. In the *American Journal of Public Health*, Andrew Golub and Bruce Johnson of the National Development and Research Institute in New York wrote that young people who smoked marijuana in the generations before and after the baby boomers do not appear to be likely to move on to harder drugs. The researchers said that these findings suggest that the gateway phenomenon reflects norms prevailing among youths at a specific place and time.

> "The recent increase in youthful marijuana use has been offset by lower rates of progression to hard drug use among youths born in the 1970s. Dire predictions of future hard drug abuse by youths who came of age in the 1990s may be greatly overstated" (Golub & Johnson 2001).

Research also suggests that the "gateway theory" does not describe the behavior of serious drug users:

> "The serious drug users were substantially different from high school samples in their progression of drug use. The serious drug users were less likely to follow the typical sequence identified in previous studies (alcohol, then marijuana, followed by other illicit drugs). They were more likely to have used marijuana before using alcohol, and more likely to have used other illicit drugs before using marijuana. We also found that atypical sequencing was associated with earlier initiation of the use of illicit drugs other than marijuana and greater lifetime drug involvement. These findings suggest that for a large number of serious drug users, marijuana does not play the role of a 'gateway drug'. We conclude that prevention efforts which focus on alcohol and marijuana may be of limited effectiveness for youth who are at risk for serious drug abuse" (Mackesy-Amiti et al. 1997)

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III. Dependence liability

13) Basic research on rewarding, tolerance and withdrawal.

In recent years, scientists were able to show that animals do self-administer THC under certain conditions. Basic animal research also shows that cannabis produces tolerance and withdrawal. This research helps explain abuse of cannabis and dependency in humans. However, basic research cannot predict how pronounced these effects will be in humans and whether they are stronger or less strong compared to other drugs such as caffeine, nicotine and heroin.

Tanda et al. (2000) demonstrated for the first time that animals self-administer THC. They write in their abstract:

> "Many attempts to obtain reliable self-administration behavior by laboratory animals with delta-9-tetrahydrocannabinol (THC), the psychoactive ingredient in marijuana, have been unsuccessful. Because self-administration behavior has been demonstrated in laboratory animals for almost all other psychoactive drugs abused by humans, as well as for nicotine, the psychoactive ingredient in tobacco, these studies would seem to indicate that marijuana has less potential for abuse. Here we show persistent intravenous self-administration behavior by monkeys for doses of THC lower than doses used in previous studies, but comparable to doses in marijuana smoke inhaled by humans" (Tanda et al. 2000).

In this study Tanda, Munzar and Goldberg used a low but clinically relevant dose of THC administered intravenously in a clear solution. This solution rapidly distributed THC to the brain. Previous attempts to show self-administration, using much higher doses of THC held in a suspension, failed. One reason for this may be that, although higher doses were used, the suspension resulted in less brain penetration. In this study, the monkeys had previously been trained to self-administer cocaine by pressing a lever 10 times. When saline was substituted for cocaine, self administration stopped. When THC replaced the saline, the monkeys quickly started to press the lever again. The monkeys gave themselves about 30 injections during an hour-long session, which equates roughly with the dose received by a person smoking a marijuana joint.

The team went on to confirm that giving the monkeys a second drug that directly blocks cannabinoid receptors in the brain could prevent self-administration. Dr. Goldberg's team concludes from its observations that THC "has as much potential for abuse as other drugs of abuse, such as cocaine and heroin."

However, Martin Jarvis, professor of health psychology at University College London (UK) said in an interview to the *British Medical Journal* this would probably overstate the case. He said that misuse is "a judgment best made by looking at patterns of actual human use." He continued: "We shouldn't assume that unreasonable behavior in society follows from the observation of brain reward behavior in animals alone" (Berger 2000).

Ian Stolerman, professor of behavioral pharmacology at the Institute of Psychiatry in London, agreed with Jarvis and states during the interview: "This is an important study because for the first time it provides a method for studying directly the intake of THC by a laboratory animal and thus models a key behavioral feature of addictive states generally. It will lead to studies of how and where THC works in the brain to generate drug abuse. It does show that THC shares properties with other drugs of abuse, but whether it is really as potentially abusive as cocaine and heroin is not so clear" (Berger 2000).

Several studies in recent years have demonstrated that there is an interaction between the endogenous cannabinoid system and several other transmitter and modulator systems in the brain, among them the opioid system.

Lichtmann et al. (2001) have shown that there seems to be a reciprocal relationship between the cannabinoid and opioid system relative to dependency. THC was able to block some of the withdrawal symptoms in morphine dependent mice, and morphine was able to reduce some of the withdrawal symptoms in THC dependent mice. The mu-opioid receptor seems to be involved in THC dependence. These findings are consistent with the results of a study by Yamaguchi et al. (2001). Their study in mice suggests that in morphine dependence, upregulation of cannabinoid CB1 receptors occurs. Thus, CB1 receptor agonists may have potential as therapeutic drugs for opiate withdrawal symptoms. Successful treatment of withdrawal from opiates has already been described by physicians of the 19th century and also in contemporary case reports.

Valverde et al. (2001) support the concept of an interaction between the cannabinoid and the opiate systems. They found several effects of THC on the opiate system in mice including facilitation of the antinociceptive and antidepressant-like responses elicited by the endogenous enkephalins and increased release of Met-enkephalin-like material in the nucleus accumbens. However, there was no modification of the rewarding responses produced by morphine from the acute or chronic administration of THC.

> "Recent studies have suggested that cannabinoids might initiate the consumption of other highly addictive substances, such as opiates. In this work, we show that acute administration of Delta9-tetrahydrocannabinol in mice facilitates the antinociceptive and antidepressant-like responses elicited by the endogenous enkephalins protected from their degradation by RB 101, a complete inhibitor of enkephalin catabolism. This emphasizes the existence of a physiological interaction between endogenous opioid and cannabinoid systems. Accordingly, Delta9-tetrahydrocannabinol increased the release of Met-enkephalin-like material in the nucleus accumbens of awake and freely moving rats measured by microdialysis. In addition, this cannabinoid agonist displaced the in vivo [3H]diprenorphine binding to opioid receptors in total mouse brain. The repetitive pretreatment during 3 weeks of Delta9-tetrahydrocannabinol in mice treated chronically with morphine significantly reduces the naloxone-induced withdrawal syndrome. However, this repetitive administration of Delta9-

> tetrahydrocannabinol did not modify or even decrease the rewarding responses produced by morphine in the place preference paradigm. Taken together, these behavioral and biochemical results demonstrate the existence of a direct link between endogenous opioid and cannabinoid systems. However, chronic use of high doses of cannabinoids does not seem to potentiate the psychic dependence to opioids" (Valverde et al. 2001).

The neurotransmitter dopamine seems to play a major role in rewarding by drugs and physical activities, such as sex and sports. It has been suggested that the use of cannabis, like that of caffeine, tobacco and other drugs, is associated with increased mesolimbic dopamine activity (Brody & Preut 2002). "However, evidence for such an effect is inconsistent" (Stanley-Cary et al. 2002). E.g. Stanley-Cary et al. (2002) investigated whether or not the cannabinoid agonist CP 55,940, which binds to the CB1 receptor, mimicked the effects of amphetamine, a drug which increases dopamine release, on prepulse inhibition (PPI) of the acoustic startle reflex. They write:

> "The first experiment measured the PPI of 16 male Wistar rats injected (i.p.) with different doses of CP 55,940 in a Latin-square design. A second experiment replicated the effects of the first experiment in a between-subjects design, and also examined the effects of using a 5% alcohol solution as a solvent for cannabinoid agonists, in comparison to the more inert detergent, Tween 80. In both experiments, CP 55,940 in Tween 80 significantly reduced basal activity, increased startle onset latencies and increased PPI, effects opposite to those of amphetamine. These results suggest that the net behavioral effects of cannabinoids are opposite to those of amphetamine. In addition, it was found that 1 ml/kg of a 5% alcohol solution has significant behavioral effects on its own, and reverses the effects of CP 55,940 on PPI" (Stanley-Cary et al. 2002).

Effects of cannabis use on dopamine may be complex and are not fully understood today. Studies showed that activation of dopamine receptors with a dopamine-2(D2)-like receptor ligand in the striatum (a region that controls planning and execution of motor behaviors) led to a strong stimulation of anandamide (an endocannabinoid) outflow (Giuffrida et al. 1999). The researchers concluded that the physiological role of anandamide may be

> "...to counter dopamine stimulation of motor activity. (...) Thus, our findings may have implications for neuropsychiatric disorders such as schizophrenia, Tourette's syndrome and Parkinson's disease and may point to novel therapeutic approaches for these conditions."

In another study of this group, elevated endocannabinoid levels were found in the cerebrospinal fluid of people with schizophrenia. One explanation for the higher levels in schizophrenics is that the brain is attempting to compensate for a hyperactive dopamine system. "It's the brain's response to bring this dopamine activity down," said Daniele

Piomelli, professor at the University of California at Irvine in the New Scientist of May 29, 1999. But, he added, the brain cannot keep the amount of anandamide high enough to lower dopamine levels.

In summary, animal studies show that THC and other ligands to the CB1 receptor are rewarding, that they are self-administered by animals under certain conditions, and that CB1 receptor ligands exert complex interactions with the opiate and the dopamine system. However, determining the relevance and implications of these findings to humans requires clinical studies.

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14) Dependency compared to other drugs.

Compared to other widely used drugs (alcohol, tobacco, opiates) a smaller percentage of cannabis users become dependent. Dependency is also less severe compared to many other legal and illegal drugs. The relatively low dependence liability of cannabis is widely recognized.

Withdrawal from THC has been described in animal research and humans. For example, people who smoke marijuana daily become more aggressive when they quit. Dr. Elena Kouri and colleagues at Harvard University write in the *Journal of Psychopharmacology* that they had shown objectively that when people stop smoking marijuana, there is a clear withdrawal syndrome (Kouri and Pope 2000).

The withdrawal symptoms are relatively mild. In a review of the published literature regarding cannabis withdrawal symptoms in humans, Smith (2002) stated:

> "It is suggested that the studies conducted to date do not provide a strong evidence base for the drawing of any conclusions as to the existence of a cannabis withdrawal syndrome in human users, or as to the cause of symptoms reported by those abstaining from the drug. On the basis of current research, cannabis cannot be said to provide as clear a withdrawal pattern as other drugs of abuse, such as opiates. However, cannabis also highlights the need for a further defining of withdrawal, in particular the position that rebound effects occupy in this phenomenon. It is concluded that more controlled research might uncover a diagnosable withdrawal syndrome in human users and that there may be a precedent for the introduction of a cannabis withdrawal syndrome before the exact root of it is known" (Smith 2002).

Tolerance and rebound phenomena in humans have been described for cannabis. These are other indications of dependency caused by cannabis:

> "Tolerance develops to the receptor-mediated effects of THC with continued usage. However, there are distinctions in their degree with different effects. Discontinuation of chronic THC use may cause rebound phenomena (transient increase in intraocular pressure, loss of appetite, etc.). Some chronic users report withdrawal symptoms after abrupt cessation. This withdrawal syndrome is characterized by irritability, agitation, sleep disorder, hyperhidrosis and loss of appetite. It is generally mild. Cannabis dependency is less determined by physical than by psychological factors. Dependency and abuse potential of therapeutically employed Δ^9-THC is low" (Grotenhermen 2002).

Dependency rates are reported to be lower than with many other drugs. In a German study of 1,458 current or previous cannabis users, ordered by the German Federal Health Ministry, 2-10% of those using exclusively cannabis were classified as substance dependent (Kleiber et al. 1997). If those who also used other illegal drugs were included, 8% of cannabis users were regarded as dependent, including 1% of the "occasional users," 7% of the "individual users," 10% of the "recreational users," and 28% of the "permanent users." Duration of consumption had no influence on the likelihood of the subject to quit use, an indication that the risk of dependency was independent of duration of use, and that users generally had no problems quitting.

Similar percentages were reported by Hall et al. (1999):

> "A variety of estimates have been derived from U.S. studies in the late 1970s and early 1980s, which defined cannabis use and dependence in a variety of ways. These studies suggested that between 10 and 20 per cent of those who have ever used cannabis, and between 33 and 50 per cent of those who have had a history of daily cannabis use, showed symptoms of cannabis dependence (see Hall, Solowij & Lemon, 1994). A more recent and better estimate of the risk of meeting DSM-R.III criteria for cannabis dependence was obtained from data collected in the National Comorbitity Study (Anthony, Warner & Kessler, 1994). This indicated that 9 per cent of lifetime cannabis users met DSM-R-III criteria for dependence at some time in their life, compared to 32 per cent of tobacco users, 23 per cent of opiate users and 15 per cent of alcohol users" (Hall et al. 1999)

In the recent past, several studies have attempted to compare the health risks of the most common legal and illegal drugs. Two studies received special attention: a report by order of the French Health Ministry, the so-called "Roques-Report" (Roques 1998), and a study prepared for the World Health Organization (Hall et al. 1999). Major attention was paid to dependency/addiction caused by these drugs. The main results of these studies are summarized in Tables 1 and 2 below.

Table 1. Comparison of hazards of different drugs (modified according to Roques et al. 1998).

	Opiates	Cocaine	Alcohol	Benzodia zepines	Cannabis	Tobacco
Physical dependency	*****	**	*****	***	**	****
Psychological dependency	*****	****	*****	****	**	*****
Nerve damage	**	****	****	–	–	–
Overall toxicity	**** (not in therapy)	****	****	*	*	***** (cancer)
Social hazards	*****	*****	****	**	**	–

– = no effects, * = very weak effects, ** = weak effects,
*** = moderate effects, **** = strong effects, ***** = very strong effects

Table 2. Comparison of adverse effects on health for heavy users of the most harmful common form of each substance (according to Hall et al. 1999).

	Marijuana	Alcohol	Tobacco	Heroin
Traffic and other accidents	*	**		*
Violence and suicide		**		
Overdose death		*		**
HIV and liver infections		*		**
Liver cirrhosis		**		
Heart disease		*	**	
Respiratory diseases	*		**	
Cancer	*	*	**	
Mental illness	*	**		
Dependency/addiction	**	**	**	**
Lasting effect on the fetus	*	**	*	*

* = less common or less well-established effect
** = important effect

Both reports concluded that heavy cannabis consumption causes less harm than heavy use of the most common other legal and illegal drugs. Special attention was paid to the question of dependency and abuse. Hall et al. (1999) concluded that all drugs under investigation can cause dependency. The main health risks to exclusive users of cannabis would be limited to daily users who consume the drug over a period of several years. These risks included the risk of a dependency syndrome, development of a chronic bronchitis, and involvement in motor vehicle accidents if the user drives under acute influence of the drug. The latter could also affect occasional users. With regard to dependency Hall et al. (1999) conclude (as quoted above):

> "A variety of estimates have been derived from U.S. studies in the late 1970s and early 1980s, which defined cannabis use and dependence in a variety of ways. These studies suggested that between 10 and 20 per cent of those who have ever used cannabis, and between 33 and 50 per cent of those who have had a history of daily cannabis use, showed symptoms of cannabis dependence (see Hall, Solowij & Lemon, 1994). A more recent and better estimate of the risk of meeting DSM-R.III criteria for cannabis dependence was obtained from data collected in the National Comorbidity Study (Anthony, Warner & Kessler, 1994). This indicated that 9 per cent of lifetime cannabis users met DSM-R-III criteria for dependence at some time in their life, compared to 32 per cent of tobacco users, 23 per cent of opiate users and 15 per cent of alcohol users" (Hall et al. 1999).

Eminent addictions specialist Jack Henningfeld was asked to rate the addictive qualities of popular drugs for the New York Times, and produced the following ratings according to five general indicators of abuse potential.

Comparing Addictive Qualities of Popular Drugs (Higher score indicates more serious effect)					
Drug	Dependence	Withdrawal	Tolerance	Reinforcement	Intoxication
Nicotine	6	4	5	3	2
Heroin	5	5	6	5	5
Cocaine	4	3	3	6	4
Alcohol	3	6	4	4	6
Caffeine	2	2	2	1	1
Marijuana	1	1	1	2	3

Withdrawal: Presence and severity of characteristic withdrawal symptoms.

Reinforcement: A measure of the substance's ability, in human and animal tests, to get users to take it again and again, and in preference to other substances.

> Tolerance: How much of the substance is needed to satisfy increasing cravings for it, and the level of stable need that is eventually reached.
>
> Dependence: How difficult it is for the user to quit, the relapse rate, the percentage of people who eventually become dependent, the rating users give their own need for the substance and the degree to which the substance will be used in the face of evidence that it causes harm.
>
> Intoxication: Though not usually counted as a measure of addiction in itself, the level of intoxication is associated with addiction and increases the personal and social damage a substance may do. (Heningfeld, Hilts, 1994)

This assessment agrees with those cited above in that marijuana ranks low on all indicators of additive potential compared to other commonly used drugs.

Adolescents are much more susceptible to marijuana dependence and to problems related to marijuana abuse than adults.

> "Adolescents are dependent at a lower frequency and quantity of use than adults: the differences diverge as level of use increases. Twice as many adolescents as adults who used marijuana near-daily or daily within the last year were identified as being dependent (35% versus 18%). Frequency and quantity of use each retained a unique effect on dependence, but frequency appeared to be more important than quantity in predicting last year dependence." (Chen et al, 1997)

This higher dependence liability of adolescents is sometimes used as an argument against the medical use of cannabis. However, this argument is not used with other medicines, such as the opiates. The IOM report states that permitting the medical use of marijuana would not increase non-medical uses. The report also addresses the suggestion by opponents of medical use that approving marijuana as a medicine "sends the wrong message." The authors say there is "no convincing data to support this concern," and they note that "this question is beyond the issues normally considered for medical uses of drugs." (Joy et al. 1999).

Kandel et al. (1997) analyzed dependency rates in a sample of about 88,000 individuals. They found that nicotine was the most addictive drug. Analyses were based on three aggregated waves (1991, 1992 and 1993) of the nationally representative samples of the general population, at or above 12 years of age, interviewed in the National Household Surveys on Drug Abuse (n = 87915).

> "The five major findings are that: (1) nicotine is the most addictive of the four drugs we examined; (2) among female last year users of alcohol and marijuana, adolescents are significantly more at risk for dependence than any other age group of women; (3) conditional prevalences of last year dependence on alcohol, marijuana and cocaine are higher

> among adolescent females than adolescent males but significantly different only for cocaine; (4) among adults, the rates of dependence are higher among males than among females for alcohol and marijuana, but lower for nicotine; and (5) among last year users, whites are more likely than any other ethnic group to be dependent on nicotine and blacks to be dependent on cocaine" (Kandel et al. 1997).

If selected samples of individuals are investigated, it is necessary to avoid any generalization of the results. Crowley et al. (1998) investigated a sample of young cannabis users (age: 13-19 years) with serious cannabis-use disorders and problems and noted:

> "The prevalence of cannabis use is rising among adolescents, many of whom perceive little risk from cannabis. However, clinicians who treat adolescent substance users hear frequent reports of serious cannabis-use disorders and problems. (...) The data indicate that for adolescents with conduct problems cannabis use is not benign, and that the drug potently reinforces cannabis-taking, producing both dependence and withdrawal. However, findings from this severely affected clinical population should not be generalized broadly to all other adolescents."

In conclusion, cannabis can cause dependency but withdrawal is milder than withdrawal from several other legal and illegal drugs, and dependency is less frequent than with most other common legal and illegal drugs.

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IV. Abuse potential

15) Use and Abuse.

The government's review of the 1995 marijuana rescheduling petition did not distinguish between use and abuse according to professional standards, such as those in use by the medical and scientific community. Widespread use of cannabis is not an indication of its abuse potential, and widespread use of marijuana without dependency supports the argument that marijuana is safe for use under medical supervision.

Since marijuana, heroin and other drugs are often referred to as "drugs of abuse", many consider each use of these drugs "abuse". That a clear differentiation between the two terms if often lacking is suggested by Wish (1990), who noted in an editorial of *the Journal of the American Medical Association* on drug screenings in the workplace that a discussion on the difference between drug use and drug abuse was often regarded as "anachronistic and unpatriotic."

However, the term "substance abuse" is clearly defined and should be differed from simple and unproblematic use, which is the rule and not the exception with most drugs, even in adolescents. Scientists usually differentiate between use, and forms of problematic use. The most frequent terms for problematic or pathological use are abuse, misuse, harmful use and dependency (e.g. Gorman and Derzon 2002, Swift et al. 2001). Definitions for these terms vary so that samples determined using different definitions overlap. Swift et al. (2001) compared dependency according to the DSM-IV (Diagnostic Manual of Diseases) to the concept of dependency in the ICD-10 (The International Classification of Diseases, 10th Revision) in a sample of 10,641 representative Australian adults:

> The prevalence of DSM-IV (1.5%) and ICD-10 (1.7%) cannabis dependence was similar. DSM-IV and ICD-10 dependence criteria comprised unidimensional syndromes. The most common symptoms among dependent and non-dependent users were difficulties with controlling use and withdrawal, although there were marked differences in symptom prevalence. Dependent users reported a median of four symptoms. There was good to excellent diagnostic concordance (kappas = 0.7-0.9) between systems for dependence but not for abuse/harmful use (Y = 0.4). These findings provide some support for the validity of cannabis dependence.

According to the newer DSM-IV definition cannabis abuse and dependency will be observed more often than according to the criteria of the earlier DSM-III-R:

> "We assessed a clinical sample of 102 adolescents using CIDI-SAM. Prevalence of either an abuse or dependence diagnosis was lower with DSM-IV than DSM-III-R except for cannabis and alcohol, and concordance rates were better for dependence than for abuse. For most substances, rates of DSM-IV withdrawal were lower than in DSM-III-R, but rates of DSM-

> IV physiological dependence remained high. Changes in DSM-IV criteria appear to have impacted diagnoses in these adolescents, particularly for the substances they use most--i.e. alcohol, tobacco, and cannabis" (Mikulich et al. 2001).

Clinical criteria for substance abuse according to DSM-IV are:

> A. A maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by one or more of the following occurring within a twelve-month period.
>
> > (1) Recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home (e.g. repeated absences or poor work performance related to substance use, substance related absences, suspension, or expulsions from school; neglect of children or household).
> >
> > (2) Recurrent substance use in situations in which it is physically hazardous (e.g. driving an automobile or operating a machine when impaired by substance use).
> >
> > (3) Recurrent substance related legal problems (e.g. arrest for substance related disorder conduct).
> >
> > (4) Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by effects of substance (e.g. arguments with spouse about consequences of intoxication, physical fights).
>
> B. Symptoms have never met the criteria for substance dependence for this class of substance.

When talking about the gateway theory, the Institute of Medicine (1999) pointed out that it is necessary to differentiate between use and dependency or abuse to draw the right conclusions from given data:

> "Many of the data on which the gateway theory is based do not measure dependence; instead, they measure use -even once-only use. Thus, they show only that marijuana users are more likely to use other illicit drugs (even if only once) than are people who never use marijuana, not that they become dependent or even frequent users. The authors of these studies are careful to point out that their data should not be used as evidence of an inexorable *causal* progression; rather they note that identifying stage-based user groups makes it possible to identify the specific risk factors that predict movement from one stage of drug use to the next -the real issue in the gateway discussion" (Joy et al. 1999).

Modern epidemiological studies have shown that many people who use cannabis do not differ from other people, that they do not abuse the drug but use it. A survey of 15,000 British children aged 14 and 15 found that young people with high self-esteem are more likely to take illicit drugs than those whose self-confidence is low (Observer of 11 February 2001). The results contradict the concept that drug use is most prevalent among anxious or insecure youth looking for an escape from poor conditions or a way to feel better about themselves. Heather Ashton, a professor of pharmacology at Newcastle University, said that the results of the survey did not surprise her: "Students all report they take drugs for pleasure and that it has nothing to do with anxiety or stress. Years ago young people who take drugs were seen as psychotic or low risk-takers. Now that is not the case."

A report published by the Institute of Medicine provides an equally clear assessment of contemporary scientific standards for defining drug use, abuse, and dependency. The report "Pathways of Addiction, Opportunities in Drug Abuse Research" was published in 1996. According to its introduction:

> "The report employs the standard three-stage conceptualization of drug-taking behavior that applies to all psychoactive drugs, whether licit of illicit. Each stage -- use, abuse, dependence -- is marked by higher levels of use and increasing serious consequences. Thus, when the report refers to the "use" of drugs, the term is usually employed in a narrow sense to distinguish it from intensified patterns of use. Conversely, the term "abuse" is used to refer to any harmful use, irrespective of whether the behavior constitutes a "disorder" in the DSM-IV diagnostic nomenclature. . . . It bears emphasizing that adverse consequences can be associated with patterns of drug use that do not amount to abuse or dependence in a clinical sense, although the focus of this report and the committee's recommendations is on the more intensified patterns of use (i.e, abuse and dependence) since they cause the majority of serious consequences." (Committee on Opportunities in Drug Abuse Research, 1996)

The findings above clarify marijuana's abuse potential relative to other drugs; the use of more dangerous drugs is not a significant risk for most individuals whose consumption of marijuana can be described as use rather than abuse or dependence. These findings affirm that medical users of marijuana are not at risk to use of other illicit drugs due to their regular use of cannabis.

The College on the Problems on Drug Dependence recognizes that marijuana is not a harmless drug, but they note a basis for distinguishing marijuana from drugs such as cocaine and heroin. They also note that serious questions have been raised as to whether marijuana is sufficiently dangerous to justify criminal sanctions, and are critical of DEA's irrational scheduling decisions with respect to marijuana:

> "Despite these significant adverse effects, questions have been raised by various investigative commissions about whether the

> social costs associated with the prohibition of marijuana are warranted by its actual harm to individuals and society, and especially whether imprisonment for mere possession unaccompanied by other crimes -- the law in some states -- is appropriate. It can be argued that placing marijuana in the same category as heroin and cocaine also sends a counterproductive message because it erases distinctions among drugs with very different degrees of hazard." (College on the Problems of Drug Dependence, 1997).

Gorman (2002) uses data from several prospective longitudinal studies (N= 3206) to examine the association between three psychological constructs on the use, misuse, and abuse of marijuana – providing an example of research and analytical strategies that incorporate the distinctions discussed above. Many drug users not only do not move on to more dangerous drugs, many of them also stop using drugs on their own as they age.

> "[This research] examined patterns of illicit drug use, abuse, and remission over a 25-year period and recent treatment use. . . .[utilizing] Retrospectively obtained year-to-year measures from the 1996-1997 survey included use and remission of sedatives, stimulants, marijuana, cocaine, and opiates, as well as substance abuse and psychiatric treatment use. . . . Most drug abusers who had started using drugs by their early 20s appeared to gradually achieve remission. Spontaneous remission was the rule rather than the exception. Nonetheless, considerable unmet needs existed for those who had continued use into middle age." (Price et al, 2001)

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16) Abuse of cannabis

Several studies demonstrate that abuse rates for cannabis are lower than rates for other common drugs. Cannabis use is usually not problematic use and cannabis users usually have no social problems which can be attributed to cannabis. The abuse potential of cannabis is insufficient to justify prohibition of medical use.

In a sample of 10,641 Australians aged 18 years and older, 2.2% of adults were diagnosed with DSM-IV cannabis use disorder, comprising cannabis dependence (1.5%) and cannabis abuse (0.7%) (Swift et al. 2001). In this sample, 21% of cannabis users met criteria for cannabis dependence and 10.7% for abuse. Thus, there was a considerable number of cannabis users in this sample with substance use disorders without being dependent. In this sample, cannabis dependence was twice as likely to occur as cannabis abuse.

Most cannabis use is not problematic even for adolescents. In a survey of 2641 UK school students aged 15-16 years, 201 students reported having used cannabis 40 times or more. They were examined using cluster analysis and also compared to other students.

> "Three clusters of heavy cannabis users emerged. The smallest was largely distinguished by antisocial behaviour. Another cluster were clearly unhappy, with little support from parents and friends, high levels of depressed mood and low levels of self-esteem. The largest cluster were 'ordinary' and had little to distinguish them apart from a belief that their environment was stable and predictable and that society's rules should be obeyed. Although clear relationships emerged between heavy cannabis use and heavy use of other substances, the 'ordinary' cluster of heavy cannabis users were less likely than the others to have used other illicit drugs. It is therefore concluded that teenage heavy cannabis users have varied motivations and contexts for their usage. They should not be seen as a homogeneous group and many do not appear to use other illicit drugs" (Miller and Plant 2002).

Often cannabis users are treated as a homogeneous group, usually when attempting to analyze a correlation with the use of other drugs, with mental illnesses (depression, schizophrenia), or to find predictors for a certain development (e.g. Griffin et al. 2002, Degenhardt et al. 2001a). Degenhardt et al. (2001a) analyzed relationships between alcohol, cannabis and tobacco and indicators of mental health problems. Alcohol users had lower rates of affective and anxiety disorders than non-users of alcohol, while those meeting criteria for alcohol dependence had the highest rates. Tobacco and cannabis use were both associated with increased rates of all mental health problems examined. However, after controlling for demographics, neuroticism and other drug use, cannabis was not associated with anxiety or affective disorders. Alcohol dependence and tobacco use remained associated with both of these indicators of mental health. All three types of drug use were associated with higher rates of other substance use problems, with cannabis having the strongest association. It should be noted that researchers differentiated alcohol use and alcohol dependence and found very different results, while no such differentiation was made for cannabis.

It is well established that most users of legal drugs, notably alcohol, tobacco and caffeine, control their use and are not abusing the drug. It appears from cluster analyses that this is also the case with cannabis and that studies which do not use cluster analyses and do not distinguish use from problematic use will overlook relevant information.

The associations that are found with cannabis have also been found with legal drugs. Degenhardt and Hall (2001) examined the comorbidity between tobacco use, substance-use disorders and mental health problems among Australian adults aged 18 years and over. DSM-IV diagnoses of substance use, anxiety, and affective disorders were derived using the Composite International Diagnostic Interview (CIDI). Other measures included a screener for psychosis and measures of psychological distress and disability. Researchers found that current tobacco use was strongly associated with abuse/dependence upon alcohol, cannabis, and other substances, and with higher rates of anxiety and affective disorders. Current smokers were more likely to screen positively for psychosis and reported greater psychological distress and disability than non-smokers and persons who had never smoked. These higher rates of other problems were not explained by differences in demographic characteristics, neuroticism scores, or by use of other drugs. The authors concluded:

> "Current tobacco use is associated with a range of other substance-use and mental health problems. These are likely to reduce the success of attempts to quit smoking. The presence of these other problems needs to be considered when considering smoking-cessation treatment, and further research may provide information on more effective treatment strategies for persons with co-existing substance-use and mental health problems."

Degenhardt et al (2001b) found that psychosis in a sample of 6,722 Australian adults were associated with the regular use of tobacco, alcohol, cannabis and opiates.

> "Ninety-nine persons (1.4%) screened positively for psychosis. Regular tobacco, alcohol and cannabis use were much more common among persons screening positively, as were alcohol, cannabis and other drug use disorders. Among alcohol and cannabis users, psychosis 'cases' were much more likely to be dependent. Ordinal logistic regressions revealed that regular tobacco use, cannabis and alcohol dependence, and opiate abuse were predictors of psychosis scores."

For marijuana, even simple associations between an undifferentiated group of users and commonly believed attributes, for example that cannabis users are not ambitious in sports or at work, cannot generally be established. The French Monitoring Centre for Drugs and Drug Addictions (OFDT) conducted a national school survey on the relationship between sporting activities and alcohol, cigarette and cannabis use among adolescents (Peretti-Watel et al. 2002). Respondents were asked confidentially by self-administered questionnaire (pen and paper) about their use of licit and illicit drugs and life-style (including sporting activities outside school: hours per week, registration in a club, type of sport).

> "FINDINGS: The U-shaped curve between the intensity of physical activities and licit and illicit drug use appeared not to be systematic. It depended mainly on the product and the level of use. It only remained significant for boys and heavy smoking once gender and age effect were taken into account.
>
> CONCLUSION: The results stress the need to control for age and gender when the survey participants are teenagers. The relationship between drug use and sporting activity also depends on the type of sport" (Peretti-Watel et al. 2002).

One criteria of substance abuse deals with the "failure to fulfill major role obligations at work, school, or home." There are several studies dealing with the effects of cannabis use on school and work performance, with conflicting results.

McDaniel (1988) analyzed the relationship between pre-employment drug use and on-the-job performance. He found only a small positive correlation. Blank and Fenton (1989) found a positive association between positive pre-employment testing for marijuana and later dismissals. On the other side, Parish (1989) did not find any relation between pre-employment drug testing result and performance at work. Normand et al. (1990) did not find any association between drug test results and subsequent change in employment. Zwerling et al. (1990) noted a positive association between cannabis use and change of occupation, absenteeism and discipline related problems at work. One year later they reassessed the same cohort and found that there was no longer an association between cannabis use and absence from work, while discipline-related problems had decreased (Ryan et al. 1992). These results from studies that all relied on results from pre-employment drug testing suggests that only a minor sub-set of cannabis users suffers from problems at work.

A recent study by Braun et al. (2000) demonstrated that the cannabis effect is modulated by cultural aspects. This was a nearly population based study on the prospective interrelationship of smoking, alcohol intake, marijuana use, and educational and occupational attainment of black and white young adults. Researchers used data from the U.S. CARDIA study (Coronary Artery Risk Development in Young Adults) which involved 5,115 persons 18-30 years of age during the 1985-86 period, who were reevaluated in 1987/88, 1990/91, 1992/93 and 1995. At the start of the study, 28.0% stated that they had used cannabis in the past month. In the following 10 years, cannabis use was negatively associated with completion of college. However, this negative association was only found in the younger sub-set aged 18-24 years at the start of the study, while in the older sub-set there was only a negative assocation between tobacco use and college completion. Associations of substance use with occupational measures were dependent on skin colour.

> "In Whites, marijuana use was associated with less prestigious occupations and lower family income, while smoking was unrelated and moderate daily drinking was positively associated. In Blacks, marijuana use was generally unrelated to occupational measures, while smoking and daily alcohol consumption were negatively associated" (Braun et al. 2000)

Another criteria of substance abuse deals with "recurrent substance use in situation in which it is physically hazardous (e.g. driving an automobile or operating a machine when impaired by substance use)." Culpability studies provide the best data on the problems cannabis can cause in the context of driving. This method studies crashes *post hoc* based upon information (usually from coroners and/or police data) about the causative factors of a crash and blood analyzes on drugs. Examination of these causative factors permits the researchers to apportion a score for each crash-involved driver to determine culpability for the crash. Although there are some differences between studies, these scores classify each driver as "culpable", or "not culpable" for the crash. The cases are then divided into groups according to the results of the blood analysis. Those drivers who had no detectable drugs in blood constitute the control group. A recent analyzes summarizes:

> "To date (September 1999), seven studies using culpability analysis have been reported, involving a total of 7,934 drivers. Alcohol was detected as the only drug in 1,785 drivers and together with cannabis in 390 drivers. Cannabis was detected in 684 drivers and in 294 of these was the only drug detected. (...) Using the culpability analysis method the dominant role of alcohol in motor vehicle accidents is clearly demonstrated, confirming the results with the case-control method. Indeed, in three of the studies outlined in Table 28.2 the concentration-dependence of alcohol was exhibited. At BAC ≥0.1 the culpability ratios were significant, whereas BAC <0.1 did not achieve significance.
>
> The results to date of crash culpability studies have failed to demonstrate that drivers with cannabinoids in blood are significantly more likely than drug-free drivers to be culpable in road crashes" (Chesher and Longo 2002).

If urine instead of blood is analyzed, predominantly drivers with regular cannabis use will be found and not those actually impaired since cannabis use can be detected for some weeks in the urine of heavy users. In a U.S. study with 414 injured drivers, 32 of the urine samples were positive for at least one potentially impairing drug (Lowenstein and Koziol-McLain 2001). Marijuana was detected most frequently (17%), surpassing alcohol (14%). Compared with drug- and alcohol-free drivers, the odds of crash responsibility were higher in drivers testing positive for alcohol alone (odds radio [OR] = 3.2) and in drivers testing positive for alcohol in combination with other drugs (OR = 3.5). Marijuana alone was not associated with crash responsibility (OR = 1.1). In a multivariate analysis, controlling for age, gender, seat belt use, and other confounding variables, only alcohol predicted crash responsibility. Researchers concluded:

> "Alcohol remains the dominant drug associated with injury-producing traffic crashes. Marijuana is often detected, but in the absence of alcohol, it is not associated with crash responsibility" (Lowenstein and Koziol-McLain 2001).

The first controlled, population based study on accidents on cannabis users compared to non-users was conducted by Braun et al. (1998) in the U.S. Researchers compared 4,462

individuals with different cannabis use status (never, former, current use) with regard to frequency of injuries within three years. Participants were randomly selected from 64,862 patients of a health maintenance program aged 15 to 49 years. All injuries independently of cause and severity were included. A total of 2,524 accident victims were treated outpatient, 22 were treated inpatient and 3 were fatalities. There was no association between cannabis use and injuries.

The abuse potential of a certain substance can also be determined from the variation in the intensity of use over the course of several years. A high variability in intensity indicates a weak potential for dependency and abuse. Von Sydow et al. (2001) determined incidence and patterns of the course of cannabis use and disorders as well as cohort effects in a community sample of adolescents and young adults (n=2,446) aged 14-24 years at the outset of the study. Patterns of cannabis use, abuse and dependence (DSM-IV) were assessed using the Composite International Diagnostic Interview (M-CIDI). They reported the following results: (1) Cumulative lifetime incidence for cannabis use (at second follow-up): 47%; 5.5% for cannabis abuse, 2.2% for dependence. (2) Men used and abused cannabis more often than women. (3) The majority of the older participants (18-24 years at baseline) had reduced their cannabis use at follow-up, while younger participants (14-17 years at baseline) more often had increased their use and developed abuse or dependence. (4) The younger birth cohort (born 1977-1981) tended to start earlier with substance (ab)use compared to the older birth cohort (1970-1977). (5) Cannabis use was associated with increasing rates of concomitant use of other licit and illicit drugs. The authors concluded:

> "Cannabis use is widespread in our sample, but the probability of developing cannabis abuse or dependence is relatively low (8%). The natural course of cannabis use is quite variable: about half of all cannabis users stopped their use spontaneously in their twenties, others report occasional or more frequent use of cannabis" (Von Sydow et al. 2001)

Felder and Glass (2001) explain that the abuse potential of cannabis is not sufficient to preclude its medical use. Their assessment of the relative abuse potential of cannabis suggests that it does not have the high potential for abuse required for Schedule I or II status..

> Much of the political and public objection to the use of [Delta][9] THC or marijuana as a therapy centers around its abuse potential and the belief by some that it serves as a "gateway" drug leading users to "harder" drugs of abuse. Many therapeutic drugs have abuse potential, yet this does not invalidate their role in current therapies. While there is some preliminary evidence for cannabinoids activating the reward pathways in the brain (Tanda et al. 1998), most investigators have failed to find addictive or reinforcing effects of cannabinoids in animal models. Unlike cocaine or heroin, cannabinoid agonists produce conditioned place aversion even at low doses (McGregor et al. 1996; Parker and Gilles 1995) and anxiogenic effects (Onavi et al 1990). Furthermore, animals will not self-administer cannabinoids (Harris et al 1974; Leite and Carlina 1974; Cocoran and Amit 1974), and a

> lack of cross-sensitization between cocaine (McGregor et al 1995) or amphetamines (Takahashi and Singer 1981) and cannabinoids has also been demonstrated. (Felder and Glass 1998, 192)

A considerable number of cannabis users suffer from problems that meet the criteria for abuse. However, the large majority of cannabis users do not experience any relevant problems related to their use. When compared to legal drugs, abuse problems with cannabis are generally less severe. The abuse of cannabis does not preclude its medical use. Relative to other scheduled drugs cannabis does not have a high potential for abuse.

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17) Emergency room admissions

Data on both drug treatment and emergency room admissions also distinguish the abuse potential of marijuana from that of other drugs, and establishes its relative abuse potential as lower than Schedule I drugs such as heroin and Schedule II drugs such as cocaine.

According to the Treatment Episodes Data Set, nearly 54% of all marijuana treatment admissions are referred to by the criminal justice system, compared to much smaller percentages for heroin and cocaine. The abuse potential of the more dangerous drugs is so severe that addicts seek treatment on their own or through persuasion from the people they have contact with. Furthermore, marijuana treatment admissions are much more likely to receive ambulatory drug treatment such as outpatient care than opiate or cocaine admissions, another indication that marijuana has a lower potential for abuse (see table 3)

The relative abuse potential of drugs can also be evaluated by comparing the likelihood of the respective user populations to be admitted to emergency rooms as a result of their drug use. According to the 1998 National Household Survey, there were 18.7 million annual marijuana users, 3.8 million annual cocaine users, and 253,000 annual heroin users. According to 1998 data from the Drug Abuse Warning Network (DAWN), based on reports from participating hospital emergency rooms, there were 76,870 emergency room mentions for marijuana, 172,014 mentions of cocaine, and 77,645 mentions of heroin/morphine. Incorporating both sets of data indicates that rates of emergency room mentions per 100,000 users is 411 for marijuana, 4,514 for cocaine, and 30,690 for heroin. The table demonstrates that users of marijuana in the U.S. are much less likely to be admitted to emergency rooms than those of cocaine and heroin.

Table 3. Selected Drug Use Statistics - 1998

	Estimated Annual Users (1)	Emergency Room (ER) Mentions (2)	ER Mentions/ 100,000 users	Percent of Treatment Admissions Referred by Criminal Justice System (3)	Percent of Treatment Admissions Receiving Ambulatory Care (3)
Marijuana/Hashish	18,710,000	76,870	410.85	53.9%	80.4%
Heroin/Morphine	253,000	77,645	30,689.72	11.1% - 17.0%	59.5%-61.8%
Cocaine	3,811,000	172,014	4,513.62	25.7% - 29.3%	52.2% - 57.1%

Thus, national survey data provide additional evidence that marijuana does not have a high potential for abuse relative to other controlled substances.

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18) Cannabis and dronabinol.

There is growing evidence that there is no relevant difference in subjective effects between (Schedule III) dronabinol and cannabis. Thus, it can be expected that the abuse liability is similar for both agents.

In 1999, the Drug Enforcement Administration (DEA) reclassified Marinol™ from a "Schedule II" drug to the less restrictive "Schedule III" category according to the Controlled Substances Act. This essentially means that instead of being classified with drugs like morphine, Marinol™ is now classified with more widely used drugs like codeine. According to the Associated Press of July 3, 1999, Barry McCaffrey, director of the White House Office of National Drug Control Policy, said the capsule form of Marinol™ is the "safe and proper way" to make components of marijuana available to the public. "This action will make Marinol™, which is scientifically proven to be safe and effective for medical use, more widely available," he said. Geoff Sugerman, a medical marijuana advocate in Oregon, said "Here is more proof that the properties in marijuana really do work as medicine." Oregon along with other states approved the use of marijuana with a doctor's consent, an action McCaffrey has opposed.

There are not many direct comparisons of the subjective and medicinal effects of cannabis and dronabinol (THC, Marinol™). Recent experimental research has shown that the subjective effects of cannabis and THC are very similar (Wachtel et al. 2002). Authors write:

> "There has been controversy about whether the subjective, behavioral or therapeutic effects of whole plant marijuana differ from the effects of its primary active ingredient, Delta(9)-tetrahydrocannabinol (THC). However, few studies have directly compared the effects of marijuana and THC using matched doses administered either by the smoked or the oral form. (...)
>
> Two studies were conducted to compare the subjective effects of pure THC to whole-plant marijuana containing an equivalent amount of THC in normal healthy volunteers. In one study the drugs were administered orally and in the other they were administered by smoking. (...)
>
> In each study, marijuana users (oral study: n=12, smoking study: n=13) participated in a double-blind, crossover design with five experimental conditions: a low and a high dose of THC-only, a low and a high dose of whole-plant marijuana, and placebo. In the oral study, the drugs were administered in brownies, in the smoking study the drugs were smoked. Dependent measures included the Addiction Research Center Inventory, the Profile of Mood States, visual analog items, vital signs, and plasma levels of THC and 11-nor-9-carboxy-THC. (...)

> In both the oral study and the smoking study, THC-only and whole plant marijuana produced similar subjective effects, with only minor differences.
>
> CONCLUSION: These results support the idea that the psychoactive effects of marijuana in healthy volunteers are due primarily to THC" (Wachtel et al. 2002).

Since the abuse potential of a drug is mainly attributed to its subjective effects it can be assumed that the the abuse potential of THC and cannabis are quite similar.

Clinical research has also demonstrated similar properties of THC and cannabis with regard to therapeutic effects. This is shown in the data from marijuana research programs on the anti-emetic effects of marijuana in 6 states (Musty & Rossi 2001, see above), where patients who smoked marijuana experienced 70-100% relief from nausea and vomiting, and those who used the THC capsule experienced 76-88% relief. In the study by Abrams et al. (2002) that investigated the interaction of smoked cannabis and Marinol™ (THC) with HIV medication, very similar effects were observed with regard to weight gain. The participants had been divided into three groups, with one set smoking marijuana (3.95% THC), another taking oral dronabinol capsules (3x2.5 mg daily), and a third taking oral placebo capsules. Researchers found that those using dronabinol (THC) or marijuana experienced significant increases in caloric intake and gained an average of 3.5 kg (marijuana group) and 3.2 kg. (THC group) compared to 1.3 kg in the placebo group. There was no significant difference between marijuana and THC with regard to side effects and benefits.

Leo Hollister stated in a recent review on the medical use of marijuana:

> "Marinol™ or dronabinol, is available for treating nausea and vomiting associated with cancer chemotherapy and as an adjunct to weight loss in patients with wasting syndrome associated with AIDS. Although such approval currently applies only to orally administered THC, for practical purposes smoked marijuana should also be expected to be equally effective. Promising leads, also often fragile, suggest possible uses for treating chronic pain syndromes, neurological disease with spasticity and other causes of weight loss. These indications require more study."

The American public notes that the difference between cannabis and dronabinol with regard to classification is hypocritical and polotical. Journalist Cynthia Cotts commented the reclassification of Marinol™ from Schedule II to Schedule III in the Nation on September 20, 1999:

> "For more than half a century, the U.S. government has maintained a hard line on marijuana, denying that the plant has any medical value at all. But in the period since 1996, during which voters in several states have approved the medical use of marijuana and the Institute of Medicine has hailed the

therapeutic effects of THC (one of the cannabinoids found in the natural plant), the Feds have scrambled to revise their position. Now, the drug warriors' line goes something like this: Who needs pot, an illegal substance that burns up your lungs, when you can take Marinol™, a little white pill that contains synthetic THC?

The government threw its weight behind Marinol™ this past July, when the Drug Enforcement Administration moved the drug into Schedule III, lifting its dangerous stigma and making it easier for doctors to prescribe. While drug czar Barry McCaffrey insisted the move was based on "pure science," a review of the players involved suggests that the rise of Marinol™ is more the result of politics and profiteering" (Cotts 1999).

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