To: All members of Congress  
From: Americans for Safe Access  
Date: February 22, 2016  
Re: The Dangers and Consequences of Misinformation on Marijuana (cannabis)

Forty-four states now allow patients under their physician’s care to use medical cannabis (marijuana) in some form, and most of the rest of the states are discussing medical cannabis in their current legislative sessions. In addition, three cannabis related budget amendments and four bills have been introduced so far in the 115th Congress.

We know that you rely on the Drug Enforcement Administration (DEA) to provide current and accurate information when you are making decisions about cannabis policy. Americans for Safe Access (ASA) has prepared this memo to inform you about four important changes in the DEA’s positions on medical cannabis that could have an impact on your policy making decisions this session.

In August 2016, the DEA issued the “Denial of Petition to Initiate Proceedings to Reschedule Marijuana,” (see enclosure A) in response to Washington and Rhode Island’s attempts to reschedule cannabis. While the DEA did not move forward with rescheduling cannabis, the report did clarify four important misconception about medical cannabis: that cannabis was a “gateway drug”, and that it caused cognitive decline, psychosis and lung cancer based on new research (see enclosures F i-viii). This new report contradicted two previous reports from the DEA, “The Dangers and Consequences of Marijuana Abuse” and “Drugs of Abuse” that are often cited by policy makers.

In response to the DEA’s new report, Americans for Safe Access (ASA) released “The DEA’s Denial of Existing Medical Cannabis Research” (see enclosure B) which called upon the Department of Justice (DOJ) and the DEA to update contradicting information in the DEA publications. On December 5th, 2016, utilizing rights granted to our members and patients under the Information Quality Act (IQA), ASA filed a petition with the DOJ (see enclosure C) requesting the DEA to remove or update several items from their website which contained this misinformation.

ASA’s “IQA Request for Correction of Information Disseminated by DEA Regarding Marijuana (Cannabis)” identified 25 violations of the IQA on the DEA’s website and publications and included suggested changes based on the DEA’s finding from their August report. Despite the DOJ Information Quality Guidelines requirements for a 60-calendar day response, neither the DEA nor the DOJ has responded directly to ASA’s request (see enclosure D).

The DEA has removed the document, “The Dangers and Consequences of Marijuana Abuse,” which contained the majority of the inaccurate statements outlined in ASA’s Request, but there is still more that needs to be corrected, and ASA is working to make sure it is.
While we are waiting for the final response from DEA on their plans to update their information on their website, we know that policy makers are being asked to make decisions on cannabis policy now. It is our hope that the enclosed documents will provide a better understanding of the status of science on these important matters.

Enclosures:

B. ASA Report: “The DEA’s Denial of Existing Medical Cannabis Research” (August 2016)
C. ASA’s “IQA Request for Correction of Information Disseminated by DEA Regarding Marijuana (Cannabis)”
D. ASA’s IQA Deadline Letter to DEA
E. Relevant research studies from “Denial of Petition to Initiate Proceedings to Reschedule Marijuana”
Enclosure A: “Denial of Petition to Initiate Proceedings to Reschedule Marijuana” (August 2016)
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Part IV

Department of Justice

Drug Enforcement Administration
21 CFR Chapter II and Part 1301
Denial of Petition To Initiate Proceedings To Reschedule Marijuana; Proposed Rules and Applications To Become Registered Under the Controlled Substances Act To Manufacture Marijuana To Supply Researchers in the United States; Policy Statement
DEPARTMENT OF JUSTICE
Drug Enforcement Administration

21 CFR Chapter II
[Docket No. DEA–426]

Denial of Petition To Initiate Proceedings To Reschedule Marijuana

AGENCY: Drug Enforcement Administration, Department of Justice.

ACTION: Denial of petition to initiate proceedings to reschedule marijuana.

SUMMARY: By letter dated July 19, 2016 the Drug Enforcement Administration (DEA) denied a petition to initiate rulemaking proceedings to reschedule marijuana. Because the DEA believes that this matter is of particular interest to members of the public, the agency is publishing below the letter sent to the petitioner which denied the petition, along with the supporting documentation that was attached to the letter.

DATES: August 12, 2016.

FOR FURTHER INFORMATION CONTACT: Michael J. Lewis, Office of Diversion Control, Drug Enforcement Administration; Mailing Address: 8701 Morrissette Drive, Springfield, Virginia 22152; Telephone: (202) 598–6812.

SUPPLEMENTARY INFORMATION:
July 19, 2016

Dear Ms. Raimondo and Mr. Inslee:

On November 30, 2011, your predecessors, The Honorable Lincoln D. Chafee and The Honorable Christine O. Gregoire, petitioned the Drug Enforcement Administration (DEA) to initiate rulemaking proceedings under the rescheduling provisions of the Controlled Substances Act (CSA). Specifically, your predecessors petitioned the DEA to have marijuana and “related items” removed from Schedule I of the CSA and rescheduled as medical cannabis in Schedule II.

Your predecessors requested that the DEA remove marijuana and related items from Schedule I based on their assertion that:

1. Cannabis has accepted medical use in the United States;
2. Cannabis is safe for use under medical supervision;
3. Cannabis for medical purposes has a relatively low potential for abuse, especially in comparison with other Schedule II drugs.

In accordance with the CSA rescheduling provisions, after gathering the necessary data, the DEA requested a scientific and medical evaluation and scheduling recommendation from the Department of Health and Human Services (HHS). The HHS concluded that marijuana has a high potential for abuse, has no accepted medical use in the United States, and lacks an acceptable level of safety for use even under medical supervision. Therefore, the HHS recommended that marijuana remain in Schedule I.

The scientific and medical evaluation and scheduling recommendation that the HHS submitted to the DEA is enclosed with this letter. Based on the HHS evaluation and all other relevant data, the DEA has concluded that there is no substantial evidence that marijuana should be removed from Schedule I.

A document prepared by the DEA addressing these materials in detail also is enclosed. In short, marijuana continues to meet the criteria for Schedule I control under the CSA because:

1. Marijuana has a high potential for abuse. The HHS evaluation and the additional data gathered by the DEA show that marijuana has a high potential for abuse.

2. Marijuana has no currently accepted medical use in treatment in the United States. Based on the established five-part test for making such determination, marijuana has no “currently accepted medical use” because: As detailed in the HHS evaluation, the drug’s chemistry is not known and reproducible; there are no adequate safety studies; there are no adequate and well-controlled studies proving efficacy; the drug is not accepted by qualified experts; and the scientific evidence is not widely available.

3. Marijuana lacks accepted safety for use under medical supervision. At present, there are no marijuana products approved by the U.S. Food and Drug Administration (FDA), nor is marijuana under a New Drug Application (NDA) evaluation at the FDA for any indication. The HHS evaluation states that marijuana does not have a currently accepted medical use in treatment in the United States or a currently accepted medical use with severe restrictions. At this time, the known risks of marijuana use have not been shown to be outweighed by specific benefits in well-controlled clinical trials that scientifically evaluate safety and efficacy.

The statutory mandate of Title 21 United States Code, Section 812(b) (21 U.S.C. 812(b)) is dispositive. Congress established only one schedule, Schedule I, for drugs of abuse with “no currently accepted medical use in treatment in the United States” and “lack of accepted safety for use . . . under medical supervision.” 21 U.S.C. 812(b).

Although the HHS evaluation and all other relevant data lead to the conclusion that marijuana must remain in schedule I, it should also be noted that, in view of United States obligations under international drug control treaties, marijuana cannot be placed in a schedule less restrictive than schedule II. This is explained in detail in accompanying documents titled “Preliminary Note Regarding Treaty Considerations.”

Accordingly, and as set forth in detail in the accompanying HHS and DEA documents, there is no statutory basis under the CSA for the DEA to grant your predecessors’ petition to initiate rulemaking proceedings to reschedule marijuana. The petition is, therefore, hereby denied.

Sincerely,
Chuck Rosenberg,
Acting Administrator.

Preliminary Note Regarding Treaty Considerations

Cover Letter from HHS to DEA
Summarizing the Scientific and Medical Evaluation and Scheduling Recommendation for Marijuana.

U.S. Department of Health and Human Services (HHS)— Basis for the Recommendation for Maintaining Marijuana in Schedule I of the Controlled Substances Act

U.S. Department of Justice—Drug Enforcement Administration (DEA), Schedule of Controlled Substances—Maintaining Marijuana in Schedule I of the Controlled Substances Act, Background, Data, and Analysis: Eight Factors Determinative of Control and Findings Pursuant to 21 U.S.C. 812(b)

Dated: July 19, 2016.

Chuck Rosenberg,
Acting Administrator, Preliminary Note Regarding Treaty Considerations.

As the Controlled Substances Act (CSA) recognizes, the United States is a party to the Single Convention on Narcotic Drugs, 1961 (referred to here as the Single Convention or the treaty). 21 U.S.C. 801(7). Parties to the Single Convention are obligated to maintain various control provisions related to the drugs that are covered by the treaty. Many of the provisions of the CSA were enacted by Congress for the specific purpose of ensuring U.S. compliance with the treaty. Among these is a scheduling provision, 21 U.S.C. 811(d)(1). Section 811(d)(1) provides that, where a drug is subject to control under the Single Convention, the DEA Administrator (by delegation from the Attorney General) must “issue an order controlling such drug under the schedule he deems most appropriate to carry out such [treaty] obligations, without regard to the findings required by [21 U.S.C. 811(a) or 812(b)] and without regard to the procedures prescribed by [21 U.S.C. 811(a) and (b)].”

Marijuana is a drug listed in the Single Convention. The Single Convention uses the term “cannabis” to refer to marijuana. Thus, the DEA

1 Under the Single Convention, “cannabis plant” means any plant of the genus Cannabis.” Article 1(c). The Single Convention defines “cannabis” to include “the flowering or fruiting tops of the cannabis plant (excluding the seeds and leaves when not accompanied by the tops) from which the resin has not been extracted, by whatever name they may be designated.” Article 1(b). This definition of “cannabis” under the Single Convention is slightly less inclusive than the CSA definition of “marijuana,” which includes all parts of the cannabis plant except for the mature stalks, sterilized seeds, oil from the seeds, and certain derivatives thereof. See 21 U.S.C. 802(16). Cannabis and cannabis resin are included in the list of drugs in Schedule I and Schedule IV of the Single Convention. In contrast to the CSA, the drugs listed in Schedule IV of the Single Convention are also
Administrator is obligated under section 811(d) to control marijuana in the schedule that he deems most appropriate to carry out the U.S. obligations under the Single Convention. It has been established in prior marijuana rescheduling proceedings that placement of marijuana in either schedule I or schedule II of the CSA is “necessary as well as sufficient to satisfy our international obligations” under the Single Convention. NORMAL v. DEA, 559 F.2d 735, 751 (D.C. Cir. 1977). As the United States Court of Appeals for the DC Circuit has stated, “several requirements imposed by the Single Convention would not be met if cannabis and cannabis resin were placed in CSA schedule III, IV, or V.” 2 Id. Therefore, in accordance with section 811(d)(1), DEA must place marijuana in either schedule I or schedule II.

Because schedules I and II are the only possible schedules in which marijuana may be placed, for purposes of evaluating this scheduling petition, it is essential to understand the differences between the criteria for placement of a substance in schedule I and those for placement in schedule II. These criteria are set forth in 21 U.S.C. 812(b)(1) and (b)(2), respectively. As indicated therein, substances in both schedule I and schedule II share the characteristic of “a high potential for abuse.” Where the distinction lies is that schedule I drugs have “no currently accepted medical use in treatment in the United States” and “a lack of accepted safety for use of the drug . . . under medical supervision,” while schedule II drugs have “a currently accepted medical use in treatment in the United States.” 3 Accordingly, in view of section 811(d)(1), this scheduling petition turns on whether marijuana has a currently accepted medical use in treatment in the United States. If it does not, DEA must, pursuant to section 811(d), deny the petition and keep marijuana in schedule I.

As indicated, where section 811(d)(1) applies to a drug that is the subject of a rescheduling petition, the DEA Administrator must issue an order controlling the drug under the schedule he deems most appropriate to carry out United States obligations under the Single Convention, without regard to the findings required by sections 811(a) or 812(b) and without regard to the procedures prescribed by sections 811(a) and (b). Thus, since the only determinative issue in evaluating the present scheduling petition is whether marijuana has a currently accepted medical use in treatment in the United States, DEA need not consider the findings of sections 811(a) or 812(b) that have no bearing on that determination, and DEA likewise need not follow the procedures prescribed by sections 811(a) and (b) with respect to such irrelevant findings. Specifically, DEA need not evaluate the relative abuse potential of marijuana or the relative extent to which abuse of marijuana may lead to physical or psychological dependence.

As explained below, the medical and scientific evaluation and scheduling recommendation issued by the Secretary of Health and Human Services concludes that marijuana has no currently accepted medical use in treatment in the United States, and the DEA Administrator likewise so concludes. For the reasons just indicated, no further analysis beyond this consideration is required. Nonetheless, because of the widespread public interest in understanding all the facts relating to the harms associated with marijuana, DEA is publishing here the entire medical and scientific analysis and scheduling evaluation issued by the Secretary, as well as DEA's additional analysis.

Department of Health and Human Services, Office of the Secretary Assistant Secretary for Health, Office of Public Health and Science, Washington, DC 20201.

June 25, 2015.

The Honorable Chuck Rosenberg
Acting Administrator, Drug Enforcement Administration, U.S. Department of Justice, 8701 Morrissette Drive, Springfield, VA 22152.

Dear Mr. Rosenberg:

Pursuant to the Controlled Substances Act (CSA, 21 U.S.C. § 811(b), (c), and (f)), the Department of Health and Human Services (HHS) is recommending that marijuana continue to be maintained in Schedule I of the CSA.

The Food and Drug Administration (FDA) has considered the abuse potential and dependence-producing characteristics of marijuana.

Marijuana meets the three criteria for placing a substance in Schedule I of the CSA under 21 U.S.C. 812(b)(1). As discussed in the enclosed analyses, marijuana has a high potential for abuse, no currently accepted medical use in treatment in the United States, and a lack of acceptability for use under medical supervision. Accordingly, HHS recommends that marijuana be maintained in Schedule I of the CSA.

Enclosed are two documents prepared by FDA’s Controlled Substance Staff in response to petitions filed on February 2009 by Mr. Bryan Krumm and in 2011 by Governors Lincoln D. Chafee and Christine O. Gregoire that form the basis for the recommendation. Pursuant to the requests in the petitions, FDA broadly evaluated marijuana, and did not focus its evaluation on particular strains of marijuana or components or derivatives of marijuana.

FDAs Center for Drug Evaluation and Research’s current review of the available evidence and the published clinical studies on marijuana demonstrated that since our 2006 scientific and medical evaluation and scheduling recommendation responding to a previous DEA petition, research with marijuana has progressed. However, the available evidence is not sufficient to determine that marijuana has an accepted medical use. Therefore, more research is needed into marijuana’s effects, including potential medical uses for marijuana and its derivatives. Based on the current review, we identified several methodological challenges in the marijuana studies published in the literature. We recommend they be addressed in future clinical studies with marijuana to ensure that valid scientific data are generated in studies evaluating marijuana’s safety and efficacy for therapeutic use. For example, we recommend that studies need to focus on consistent administration and reproducible dosing of marijuana, potentially through the use of administration methods other than smoking. A summary of our review of the published literature on the clinical uses of marijuana, including recommendations for future studies, is attached to this document.

FDA and the National Institutes of Health’s National Institute on Drug Abuse (NIDA) also believe that work continues to be needed to ensure support by the federal government for the efficient conduct of clinical research using marijuana. Concerns have been raised about whether the existing federal regulatory system is flexible enough to respond to increased interest in research into the potential therapeutic uses of marijuana and marijuana-derived drugs. HHS welcomes an opportunity to continue to explore these concerns with DEA.

Should you have any questions regarding these recommendations, please contact Corinne P. Moody, Science Policy Analyst, Controlled Substances Staff, Center for Drug Evaluation and Research, FDA, at (301) 796–3152.

Sincerely yours,

Karen B. DeSalvo, MD, MPH, MSc
Acting Assistant Secretary for Health
Enclosure: Basis for the Recommendation for Maintaining Marijuana in Schedule I of the Controlled Substances Act
Basis for the Recommendation for Maintaining Marijuana in Schedule I of the Controlled Substances Act

On November 30, 2011, Governors Lincoln D. Chafee of Rhode Island and Christine O. Gregoire of Washington submitted a petition to the Drug Enforcement Administration (DEA) requesting that proceeding be initiated to repeal the rules and regulations that place marijuana in Schedule I of the Controlled Substances Act (CSA). The petition contends that cannabis has an accepted medical use in the United States, is safe for use under medical supervision, and has a relatively low abuse potential compared to other Schedule II drugs. The petition requests that marijuana and “related items” be rescheduled in Schedule II of the CSA.

In June 2013, the DEA Administrator requested that the U.S. Department of Health and Human Services (HHS) provide a scientific and medical evaluation of the available information and a scheduling recommendation for marijuana, in accordance with the provisions of 21 U.S.C. 811(b).

In accordance with 21 U.S.C. 811(b), DEA has gathered information related to the control of marijuana (Cannabis sativa) under the CSA. Pursuant to 21 U.S.C. 811(b), the Secretary of HHS is required to consider in a scientific and medical evaluation eight factors determinative of control under the CSA. Following consideration of the eight factors, if it is appropriate, the Secretary must make three findings to recommend scheduling a substance in the CSA. The findings relate to a substance’s abuse potential, legitimate medical use, and safety or dependence liability.

Administrative responsibilities for evaluating a substance for control under the CSA are performed by the Food and Drug Administration (FDA), with the concurrence of the National Institute on Drug Abuse (NIDA), as described in the Memorandum of Understanding (MOU) of March 8, 1985 (50 FR 9518–20).

In this document, FDA recommends the continued control of marijuana in Schedule I of the CSA. Pursuant to 21 U.S.C. 811(c), the eight factors pertaining to the scheduling of marijuana are considered below.

1. Its Actual or Relative Potential for Abuse

Under the first factor the Secretary must consider marijuana’s actual or relative potential for abuse. The CSA does not define the term “abuse.” However, the CSA’s legislative history suggests the following in determining whether a particular drug or substance has a potential for abuse:

a. There is evidence that individuals are taking the drug or drugs containing such a substance in amounts sufficient to create a hazard to their health or to the safety of other individuals or to the community.

b. There is a significant diversion of the drug or drugs containing such a substance from legitimate drug channels.

c. Individuals are taking the drug or drugs containing such a substance on their own initiative rather than on the basis of medical advice from a practitioner licensed by law to administer such drugs in the course of his professional practice.

d. The drugs or substances containing such a substance are new drugs so related in their action to a drug or drugs already listed as having a potential for abuse to make it likely that the drug will have the same potentiality for abuse as such drugs, thus making it reasonable to assume that there may be significant diversions from legitimate channels, significant use contrary to or without medical advice, or that it has a substantial capability of creating hazards to the health of the user or to the safety of the community.

In the development of this scientific and medical evaluation for the purpose of scheduling, the Secretary analyzed considerable data related to the substance’s abuse potential. The data include a discussion of the prevalence and frequency of use, the amount of the substance available for illicit use, the ease of obtaining or manufacturing the substance, the reputation or status of the substance “on the street,” and evidence relevant to at-risk populations.

Importantly, the petitioners define marijuana as including all Cannabis cultivated strains. Different marijuana samples derived from various cultivated strains may have very different chemical constituents, thus the analysis is based on what is known about the range of these constituents across all cultivated strains.

Determining the abuse potential of a substance is complex with many dimensions, and no single test or assessment provides a complete characterization. Thus, no single measure of abuse potential is ideal. Scientifically, a comprehensive evaluation of the relative abuse potential of a substance can include consideration of the following elements: Receptor binding affinity, preclinical pharmacology, reinforcing effects, discriminative stimulus effects, dependence producing potential, pharmacokinetics, route of administration, toxicity, data on actual abuse, clinical abuse potential studies, and public health risks. Importantly, abuse can exist independently from tolerance or physical dependence because individuals may abuse drugs in doses or patterns that do not induce these phenomena. Additionally, evidence of clandestine population and illicit trafficking of a drug can shed light on both the demand for a substance as well as the ease of obtaining a substance. Animal and human laboratory data and epidemiological data are all used in determining a substance’s abuse potential. Moreover, epidemiological data can indicate actual abuse.

The petitioners compare the effects of marijuana to currently controlled Schedule II substances and make repeated claims about their comparative effects. Comparisons between marijuana and the diverse array of Schedule II substances is difficult, because of the pharmacologically dissimilar actions of substances of Schedule II of the CSA. For example, Schedule II substances include stimulant-like drugs (e.g., cocaine, methylphenidate, and amphetamine), opioids (e.g., oxycodone, fentanyl), sedatives (e.g., pentobarbital, amobarbital), dissociative anesthetics (e.g., PCP), and naturally occurring plant components (e.g., coca leaves and poppy straw). The mechanism(s) of action of the above Schedule II substances are wholly different from one another, and they are different from tetrahydrocannabinol (THC) and marijuana as well. For example, Schedule II stimulants typically function by increasing monoaminergic tone via an increase in dopamine and norepinephrine (Schmitt et al., 2013). In contrast, opioid analgesics function via mu-opioid receptor agonist effects. These differing mechanism(s) of action result in vastly different behavioral and adverse effect profiles, making comparisons across the range of

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4 Note that “marijuana” is the spelling originally used in the Controlled Substances Act (CSA). This document uses the spelling that is more common in current usage, “marijuana.”

5 The CSA defines marijuana as the following: All parts of the plant Cannabis Sativa L., whether growing or not; the seeds thereof; the resin extracted from any part of such plant; and every compound, manufacture, salt, derivative, mixture, or preparation of such plant, its seeds or resin. Such term does not include the mature stalks of such plant, fiber produced from such stalks, oil or cake made from the seeds of such plant, any other compound, manufacture, salt, derivative, mixture, or preparation of such mature stalks (except the resin extracted therefrom), fiber, oil, or cake, or the sterilized seed of such plant which is incapable of germination (21 U.S.C. 802(16)).
pharmacologically diverse C-II substances inappropriate. In addition, many substances scheduled under the CSA are reviewed and evaluated within the context of commercial drug development, using data submitted in the form of a new drug application (NDA). A new analgesic drug might be compared to a currently scheduled analgesic drug as part of the assessment of its relative abuse potential. However, because the petitioners have not identified a specific indication for the use of marijuana, identifying an appropriate comparator based on indication cannot be done.

a. There is evidence that individuals are taking the substance in amounts sufficient to create a hazard to their health or to the safety of other individuals or to the community. Evidence shows that some individuals are taking marijuana in amounts sufficient to create a hazard to their health and to the safety of other individuals in the community. A large number of individuals use marijuana.

HHS provides data on the extent of marijuana abuse through NIDA and the Substance Abuse and Mental Health Services Administration (SAMHSA). According to the most recent data from SAMHSA’s 2012 National Survey on Drug Use and Health (NSDUH), which estimates the number of individuals who have used a substance within a month prior to the study (described as “current use”), marijuana is the most commonly used illicit drug among Americans aged 12 years and older, with an estimated 18.9 million Americans having used marijuana within the month prior to the 2012 NSDUH. Compared to 2004, when an estimated 14.6 million individuals reported using marijuana within the month prior to the study, the estimated rates in 2012 show an increase of approximately 4.3 million individuals. The 2013 Monitoring the Future (MTF) survey of 8th, 10th, and 12th grade students also indicates that marijuana is the most widely used illicit substance in this age group. Specifically, current month use was at 7.0 percent of 8th graders, 18.0 percent of 10th graders and 22.7 percent of 12th graders. Additionally, the 2011 Treatment Episode Data Set (TEDS) reported that primary marijuana abuse accounted for 18.1 percent of non-private substance abuse treatment facility admissions, with 24.3 percent of those admitted reporting daily use. However, of these admissions for primary marijuana abuse, the criminal justice system referred 91.7 percent to treatment. SAMHSA’s Drug Abuse Warning Network (DAWN) was a national probability survey of U.S. hospitals with emergency departments (EDs) and was designed to obtain information on ED visits in which marijuana was mentioned, accounting for 36.4 percent of illicit drug related ED visits. There are some limitations related to DAWN data on ED visits, which are discussed in detail in Factor 4, “Its History and Current Pattern of Abuse;” Factor 5, “The Scope, Duration, and Significance of Abuse;” and Factor 6, “What, if any, Risk There is to the Public Health.” These factors contain detailed discussions of these data.

A number of risks can occur with both acute and chronic use of marijuana. Detailed discussions of the risks are addressed in Factor 2, “Scientific Evidence of its Pharmacological Effect, if Known,” and Factor 6, “What, if any, Risk There is to the Public Health.” There is significant diversion of the substance from legitimate drug channels. There is a lack of evidence of significant diversion of marijuana from legitimate drug channels, but this is likely due to the fact that marijuana is more widely available from illicit sources rather than through legitimate channels. Marijuana is not an FDA-approved drug product, as an NDA or biologics license application (BLA) has not been approved for marketing in the United States. Numerous states and the District of Columbia have state-level medical marijuana laws that allow for marijuana use within that state. These state-level drug channels do not have sufficient collection of data related to medical treatment, including efficacy and safety.

Marijuana is used by researchers for nonclinical research as well as clinical research under investigational new drug (IND) applications; this represents the only legitimate drug channel in the United States. However, marijuana used for research represents a very small contribution of the total amount of marijuana available in the United States, and thus provides limited information about diversion. In addition, the lack of significant diversion of investigation supplies is likely because of the widespread availability of illicit marijuana of equal or greater amounts of delta-9-THC. The data originating from the DEA on seizure statistics demonstrate the magnitude of the availability for illicit marijuana. DEA’s System to Retrieve Information From Drug Evidence (STRIDE) provides information on total domestic drug seizures. STRIDE reports a total domestic distribution of marijuana in 2011, the most recent year with complete data that is currently publically available (DEA Domestic Drug Seizures, n.d.).

c. Individuals are taking the substance on their own initiative rather than on the basis of medical advice from a practitioner licensed by law to administer such substances.

Because the FDA has not approved an NDA or BLA for a marijuana drug product for any therapeutic indication, the only way an individual can take marijuana on the basis of medical advice through legitimate channels at the federal level is by participating in research under an IND application. That said, numerous states and the District of Columbia have passed state-level medical marijuana laws allowing for individuals to use marijuana under certain circumstances. However, data are not yet available to determine the number of individuals using marijuana under these state-level medical marijuana laws. Regardless, according to the 2012 NSDUH data, 18.9 million Americans used marijuana (SAMHSA, 2013). Based on the large number of individuals reporting current use of marijuana and the lack of an FDA-approved drug product in the United States, one can assume that it is likely that the majority of individuals using marijuana do so on their own initiative rather than on the basis of medical advice from a licensed practitioner.

d. The substance is so related in its action to a substance already listed as having a potential for abuse to make it likely that it will have the same potential for abuse as such substance, thus making it reasonable to assume that there may be significant diversions from legitimate channels, significant use contrary to or without medical advice, or that it has a substantial capability of creating hazards to the health of the user or to the safety of the community. FDA has approved two drug products containing cannabinoid compounds that are structurally related to the active components in marijuana. These two marketed products are controlled under the CSA. Once a specific drug product containing cannabinoids becomes approved, that specific drug product may be moved from Schedule I to a different Schedule (II-V) under the CSA. Firstly, Marinol—generically known as dronabinol—is a Schedule III drug product containing synthetic delta-9-THC. Marinol, which is formulated in sesame oil in soft gelatin capsules, was first placed in Schedule II under the CSA following its approval by the FDA. Marinol was later rescheduled to Schedule III under the CSA because of low numbers of reports of abuse relative to marijuana. Dronabinol is
listed in Schedule I under the CSA. FDA approved Marinol in 1985 for the
treatment of nausea and vomiting associated with cancer chemotherapy in
patients who failed to respond
adequately to conventional anti-emetic
treatments. In 1992, FDA approved
Marinal for anorexia associated with
weight loss in patients with acquired
immunodeficiency syndrome (AIDS).
Secondly, in 1985, FDA approved
Cesamet, a drug product containing the
Schedule II substance nabilone, for the
treatment of nausea and vomiting
associated with cancer chemotherapy.
Besides the two cannabinoid-containing
drug products FDA approved for
marketing, other naturally occurring
cannabinoids and their derivatives
(from Cannabis) and their synthetic
equivalents with similar chemical
structure and pharmacological activity
are included in the CSA as Schedule I
substances.

2. Scientific Evidence of Its
Pharmacological Effects, if Known

Under the second factor, the Secretary
must consider the scientific evidence of
marijuana’s pharmacological effects.
Abundant scientific data are available
on the neurochemistry, toxicology, and
pharmacology of marijuana. This
section includes a scientific evaluation
of marijuana’s neurochemistry;
pharmacology; and human and animal
behavioral, central nervous system,
cognitive, cardiovascular, autonomic,
endocrinological, and immunological
system effects. The overview presented
below relies upon the most current
research literature on cannabinoids.

Neurochemistry and Pharmacology of
Marijuana

Marijuana is a plant that contains
numerous natural constituents, such as
cannabinoids, that have a variety of
pharmacological actions. The petition
defines marijuana as including all
Cannabis cultivated strains. Different
marijuana samples derived from various
cultivated strains may have very
different chemical constituents
including delta^8^-THC and other
cannabinoids (Appendino et al., 2011).
As a consequence, marijuana products
from different strains will have different
biological and pharmacological profiles.
According to ElSohly and Slade
(2005) and Appendino et al. (2011),
marijuana contains approximately 525
identified natural constituents,
including approximately 100
compounds classified as cannabinoids.
Cannabinoids primarily exist in
Cannabis and published data suggests
that most major cannabinoid
compounds occurring naturally have
been identified chemically. New and
minor cannabinoids and other new
compounds are continuously being
characterized (Pollastro et al., 2011).
So far, only two cannabinoids
(cannabinergic and its corresponding
acid) have been obtained from a non-
Cannabis source. A South African
Helichrysum (H. umbracluligerum)
accumulates these compounds
(Appendino et al., 2011). The chemistry
of marijuana is described in more detail
in Factor 3, “The State of Current
Scientific Knowledge Regarding the
Drug or Other Substance.”
The site of cannabinoid action is at
the cannabinoid receptors. Cloning of
cannabinoid receptors, first from rat
brain tissue (Matsuda et al., 1990) and
then from human brain tissue (Gerard et
al., 1991), has verified the site of action.
Two cannabinoid receptors, CB1 and
CB2, were characterized (Battista et
al., 2012; Piomelli, 2005). Evidence of
a third cannabinoid receptor exists, but it
has not been identified (Battista et
al., 2012).
The cannabinoid receptors, CB1 and
CB2, belong to the family of G-protein-
coupled receptors, and present a typical
seven transmembrane-spanning domain
structure. Cannabinoid receptors link to
an inhibitory G-protein (Gi), such that
adenylate cyclase activity is inhibited
when a ligand binds to the receptor.
This, in turn, prevents the conversion of
ATP to the second messenger, cyclic
AMP (cAMP). Examples of inhibitory
coupled receptors include opioid,
muscarinic cholinergic, alpha2
adrenoreceptors, dopamine (D2), and
serotonin (5-HT).

Cannabinoid receptor activation
inhibits N- and P/Q-type calcium
channels and activates inwardly
rectifying potassium channels (Mackie
et al., 1995; Twitchell et al., 1997).
N-type calcium channel inhibition
decreases neurotransmitter release from
several tissues. Thus, calcium channel
inhibition may be the mechanism by
which cannabinoids inhibit
acetylcholine, norepinephrine, and
glutamate release from specific areas of
the brain. These effects may represent a
potential cellular mechanism
underlying cannabinoids’
antinociceptive and psychoactive
effects (Ameri, 1999).

CB1 receptors are found primarily
in the central nervous system, but are also
present in peripheral tissues. CB1
receptors are located mainly in the basal
ganglia, hippocampus, and cerebellum of
the brain (Howlett et al., 2004). The
localization of these receptors may
explain cannabinoid interference with
movement coordination and effects on
memory and cognition. Additionally,
CB2 receptors are found in the immune
system and numerous other peripheral
tissues (Petrocellis and Di Marzo, 2009).
However, the concentration of CB1
receptors is considerably lower in
peripheral tissues than in the central
nervous system (Herkenham et al., 1990

CB2 receptors are found primarily
in the immune system, but are also present
in the central nervous system and other
peripheral tissues. In the immune
system, CB2 receptors are found
predominantly in B lymphocytes and
natural killer cells (Bouabala et al.,
1993). CB2 receptors may mediate
cannabinoids’ immunological effects
(Galiegue et al., 1995). Additionally, CB2
receptors have been localized in the
brain, primarily in the cerebellum and
hippocampus (Gong et al., 2006). The
distribution of CB2 receptors throughout
the body is less extensive than the
distribution of CB1 receptors (Petrocellis
and Di Marzo, 2009). However, both CB1
and CB2 receptors are present in
numerous tissues of the body.

Cannabinoid receptors have
endoogenous ligands. In 1992 and 1995,
two endogenous cannabinoid receptor
agonists, anandamide and arachidonyl
glycerol (2-AG), respectively, were
identified (Di Marzo, 2006).
Anandamide is a low efficacy agonist
(Breivogel and Childers, 2000) and 2-AG
is a high efficacy agonist (Goniserek
et al., 2000). Cannabinoid endogenous
ligands are present in central as well as
peripheral tissues. A combination of
uptake and hydrolysis terminate the
action of the endogenous ligands. The
endogenous cannabinoid system is a
locally active signaling system that, to
help restore homeostasis, is activated
“on demand” in response to changes to
the local homeostasis (Petrocellis and
Di Marzo, 2009). The endogenous
cannabinoid system, including the
endogenous cannabinoids and the
cannabinoid receptors, demonstrate
substantial plasticity in response to
several physiological and pathological
stimuli (Petrocellis and Di Marzo, 2009).
This plasticity is particularly evident in
the central nervous system.

Delta^8^-THC and cannabidiol (CBD) are
two abundant cannabinoids present in
marijuana. Marijuana’s major
psychoactive cannabinoid is delta^8^-THC
(Wachtel et al., 2002). In 1964, Gaoni
and Mechoularn first described delta^8-
THC’s structure and function. In 1963,
Mechoularn and Shvo first described
CBD’s structure. The pharmacological
actions of CBD have not been fully
studied in humans.
Delta^8^-THC and CBD have varying
affinity and effects at the cannabinoid
receptors. Delta^8^-THC displays similar
affinity for CB1 and CB2 receptors, but behaves as a weak agonist for CB2 receptors. The identification of synthetic cannabinoid ligands that selectively bind to CB2 receptors but do not have the typical delta*-THC-like psychoactive properties suggests that the activation of CB1-receptors mediates cannabinoids’ psychotropic effects (Hanus et al., 1999). CBD has low affinity for both CB1 and CB2 receptors (Mechoulam et al., 2007). According to Mechoulam et al. (2007), CBD has antagonistic effects at CB1 receptors and some inverse agonistic properties at CB2 receptors. When cannabinoids are given subacutely to rats, CB1 receptors down-regulate and the binding of the second messenger system coupled to CB1 receptors, GTPgammaS, decreases (Breivogel et al., 2001).

Animal Behavioral Effects
Self-Administration
Self-administration is a method that assesses the ability of a drug to produce rewarding effects. The presence of rewarding effects increases the likelihood of behavioral responses to obtain additional drug. Animal self-administration of a drug is often useful in predicting rewarding effects in humans, and is indicative of abuse liability. A good correlation is often observed between those drugs that rhesus monkeys self-administer and those drugs that humans abuse (Balster and Bigelow, 2003). Initially, researchers could not establish self-administration of cannabinoids, including delta*-THC, in animal models. However, self-administration of delta*-THC can now be established in a variety of animal models under specific training paradigms (Justinova et al., 2003, 2004, 2005).

Squirrel monkeys, with and without prior exposure to other drugs of abuse, self-administer delta*-THC under specific conditions. For instance, Tanda et al. (2000) observed that when squirrel monkeys are initially trained to self-administer intravenous cocaine, they will continue to bar-press delta*-THC at the same rate as they would with cocaine. The doses were notably comparable to those doses used by humans who smoke marijuana. SR141716, a CB1 cannabinoid receptor agonist-antagonist, can block this rewarding effect. Other studies show that naive squirrel monkeys can be successfully trained to self-administer delta*-THC intravenously (Justinova et al., 2003). The maximal responding rate is 4 µg/kg per injection, which is 2–3 times greater than observed in previous studies using cocaine-experienced monkeys. Naltrexone, a mu-opioid antagonist, partially antagonizes these rewarding effects of delta*-THC (Justinova et al., 2004).

Additionally, data demonstrate that under specific conditions, rodents self-administer cannabinoids. Rats will self-administer delta*-THC when applied intracerebroventricularly (i.e.,), but only at the lowest doses tested (0.01–0.02 µg/infusion) (Braida et al., 2004). SR141716 and the opioid antagonist naloxone can antagonize this effect. However, most studies involve rodents self-administering the synthetic cannabinoid WIN 55212, a CB1 receptor agonist with a non-cannabinoid structure (Deiana et al., 2007; Fattore et al., 2007; Martellotta et al., 1998; Mendizabal et al., 2006).

Aversive effects, rather than reinforcing effects, occur in rats that received high doses of WIN 55212 (Chaperon et al., 1998) or delta*-THC (Sanudo-Pena et al., 1997), indicating a possible critical dose-dependent effect. In both studies, SR141716 reversed these aversive effects.

Conditioned Place Preference
Conditioned place preference (CPP) is a less rigorous method than self-administration for determining whether or not a drug has rewarding properties. In this behavioral test, animals spend time in two distinct environments: one where they previously received a drug and one where they received a placebo. If the drug is reinforcing, animals will choose to spend more time in the environment paired with the drug, rather than with the placebo, when presented with both options simultaneously.

Animals show CPP to delta*-THC, but only at the lowest doses tested (0.075–1.0 mg/kg, intraperitoneal i.p.) (Braida et al., 2004). SR141716 and naloxone antagonize this effect (Braida et al., 2004). As a partial agonist, SR141716 can induce CPP at doses of 0.25, 0.5, 2 and 3 mg/kg (Cheer et al., 2000). In knockout mice, those without µ-opioid receptors do not develop CPP to delta*-THC (Ghozland et al., 2002).

Drug Discrimination Studies
Drug discrimination is a method where animals indicate whether a test drug produces physical or psychic perceptions similar to those produced by a known drug of abuse. In this test, an animal learns to press one bar when it receives the known drug of abuse and another bar when it receives placebo. To determine whether the test drug is like the known drug of abuse, a challenge session with the test drug demonstrates which of the two bars the animal presses more often.

In addition to humans (Lile et al., 2009; Lile et al., 2011), it has been noted that animals, including monkeys (McMahon et al., 2009), mice (McMahon et al., 2008), and rats (Gold et al., 1992), are able to discriminate cannabinoids from other drugs or placebo. Moreover, the major active metabolite of delta*-THC, 11-hydroxy-delta*-THC, also generalizes (following oral administration) to the stimulus cues elicited by delta*-THC (Browne and Weissman, 1981). Twenty-two other cannabinoids found in marijuana also fully substitute for delta*-THC. However, CBD does not substitute for delta*-THC in rats (Vann et al., 2008).

Discriminative stimulus effects of delta*-THC are pharmacologically specific for marijuana containing cannabinoids (Balster and Prescott, 1992; Browne and Weissman, 1981; Wiley et al., 1993, 1995). The discriminative stimulus effects of the cannabinoid group appear to provide unique effects because stimulants, hallucinogens, opioids, benzodiazepines, barbiturates, NMDA antagonists, and antipsychotics do not fully substitute for delta*-THC.

Central Nervous System Effects
Human Physiological and Psychological Effects
Psychoactive Effects
Below is a list of the common subjective responses to cannabinoids (Adams and Martin, 1996; Gonzalez, 2007; Hollister 1986; 1986; Institute of Medicine, 1982). According to Maldonado (2002), these responses to marijuana are pleasurable to many humans and are often associated with drug-seeking and drug-taking. High levels of positive psychoactive effects are associated with increased marijuana use, abuse, and dependence (Scherrer et al., 2009; Zeiger et al., 2010).

- (1) Disinhibition, relaxation, increased sociability, and talkativeness.
- (2) Increased merriment and appetite, and even exhilaration at high doses.
- (3) Enhanced sensory perception, which can generate an increased appreciation of music, art, and touch.
- (4) Heightened imagination, which can lead to a subjective sense of increased creativity.
- (5) Initial dizziness, nausea, tachycardia, facial flushing, dry mouth, and tremor.
- (6) Disorganized thinking, inability to converse logically, time distortions, and short-term memory impairment.
- (7) Ataxia and impaired judgment, which can impede driving ability or...
lead to an increase in risk-tasking behavior. Illusions, delusions, and hallucinations that intensify with higher doses. Emotional lability, incongruity of affect, dysphoria, agitation, paranoia, confusion, drowsiness, and panic attacks, which are more common in inexperienced or high-dosed users.

As with many psychoactive drugs, a person’s medical, psychiatric, and drug-taking history can influence the individual’s response to marijuana. Dose preferences to marijuana occur in that marijuana users prefer higher concentrations of the principal psychoactive substance (1.95 percent delta-9-THC) over lower concentrations (0.63 percent delta-9-THC) (Chait and Burke, 1994). Nonetheless, frequent marijuana users (>100 times of use) were able to identify a drug effect from low-dose delta-9-THC better than occasional users (<10 times of use) while also experiencing fewer sedative effects from marijuana (Kirk and de Wit, 1999).

The petitioners contend that many of marijuana’s naturally occurring cannabinoids mitigate the psychoactive effects of delta-9-THC, and therefore that marijuana lacks sufficient abuse potential to warrant Schedule I placement, because Marinol, which is in Schedule III, contains only delta-9-THC. This theory has not been demonstrated in controlled studies. Moreover, the concept of abuse potential encompasses all properties of a substance, including its chemistry, pharmacology, and pharmacokinetics, as well as usage patterns and diversion history. The abuse potential of a substance is associated with the repeated or sporadic use of a substance in nonmedical situations for the psychoactive effects the substance produces. These psychoactive effects include euphoria, perceptual and other cognitive distortions, hallucinations, and mood changes. However, as stated above, the abuse potential not only includes the psychoactive effects, but also includes other aspects related to a substance.

DEA’s final published rule entitled “Rescheduling of the Food and Drug Administration Approved Product Containing Synthetic Dronabinol [(−)-delta-9-(trans)-Tetrahydrocannabinol] in Sesame Oil and Encapsulated in Soft Gelatin Capsules From Schedule II to Schedule III” (64 FR 35928, July 2, 1999) rescheduled Marinol from Schedule II to Schedule III. The HHS assessment of the abuse potential and subsequent recommendation compared Marinol to marijuana on different aspects related to abuse potential. Major differences in formulation, availability, and usage between marijuana and the drug product, Marinol, contribute to their differing abuse potentials. Hollister and Gillespie (1973) estimated that delta-9-THC by smoking is 2.6 to 3 times more potent than delta-9-THC ingested orally. The intense psychoactive drug effect achieved, rapidly by smoking is generally considered to produce the effect desired by the abuser. This effect explains why abusers often prefer to administer certain drugs by inhalation, intravenously, or intranasally rather than orally. Such is the case with cocaine, opium, heroin, phencyclidine, methamphetamine, and delta-9-THC from marijuana (0.1–9.5 percent delta-9-THC range) or hashish (10–30 percent delta-9-THC range) (Wesson and Washburn, 1990). Thus, the delayed onset and longer duration of action for Marinol may be contributing factors limiting the abuse or appeal of Marinol as a drug of abuse relative to marijuana. The formulation of Marinol is a factor that contributes to differential scheduling of Marinol and marijuana. For example, extraction and purification of dronabinol from the encapsulated sesame oil mixture of Marinol is highly complex and difficult. Additionally, the presence of sesame oil mixture in the formulation may preclude the smoking of Marinol-laced cigarettes.

Additionally, there is a dramatic difference between actual abuse and illicit trafficking of Marinol and marijuana. Despite Marinol’s availability in the United States, there have been no significant reports of abuse, diversion, or public health problems due to Marinol. By comparison, 18.9 million American adults report currently using marijuana (SAMHSA, 2013). In addition, FDA’s approval of an NDA for Marinol allowed for Marinol to be rescheduled to Schedule II, and subsequently to Schedule III of the CSA. In conclusion, marijuana and Marinol differ on a wide variety of factors that contribute to each substance’s abuse potential. These differences are major reasons distinguishing the higher abuse potential for marijuana and the different scheduling determinations of marijuana and Marinol.

In terms of the petitioners’ claim that different cannabinoids present in marijuana mitigate the psychoactive effects of delta-9-THC, only three of the cannabinoids present in marijuana were simultaneously administered with delta-9-THC to the combination of these cannabinoids such as CBD, cannabichromene (CBC) and cannabidiol (CBN) influence delta-9-THC’s psychoactive effects. Dalton et al. (1976) observed that smoked administration of placebo marijuana cigarettes containing injections of 0.15 mg/kg CBD with 0.025mg/kg of delta-9-THC, in a 7:1 ratio of CBD to delta-9-THC, significantly decreased ratings of acute subjective effects and “high” when compared to smoking delta-9-THC alone. In contrast, Ilan et al. (2005) calculated the naturally occurring concentrations of CBC and CBD in a batch of marijuana cigarettes with either 1.8 percent or 3.6 percent delta-9-THC concentration by weight. For each strength of delta-9-THC in marijuana cigarettes, the concentrations of CBC and CBD were classified in groups of either low or high. The study varied the amount of CBC and CBD within each strength of delta-9-THC marijuana cigarettes, with administrations consisting of either low CBD (between 0.1–0.2 percent CBC concentration by weight) and low CBD (between 0.1–0.4 percent CBD concentration by weight), high CBC (>0.5 percent CBC concentration by weight) and low CBD, or low CBC and high CBD (>1.0 percent CBD concentration by weight). Overall, all combinations scored significantly greater than placebo on ratings of subjective effects, and there was no significant difference between any combinations.

The oral administration of a combination of either 15, 30, or 60 mg CBD with 30 mg delta-9-THC dissolved in liquid (in a ratio of at least 2:1 to delta-9-THC) reduced the subjective effects produced by delta-9-THC alone (Karniol et al., 1974). Additionally, orally administering a liquid mixture combining 1 mg/kg CBD with 0.5 mg/kg of delta-9-THC (ratio of 2:1 CBD to delta-9-THC) decreased scores of anxiety and marijuana drug effect on the Addiction Research Center Inventory (ARCI) compared to delta-9-THC alone (Zuardi et al., 1982). Lastly, orally administration of either 12.5, 25, or 50 mg CBN combined with 25 mg delta-9-THC dissolved in liquid (in a ratio of at least 1:2 CBN to delta-9-THC) significantly increased subjective ratings of “drugged,” “drowsy,” “dizzy,” and “drunk,” compared to delta-9-THC alone (Karniol et al., 1975).

Even though some studies suggest that CBD may decrease some of delta-9-THC’s psychoactive effects, the ratios of CBD to delta-9-THC administered in these studies are not present in marijuana used by most people. For example, in one study, researchers used smoked marijuana with ratios of CBD to delta-9-THC naturally present in marijuana
plant material and they found out that varying the amount of CBD actually had no effect on delta^*-THC's psychoactive effects (Ilan et al., 2005). Because most marijuana currently available on the street has high amounts of delta^*-THC with low amounts of CBD and other cannabinoids, most individuals use marijuana with low levels of CBD present (Mehmedic et al., 2010). Thus, any possible mitigation of delta^*-THC's psychoactive effects by CBD will not occur for most marijuana users. In contrast, one study indicated that another cannabinoid present in marijuana, CBN, may enhance delta^*-THC's psychoactive effects (Karniol et al., 1975).

Behavioral Impairment

Marijuana induces various psychoactive effects that can lead to behavioral impairment. Marijuana’s acute effects can significantly interfere with a person’s ability to learn in the classroom or to operate motor vehicles. Acute administration of smoked marijuana impairs performance on learning, associative processes, and psychomotor behavioral tests (Block et al., 1992). Ramaekers et al. (2006a) showed that acute administration of 250 µg/kg and 500 µg/kg of delta^*-THC in smoked marijuana dose-dependently impairs cognition and motor control, including motor impulsivity and tracking impairments (Ramaekers et al., 2006b). Similarly, administration of 290 µg/kg delta^*-THC in a smoked marijuana cigarette resulted in impaired perceptual motor speed and accuracy: Two skills which are critical to driving ability (Kurthzhaler et al., 1999). Lastly, administration of 3.95 percent delta^*-THC in a smoked marijuana cigarette not only increased disequilibrium measures, but also increased the latency in a task of simulated vehicle braking at a rate comparable to an increase in stopping distance of five feet at 60 mph (Liguori et al., 1998). However, acute administration of marijuana containing 2.1 percent delta^*-THC does not produce “hangover effects” (Chait, 1990).

In addition to measuring the acute effects immediately following marijuana administration, researchers have conducted studies to determine how long behavioral impairments last after abstinence. Some of marijuana’s acute effects may not fully resolve until at least one day after the acute psychoactive effects have subsided. Heishman et al. (1990) showed that impairment on memory tasks persists for 24 hours after smoking marijuana cigarettes containing 2.57 percent delta^*-THC. However, Fant et al. (1998) showed that the morning after exposure to 1.8 percent or 3.6 percent smoked delta^*-THC, subjects had minimal residual alterations in subjective or performance measures.

A number of factors may influence marijuana’s behavioral effects including the duration of use (chronic or short term), frequency of use (daily, weekly, or occasionally), and amount of use (heavy or moderate). Researchers also have examined how long behavioral impairments last following chronic marijuana use. These studies used self-reported histories of past duration, frequency, and amount of past marijuana use, and administered a variety of performance and cognitive measures at different time points following marijuana abstinence. In chronic marijuana users, behavioral impairments may persist for up to 28 days of abstinence. Solowij et al. (2002) demonstrated that after 17 hours of abstinence, 51 adult heavy chronic marijuana users performed worse on memory and attention tasks than 33 non-using controls or 51 heavy, short-term users. Another study noted that heavy, frequent marijuana users, abstinent for at least 24 hours, performed significantly worse than the controls on verbal memory and psychomotor speed tests (Messinis et al., 2006). Additionally, after at least 1 week of abstinence, young adult frequent marijuana users, aged 18–28, showed deficits in psychomotor speed, sustained attention, and cognitive inhibition (Lisdahl and Price, 2012). Adult heavy, chronic marijuana users showed deficits on memory tests after 7 days of supervised abstinence (Pope et al., 2002). However, when these same individuals were again tested after 28 days of abstinence, they did not show significant memory deficits. The authors concluded, “cannabis-associated cognitive deficits are reversible and related to recent cannabis exposure, rather than irreversible and related to cumulative lifetime use.” However, other researchers reported neuropsychological deficits in memory, executive functioning, psychomotor speed and manual dexterity in heavy marijuana users abstinent for 28 days (Bolla et al., 2002). Furthermore, a follow-up study of heavy marijuana users noted decision-making deficits after 25 days of supervised abstinence. (Bolla et al., 2005). However, moderate marijuana users did not show decision-making deficits after 25 days of abstinence, suggesting the amount of marijuana use may impact the duration of residual impairment.

The effects of chronic marijuana use do not seem to persist after more than 1 to 3 months of abstinence. After 3 months of abstinence, any deficits observed in IQ, immediate memory, delayed memory, and information-processing speeds following heavy marijuana use compared to pre-drug use scores were no longer apparent (Fried et al., 2005). Marijuana did not appear to have lasting effects on performance of a comprehensive neuropsychological battery when 34 monozygotic male twins (one of whom used marijuana, one of whom did not) were compared 1–20 years after cessation of marijuana use (Lyons et al., 2004). Similarly, following abstinence for a year or more, both light and heavy adult marijuana users did not show deficits on scores of verbal memory compared to non-using controls (Tait et al., 2011). According to a recent meta-analysis looking at non-acute and long-lasting effects of marijuana use on neurocognitive performance, any deficits seen within the first month following abstinence are generally not present after about 1 month of abstinence (Schreiner and Dunn, 2012).

Another aspect that may be a critical factor in the intensity and persistence of impairment resulting from chronic marijuana use is the age of first use. Individuals with a diagnosis of marijuana misuse or dependence who were seeking treatment for substance use, who initiated marijuana use before the age of 15 years, showed deficits in performance on tasks assessing sustained attention, impulse control, and general executive functioning compared to non-using controls. These deficits were not seen in individuals who initiated marijuana use after the age of 15 years (Fontes et al., 2011). Similarly, heavy, chronic marijuana users who began using marijuana before the age of 16 years had greater decrements in executive functioning tasks than heavy, chronic marijuana users who started using after the age of 16 years and non-smokers (Gruber et al., 2012). Additionally, in a prospective longitudinal birth cohort study of 1,037 individuals, marijuana dependence or chronic marijuana use was associated with a decrease in IQ and general neuropsychological performance compared to pre-marijuana exposure levels in adolescent onset users (Meier et al., 2012). The decline in adolescent-onset user’s IQ persisted even after reduction or abstinence of marijuana use for at least 1 year. In contrast, the adult-onset chronic marijuana users showed no significant changes in IQ compared to pre-exposure.
levels whether they were current users or abstinent for at least 1 year (Meier et al., 2012).

In addition to the age of onset of use, some evidence suggests that the amount of marijuana used may relate to the intensity of impairments. In the above study by Gruber et al. (2012), where early-onset users had greater deficits than late-onset users, the early-onset users reported using marijuana twice as often and using three times as much marijuana per week than the late-onset users. Meier et al. (2012) showed that the deficits in IQ seen in adolescent-onset users increased with the amount of marijuana used. Moreover, when comparing scores for measures of IQ, immediate memory, delayed memory, and information-processing speeds to pre-drug-use levels, the current, heavy, chronic marijuana users showed deficits in all three measures while current, occasional marijuana users did not (Fried et al., 2005).

Behavioral Effects of Prenatal Exposure

Studies with children at different stages of development are used to examine the impact of prenatal marijuana exposure on performance in a series of cognitive tasks. However, many pregnant women who reported marijuana use were more likely to also report use of alcohol, tobacco, and cocaine (Goldschmidt et al., 2008). Thus, with potential exposure to multiple drugs, it is difficult to determine the specific impact of prenatal marijuana exposure.

Most studies assessing the behavioral effects of prenatal marijuana exposure included women who, in addition to using marijuana, also reported using alcohol and tobacco. However, some evidence suggests an association between heavy prenatal marijuana exposure and deficits in some cognitive domains. In both 4-year-old and 6-year-old children, heavy prenatal marijuana use is negatively associated with performance on tasks assessing memory, verbal reasoning, and quantitative reasoning (Fried and Watkinson, 1987; Goldschmidt et al., 2008). Additionally, heavy prenatal marijuana use is associated with deficits in measures of sustained attention in children at the ages of 6 years and 13–16 years (Fried et al., 1992; Fried, 2002). In 9- to 12-year-old children, prenatal marijuana exposure is negatively associated with executive functioning tasks that require impulse control, visual analysis, and hypothesis (Fried et al., 1998).

Association of Marijuana Use With Psychosis

This analysis evaluates only the evidence for a direct link between prior marijuana use and the subsequent development of psychosis. Thus, this discussion does not consider issues such as whether marijuana’s transient effects are similar to psychotic symptoms in healthy individuals or exacerbate psychotic symptoms in individuals already diagnosed with schizophrenia.

Extensive research has been conducted to investigate whether exposure to marijuana is associated with the development of schizophrenia or other psychoses. Although many studies are small and inferential, other studies in the literature use hundreds to thousands of subjects. At present, the available data do not suggest a causative link between marijuana use and the development of psychosis (Minozzi et al., 2010). Numerous large, longitudinal studies show that subjects who used marijuana do not have a greater incidence of psychotic diagnoses compared to those who do not use marijuana (Fergusson et al., 2005; Kuepper et al., 2011; Van Os et al., 2002).

When analyzing the available evidence of the connection between psychosis and marijuana, it is critical to determine whether the subjects in the studies are patients who are already diagnosed with psychosis or individuals who demonstrate a limited number of symptoms associated with psychosis without qualifying for a diagnosis of the disorder. For example, instead of using a diagnosis of psychosis, some researchers relied on non-standard methods of representing symptoms of psychosis including “schizophrenic cluster” (Maremmani et al., 2004), “subclinical psychotic symptoms” (Van Gastel et al., 2012), “pre-psychotic clinical high risk” (Van der Meer et al., 2012), and symptoms related to “psychosis vulnerability” (Griffith-Lendering et al., 2012). These groupings do not conform to the criteria in the Diagnostic and Statistical Manual (DSM-5) or the International Classification of Diseases (ICD–10) for a diagnosis of psychosis. Thus, these groupings are not appropriate for use in evaluating marijuana’s impact on the development of actual psychosis.

Accordingly, this analysis includes only those studies that use subjects diagnosed with a psychotic disorder.

In the largest study evaluating the link between psychosis and drug use, 274 of the approximately 45,500 Swedish conscripts in the study population (<0.01 percent) received a diagnosis of schizophrenia within the 14-year period following military induction from 1969 to 1983 (Andreason et al., 1987). Of the conscripts diagnosed with psychosis, 7.7 percent (21 of the 274 conscripts with psychosis) had used marijuana more than 50 times at induction, while 72 percent (197 of the 274 conscripts with psychosis) had never used marijuana. Although high marijuana use increased the relative risk for schizophrenia to 6.0, the authors note that substantial marijuana use history “accounts for only a minority of all cases” of psychosis (Andreason et al., 1987). Instead, the best predictor for whether a conscript would develop psychosis was a non-psychotic psychiatric diagnosis upon induction. The authors concluded that marijuana use increased the risk for psychosis only among individuals predisposed to develop the disorder. In addition, a 35-year follow up to this study reported very similar results (Manrique-Garcia et al., 2012). In this follow up study, 354 conscripts developed schizophrenia; of these 354 conscripts, 32 used marijuana more than 50 times at induction (9 percent, an odds ratio of 6.3), while 255 had never used marijuana (72 percent).

Additionally, the conclusion that the impact of marijuana may manifest only in individuals likely to develop psychotic disorders has been shown in many other types of studies. For example, although evidence shows that marijuana use may precede the presentation of symptoms in individuals later diagnosed with psychosis (Schimmelmann et al., 2011), most reports conclude that prodromal symptoms of schizophrenia appear prior to marijuana use (Schiffman et al., 2005). Similarly, a review of the gene-environment interaction model for marijuana and psychosis concluded that some evidence supports marijuana use as a factor that may influence the development of psychosis, but only in those individuals with psychotic liability (Pelayo-Teran et al., 2012). A similar conclusion was drawn when the prevalence of schizophrenia was modeled against marijuana use across eight birth cohorts in Australia in individuals born between the years 1940 to 1979 (Degenhardt et al., 2003). Although marijuana use increased over time in adults born during the four-decade period, there was not a corresponding increase in diagnoses for psychosis in these individuals. The authors conclude that marijuana may precipitate schizophrenic disorders only in those individuals who are vulnerable to developing psychosis. Thus, marijuana per se does not appear to
induce schizophrenia in the majority of individuals who have tried or continue to use marijuana. However, in individuals with a genetic vulnerability for psychosis, marijuana use may influence the development of psychosis.

Cardiovascular and Autonomic Effects

Single smoked or oral doses of delta-9-THC produce tachycardia and may increase blood pressure (Caprioni et al., 1988; Benowitz and Jones, 1975). Some evidence associates the tachycardia produced by delta-9-THC with excitation of the sympathetic and depression of the parasympathetic nervous systems (Malinowska et al., 2012). During chronic marijuana ingestion, a tolerance to tachycardia develops (Malinowska et al., 2012).

However, prolonged delta-9-THC ingestion produces bradycardia and hypotension (Benowitz and Jones, 1975). Plant-derived cannabinoids and endocannabinoids elicit hypotension and bradycardia via activation of peripherally-located CB1 receptors (Wagner et al., 1998). Specifically, the mechanism of this effect is through presynaptic CB1 receptor-mediated inhibition of norepinephrine release from peripheral sympathetic nerve terminals, with possible additional direct vasodilation via activation of vascular cannabinoid receptors (Pacher et al., 2006). In humans, tolerance can develop to orthostatic hypotension (Jones, 2002; Sidney, 2002) possibly related to plasma volume expansion, but tolerance does not develop to the supine hypotensive effects (Benowitz and Jones, 1975). Additionally, electrocardiographic changes are minimal, even after large cumulative doses of delta-9-THC are administered. (Benowitz and Jones, 1975).

Marijuana smoking by individuals, particularly those with some degree of coronary artery or cerebrovascular disease, poses risks such as increased cardiac work, catecholamines and carboxyhemoglobin, myocardial infarction, and postural hypotension (Benowitz and Jones, 1981; Hollister, 1988; Mithen et al., 2001; Malinowska et al., 2012).

Respiratory Effects

After acute exposure to marijuana, transient bronchodilation is the most typical respiratory effect (Gong et al., 1984). A recent 20-year longitudinal study with over 5,000 individuals collected information on the amount of marijuana use and pulmonary function data at years 0, 2, 5, 10, and 20 (Pletcher et al., 2012). By the more than 5,000 individuals who participated in the study, almost 800 of them reported current marijuana use but not tobacco use at the time of assessment. Pletcher et al. (2012) found that the occasional use of marijuana is not associated with decreased pulmonary function. However, some preliminary evidence suggests that heavy marijuana use may be associated with negative pulmonary effects (Pletcher et al., 2012). Long-term use of marijuana can lead to chronic cough and increased sputum, as well as an increased frequency of chronic bronchitis and pharyngitis. In addition, pulmonary function tests reveal that large-airway obstruction can occur with chronic marijuana smoking, as can cellular inflammatory histopathological abnormalities in bronchial epithelium (Adams and Martin 1996; Hollister 1986).

Evidence regarding marijuana smoking leading to cancer is inconsistent, as some studies suggest a positive correlation while others do not (Lee and Hancock, 2011; Tashkin, 2005). Several lung cancer cases have been reported in young marijuana users with no tobacco smoking history or other significant risk factors (Fung et al., 1999). Marijuana use may dose-dependently interact with mutagenic sensitivity, cigarette smoking, and alcohol use to increase the risk of head and neck cancer (Zhang et al., 1999). However, in a large study with 1,650 subjects, a positive association was not found between marijuana and lung cancer (Tashkin et al., 2006). This finding remained true, regardless of the extent of marijuana use, when controlling in tobacco use and other potential confounding variables. Overall, new evidence suggests that the effects of marijuana smoking on respiratory function and carcinogenicity differ from those of tobacco smoking (Lee and Hancock, 2011).

Endocrine System

Experimental marijuana administration to humans does not consistently alter many endocrine parameters. In an early study, male subjects who experimentally received smoked marijuana showed a significant depression in luteinizing hormone and a significant increase in cortisol (Cone et al., 1986). However, two later studies showed no changes in hormones. Male subjects experimentally exposed to smoked delta-9-THC (18 mg/marijuana cigarette) or oral delta-9-THC (10 mg three times per day for 3 days and on the morning of the fourth day) showed no changes in plasma adrenocorticotropic hormone (ACTH), the cortisol, luteinizing hormone, or testosterone levels (Dax et al., 1989). Similarly, a study with 93 men and 56 women showed that chronic marijuana use did not significantly alter concentrations of testosterone, luteinizing hormone, follicle stimulating hormone, prolactin, or cortisol (Block et al., 1991). Additionally, chronic marijuana use did not affect serum levels of thyrotropin, thyroxine, and triiodothyronine (Bonnet, 2013).

However, in a double-blind, placebo-controlled, randomized clinical trial of HIV-positive men, smoking marijuana dose-dependently increased plasma levels of ghrelin and leptin, and decreased plasma levels of peptide YY (Riggs et al., 2012). The effects of marijuana on female reproductive system functionality differ between humans and animals. In monkeys, delta-9-THC administration suppressed ovulation (Asch et al., 1981) and reduced progesterone levels (Almirez et al., 1983). However, in women, smoked marijuana did not alter hormone levels or the menstrual cycle (Mendelson and Mello, 1984). Brown and Dobs (2002) suggest that the development of androgen insensitivity in humans may be the cause of the discrepancies between animal and human hormonal response to cannabinoids.

The presence of in vitro delta-9-THC reduces binding of the corticosteroid, dexamethasone, in hippocampal tissue from adrenalectomized rats, suggesting an interaction with the glucocorticoid receptor (Eldridge et al., 1991). Although acute delta-9-THC presence releases corticosterone, tolerance develops in rats with chronic administration (Eldridge et al., 1991). Some studies suggest a possible association between frequent, long-term marijuana use and increased risk of testicular germ cell tumors (Trabert et al., 2011). On the other hand, recent data suggest that cannabinoid agonists may have therapeutic value in the treatment of prostate cancer, a type of carcinoma in which growth is stimulated by androgens. Research with prostate cancer cells shows that the mixed CB1/CB2 agonist, WIN-55212–2, induces apoptosis in prostate cancer cells, as well as decreases the expression of androgen receptors and prostate-specific antigens (Sarfaraz et al., 2005).

Immune System

Cannabinoids affect the immune system in many different ways. Synthetic, natural, and endogenous cannabinoids often cause different effects in a dose-dependent biphasic manner (Croxford and Yamamura, 2005; Tanasecu and Constantinescu, 2010). Studies in humans and animals give conflicting results about cannabinoid
effects on immune functioning in subjects with compromised immune systems. Abrams et al. (2003) investigated marijuana’s effect on immunological functioning in 62 AIDS patients taking protease inhibitors. Subjects received one of the following three times a day: A smoked marijuana cigarette containing 3.95 percent delta-^9^-THC, an oral tablet containing delta-^9^-THC (2.5 mg oral dronabinol), or an oral placebo. The results showed no changes in CD4+ and CD8+ cell counts, HIV RNA levels, or protease inhibitor levels between groups. Thus, the use of cannabinoids showed no short-term adverse virologic effects in individuals with compromised immune systems. However, these human data contrast with data generated in immunodeficient mice, which demonstrated that exposure to delta-^9^-THC in vivo suppresses immune function, increases HIV co-receptor expression, and acts as a cofactor to enhance HIV replication (Roth et al., 2003).

3. The State of Current Scientific Knowledge Regarding the Drug or Other Substance

Under the third factor, the Secretary must consider the state of current scientific knowledge regarding marijuana. Thus, this section discusses the chemistry, human pharmacokinetics, and medical uses of marijuana.

Chemistry

Marijuana is one of the common names of Cannabis sativa L. in the family Cannabaceae. Cannabis is one of the oldest cultivated crops, providing a source of fiber, food, oil, and drug. Botanists still debate whether Cannabis should be considered as a single (The Plant List, 2010) or three species, i.e., C. sativa, C. indica, and C. ruderalis (Hillig, 2005). Specifically, marijuana is developed as sativa and indica cultivated varieties (strains) or various hybrids.

The petition defines marijuana as including all Cannabis cultivated strains. Different marijuana samples derived from various cultivated strains may have very different chemical constituents including delta^9^-THC and other cannabinoids (Appendino et al., 2011). As a consequence, marijuana products from different strains will have different safety, biological, pharmaceutical, and toxicological profiles. Thus, all Cannabis strains cannot be considered together because of the varying chemical constituents between strains.

Marijuana contains numerous naturally occurring constituents including cannabinoids. Overall, various Cannabis strains contain more than 525 identified natural constituents. Among those constituents, the most important ones are the 21 (or 22) carbon terpenoids found in the plant, as well as their carboxylic acids, analogues, and transformation products, known as cannabinoids (Agurell et al., 1984, 1986; Mechoulam, 1973; Appendino et al., 2011). Thus far, more than 100 compounds classified as cannabinoids have been characterized (ElSohly and Slade, 2005; R. W. E. ElSohly et al., 2009; Appendino et al. 2011). Cannabinoids primarily exist in Cannabis, and published data suggest that most major cannabinoid compounds occurring naturally have been chemically identified. New and minor cannabinoids and other new compounds are continuously being characterized (Pollastro et al., 2011). So far, only two cannabinoids (cannabigerol and its corresponding acid) have been obtained from a non-^9^-Cannabis source. A South African Helitonia sum (Helitonia aculeigerum) accumulates these compounds (Appendino et al. 2011).

Among the cannabinoids found in marijuana, delta^9^-THC (alternate name delta^1^-THC) and delta-^8^-tetrahydrocannabinol (delta^9^-THC, alternate name delta^9^-THC) produce marijuana’s characteristic psychoactive effects. Because delta^9^-THC is more abundant than delta^8^-THC, marijuana’s psychoactivity is largely attributed to the former. Only a few varieties of marijuana analyzed contain delta^9^-THC at significant amounts (Hively et al., 1966). Delta^9^-THC is an optically active resinous substance, insoluble in water, and extremely lipid soluble. Chemically, delta^9^-THC is (6aR-trans)-6,7,8,9-tetrahydro-6,6,9-trimethyl-3-pentyl-H6-dibenzo-[b,d]pyran-1-ol, or (--)delta^9^-trans-tetrahydrocannabinol. The (--)—isomer of delta^9^-THC is pharmacologically 6—100 times more potent than the (+)—isomer (Dewey et al., 1984).

Other cannabinoids present in marijuana include CBD, CBC, and CBN. CBD, a major cannabinoid of marijuana, is insoluble in water and lipid-soluble. Chemically, CBD is 2-[(1R,6R)-3-methyl-6-prop-1-en-2-ylcyclohex-2-en-1-yl]-5-pentylbenzene-1,3-diol. CBD does not have cannabinol-like psychoactivity (Adams and Martin, 1996; Agurell et al., 1984, 1986; Hollister, 1986). CBC is another major cannabinoid in marijuana. Chemically, CBC is 2-methyl-2-(4-methylpent-3-enyl)-7-pentyl-1,3-diol. CBN, a major metabolite of delta^9^-THC, is also a minor naturally-occurring cannabinoid with weak psychoactivity. Chemically, CBN is 6,6,9-trimethyl-3-pentylbenzo[c]chromen-1-ol.

Different marijuana samples derived from various cultivated strains may differ in chemical constituents including delta^9^-THC and other cannabinoids (Appendino et al. 2011). As a consequence, marijuana products from different strains may have different safety, biological, pharmacological, and toxicological profiles. In addition to differences between cultivated strains, the concentration of delta^9^-THC and other cannabinoids in marijuana may vary with growing conditions and processing after harvest. In addition to genetic differences among Cannabis species, the plant parts collected—for example, flowers, leaves, and stems—can influence marijuana’s potency, quality, and purity (Adams and Martin, 1996; Agurell et al., 1984; Mechoulam, 1973). All these variations produce marijuana with potencies, as indicated by cannabinoid content, on average from as low as 1—2 percent to as high as 17 percent.

Overall, these variations in the concentrations of cannabinoids and other chemical constituents in marijuana complicate the interpretation of clinical data using marijuana. The lack of consistent concentrations of delta^9^-THC and other substances in marijuana from diverse sources makes interpreting the effect of different marijuana constituents difficult. In addition to different cannabinoid concentrations having different pharmacological and toxicological profiles, the non-cannabinoid components in marijuana, such as other terpenoids and flavonoids, might also contribute to the overall pharmacological and toxicological profiles of various marijuana strains and products derived from those strains.

The term marijuana is often used to refer to a mixture of the dried flowering tops and leaves from Cannabis. Marijuana in this limiting definition is one of three major derivatives sold as separate illicit products, which also include hashish and hash oil. According to the DEA, Cannabis sativa is the primary species of Cannabis currently marketed illegally in the United States. Marijuana can vary in cannabinoid content and potency (Agurell et al., 1984, 1986; Mechoulam 1973, Cascini et al., 2012). In the usual mixture of leaves and stems distributed as marijuana, the concentration of delta^9^-THC averages over 12 percent by weight. However, specially grown and selected marijuana can contain 15 percent delta^9^-THC (Appendino et al., 2011). Thus, a 1-gram marijuana cigarette might
contain delta*-THC in a range from as little as 3 milligrams to as much as 150 milligrams or more. Additionally, a recent systematic review and meta-analysis found that marijuana’s delta*-THC content has increased significantly from 1979–2009 (Cascini et al., 2012). In addition to smoking marijuana, individuals ingest marijuana through food made with butter or oil infused with marijuana and its extracts. These marijuana butters are generally made by adding marijuana to butter and heating it. The resultant butter is then used to cook a variety of foods. There are no published studies measuring the concentrations of cannabinoids in these marijuana products.

Hashish consists of the dried and compressed cannabinoid-rich resinous material of Cannabis and comes in a variety of forms (e.g., balls and cakes). Individuals may break off pieces, place it into a pipe and smoke it. DEA reports that cannabinoid content in hashish averages six percent (DEA, 2005). With the development and cultivation of more high potency Cannabis strains, the average cannabinoid content in hashish will likely increase.

Hash oil is produced by solvent extraction of the cannabinoids from plant material. The extract’s color and odor vary, depending on the solvent type used. Hash oil is a viscous brown- or amber-colored liquid containing approximately 50 percent cannabinoids. One or two droplets of the liquid placed on a cigarette purportedly produce the equivalent of a single marijuana cigarette (DEA, 2005).

In conclusion, marijuana has hundreds of cultivars containing variable concentrations of delta*-THC, cannabinoids, and other compounds. Thus, marijuana is not a single chemical with a consistent and reproducible chemical profile or predictable and consistent clinical effects. A guidance for industry, entitled Botanical Drug Products, provides information on the approval of botanical drug products. To investigate marijuana for medical use in a manner acceptable as support for marketing approval under an NDA, clinical studies under an IND of consistent batches of a particular marijuana product for particular disease indications should be conducted. In addition, information and data regarding the marijuana product’s chemistry, manufacturing and control, pharmacology, and animal toxicology data, among others must be provided and meet the requirements for new drug approval (See 21 CFR 314.50).

**Human Pharmacokinetics**

Marijuana can be taken in a variety of formulations by multiple routes of administration. Individuals smoke marijuana as a cigarette, weighing between 0.5 and 1.0 gram, or in a pipe. Additionally, individuals take marijuana orally in foods or as an extract in ethanol or other solvents. More recently, access to vaporizers provides another means for abusers to inhale marijuana.

The absorption, metabolism, and pharmacokinetic profile of delta*-THC, cannabinoids, and drug products containing delta*-THC vary with route of administration and formulation (Adams and Martin, 1996; Agurell et al., 1984, 1986).

**Pharmacokinetics of Smoked Administration of Cannabinoids**

Characterization of the pharmacokinetics of delta*-THC and other cannabinoids from smoked marijuana is difficult because a subject’s smoking behavior during an experiment varies (Agurell et al., 1986; Heming et al., 1986; Huestis et al., 1992a). Each puff delivers a discrete dose of delta*-THC. An experienced marijuana smoker can titrate and regulate the dose to obtain the desired acute psychological effects and minimize undesired effects. For example, under naturalistic conditions, users hold marijuana smoke in their lungs for an extended period of time which causes prolonged absorption and increases psychoactive effects. The effect of experience in the psychological response may explain why delta*-THC venous blood levels correlate poorly with intensity of effects and intoxication level (Agurell et al. 1986; Barnett et al. 1985; Huestis et al., 1992a). Puff and inhalation volumes should be recorded in studies as the concentration (dose) of cannabinoids administered can vary at different stages of smoking.

Smoked marijuana results in absorption of delta*-THC in the form of an aerosol within seconds. Psychoactive effects occur immediately following absorption, with mental and behavioral effects measurable for up to 6 hours (Grotenhermen, 2003; Hollister 1986, 1988). Delta*-THC is delivered to the brain rapidly and efficiently as expected of a very lipid soluble drug. The bioavailability of the delta*-THC, from marijuana in a cigarette or pipe, can range from 1 to 24 percent with the fraction absorbed rarely exceeding 10 to 20 percent (Agurell et al., 1986; Hollister, 1988). The relatively low and variable bioavailability results from significant loss of delta*-THC in sidestream smoke, variation in individual smoking behaviors, cannabinoid pyrolysis, incomplete absorption of inhaled smoke, and metabolism in the lungs. An individual’s experience and technique with smoking marijuana also determines the dose absorbed (Heming et al., 1986; Johansson et al., 1989).

After smoking, delta*-THC venous levels decline precipitously within minutes, and continue to go down to about 5 to 10 percent of the peak level within an hour (Agurell et al., 1986; Huestis et al. 1992a, 1992b).

**Pharmacokinetics for Oral Administration of Cannabinoids**

After oral administration of delta*-THC or marijuana, the onset of effects starts within 30 to 90 minutes, reaches its peak after 2 to 3 hours and then remains for 4 to 12 hours (Grotenhermen, 2003; Adams and Martin, 1996; Agurell et al., 1984, 1986). Due to the delay in onset of effects, users have difficulty in titrating oral delta*-THC doses compared to smoking marijuana. Oral bioavailability of delta*-THC, whether pure or in marijuana, is low and extremely variable, ranging between 5 and 20 percent (Agurell et al., 1984, 1986). Following oral administration of radioactive-labeled delta*-THC, delta*-THC plasma levels are low relative to plasma levels after smoking or intravenous administration. Inter- and intra-subject variability occurs even with repeated dosing under controlled conditions. The low and variable oral bioavailability of delta*-THC is a consequence of its first-pass hepatic elimination from blood and erratic absorption from stomach and bowel.

**Cannabinoid Metabolism and Excretion**

Cannabinoid metabolism is complex. Delta*-THC is metabolized via microsomal hydroxylation to both active and inactive metabolites (Lemberger et al., 1970, 1972a, 1972b; Agurell et al., 1986; Hollister, 1988). The primary active metabolite of delta*-THC following oral ingestion is 11-hydroxy-delta*-THC. This metabolite is approximately equipotent to delta*-THC in producing marijuana-like subjective effects (Agurell et al., 1986, Lemberger and Rubin, 1975). After oral administration, metabolite levels may exceed that of delta*-THC and thus contribute greatly to the pharmacological effects of oral delta*-THC or marijuana.

Plasma clearance of delta*-THC approximates hepatic blood flow at about 950 ml/min or greater. The rapid disappearance of delta*-THC from blood...
is largely due to redistribution to other tissues in the body, rather than to metabolism (Agurell et al., 1984, 1986). Metabolism in most tissues is relatively slow or absent. Slow release of delta*-THC and other cannabinoids from tissues and subsequent metabolism results in a long elimination half-life. The terminal half-life of delta*-THC ranges from approximately 20 hours to as long as 10 to 13 days, though reported estimates vary as expected with any slowly cleared substance and the use of assays with variable sensitivities (Hunt and Jones, 1980). Lemberger et al. (1970) determined the half-life of delta*-THC to range from 23 to 28 hours in heavy marijuana users to 60 to 70 hours in naive users. In addition to 11-hydroxy-delta*-THC, some inactive carboxy metabolites have terminal half-lives of 50 hours to 6 days or more. The latter substances serve as long-term markers in urine tests for earlier marijuana use.

The majority of the absorbed delta*-THC dose is eliminated in feces, and about 3 percent in urine. Delta*-THC enters enterobacterial circulation and undergoes hydroxylation and oxidation to 11-nor-9-carboxy-delta*-THC. The glucuronide is excreted as the major urine metabolite along with about 18 non-conjugated metabolites. Frequent and infrequent marijuana users metabolize delta*-THC similarly (Agurell et al., 1986).

**Status of Research Into the Medical Uses for Marijuana**

State-level public initiatives, including laws and referenda in support of the medical use of marijuana, have generated interest in the medical community and the need for high quality clinical investigation as well as comprehensive safety and effectiveness data. In order to address the need for high quality clinical investigations, the state of California established the Center for Medicinal Cannabis Research (CMCR, [www.cmcr.ucsd.edu](http://www.cmcr.ucsd.edu)) in 2000 “in response to scientific evidence for therapeutic possibilities of cannabis and related initiatives in favor of compassionate use” (Grant, 2005). State legislation establishing the CMCR called for high quality medical research that would “enhance understanding of the efficacy and adverse effects of marijuana as a pharmacological agent,” but stressed the project “should not be construed as encouraging or sanctioning the social or recreational use of marijuana.” The CMCR funded many of the published studies on marijuana’s potential use for treating multiple sclerosis, neuropathic pain, appetite suppression and cachexia. However, aside from the data produced by CMCR, no state-level medical marijuana laws have produced scientific data on marijuana’s safety and effectiveness.

FDA approves medical use of a drug following a submission and review of an NDA or BLA. The FDA has not approved any drug product containing marijuana for marketing. Even so, results of small clinical exploratory studies have been published in the current medical literature. Many studies describe human research with marijuana in the United States under FDA-regulated IND applications. However, FDA approval of an NDA is not the only means through which a drug can have a currently accepted medical use in treatment in the United States. In general, a drug may have a “currently accepted medical use” in treatment in the United States if the drug meets a five-part test. Established case law (Alliance for Cannabis Therapeutics v. DEA, 15 F.3d 1131, 1135 (D.C. Cir. 1994)) upheld the Administrator of DEA’s application of the five-part test to determine whether a drug has a “currently accepted medical use.” The following describes the five elements that characterize “currently accepted medical use” for a drug:  

i. the drug’s chemistry must be known and reproducible.

“the substance’s chemistry must be scientifically established to permit it to be reproduced into dosages which can be standardized.” The listing of the substance in a current edition of one of the official compendia, as defined by section 201 G of the Food, Drug and Cosmetic Act, 21 U.S.C. 321(g), is sufficient to meet this requirement.”

ii. there must be adequate safety studies.

“there must be adequate pharmacological and toxicological studies, done by all methods reasonably applicable, on the basis of which it could fairly and responsibly be concluded that the drug is safe for use in treating a specific, recognized disorder.”

iii. there must be adequate and well-controlled studies proving efficacy.

“there must be adequate, well-controlled, well-designed, well-conducted, and well-documented studies, including clinical investigations, by experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, that the substance is safe for use in treating a specific, recognized disorder.”

iv. the drug must be accepted by qualified experts.

“The drug has a New Drug Application (NDA) approved by the Food and Drug Administration, pursuant to the Food, Drug and Cosmetic Act, 21 U.S.C. 355. Or, a consensus of the national community of experts, qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, accepts the safety and effectiveness of the substance for use in treating a specific, recognized disorder. A material conflict of opinion among experts precludes a finding of consensus.”

v. the scientific evidence must be widely available.

“In the absence of NDA approval, information concerning the chemistry, pharmacology, toxicology, and effectiveness of the substance must be reported, published, or otherwise widely available, in sufficient detail to permit experts, qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, to fairly and responsibly conclude that the substance is safe and effective for use in treating a specific, recognized disorder.”

Marijuana does not meet any of the five elements necessary for a drug to have a “currently accepted medical use.”

Firstly, the chemistry of marijuana, as defined in the petition, is not reproducible in terms of creating a standardized dose. The petition defines marijuana as including all *Cannabis* cultivated strains. Different marijuana samples derived from various cultivated strains may have very different chemical constituents including delta*-THC and other cannabinoids (Appendino et al., 2011). As a consequence, marijuana products from different strains will have different safety, biological, pharmacological, and toxicological profiles. Thus, when considering all *Cannabis* strains together, because of the varying chemical constituents, reproducing consistent standardized doses is not possible. Additionally, smoking marijuana currently has not been shown to allow delivery of consistent and reproducible doses. However, if a specific *Cannabis* strain is grown and processed under strictly controlled conditions, the plant chemistry may be kept consistent enough to produce reproducible and standardized doses.

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*In this quotation the term cannabis is interchangeable with marijuana.*
As to the second and third criteria; there are neither adequate safety studies nor adequate and well-controlled studies proving marijuana’s efficacy. To support the petitioners’ assertion that marijuana has accepted medical use, the petitioners cite the American Medical Association’s (AMA) 2009 report entitled “Use of Cannabis for Medicinal Purposes.” The petitioners claim the AMA report is evidence the AMA accepts marijuana’s safety and efficacy. However, the 2009 AMA report clarifies that the report “should not be viewed as an endorsement of state-based medical cannabis programs, the legalization of marijuana, or that scientific evidence on the therapeutic use of cannabis meets the same and current standards for a prescription drug product.”

Currently, no published studies conducted with marijuana meet the criteria of an adequate and well-controlled efficacy study. The criteria for an adequate and well-controlled study for purposes of determining the safety and efficacy of a human drug are defined under the Code of Federal Regulations (CFR) in 21 CFR 314.126. In order to assess this element, FDA conducted a review of clinical studies published and available in the public domain before February, 2013. Studies were identified through a search of PubMed for articles published from inception to February 2013, for randomized controlled trials using marijuana to assess marijuana’s efficacy in any therapeutic indication. Additionally, the review included studies identified through a search of bibliographic references in relevant systematic reviews and identified studies presenting original research in any language. Selected studies needed to be placebo-controlled and double-blinded. Additionally, studies needed to encompass administered marijuana plant material. There was no requirement for any specific route of administration, nor any age limits on study subjects. Studies were excluded that used placebo marijuana supplemented by the addition of specific amounts of THC or other cannabinoids. Additionally, studies administering marijuana plant extracts were excluded.

The PubMed search yielded a total of 556 abstracts of scientific articles. Of these abstracts, a full-text review was conducted with 85 papers to assess eligibility. Of the studies identified through the search of the references and the 556 abstracts from the PubMed search, only 11 studies met all the criteria for selection (Abrams et al., 2007; Corey-Bloom et al., 2012; Crawford and Merritt, 1979; Ellis et al., 2009; Haney et al., 2005; Haney et al., 2007; Merritt et al., 1980; Tashkin et al., 1974; Ware et al., 2010; Wilsey et al., 2008; Wilsey et al., 2013). These 11 studies were conducted between 1974 and 2013. Ten of these studies were conducted in the United States and one study was conducted in Canada. The identified studies examine the effects of smoked and vaporized marijuana for the indications of chronic neuropathic pain, spasticity related to Multiple Sclerosis (MS), appetite stimulation in human immunodeficiency virus (HIV) patients, glaucoma, and asthma. All studies used adult subjects.

The 11 identified studies were individually evaluated to determine if these successfully met accepted scientific standards. Specifically, they were evaluated on study design including subject selection criteria, sample size, blinding techniques, dosing paradigms, outcome measures, and the statistical analysis of the results. The analysis relied on published studies, thus information available about protocols, procedures, and results were limited to documents published and widely available in the public domain. The review found that all 11 studies that examined effects of smoked marijuana do not currently prove efficacy of marijuana in any therapeutic indication based on a number of limitations in their study design; however, they may be considered proof of concept studies. Proof of concept studies provide preliminary evidence on a proposed hypothesis involving a drug’s effect. For drugs under development, the effect often relates to a short-term clinical outcome being investigated. Proof of concept studies often serve as the link between preclinical studies and dose ranging clinical trials. Thus, proof of concept studies generally are not sufficient to prove efficacy of a drug because they provide only preliminary information about the effects of a drug. In addition to the lack of published adequate and well-controlled efficacy studies proving efficacy, the criteria for adequate safety studies has also not been met. Importantly, in its discussion of the five-part test used to determine whether a drug has a “currently accepted medical use,” DEA said, “No drug can be considered safe in the abstract. Safety has meaning only when judged against the intended use of the drug, its known effectiveness, its known and potential risks, the severity of the illness to be treated, and the availability of alternative remedies” (57 FR 10504). When determining whether a drug product is safe and effective for any indication, FDA performs an extensive risk-benefit analysis to determine whether the risks posed by the drug product’s side effects are outweighed by the drug product’s potential benefits for a particular indication. Thus, contrary to the petitioners’ assertion that marijuana has accepted safety, in the absence of an accepted therapeutic indication which can be weighed against marijuana’s risks, marijuana does not satisfy the element for having adequate safety studies such that experts may conclude that it is safe for treating a specific, recognized disorder.

The fourth of the five elements for determining “currently accepted medical use” requires that the national community of experts, qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, accepts the safety and effectiveness of the substance for use in treating a specific, recognized disorder. A material conflict of opinion among experts precludes a finding of consensus. Medical practitioners who are not experts in evaluating drugs are not qualified to determine whether a drug is generally recognized as safe and effective or meets NDA requirements (57 FR 10499–10505). There is no evidence that there is a consensus among qualified experts that marijuana is safe and effective for use in treating a specific, recognized disorder. As discussed above, there are not adequate scientific studies that show marijuana is safe and effective in treating a specific, recognized disorder. In addition, there is no evidence that a consensus of qualified experts have accepted the safety and effectiveness of marijuana for use in treating a specific, recognized disorder. Although medical practitioners are not qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, we also note that the AMA’s report, entitled “Use of Cannabis for Medicinal Purposes,” does not accept that marijuana currently has accepted medical use. Furthermore, based on the above definition of a “qualified expert,” who is an individual qualified by scientific training and experience to evaluate the safety and effectiveness of a drug, state-level medical marijuana laws do not provide evidence of a consensus among qualified experts that marijuana is safe and effective for use in treating a specific, recognized disorder.
As to the fifth part of the test, which requires that information concerning the chemistry, pharmacology, toxicology, and effectiveness of marijuana to be reported in sufficient detail, the scientific evidence regarding all of these aspects is not available in sufficient detail to allow adequate scientific scrutiny. Specifically, the scientific evidence regarding marijuana’s chemistry in terms of a specific Cannabis strain that could produce standardized and reproducible doses is not currently available.

Alternately, a drug can be considered to have a “currently accepted medical use with severe drug” (21 U.S.C. 812(b)(2)(B)), as allowed under the stipulations for a Schedule II drug. Yet, as stated above, currently marijuana does not have any accepted medical use, even under conditions where its use is severely restricted.

In conclusion, to date, research on marijuana’s medical use has not progressed to the point where marijuana is considered to have a “currently accepted medical use” or a “currently accepted medical use with severe restrictions.”

4. Its History and Current Pattern of Abuse

Under the fourth factor, the Secretary must consider the history and current pattern of marijuana abuse. A variety of sources provide data necessary to assess abuse patterns and trends of marijuana. The data indicators of marijuana use include the NSDUH, MTF, DAWN, and TEDS. The following briefly describes each data source, and summarizes the data from each source.

**National Survey on Drug Use and Health (NSDUH)**

According to 2012 NSDUH data, the most recent year with complete data, the use of illicit drugs, including marijuana, is increasing. The 2012 NSDUH estimates that 23.9 million individuals over 12 years of age (9.2 percent of the U.S. population) currently use illicit drugs, which is an increase of 4.8 million individuals from 2004 when 19.1 million individuals (7.9 percent of the U.S. population) were current illicit drug users. NSDUH reports marijuana as the most commonly used illicit drug, with 18.9 million individuals (7.3 percent of the U.S. population) currently using marijuana in 2012. This represents an increase of 4.3 million individuals from 2004, when 14.6 million individuals (6.1 percent of the U.S. population) were current marijuana users.

The majority of individuals who try marijuana at least once in their lifetime do not currently use marijuana. The 2012 NSDUH estimates that 111.2 million individuals (42.8 percent of the U.S. population) have used marijuana at least once in their lifetime. Based on this estimate and the estimate for the number of individuals currently using marijuana, approximately 16.9 percent of those who have tried marijuana at least once in their lifetime currently use marijuana; conversely, 83.1 percent do not currently use marijuana. In terms of the frequency of marijuana use, an estimated 40.3 percent of individuals who used marijuana in the past month used marijuana on 20 or more days within the past month. This amount corresponds to an estimated 7.6 million individuals who used marijuana on a daily or almost daily basis.

Some characteristics of marijuana users are related to age, gender, and criminal justice system involvement. In observing use among different age cohorts, the majority of individuals who currently use marijuana are shown to be between the ages of 18–25, with 18.7 percent of this age group currently using marijuana. In the 26 and older age group, 5.3 percent of individuals currently use marijuana. Additionally, in individuals aged 12 years and older, males reported more current marijuana use than females.

NSDUH includes a series of questions aimed at assessing the prevalence of dependence and abuse of different substances in the past 12 months. In 2012, marijuana was the most common illicit drug reported by individuals with past year dependence or abuse. An estimated 4.3 million individuals meet the NSDUH criteria for marijuana dependence or abuse in 2012. The estimated rates and number of individuals with marijuana dependence or abuse has remained similar from 2002 to 2012. In addition to data on dependence and abuse, NSDUH includes questions aimed at assessing treatment for a substance use problem. In 2012, an estimated 957,000 persons received treatment for marijuana use during their most recent treatment in the year prior to the survey.

**Monitoring the Future (MTF)**

According to MTF, rates of marijuana and illicit drug use declined for all three grades from 2005 through 2007. However, starting around 2008, rates of annual use of illicit drugs and marijuana increased through 2013 for all three grades. Marijuana remained the most widely used illicit drug during all time periods. The prevalence of annual and past month marijuana use in 10th and 12th graders in 2013 is greater than in 2005. Table 1 lists the lifetime, annual, and monthly prevalence rates of various drugs for 8th, 10th, and 12th graders in 2013.

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13 NSDUH provides national estimates of the prevalence and incidence of illicit drug, alcohol and tobacco use in the United States. NSDUH is an annual study conducted by SAMHSA. Prior to 2002, the survey was known as the National Household Survey on Drug Abuse (NHSDA). NSDUH utilizes a nationally representative sample of United States civilian, non-institutionalized population aged 12 years and older. The survey excludes homeless people who do not use shelters, active military personnel, and residents of institutional group quarters such as jails and hospitals. The survey identifies whether an individual used a drug within a specific time period, but does not identify the amount of the drug used on each occasion. NSDUH defines “current use” as having used the substance within the month prior to the study.


15 “These questions are used to classify persons as dependent on or abusing specific substances based on criteria specified in the Diagnostic and Statistical Manual of Mental Disorder, 4th edition (DSM–IV). The questions related to dependence ask about health and emotional problems associated with current use, unsuccessful attempts to cut down on use, tolerance, withdrawal, reducing other activities to use substances, spending a lot of time engaging in activities related to substance use, or using the substance in greater quantities or for longer than intended. The questions on abuse ask about problems at work, home, and school; problems with family or friends; physical danger; and trouble with the law due to substance use. Dependence is considered to be a more severe substance use problem than abuse because it involves the psychological and physiological effects of tolerance and withdrawal.” (NSDUH, 2013).

16 Monitoring the Future is a national survey that tracks drug use prevalence and trends among adolescents in the United States. MTF is reported annually by the Institute for Social Research at the University of Michigan under a grant from NIDA. Every spring, MTF surveys 8th, 10th, and 12th graders in randomly selected U.S. schools. MTF has been conducted since 1975 for 12th graders and since 1991 for 8th and 10th graders. The MTF survey presents data in terms of prevalence among the sample interviewed. For 2012, the latest year with complete data, the sample sizes were 15,200—8th graders; 13,300—10th graders; and 13,200—12th graders. In all, a total of about 41,700 students of 389 schools participated in the 2013 MTF.

17 See for example, “http://www.monitoringthefuture.org/index.html.”
Table 1: Trends in lifetime, annual, and monthly prevalence of use of various drugs for eighth, tenth, and twelfth graders. Percentages represent students in survey responding that they had used a drug at least once in their lifetime, in the past year, or in the past 30 days.

<table>
<thead>
<tr>
<th>Any illicit Drug (a)</th>
<th>Lifetime</th>
<th>Annual</th>
<th>30-Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>8th Grade</td>
<td>20.1</td>
<td>18.5</td>
<td>20.3</td>
</tr>
<tr>
<td>10th Grade</td>
<td>37.7</td>
<td>36.8</td>
<td>38.8</td>
</tr>
<tr>
<td>12th Grade</td>
<td>49.9</td>
<td>49.1</td>
<td>50.4</td>
</tr>
<tr>
<td>Marijuana/Hashish</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8th Grade</td>
<td>16.4</td>
<td>15.2</td>
<td>16.5</td>
</tr>
<tr>
<td>10th Grade</td>
<td>34.5</td>
<td>33.8</td>
<td>35.8</td>
</tr>
<tr>
<td>12th Grade</td>
<td>45.5</td>
<td>45.2</td>
<td>45.5</td>
</tr>
</tbody>
</table>

SOURCE: The Monitoring the Future Study, the University of Michigan

a. For 12th graders only: "any illicit drug" includes any use of marijuana, LSD, other hallucinogens, crack, other cocaine, or heroin; or any narcotics use other than heroin, amphetamines, sedatives (barbiturates), or tranquilizers not under a doctor's orders. For 8th and 10th graders only: the use of narcotics other than heroin and sedatives (barbiturates) was excluded.

Drug Abuse Warning Network (DAWN)\(^1\)

Importantly, many factors can influence the estimates of ED visits, including trends in overall use of a substance as well as trends in the reasons for ED usage. For instance, some drug users may visit EDs for life-threatening issues while others may visit to seek care for detoxification because they needed certification before entering treatment. Additionally, DAWN data do not distinguish the drug responsible for the ED visit from other drugs that may have been used concomitantly. As stated in a DAWN report, "Since marijuana/hashish is frequently present in combination with other drugs, the reason for the ED visit may be more relevant to the other drug(s) involved in the episode."

For 2011, DAWN\(^2\) estimates a total of 5,067,374 (95 percent confidence interval [CI]: 4,616,753 to 5,517,995) drug-related ED visits from the entire United States. Of these, approximately 2,462,948 ([CI]: 2,112,868 to 2,813,028) visits involved drug misuse or abuse.

During the same period, DAWN estimates that 1,252,500 (CI: 976,169 to 1,528,831) drug related ED visits involved illicit drugs. Thus, over half of all drug-related ED visits associated with drug misuse or abuse involved an illicit drug. For ED visits involving illicit drugs, 56.3 percent involved multiple drugs while 43.7 percent involved a single drug.

Marijuana was involved in 455,668 ED visits (CI: 370,995 to 540,340), while cocaine was involved in 555,224 (CI: 324,262 to 686,185) ED visits, heroin was involved in 258,482 (CI: 205,046 to 311,918) ED visits and stimulants including amphetamine and methamphetamine were involved in 159,840 (CI: 100,199 to 219,481) ED visits. Other illicit drugs, such as PCP, MDMA, GHB and LSD were much less frequently associated with ED visits. The number of ED visits involving marijuana has increased by 62 percent since 2004.

Marijuana-related ED visits were most frequent among young adults and minors. Individuals under the age of 18 accounted for 13.2 percent of these marijuana-related visits, whereas this age group accounted for approximately 1.2 percent of ED visits involving cocaine, and less than 1 percent of ED visits involving heroin. However, the age group with the most marijuana-related ED visits was between 25 and 29 years old. Yet, because populations differ between age groups, a standardized measure for population size is useful to make comparisons. For marijuana, the rates of ED visits per 100,000 population were highest for patients aged 18 to 20 (443.8 ED visits per 100,000) and for patients aged 21 to 24 (446.9 ED visits per 100,000).

While DAWN provides estimates for ED visits associated with the use of medical marijuana for 2009–2011, the validity of these estimates is questionable. Because the drug is not approved by the FDA, reporting medical marijuana may be inconsistent and reliant on a number of factors including whether the patient self-reports the marijuana use as medicinal, how the treating health care provider records the marijuana use, and lastly how the SAMHSA coder interprets the report. All of these aspects will vary greatly between states with medical marijuana laws and states without medical marijuana laws. Thus, even though estimates are reported for medical marijuana related ED visits, medical marijuana estimates cannot be assessed with any acceptable accuracy at this time, as FDA has not approved marijuana treatment of any medical condition. These data show the difficulty in evaluating abuse of a product that is not currently approved by FDA, but authorized for medical use, albeit inconsistently, at the state level. Thus, we believe the likelihood of the treating health care provider or SAMHSA coder attributing the ED visit to "medical marijuana” versus “marijuana” to be very low. Overall, the available data are inadequate to characterize its abuse at the community level.

\(^1\)DAWN is a national probability survey of the U.S. hospitals with ED designed to obtain information on drug related ED visits. DAWN is sponsored by SAMHSA. The DAWN system provides information on the health consequences of drug use in the United States, as manifested by drug-related visits to ED. The ED data from a representative sample of hospital emergency departments are weighted to produce national estimates. Importantly, DAWN data and estimates, starting in 2004, are not comparable to those for prior years because of vast changes in the methodology used to collect the data. Furthermore, estimates for 2004 are the first to be based on a redesigned sample of hospitals, which ended in 2011.

Treatment Episode Data Set (TEDS) 41

Primary marijuana abuse accounted for 18.1 percent of all 2011 TEDS 42 admissions. Individuals admitted for primary marijuana abuse were nearly three-quarters (73.4 percent) male, and almost half (45.2 percent) were white. The average age at admission was 24 years old, and 31.1 percent of individuals admitted for primary marijuana abuse were under the age of 18. The reported frequency of marijuana use was 24.3 percent reporting daily use. Almost all (96.8 percent) primary marijuana users utilized the substance by smoking. Additionally, 92.9 percent reported using marijuana for the first time before the age of 18.

An important aspect of TEDS admission data for marijuana is of the referral source for treatment. Specifically, primary marijuana admissions were less likely than all other admissions to either be self-referred or referred by an individual for treatment. Instead, the criminal justice system referred more than half (51.6 percent) of primary marijuana admissions.

Since 2003, the percent of admissions for primary marijuana abuse increased from 15.5 percent of all admissions in 2003 to 18.1 percent in 2011. This increase is less than the increase seen for admissions for primary opioids other than heroin, which increased from 2.8 percent in 2003 to 7.3 percent in 2011. In contrast, the admissions for primary cocaine abuse declined from 9.8 percent in 2003 to 2.0 percent in 2011.

5. The Scope, Duration, and Significance of Abuse

Under the fifth factor, the Secretary must consider the scope, duration, and significance of marijuana abuse. According to 2012 data from NSDUH and 2013 data from MTF, marijuana remains the most extensively used illegal drug in the United States, with 42.8 percent of U.S. individuals over age 12 (11.2 million) and 45.5 percent of 12th graders having used marijuana at least once in their lifetime. Although the majority of individuals over age 12 (83.1 percent) who have ever used marijuana in their lifetime do not use the drug monthly, 18.9 million individuals (7.3 percent of the U.S. population) report that they used marijuana within the past 30 days. An examination of use among various age cohorts through NSDUH demonstrates that monthly use occurs primarily among college-aged individuals, with use dropping off sharply after age 25. Additionally, NSDUH data show the number of individuals reporting past-month use of marijuana has increased by 4.3 million individuals since 2004. Data from MTF shows that annual prevalence of marijuana use declined for all three grades from 2005 through 2007, then began to rise through 2013.

Additionally, in 2013, 1.1 percent of 8th graders, 4.0 percent of 10th graders, and 6.5 percent of 12th graders reported daily use of marijuana, defined as use on 20 or more days within the past 30 days.

The 2011 DAWN data show that marijuana use was mentioned in 455,668 ED visits, which amounts to approximately 36.4 percent of all illicit drug-related ED visits. 43 TEDS data for 2011 show that 18.1 percent of all admissions were for primary marijuana abuse. 44 Between 2003 and 2011, there was a 2.6 percent increase in the number of TEDS admissions for primary marijuana use.

41 The TEDS system is part of SAMHSA’s Drug and Alcohol Services Information System (Office of Applied Science, SAMHSA). The TEDS report presents information on the demographic and substance use characteristics of the 1.8 million annual admissions to treatment for alcohol and drug abuse in facilities that report to individual state administrative data systems. Specifically, TEDS includes facilities licensed or certified by the states to provide substance abuse treatment and is required by the states to provide TEDS client-level data. Facilities that report TEDS data are those receiving State alcohol and drug agency funds for the provision of alcohol and drug treatment services. Since TEDS is based only on reports from these facilities, TEDS data do not represent the total national demand for substance abuse treatment or the prevalence of substance abuse in the general population. The primary goal for TEDS is to monitor the characteristics of treatment episodes for substance abusers. Importantly, TEDS is an admissions-based system, where admittance to treatment is counted as an anonymous tally. For instance, a given individual who is admitted to treatment twice within a given year would be counted as two admissions. The most recent year with complete data is 2011.


43 Many factors can influence the estimates of ED visits, including trends in the reasons for ED usage. For instance, some drug users may visit EDs for life-threatening issues while others may visit to seek care for detoxification because they needed certification before entering treatment. Additionally, DAWN data do not distinguish the drug responsible for the ED visit from other drugs that may have been used concomitantly. As stated in a DAWN report, “Since marijuana/hashish is frequently present in combination with other drugs, the reason for the ED visit may be more relevant to the other drug[s] involved in the episode.”

44 An important aspect of TEDS admission data for marijuana is the referral source for treatment. Specifically, primary marijuana admissions were less likely than all other admissions to either be self-referred or referred by an individual for treatment. Instead, the criminal justice system referred more than half (51.6 percent) of primary marijuana admissions.

Approximately 61.5 percent of primary marijuana admissions in 2011 were for individuals under the age of 25 years.

6. WHAT, if Any, Risk There Is to the Public Health

Under the sixth factor, the Secretary must consider the risks posed to the public health by marijuana. Factors 1, 4, and 5 include a. discussion of the risk to the public health as measured by emergency room episodes and drug treatment admissions. Additionally, Factor 2 includes a discussion of marijuana’s central nervous system, cognitive, cardiovascular, autonomic, respiratory, and immune system effects. Factor 6 focuses on the health risks to the individual user in terms of the risks from acute and chronic use of marijuana, as well as the “gateway hypothesis.”

Risks From Acute Use of Marijuana

Acute use of marijuana impairs psychomotor performance, including complex task performance, which makes operating motor vehicles or heavy equipment after using marijuana inadvisable (Ramaekers et al., 2004; Ramaekers et al., 2006a). A meta-analysis conducted by Li et al. (2011) showed an association between marijuana use by the driver and a significantly increased risk of involvement in a car accident. Additionally, in a minority of individuals who use marijuana, some potential responses include dysphoria and psychological distress, including prolonged anxiety reactions (Haney et al., 1999).

Risks From Chronic Use of Marijuana

A distinctive marijuana withdrawal syndrome following long term or chronic use has been identified. The withdrawal syndrome indicates that marijuana produces physical dependence that is mild, short-lived, and comparable to tobacco withdrawal (Budney et al., 2008). Marijuana withdrawal syndrome is described in detail below under Factor 7.

The following states how the DSM–V (2013) of the American Psychiatric Association describes the consequences of marijuana abuse:

Individuals with cannabis use disorder may use cannabis throughout the day over a period of months or years, and thus may spend many hours a day under the influence. Others may use less frequently, but their use causes recurrent problems related to family
school, work, or other important activities (e.g., repeated absences at work; neglect of family obligations). Periodic cannabis use and intoxication can negatively affect behavioral and cognitive functioning and thus interfere with optimal performance at work or school, or place the individual at increased physical risk when performing activities that could be physically hazardous (e.g., driving a car; playing certain sports; performing manual work activities, including operating machinery). Arguments with spouses or parents over the use of cannabis in the home, or its use in the presence of children, can adversely impact family functioning and are common features of those with cannabis use disorder. Last, individuals with cannabis use disorder may continue using marijuana despite knowledge of physical problems (e.g., chronic cough related to smoking) or psychological problems (e.g., excessive sedation or exacerbation of other mental health problems) associated with its use.

Marijuana as a “Gateway Drug”

Kandel (1975) proposed nearly 40 years ago the hypothesis that marijuana is a “gateway drug” that leads to the use or abuse of other illicit drugs. Since that time, epidemiological research explored this premise. Overall, research does not support a direct causal relationship between regular marijuana use and other illicit drug use. The studies examining the gateway hypothesis are limited. First, in general, studies recruit individuals influenced by a myriad of social, biological, and economic factors that contribute to extensive drug abuse (Hall & Lynskey, 2005). Second, most studies that test the hypothesis that marijuana use causes abuse of other illicit drugs use the determinative measure any use of an illicit drug, rather than DSM–5 criteria for drug abuse or dependence on an illicit drug (DSM–5, 2013). Consequently, although an individual who used marijuana may try other illicit drugs, the individual may not regularly use drugs, or have a diagnosis of drug abuse or dependence.

Little evidence supports the hypothesis that initiation of marijuana use leads to an abuse disorder with other illicit substances. For example, one longitudinal study of 708 adolescents demonstrated that early onset marijuana use did not lead to problematic drug use (Kandel & Chen, 2000). Similarly, Nace et al. (1975) examined Vietnam-era soldiers who extensively abused marijuana and heroin in the military, and found a lack of correlation of a causal relationship demonstrating marijuana use leading to heroin addiction. Additionally, in another longitudinal study of 2,446 adolescents, marijuana dependence was uncommon but when it did occur, the common predictors of marijuana dependence were the following: Parental death, deprived socio-economic status, and baseline illicit drug use other than marijuana (von Sydow et al., 2002).

When examining the association between marijuana and illicit drugs, focusing on drug use versus abuse or dependence, different patterns emerge. For example, a study examining the possible causal relationship of the gateway hypothesis found a correlation between marijuana use in adolescents and other illicit drug use in early adulthood and, adjusting for age-linked experiences, did not effect this correlation (Van Gundy and Rebello, 2010). However, when examining the association in terms of development of drug abuse; age-linked stressors and social roles moderated the correlation between marijuana use in adolescents and other illicit drug use. Similarly, Degenhardt et al. (2009) examined the development of drug dependence and found an association that did not support the gateway hypothesis. Specifically, drug dependence was significantly associated with the use of other illicit drugs prior to marijuana use.

Interestingly, the order of initiation of drug use seems to depend on the prevalence of use of each drug, which varies by country. Based on the World Health Organization (WHO) World Mental Health Survey that includes data from 17 different countries, the order of drug use initiation varies by country and relates to prevalence of drug use in each country (Degenhardt et al., 2010). Specifically, in the countries with the lowest prevalence of marijuana use, use of other illicit drugs before marijuana was common. This sequence of initiation is less common in countries with higher prevalence of marijuana use. A study of 9,282 households in the United States found that marijuana use often preceded the use of other illicit drugs; however, prior non-marijuana drug dependence was also frequently correlated with higher levels of illicit drug abuse (Degenhardt et al., 2009). Additionally, in a large 25-year longitudinal study of 1,256 New Zealand children, the author concluded that marijuana use correlated to an increased risk of abuse of other drugs, including cocaine and heroin (Fergusson et al., 2005). Therefore, individuals with a drug abuse disorder may have used marijuana as one of their first illicit drugs, this fact does not correctly lead to the reverse inference that most individuals who used marijuana will inherently go on to try or become regular users of other illicit drugs. Specifically, data from the 2011 NSDUH survey illustrates this issue (SAMHSA, 2012). NSDUH data estimates 107.8 million individuals have a lifetime history of marijuana use, which indicates use on at least one occasion, compared to approximately 36 million individuals having a lifetime history of cocaine use and approximately 4 million individuals having a lifetime history of heroin use. NSDUH data do not provide information about each individual’s specific drug history. However, even if one posits that every cocaine and heroin user previously used marijuana, the NSDUH data show that marijuana use at least once in a lifetime does not predict that an individual will also use another illicit drug at least once.

Finally, a review of the gateway hypothesis by Vanyukov et al. (2012) notes that because the gateway hypothesis only addresses the order of drug use initiation, the gateway hypothesis does not specify any mechanistic connections between drug “stages” following exposure to marijuana and does not extend to the risks for addiction. This concept contrasts with the concept of a common liability to addiction that involves mechanisms and biobehavioral characteristics pertaining to the entire course of drug abuse risk and disorders.

7. Its Psychic or Physiologic Dependence Liability

Under the seventh factor, the Secretary must consider marijuana’s psychic or physiological dependence liability.

Psychic or psychological dependence has been shown in response to marijuana’s psychoactive effects. Psychoactive responses to marijuana are pleasurable to many humans and are associated with drug-seeking and drug-taking (Maldonado, 2002). Moreover, high levels of psychoactive effects, notably positive reinforcement, are associated with increased marijuana use, abuse, and dependence (Scherrer et al., 2009; Zeiger et al., 2010). Epidemiological data support these findings through 2012 NSDUH statistics that show that of individuals years 12 or older who used marijuana in the past month, an estimated 40.3 percent used marijuana on 20 or more days within the past month. This equates to approximately 7.6 million individuals aged 12 or older who used marijuana on a daily or almost daily basis.
Additionally, the 2013 MTF data report the prevalence of daily marijuana use, defined as use on 20 or more days within the past 30 days, in 8th, 10th, and 12th graders is 1.1 percent, 4.0 percent, and 6.5 percent, respectively.

Tolerance can develop to some, but not all, of marijuana’s effects. Specifically, tolerance does not seem to develop in response to many of marijuana’s psychoactive effects. This lack of tolerance may relate to electroencephalogram data demonstrating that chronic delta-THC administration does not affect increased neuronal firing in the ventral tegmental area, a region known to play a critical role in drug reinforcement and reward (Wu and French, 2000). In the absence of other abuse indicators, such as rewarding properties, the presence of tolerance or physical dependence does not determine whether a drug has abuse potential.

However, humans can develop tolerance to marijuana’s cardiovascular, autonomic, and behavioral effects (Jones et al., 1981). Tolerance to some of marijuana’s behavioral effects seems to develop after heavy marijuana use, but not after occasional marijuana use. For instance, following acute administration of marijuana, heavy marijuana users did not exhibit impairments in tracking and attention tasks, as were seen in occasional marijuana users (Ramaekers et al., 2009). Furthermore, a neurophysiological assessment administered through an electroencephalograph (EEG) which measures event-related potentials (ERP) conducted in the same subjects as the previous study, found a corresponding effect in the P100 component of ERPs. Specifically, corresponding to performance on tracking and attention tasks, heavy marijuana users showed no changes in P100 amplitudes following acute marijuana administration, although occasional users showed a decrease in P100 amplitudes (Theunissen et al., 2012). A possible mechanism underlying tolerance to marijuana’s effects may be the down-regulation of cannabinoid receptors (Hirvonen et al., 2012; Gonzalez et al., 2005; Rodriguez de Fonseca et al., 1994; Oviedo et al., 1993).

Importantly, pharmacological tolerance alone does not indicate a drug’s physical dependence liability. In order for physical dependence to exist, evidence of a withdrawal syndrome is needed. Physical dependence is a state of adaptation, manifested by a drug-class specific withdrawal syndrome produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist (Ibid). Many medications not associated with abuse or addiction can produce physical dependence and withdrawal symptoms after chronic use. Discontinuation of heavy, chronic marijuana use has been shown to lead to physical dependence and withdrawal symptoms (American Psychiatric Association DSM-V, 2013; Budney and Hughes, 2006; Haney et al., 1999). In heavy, chronic marijuana users, the most commonly reported withdrawal symptoms are sleep difficulties, decreased appetite, weight loss, irritability, anger, anxiety or nervousness, and restlessness. Some less commonly reported withdrawal symptoms are depressed mood, sweating, shakiness, physical discomfort, and chills (Budney and Hughes, 2006; Haney et al., 1999). The occurrence of marijuana withdrawal symptoms in light or non-daily marijuana users has not been established. The American Psychiatric Association’s DSM–V (2013) includes a list of symptoms of ‘cannabis withdrawal’. Of marijuana withdrawal symptoms begin within 24–48 hours of discontinuation, peak within 4–6 days, and last for 1–3 weeks. Marijuana withdrawal syndrome has been reported in adolescents and adults admitted for substance abuse treatment. Based on clinical descriptions, this syndrome appears to be mild compared to classical alcohol and barbiturate withdrawal syndromes, which can include more serious symptoms such as agitation, paranoia, and seizures.

Multiple studies comparing marijuana and tobacco withdrawal symptoms in humans demonstrate that the magnitude and time course of the two withdrawal syndromes are similar (Budney et al., 2008; Vandrey et al., 2005, 2008).

8. Whether the Substance Is an Immediate Precursor of a Substance Already Controlled Under This Article

Under the eight factor analysis, the Secretary must consider whether marijuana is an immediate precursor of a controlled substance. Marijuana is not an immediate precursor of another controlled substance.

Recommendation

After consideration of the eight factors discussed above, FDA recommends that marijuana remain in Schedule I of the CSA. NIDA concurs with this scheduling recommendation. Marijuana meets the three criteria for placing a substance in Schedule I of the CSA under 21 U.S.C. 812(b)(I):

1. Marijuana has a high potential for abuse:

A number of factors indicate marijuana’s high abuse potential, including the large number of individuals regularly using marijuana, marijuana’s widespread use, and the vast amount of marijuana available for illicit use. Approximately 18.9 million individuals in the United States (7.3 percent of the U.S. population) used marijuana monthly in 2012. Additionally, approximately 4.3 million individuals met diagnostic criteria for marijuana dependence or abuse in the year prior to the 2012 NSDUH survey. A 2013 survey indicates that by 12th grade, 36.4 percent of students report using marijuana within the past year, and 22.7 percent report using marijuana monthly. In 2011, 457,668 ED visits were marijuana-related, representing 36.4 percent of all illicit drug-related episodes. Primary marijuana use accounted for 16.1 percent of admissions to drug treatment programs in 2011. Additionally, marijuana has dose-dependent reinforcing effects, as demonstrated by data showing that humans prefer relatively higher doses to lower doses. Furthermore, marijuana use can result in psychological dependence.

2. Marijuana has no currently accepted medical use in treatment in the United States:

FDA has not approved a marketing application for a marijuana drug product for any indication. The opportunity for scientists to conduct clinical research with marijuana exists, and there are active INDs for marijuana; however, marijuana does not have a currently accepted medical use for treatment in the United States, nor does marijuana have an accepted medical use with severe restrictions.

A drug has a “currently accepted medical use” if all of the following five elements have been satisfied:

a. the drug’s chemistry is known and reproducible;

b. there are adequate safety studies;

c. there are adequate and well-controlled studies proving efficacy;

d. the drug is accepted by qualified experts; and

e. the scientific evidence is widely available.
Marijuana does not meet any of the elements for having a "currently accepted medical use." First, FDA broadly evaluated marijuana, and did not focus its evaluation on particular strains of marijuana or components or derivatives of marijuana. Since different strains may have different chemical constituents, marijuana, as identified in this petition, does not have a known and reproducible chemistry, which would be needed to provide standardized doses. Second, there are not adequate safety studies on marijuana in the medical literature in relation to a specific, recognized disorder. Third, there are no published, hand and well controlled studies proving efficacy of marijuana. Fourth, there is no evidence that qualified experts accept marijuana for use in treating a specific, recognized disorder. Lastly, the scientific evidence regarding marijuana's chemistry in terms of a specific Cannabis strain that could produce standardized and reproducible doses is not currently available, so the scientific evidence on marijuana is not widely available.

Alternately, a Schedule II drug can be considered to have a "currently accepted medical use with severe restrictions" [21 U.S.C. 812(b)(2)(B)]. Yet as stated above, the lack of accepted medical use for a specific, recognized disorder precludes the use of marijuana even under conditions where its use is severely restricted.

In conclusion, to date, research on marijuana's medical use has not developed to the point where marijuana is considered to have a "currently accepted medical use" or a "currently accepted medical use with severe restrictions."

(3) There is a lack of accepted safety for use of marijuana under medical supervision:

There are currently no FDA-approved marijuana drug products. Marijuana does not have a currently accepted medical use in the United States or a currently accepted medical use with severe restrictions. Thus, FDA has not determined that marijuana is safe for use under medical supervision.

In addition, FDA cannot conclude that marijuana has an acceptable level of safety relative to its effectiveness in treating a specific, recognized disorder without evidence that the substance is contamination free, and assurance of a consistent and predictable dose.

Investigation into the medical use of marijuana should include information and data regarding the chemistry, manufacturing, and specifications of marijuana. Additionally, a procedure for delivering a consistent dose of marijuana should also be developed. Therefore, FDA concludes marijuana does not currently have an accepted level of safety for use under medical supervision.

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The Medical Application of Marijuana: A Review of Published Clinical Studies

March 19, 2015
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Controlled Substance Staff (CSS)

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Executive Summary

Marijuana is a Schedule I substance under the Controlled Substances Act (CSA). Schedule I indicates a high potential for abuse, no currently accepted medical use in the United States, and a lack of accepted safety for use under medical supervision. To date, marijuana has not been subject to an approved new drug application (NDA) that demonstrates its safety and efficacy for a specific indication under the Food Drug and Cosmetic Act (FDCA).

Nevertheless, as of October 2014, twenty-three states and the District of Columbia have passed state-level medical marijuana laws that allow for marijuana use within that state; similar bills are pending in other states.

The present review was undertaken by the Food and Drug Administration (FDA) to analyze the clinical studies published in the medical literature investigating the use of marijuana in any therapeutic areas. First, we discuss the context for this scientific review. Next, we describe the methods used in this review to identify adequate and well-controlled studies evaluating the safety and efficacy of marijuana for particular therapeutic uses.

The FDA conducted a systematic search for published studies in the medical literature that meet the described criteria for study design and outcome measures prior to February 2013. While not part of our systematic review, we have continued to routinely follow the literature beyond that date for subsequent studies. Studies were considered to be relevant to this review if the investigators administered marijuana to patients with a diagnosed medical condition in a well-controlled, double-blind, placebo-controlled clinical trial. Of the eleven studies that met the criteria for review, five different therapeutic areas were investigated:

- Five studies examined chronic neuroprotective pain
- Two studies examined appetite stimulation in human immunodeficiency virus (HIV) patients
- Two studies examined glaucoma
- One study examined spasticity and pain in multiple sclerosis (MS)
- One study examined asthma

For each of these eleven clinical studies, information is provided regarding the subjects studied, the drug conditions tested (including dose and method of administration), other drugs used by subjects during the study, the physiological and subjective measures collected, the outcome of these measures comparing treatment with marijuana to placebo, and the reported and observed adverse events. The conclusions drawn by the investigators are then described, along with potential limitations of these conclusions based on the study design. A brief summary of each study’s findings and limitations is provided at the end of the section.

The eleven clinical studies that met the criteria and were evaluated in this review showed positive signals that marijuana may produce a desirable therapeutic outcome, under the specific experimental conditions tested. Notably, it is beyond the scope of this review to determine whether these data demonstrate that marijuana has a currently accepted medical use in the United States. However, this review concludes that these eleven clinical studies serve as proof-of-concept studies, based on the limitations of their study designs, as described in the study summaries. Proof-of-concept studies provide preliminary evidence on a proposed hypothesis regarding a drug’s effect. For drugs under development, the effect often relates to a short-term clinical outcome being investigated. Proof-of-concept studies serve as the link between preclinical studies and dose ranging clinical studies. Therefore, proof-of-concept studies are not sufficient to demonstrate efficacy of a drug because they provide only preliminary information about the effects of a drug. However, the studies reviewed produced positive results, suggesting marijuana should be further evaluated as an adjunct treatment for neuropathic pain, appetite stimulation in HIV patients, and spasticity in MS patients.

The main limitations identified in the eleven studies testing the medical applications of marijuana are listed below:

- The small numbers of subjects enrolled in the studies, which limits the statistical analyses of safety and efficacy.
- The evaluation of marijuana only after acute administration in the studies, which limits the ability to determine efficacy following chronic administration.
- The administration of marijuana typically through smoking, which exposes ill patients to combusted material and introduces problems with determining the doses delivered.
- The potential for subjects to identify whether they received marijuana or placebo, which breaks the blind of the studies.
- The small number of cannabinoid naïve subjects, which limits the ability to determine safety and tolerability in these subjects.
- The low number of female subjects, which makes it difficult to generalize the study findings to subjects of both genders.

Thus, this review discusses the following methodological changes that may be made in order to resolve these limitations and improve the design of future studies which examine the safety and efficacy of marijuana for specific therapeutic indications:

- Determine the appropriate number of subjects studied based on recommendations in various FDA Guidance for Industry regarding the conduct of clinical trials for specific medical indications.
- Evaluate the effects of marijuana under therapeutic conditions following both acute and chronic administration.
- Consider alternatives to smoked marijuana (e.g., vaporization).
- Address and improve whenever possible the difficulty in blinding of marijuana and placebo treatments in clinical studies.
- Evaluate the effect of prior experience with marijuana with regard to the safety and tolerability of marijuana.

- Strive for gender balance in the subjects used in studies.

In conclusion, the eleven clinical studies conducted to date do not meet the criteria required by the FDA to determine if marijuana is safe and effective in specific therapeutic areas. However, the studies can serve as proof-of-concept studies and support further research into the use of marijuana in these therapeutic indications. Additionally, the clinical outcome data and adverse event profiles reported in these published studies can beneficially inform how future research in this area is conducted. Finally, application of the recommendations listed above by investigators when designing future studies could greatly improve the available clinical data that can be used to determine if marijuana has validated and reliable medical applications.

1. Introduction

In response to citizen petitions submitted to the Drug Enforcement Administration (DEA) requesting DEA to reschedule marijuana, the DEA Administrator requested that the U.S. Department of Health and Human

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27 This Guidance is available on the internet at http://www.fda.gov/Drugs/default.htm under Guidance (Drugs).
Services (HHS) provide a scientific and medical evaluation of the available information and a scheduling recommendation for marijuana, in accordance with 21 U.S.C. 811(b). The Secretary of HHS is required to consider in a scientific and medical evaluation eight factors determinative of control under the Controlled Substance Act (CSA). Administrative responsibilities for evaluating a substance for control under the CSA are performed by the Food and Drug Administration (FDA), with the concurrence of the National Institute on Drug Abuse (NIDA). Part of this evaluation includes an assessment of whether marijuana has a currently accepted medical use in the United States. This assessment necessitates a review of the available data from published clinical studies to determine whether there is adequate scientific evidence of marijuana’s effectiveness.

Under Section 202 of the CSA, marijuana is currently controlled as a Schedule I substance (21 U.S.C. 812). Schedule I includes those substances that have a high potential for abuse, have no currently accepted medical use in treatment in the United States, and lack accepted safety for use under medical supervision (21 U.S.C. §812(b)(1)(A)–(C)).

A drug product which has been approved by FDA for marketing in the United States is considered to have a “currently accepted medical use.”

Marijuana is not an FDA-approved drug product, as a New Drug Application (NDA) or Biologics License application (BLA) for marijuana has not been approved by FDA. However, FDA approval of an NDA is not the only means through which a drug can have a currently accepted medical use in the United States.

In general, a drug may have a “currently accepted medical use” in the United States if the drug meets a five-part test. Established case law (Alliance for Cannabis Therapeutics v. DEA, 15 F.3d 1131, 1135 (D.C. Cir. 1994)) upheld the Administrator of DEA’s application of the five-part test to determine whether a drug has a “currently accepted medical use.” The following describes the five elements that characterize “currently accepted medical use” for a drug: 24

i. The drug’s chemistry must be known and reproducible.

“...”

section 201(j) of the Food, Drug and Cosmetic Act, 21 U.S.C. 321(j), is sufficient to meet this requirement.” ii. There must be adequate safety studies.

“There must be adequate pharmacological and toxicological studies, done by all methods reasonably applicable, on the basis of which it could fairly and responsibly be concluded, by experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, that the substance is safe for treating a specific, recognized disorder.” iii. There must be adequate and well-controlled studies proving efficacy.

“There must be adequate, well-controlled, well-designed, well-conducted, and well-documented studies, including clinical investigations, by experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, on the basis of which it could be fairly and responsibly concluded by such experts that the substance will have the intended effect in treating a specific, recognized disorder.” iv. The drug must be accepted by qualified experts.

“The drug has a New Drug Application (NDA) approved by the Food and Drug Administration, pursuant to the Food, Drug and Cosmetic Act, 21 U.S.C. 355. Or, a consensus of the national community of experts, qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, accepts the safety and effectiveness of the substance for use in treating a specific, recognized disorder. A material conflict of opinion among experts precludes a finding of consensus.” and v. The scientific evidence must be widely available.

“In the absence of NDA approval, information concerning the chemistry, pharmacology, toxicology, and effectiveness of the substance must be reported, published, or otherwise widely available, in sufficient detail to permit experts, qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, to fairly and responsibly conclude the substance is safe and effective for use in treating a specific, recognized disorder.”

One way to pass the five-part test for having “currently accepted medical use” is through submission of an NDA or BLA which is approved by FDA. However, FDA approval of an NDA or BLA is not required for a drug to pass the five-part test.

This review focuses on FDA’s analysis of one element of the five-part test for determining whether a drug has “currently accepted medical use”.

Specifically, the present review assesses the 3rd criterion that addresses whether marijuana has “adequate and well-controlled studies proving efficacy”. Thus, this review evaluates published clinical studies that have been conducted using marijuana in subjects who have a variety of medical conditions by assessing the adequacy of the summarized study designs and the study data. The methodology for selecting the studies that were evaluated is delineated below.

FDA’s evaluation and conclusions regarding the remaining four criteria for whether marijuana has a “currently accepted medical use,” as well as the eight factors pertaining to the scheduling of marijuana, are outside the scope of this review. A detailed discussion of these factors is contained in FDA’s scientific and medical evaluation of marijuana.

2. Methods

The methods for selecting the studies to include in this review involved the following steps, which are described in detail in the subsections below:

1. Define the objective of the review.
2. Define “marijuana” in order to facilitate the medical literature search for studies that administered the substance.
3. Define “adequate and well-controlled studies” in order to facilitate the search for relevant data and literature.
4. Search medical literature databases and identify relevant adequate and well-controlled studies, and
5. Review and analyze the adequate and well-controlled clinical studies to determine if they demonstrate efficacy of marijuana for any therapeutic indication.

2.1 Define the Objective of the Review

The objective of this review is to assess the study designs and resulting data from clinical studies published in the medical literature that were conducted with marijuana (as defined below) as a treatment for any therapeutic indication, in order to determine if they meet the criteria of “adequate and well-controlled studies proving efficacy”.

2.2 Define “Marijuana”

In this review, the term “marijuana” refers to the flowering tops or leaves of the Cannabis plant. There were no restrictions on the route of administration used for marijuana in the studies.

Studies which administered individual cannabinoids (whether

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24 57 FR 10499, 10504–06 (March 26, 1992).
experimental substances or marketed drug products) or marijuana extracts were excluded from this review. Additionally, studies of administered neutral plant material or placebo marijuana (marijuana with all cannabinoids excluded) that had subsequently been supplemented by the addition of specific amounts of THC or other cannabinoids were also excluded (Chang et al., 1979).

2.3 Define “Adequate and Well-Controlled Clinical Studies”

The criteria for an “adequate and well-controlled study” for purposes of determining the safety and efficacy of a human drug is defined under the Code of Federal Regulations (CFR) in 21 CFR 314.126. The elements of an adequate and well-controlled study as described in 21 CFR 314.126 can be summarized as follows:

1. The main objective must be to assess a therapeutically relevant outcome.
2. The study must be placebo-controlled.
3. The subjects must qualify as having the medical condition being studied.
4. The study design permits a valid comparison with an appropriate control condition.
5. The assignment of subjects to treatment and control groups must be randomized.
6. There is minimization of bias through the use of a double-blind study design.
7. The study report contains a full protocol and primary data.
8. Analysis of the study data is appropriately conducted.

As noted above, the current review examines only those data available in the public domain and thus relies on clinical studies published in the medical literature. Published studies by their nature are summaries that do not include the level of detail required by studies submitted to FDA in an NDA.

While the majority of the elements defining an adequate and well-controlled study can be satisfied through a published paper (elements #1–6), there are two elements that cannot be met by a study published in the medical literature: element #7 (availability of a study report with full protocol and primary data) and element #8 (a determination of whether the data analysis was appropriate). Thus, for purposes of this review, only elements #1–6 will be used to qualify a study as being adequate and well-controlled.

2.4 Search Medical Literature Databases and Identify Relevant Studies

We identified randomized, double-blind, placebo-controlled clinical studies conducted with marijuana to assess marijuana’s efficacy in any therapeutic indication. Two primary medical literature databases were searched for all studies posted to the databases prior to February 2013: 29

• PubMed: PubMed is a database of published medical and scientific studies that is maintained by the U.S. National Library of Medicine (NLM) at NIH as part of the Entrez system of information retrieval. PubMed comprises more than 24 million citations for biomedical literature from MEDLINE, life science journals, and online books (http://www.ncbi.nlm.nih.gov/pubmed).

• ClinicalTrials.gov:

ClinicalTrials.gov is a database of publicly and privately supported clinical studies that is maintained by the NLM. Information about the clinical studies is provided by the Sponsor or Principal Investigator of the study. Information about the studies is submitted to the Web site ("registered")

29While not a systematic review, we have followed the recent published literature on marijuana use for possible therapeutic purposes and, as of January 2015, we found only one new study that would meet our criteria (Naltali et al., 2013). This study examined the effects of smoked marijuana on Crohn’s disease.

when the studies begin, and is updated throughout the study. In some cases, results of the study or resulting publication citations are submitted to the Web site after the study ends (https://clinicaltrials.gov/ct2/about-site/background).

ClinicalTrials.gov was searched for all studies administering marijuana. The results of this search were used to confirm that no completed studies with published data were missed in the literature search. During the literature search, references found in relevant studies and systematic reviews were evaluated for additional relevant citations. All languages were included in the search. The PubMed search yielded a total of 566 abstracts.30 Of these abstracts, a full-text review was conducted with 85 papers to assess eligibility. From this evaluation, only eleven of 85 studies met the 6 CFR elements for inclusion as adequate and well-controlled studies.

Figure 1 (below) provides an overview of the process used to identify studies from the PubMed search. The eleven studies reviewed were published between 1974 and 2013. Ten of these studies were conducted in the United States and one study was conducted in Canada. These eleven studies examined the effects of smoked and vaporized marijuana for the indications of chronic neuropathic pain, spasticity related to multiple sclerosis (MS), appetite stimulation in patients with human immunodeficiency virus (HIV), glaucoma, and asthma. All included studies used adult patients as subjects. All studies conducted in the United States were conducted under an IND as Phase 2 investigations.

30The following search strategy was used, “(cannabis OR marijuana) AND (therapeutic use OR therapy) AND (RCT OR randomized controlled trial OR “systematic review” OR clinical trial OR clinical trials) NOT (“marijuana abuse” [Mesh] OR addictive behavior OR substance related disorders)”.
Figure 1: Identification of Studies from PubMed Search

![Diagram showing the identification process from PubMed search to eligible full-text articles]

- 566 Abstracts identified in PubMed search
- 481 Excluded because either clearly irrelevant, excluded article type, or not RCT
- 85 Full-text articles assessed for eligibility
- 76 Excluded
  - 63 Administered individual cannabinoids or marijuana plant derived products
    - 27 Administered delusional THC
    - 20 Administered marijuana plant extracts
    - 4 Administered Cannabidiol
    - 4 Administered hemp seed oil
    - 1 Administered Rimonaabant
  - 6 Were mechanistic studies
  - 7 Had a primary focus on safety
- 9 Articles from the PubMed search meet inclusion criteria

Articles were deemed irrelevant if they examined safety or adverse event related outcomes, including psychoactive effects or other adverse events. Excluded article types included comments, reviews, meta-analyses, and news articles. Randomized Controlled Trials. Cannabinoids administered included synthetic cannabinoids. Rimonaabant is a cannabinoid receptor antagonist. Additional 2 studies meeting the inclusion criteria were found through

Two qualifying studies, which assessed marijuana for glaucoma, were previously reviewed in the 1999 Institute of Medicine (IOM) report entitled “Marijuana and Medicine: Assessing the Science Base.” We did our own analysis of these two studies and concurred with the conclusions in the IOM report. Thus, a detailed discussion of the two glaucoma studies is not included in the present review. The present review only discusses 9 of the identified 11 studies. For a summary of the study design for all eleven qualifying studies, see Tables 1–5 (located in the Appendix).

Based on the selection criteria for relevant studies described in Section 2.3 (Define Adequate and Well-Controlled Clinical Studies), a number of clinical studies that investigated marijuana, as defined in this review, were excluded from this review. Studies that examined the effects of marijuana in healthy subjects were excluded because they did not test a patient population with a medical condition (Flom et al., 1975; Foltin et al., 1986; Foltin et al., 1988; Hill et al., 1974; Milstein et al., 1974; Milstein et al., 1975; Soderpalm et al., 2001; Wallace et al., 2007; Greenwald and Stitzer, 2000). A 1975 study by Tashkin et al. was excluded because it had a single-blind, rather than double-blind, study design. Two other studies were excluded because the primary outcome measure assessed safety rather than a therapeutic outcome (Greenberg et al., 1994; Abrams et al., 2003).

2.5 Review and Analyze Qualifying Clinical Studies

Qualified clinical studies that evaluated marijuana for therapeutic purposes were examined in terms of adequacy of study design including method of drug administration, study size, and subject inclusion and exclusion criteria. Additionally, the measures and methods of analysis used in the studies to assess the treatment effect were examined.

3. Results and Discussion

The eleven qualifying studies in this review assessed a variety of therapeutic indications. In order to better facilitate analysis and discussion of the studies, the following sections group the studies by therapeutic area. Within each section, each individual study is summarized in terms of its design, outcome data and important limitations. This information is also provided in the Appendix in tabular form for each study.

3.1 Neuropathic Pain

Five randomized, double-blind, placebo-controlled Phase 2 clinical studies have been conducted to examine the effects of inhaled marijuana smoke on neuropathic pain associated with HIV-sensory neuropathy (Abrams et al., 2007; Ellis et al., 2009) and chronic neuropathic pain from multiple causes (Wilsey et al., 2008; Ware et al., 2010; Wilsey et al., 2013). Table 1 of the Appendix summarizes these studies.
3.1.1 Neuropathic Pain Associated with HIV-Sensory Neuropathy

Two studies examined the effect of marijuana to reduce the pain induced by HIV-sensory neuropathy. Alfons et al. (2007) conducted the first study entitled, “Cannabis in painful HIV-associated sensory neuropathy: A randomized placebo-controlled trial”. The subjects were 50 adult patients with uncontrolled HIV-associated sensory neuropathy, who had at least 6 experiences with smoking marijuana. The subjects were split into two parallel groups of 25 subjects each. More than 68% of subjects were current marijuana users, but all individuals were required to discontinue using marijuana prior to the study. Most subjects were taking medication for pain during the study, with the most common medications being opioids and gabapentin. Upon entry into the study, subjects had an average daily pain score of at least 30 on a 0–100 visual analog scale (VAS).

Subjects were randomized to receive either smoked marijuana (3.56% THC) or smoked placebo cigarettes three times per day for 5 days, using a standardized cued smoking procedure: (1) 5 second inhale, (2) 10 second holding smoke in the lungs, (3) 40 second exhale and breathing normally between puffs. The authors did not specify how many puffs the subjects smoked at each smoking session, but they stated that one cigarette was smoked per smoking session.

Primary outcome measures included daily VAS ratings of chronic pain and the percentage of subjects who reported a result of more than 30% reduction in pain intensity. The ability of smoked marijuana to induce acute analgesia was assessed using both thermal heat model and capsaicin sensitization model, while anti-hyperalgesia was assessed with brush and von Frey hair stimuli. The immediate analgesic effects of smoked marijuana was assessed using a 0–100 point VAS at 40-minute intervals three times before and three times after the first and last smoking sessions, which was done to correspond to the time of peak plasma cannabinoid levels. Notably, not all subjects completed the induced pain portion of the study (n = 11 in marijuana group, 9 in placebo group) because of their inability to tolerate the stimuli. Throughout the study, subjects also completed the Profile of Mood States (POMS).

Previous experience with marijuana was not required for participation in the study, but 27 of 28 subjects (96%) reported previous experience with marijuana. However, of these 27 experienced subjects, 63% (n = 18) reported no marijuana use within the past year.

The study procedures compared the effects of the target dose of marijuana and placebo during two treatment periods lasting 5 days, with 2 weeks washout periods. The marijuana strengths available were 1%, 2%, 4%, 6%, or 8% THC concentration by weight. Subjects smoked marijuana or placebo cigarettes four times per day, approximately 90–120 minutes apart, using a standardized cued smoking procedure: (1) 5 second smoke inhalation, (2) 10 second hold of smoke in lungs, (3) 40 second exhale and normal breathing between puffs. The investigators did not provide a description of the number of puffs taken at any smoking session. All subjects practiced the smoking procedures using placebo marijuana prior to test sessions.

On the first day of each test period, dose titration occurred throughout the four smoking sessions scheduled for that day, with a starting strength of 4% THC concentration. Subjects were allowed to titrate to a personalized “target dose”, which was defined as the dose that provided the best pain relief without intolerable adverse effects. This dose titration was accomplished by allowing subjects to either increase the dose incrementally (to 6% or 8% THC) to improve analgesia, or to decrease the dose incrementally (to 1% or 2% THC) if AEs were intolerable. For the next 4 days of each test period, the subjects smoked their target dose during each of the four daily smoking sessions. To maintain the blind, placebo marijuana was represented as containing 1%–8% THC, even though it did not contain any cannabinoids.

The primary outcome measure was the change in pain magnitude on the DDS at the end of each test period compared to baseline, with a clinically significant level of analgesia considered to be a reduction in pain of at least 30%. Additional measures included the POMS, the Sickness Impact Profile (SIP), the Brief Symptom Inventory (BSI) and the UK Side Effect Rating Scale and a subjective highness/sedation VAS.

During the marijuana treatment week, 19 subjects titrated to the 2%–4% THC dose while the 6%–8% dose was preferred by 8 subjects and 1 subject chose the 1% dose. During the placebo treatment week, all 28 subjects titrated to the highest possible

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33 The drug use is reported as percentage of THC present in the marijuana rather than milligrams of THC present in each cigarette because of the difficulty in determining the amount of THC delivered by inhalation (see discussion in the section entitled “3.7.2 Marijuana Dose Standardization”).
dose of “8% THC” that contained no actual cannabinoids, suggesting that placebo treatment provided little analgesic relief.

The degree of pain reduction was significantly greater after administration of marijuana compared to placebo (median change of 3.3 points on DDS, $p = 0.016$). The median change from baseline in VAS pain scores was −17 for marijuana treatment compared to −4 for placebo treatment ($p < 0.001$). A larger proportion of subjects who were treated with marijuana (0.46) reported a >30% reduction in pain, compared to placebo (0.18). Additionally, the authors report improvements in total mood disturbance, physical disability, and quality of life as measured on POMS, SIP, and BSI scales after both placebo and marijuana treatment (data not provided in paper).

In terms of safety, there were no alterations in HIV disease parameters in response to marijuana or placebo. The authors report that marijuana led to a greater degree of TtU responses as well as AEs such as difficulty in concentration, fatigue, sleepiness or sedation, increased duration of sleep, reduced salivation and thirst compared to placebo (data not provided in paper).

Two subjects withdrew from the study because of marijuana-related AEs: one subject developed an intractable smoking-related cough during marijuana administration and the sole marijuana-naïve subject in the study experienced an incident of acute cannabis-induced psychosis.33

The authors conclude that smoked marijuana effectively reduced chronic neuropathic pain from HIV-associated sensory neuropathy. The limitations of this study include: a lack of information about the number of puffs during each inhalation of smoke; a lack of information about the specific timing of the subjective assessments and collection of AEs relative to initiation of the smoking sessions; and the inclusion of only one marijuana-naïve subject. These limitations make it difficult to conclude that the actual AEs experienced during the study in response to marijuana are tolerable. It is especially concerning that the only marijuana-naïve subject left the study because of serious psychiatric responses to marijuana exposure at analgesic doses. However, the study produced positive results suggesting that marijuana should be studied further as an adjunct treatment for uncontrolled HIV-associated sensory neuropathy.

3.1.2 Central and Peripheral Neuropathic Pain

Three studies examined the effect of marijuana on chronic neuropathic pain. Wilsey et al. (2008) examined chronic neuropathic pain in multiple causes in the study entitled, “A Randomized, Placebo-Controlled, Crossover Trial of Cannabis Cigarettes in Neuropathic Pain”. The subjects were 32 patients with a variety of neuropathic pain conditions, including 22 with complex regional pain syndrome, 6 with spinal cord injury, 4 with multiple sclerosis, 2 with diabetic neuropathy, and 2 with ilioinguinal neuralgia, and 2 with lumbar sacral plexopathy. All subjects reported a pain intensity of at least 30 on a 0–100 VAS and were allowed to continue taking their regular medications during the study period, which included opioids, antidepressants, anticonvulsants, and NSAIDs. All subjects were required to have experience with marijuana but could not use any cannabinoids for 30 days before study sessions. The study consisted of three test sessions with an interval of 3–21 days between sessions. Treatment conditions were high-strength marijuana (7% delta-9–THC), low-strength marijuana (3.5% delta-9–THC), and placebo cigarettes, administered through a standardized cued-puff procedure: (1) “light the cigarette” (30 seconds), (2) “get ready” (5 seconds), (3) “inhale” (5 seconds), (4) “hold smoke in lungs” (10 seconds), (5) “exhale,” and (6) wait before repeating the puff cycle (40 cycles). Participants took 2 puffs after baseline measurements, 3 puffs an hour later, and 4 puffs an hour after that, for a cumulative dose of 9 puffs per test session.

Hourly assessment periods were scheduled before and after each set of puffs and for 2 additional hours during the recovery period. Plasma cannabinoids were measured at baseline, 5 minutes after the first puff and again at 3 hours after the last puff cycle. The primary outcome measure was spontaneous pain relief, as measured by a 0–100 point VAS for current pain. Pain unpleasantness was measured on a 0–100 point VAS, and degree of pain relief was measured on a 7-point Patient Global Impression of Change (PGIC) scale. Secondary measures included the Neuropathic Pain Scale (NPS), a 0–100 point VAS for allodynia, and changes in thermal pain threshold. Subjective measures were also evaluated with unipolar 0–100 point VAS for any drug effect, good drug effect, bad drug effect, high, drunk, impaired, stoned, like the drug effect, sedated, confused, nauseated, desire more of the drug, anxious, down, hungry, and bipolar 0–100 point VAS for sad/happy, anxious/relaxed, jittery/calm, bad/good, paranoid/self-assured, fearful/unafraid. Neurocognitive assessments measured attention and concentration, learning and memory, and fine motor speed.

Marijuana produced a reduction in pain compared to placebo, as measured by the pain VAS, the PGIC and on pain descriptors in the NPS, including sharp ($P < .001$), burning ($P < .001$), aching ($P < .001$), sensitive ($P = .03$), superficial ($P < .01$) and deep pain ($P < .001$). Notably, there were no additional benefits from the 7% THC strength of marijuana compared to the 3.5% THC strength, seemingly because of cumulative drug effects over time. There were no changes in allodynia or thermal pain responsivity following administration of either dose of marijuana.

Marijuana at both strengths produced increases on measures of any drug effect, good drug effect, high, stoned, impairment, sedation, confusion, and hunger. The 7% THC marijuana increased anxiety scores and bad drug effect (later in session) compared to placebo. Neither strength of marijuana affected the measures of mood. On neurocognitive measures, both the 3.5% THC and 7% THC marijuana produced impairment in learning and memory, while only the 7% THC marijuana impaired attention and psychomotor speed, compared to placebo. There were no adverse cardiovascular side effects and no subjects dropped out because of an adverse event related to marijuana. The authors conclude that marijuana may be effective at ameliorating neuropathic pain at doses that induce mild cognitive effects, but that smoking is not an optimum route of administration. The limitations of this study include: inclusion of subjects with many forms of neuropathic pain and maintenance of subjects on other analgesic medication while being tested with marijuana. These limitations make it difficult to conclude that marijuana has analgesic properties on its own and that the actual AEs experienced during the study in response to marijuana are tolerable. The authors compared pain score results by the type of pain condition, with no significant differences found. However, the sample size of this study was small thus a type II error may have been present. Thus, it

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At the time of the study, the following criteria from the Diagnostic and Statistical Manual of Mental Disorders (DSM–IV–TR, 2000) were used to diagnose substance-induced psychotic disorders: prominent hallucinations or delusions; Hallucinations and/or Delusions that develop, or within one month of, intoxication or withdrawal; The disturbance is not better accounted for by a psychotic disorder that is not substance induced. The disturbance does not occur exclusively during the course of a delirium.
is difficult to determine if any particular subset of neuropathic pain conditions would benefit specifically from marijuana administration. However, the study produced positive results suggesting that marijuana should be studied further as an adjunct treatment for uncontrolled neuropathic pain.

The second study, conducted by Ware et al. (2010) in Canada is entitled, “Smoked cannabis for chronic neuropathic pain: a randomized controlled trial”. The subjects were 21 adult patients with neuropathic pain caused by trauma or surgery, compounded with alldynia or hyperalgesia, and a pain intensity score greater than 4 on a 10 point VAS. All subjects maintained their current analgesic medication and they were allowed to use acetaminophen for breakthrough pain. Eighteen subjects had previous experience with marijuana but none of them had used marijuana within a year before the study.

The study design used a four-period crossover design using marijuana (2.5%, 6.0% and 9.4% THC) and placebo marijuana. The 2.5% and 6.0% doses of marijuana were included to increase successful blinding. Each period was 14 days in duration, beginning with 5 days on the study drug followed by a 9-day washout period. Doses were delivered as 25 mg of marijuana that was smoked in a single inhalation using a titanium pipe. The first dose of each period was self-administered using a standardized puff procedure: (1) inhale for 5 seconds, (2) hold the smoke in their lungs for 10 seconds, and (3) exhale. Subsequent doses were self-administered in the same manner for a total of three times daily at home on an outpatient basis for the first five days of each period.

The primary measure was an 11-point pain intensity scale, averaged over the 5 day treatment period, which was administered once daily for present, worst, least and average pain intensity during the previous 24 hours. Secondary measures included an acute pain 0–100 point VAS, pain quality assessed with the McGill Pain Questionnaire, sleep assessed with the Leeds Sleep Evaluation Questionnaire, mood assessed with the POMS, quality of life assessed using the EQ–5D health outcome instrument. Subjective measures included 0–100 point VAS scales for high, relaxed, and happy.

Over the first three hours after smoking marijuana, ratings of pain, high, relaxation, stress, happiness and heart rate decreased. During the five days of each study period, participants were contacted daily to administer questionnaires on pain intensity, sleep, medication and AEs. Subjects returned on the fifth day to complete questionnaires on pain quality, mood, quality of life and assessments of potency. At the end of the study, participants completed final adverse event reports and potency assessments.

The average daily pain intensity was significantly lower on 9.4% THC marijuana (5.4) than on placebo marijuana (6.1) (p = 0.023). The 9.4% THC strength also produced more drowsiness, better sleep, with less anxiety and depression, compared to placebo (all p < 0.05). However, there were no significant differences on POMS scores or on VAS scores for high, happy, relaxed or stressed between THC doses.

The most frequent drug-related adverse events reported in the group receiving 9.4% THC marijuana were headache, dry eyes, burning sensation, dizziness, numbness and cough. Reports of high and euphoria occurred on only three occasions each dose of THC. There were no significant changes in vital signs, heart-rate variability, or renal function. One subject withdrew from the study due to increased pain during administration of 6% THC marijuana.

The authors conclude that smoked marijuana reduces neuropathic pain, improves mood and aids in sleep, but that smoking marijuana is not a preferable route of administration. The limitations of this study include: The lack of information on timing of assessments during the outpatient portion of the study and maintenance of subjects on other analgesic medication while being tested with marijuana. These limitations make it difficult to conclude that marijuana has analgesic properties on its own and that the actual AEs experienced during the study in response to marijuana are tolerable. However, the study produced positive results suggesting that marijuana should be studied further as an adjunct treatment for uncontrolled neuropathic pain.

Wilsey et al. (2013) conducted the most recent study entitled, “Low-Dose Vaporized Cannabis Significantly Improves Neuropathic Pain”. This study is the only one in this review that utilized vaporization as a method of marijuana administration. The subjects were 36 patients with a neuropathic pain disorder (CRPS, thalamic pain, spinal cord injury, peripheral neuropathy, radiculopathy, or nerve injury) who were maintained on their current medications (opioids, anticonvulsants, antidepressants, and NSAIDs). Although subjects were required to have a history of marijuana use, they refrained from use of cannabinoids for 30 days before study sessions.

Subjects participated in three sessions in which they received 1.29% or 3.53% THC marijuana or placebo marijuana. The marijuana was vaporized using the Volcano vaporizer and a standardized cued-puff procedure: (1) “hold the vaporizer bag with one hand and put the vaporizer mouthpiece in their mouth” (30 seconds), (2) “get ready” (5 seconds), (3) “inhale” (5 seconds), (4) “hold vapor in lungs” (10 seconds), (5) “exhale and wait” before repeating puff cycle (40 seconds). Subjects inhaled 4 puffs at 60 minutes. At 180 minutes, the vaporizer was refilled with marijuana vapor and subjects were allowed to inhale 4 to 8 puffs using the cued procedure. Thus, cumulative dosing allowed for a range of 8 to 12 puffs in total for each session, depending on the subjects desired response and tolerance. The washout time between each session ranged from 3–14 days.

The primary outcome variable was spontaneous pain relief, as assessed using a 0–100 point VAS for current pain. Secondary measures included the Patient Global Impression of Change (PGIC), the Neuropathic Pain Scale (NPS), a 0–100 point VAS for allodynia. Acute pain threshold was measured with a thermal pain model. Subjective measures included 0–100 point unipolar VAS for any drug effect, good drug effect, bad drug effect, high, drunk, impaired, stoned, drug liking, sedated, confused, nauseated, desire more drug, anxious, down and hungry. Bipolar 0–100 point VAS included sad/happy, anxious/relaxed, jittery/calm, bad/good, paranoid/self-assured, and fearful/unafraid. Neurocognitive assessments assessed attention and concentration, learning and memory, and fine motor speed.

A 30% reduction in pain was achieved in 61% of subjects who received the 3.53% THC marijuana, in 57% of subjects who received the 1.29% THC marijuana and in 26% of subjects who received the placebo marijuana (p = 0.002 for placebo vs. 3.53% THC, p = 0.007 for placebo vs 1.29% THC; p > 0.05 1.29% THC vs. 3.53% THC). Both strengths of marijuana significantly decreased pain intensity, unpleasantness, sharpness, and deepness on the NPS, as well as pain ratings on the PGIC, compared to placebo. These effects on pain were maximal with cumulative dosing over the course of the study session, with minimal effects at the end of the 60 minutes. There were no effects of marijuana compared to placebo on measures of allodynia or
thermal pain. Subjects correctly identified the study treatment 63% of the time for placebo, 61% of the time for 1.29% THC, and 89% of the time for 3.53% THC.

On subjective measures, marijuana produced dose-dependent increases compared to placebo on ratings for: any drug effect, good drug effect, drug liking, high, stoned, sedated, confused, and hungry. Both strengths of marijuana produced similar increases in drunk or impaired compared to placebo. In contrast, desire for drug was rated as higher for the 1.29% THC marijuana compared to the 3.53% THC marijuana. There were no changes compared to placebo for bad effect, nauseous, anxiety, feeling down or any of the bipolar mood assessments. There was dose-dependent impairment on learning and memory from marijuana compared to placebo, but similar effects between the two strengths of marijuana on attention.

The authors conclude that vaporization of relatively low doses of marijuana can produce improvements in analgesia in neuropathic pain patients, especially when patients are allowed to titrate their exposure. However, this individualization of doses may account for the general lack of difference between the two strengths of marijuana. No data were presented regarding the total amount of THC consumed by each subject, so it is difficult to determine a proper dose-response evaluation. Additional limitations of this study are the inclusion of subjects with many forms of nerve pain and maintenance of subjects on other analgesic medication while being tested with marijuana. These limitations make it difficult to conclude that marijuana has analgesic properties on its own. It is also difficult to determine if any particular subset of neuropathic pain conditions would benefit specifically from marijuana administration. However, the study produced positive results suggesting that marijuana should be studied further as an adjunct treatment for uncontrolled neuropathic pain.

3.2 Appetite Stimulation in HIV

Two randomized, double-blind, placebo-controlled Phase 2 studies examined the effects of smoked marijuana on appetite in HIV-positive subjects (Haney et al., 2005; Haney et al., 2007). Table 2 of the Appendix summarizes both studies.

The first study, conducted by Haney et al. (2005) is entitled, “Dronabinol and marijuana in HIV+ marijuana smokers: acute effects on caloric intake and mood”. The subjects were 30 HIV-positive patients who were maintained on two antiretroviral medications and either had clinically significant decreases in lean muscle mass (low-BIA group, n = 15) or normal lean muscle mass (normal-BIA group, n = 15). All subjects had a history of smoking marijuana at least twice weekly for 4 weeks prior to entry into the study. On average, individuals had smoked 3 marijuana cigarettes per day, 5–6 times per week for 10–12 years.

Subjects participated in 8 sessions that tested the acute effects of 0, 10, 20, and 30 mg dronabinol oral capsules and marijuana cigarettes with 0%, 1.8%, 2.8%, and 3.9% THC concentration by weight, using a double-dummy design (with only one active drug per session). The doses of dronabinol are higher than those doses typically prescribed for appetite stimulation in order to help preserve the blinding. There was a one-day washout period between test sessions.

Marijuana was administered using a standardized cued procedure: (1) “light the cigarette” (30 seconds), (2) “prepare” (5 seconds), (3) “inhale” (5 seconds), (4) “hold smoke in lungs” (10 seconds), and (5) “exhale.” Each subject smoked three puffs in this manner, with a 40-second interval between each puff. Caloric intake was used as a surrogate measure for weight gain. Subjects received a box containing a variety of food and beverage items and were told to record consumption of these items following that day’s administration of the test drug. Subjective measures included 0–100 point VAS for feel drug effect, good effect, bad effect, take drug again, drug liking, hungry, full, nauseated, thirsty, desire to eat. Neurocognitive measures and vital signs were monitored.

The low BIA group consumed significantly more calories in the 1.8% and 3.9% THC marijuana conditions (p < 0.01) and the 10, 20, and 30 mg dronabinol conditions (p < 0.01) compared with the placebo condition. In contrast, in the normal BIA group, neither marijuana nor dronabinol significantly affected caloric intake. This lack of effect may be accountable, however, by the fact that this group consumed approximately 200 calories more than the low BIA group under baseline conditions.

Ratings of high and good drug effect were increased by all drug treatments in both the low-BIA and normal-BIA groups, except in response to the 10 mg dose of dronabinol. The 3.9% THC marijuana increased ratings of good drug effect, drug liking and desire to smoke again compared with placebo. Ratings of sedation were increased in both groups by 10 and 30 mg dronabinol, and in the normal BIA group by the 2.8% THC marijuana. Ratings of stimulation were increased in the normal BIA group by 2.8% and 3.9% THC marijuana and by 20 mg dronabinol. Increases in ratings of forgetfulness, withdrawn, dreaming, clumsy, heavy limbs, heart pounding, jittery, and decreases in ratings of energetic, social, and talkative were reported in the normal BIA group with 30 mg dronabinol. There were no significant changes in vital signs or performance on neurocognitive measures in response to marijuana. Notably, the time course of subjective effects peaked quickly and declined thereafter for smoked marijuana, while oral dronabinol responses took longer to peak and persisted longer. Additionally, marijuana but not dronabinol produced dry mouth and thirst.

In general, AEIs reported in this study were low in both drug conditions for both subject groups. In the low BIA group, nausea was reported by one subject in both the 10 and 20 mg dronabinol conditions, while an uncomfortable level of intoxication was produced by the 30 mg dose in two subjects. There were no AEIs reported in this group following marijuana at any dose. In the normal BIA group, the 30 mg dose of dronabinol produced an uncomfortable level of intoxication in three subjects and headache in one subject, while the 3.9% marijuana produced diarrhea in one subject.

The authors conclude that smoked marijuana can acutely increase caloric intake in low BIA subjects without significant cognitive impairment. However, it is possible that the low degree of cognitive impairment reported in this study may reflect the development of tolerance to cannabinoids in this patient population, since all individuals had current histories of chronic marijuana use. Additional limitations in this study include not utilizing actual weight gain as a primary measure. However, the study produced positive results suggesting that marijuana should be studied further as a treatment for appetite stimulation in HIV patients.

A second study conducted by Haney et al. (2007) is entitled, “Dronabinol and marijuana in HIV-positive marijuana smokers: Caloric intake, mood, and sleep: The design of this study was nearly identical to the one conducted by this laboratory in 2005 (see above), but
there was no stratification of subjects by BIA. The subjects were 10 HIV-positive patients who were maintained on two antiretroviral medications and had a history of smoking marijuana at least twice weekly for 4 weeks prior to entry into the study. On average, individuals had smoked 3 marijuana cigarettes per day, 5 times per week for 19 years.

Subjects participated in 8 sessions that tested the acute effects of 0, 5 and 10 mg dronabinol oral capsules and marijuana cigarettes with 0, 2.0% and 3.9% THC concentration by weight, using a double-dummy design (with 4 sessions involving only one active drug and 4 interspersed placebo sessions). Both drug and placebo sessions lasted for 4 days each, with active drug administration occurring 4 times per day (every 4 hours). Testing occurred in two 16-day inpatient stays. In the intervening outpatient period, subjects were allowed to smoke marijuana prior to re-entry to the study unit for the second inpatient stay.

Marijuana was administered using a standardized cued procedure: (1) “light the cigarette” (30 seconds), (2) “prepare” (5 seconds), (3) “inhale” (5 seconds), (4) “hold smoke in lungs” (10 seconds), and (5) “exhale.” Each subject smoked three puffs in this manner, with a 40-second interval between each puff.

Caloric intake was used as a surrogate measure for weight gain, but subjects were also weighed throughout the study (a measure which was not collected in the 2005 study by this group). Subjects received a box containing a variety of food and beverage items and were told to record consumption of these items following that day’s administration of the test drug. Subjective measures included 0–100 pointVAS for drug effect, good effect, bad effect, take drug again, drug liking, hungry, full, nauseated, thirsty, desire to eat. Neurocognitive measures and vital signs were monitored. Sleep was assessed using both the Nightcap sleep monitoring system and selected VAS measures related to sleep.

Both 5 and 10 mg dronabinol (p < 0.008) and 2.0% and 3.9% THC marijuana (p < 0.01) dose-dependently increased caloric intake compared with placebo. This increase was generally accomplished through increases in incidents of eating, rather than an increase in the calories consumed in each incident. Subjects also gained similar amounts of weight after the highest dose of each cannabinoid treatment: 1.2 kg (2.6 lbs) after 4 days of 10 mg dronabinol, and 1.1 kg (2.4 lbs) after 4 days of 3.9% THC marijuana. The 3.9% THC marijuana dose also increased the desire to eat and ratings of hunger.

Ratings of good drug effect, high, drug liking, and desire to smoke again were significantly increased by 10 mg dronabinol and 2.0% and 3.9% THC marijuana doses compared to placebo. Both marijuana doses increased ratings of stimulated, friendly, and self-confident. The 10 mg dose of dronabinol increased ratings of concentration impairment, and the 2.0% THC marijuana dose increased ratings of anxious. Dry mouth was induced by 10 mg dronabinol (10 mg) and 2.0% THC marijuana. There were no changes in neurocognitive performance or objective sleep measures from administration of either cannabinoid. However, 3.9% THC marijuana increased subjective ratings of sleep.

The authors conclude that both dronabinol and smoked marijuana increase caloric intake and produce weight gain in HIV-positive patients. However, it is possible that the low degree of cognitive impairment reported in this study may reflect the development of tolerance to cannabinoids in this subject population, since all individuals had current histories of chronic marijuana use. This study produced positive results suggesting that marijuana should be studied further as a treatment for appetite stimulation in HIV patients.

3.3 Spasticity in Multiple Sclerosis

Only one randomized, double-blind, placebo-controlled Phase 2 study examined the effects of smoked marijuana on spasticity in MS. This study was conducted by Corey-Bloom et al. (2012) and is entitled, “Smoked cannabis for spasticity in multiple sclerosis: A randomized, placebo-controlled trial”. The subjects were 30 patients with MS-associated spasticity and had moderate increase in tone (score ≥ 3 points on the modified Ashworth scale). Participants were allowed to continue other MS medications, with the exception of benzodiazepines. Eighty percent of subjects had a history of marijuana use and 33% had used marijuana within the previous year.

Subjects participated in two 3-day test sessions, with an 11 day washout period. During each test session they smoked a 4.0% THC marijuana cigarette once per day or a placebo cigarette once per day. Smoking occurred through a standardized cued-puff procedure: (1) Inhalation for 5 seconds, (2) breath-hold and exhalation for 10 seconds, (3) pause between puffs for 45 seconds. Subjects completed an average of four puffs per cigarette.

The primary outcome measure was change in spasticity on the modified Ashworth scale. Additionally, subjects were assessed using a VAS for pain, a timed walk, and cognitive tests (Paced Auditory Serial Addition Test) and AEIs. Treatment with 4.0% THC marijuana reduced subject scores on the modified Ashworth scale by an average of 2.74 points more than placebo (p < 0.0001) and reduced VAS pain scores compared to placebo (p = 0.008). Scores on the cognitive measure decreased by 8.7 points more than placebo (p = 0.003). However, marijuana did not affect scores for the timed walk compared to placebo. Marijuana increased rating of feeling high compared to placebo.

7 subjects did not complete the study due to adverse events (two subjects felt uncomfortably “high”, two had dizziness and one had fatigue). Of those 7 subjects who withdrew, 5 had little or no previous experience with marijuana. When the data were re-analyzed to include these drop-out subjects, with the prescription they did not have a positive response to treatment, the effect of marijuana was still significant on spasticity.

The authors conclude that smoked marijuana had usefulness in reducing pain and spasticity associated with MS. It is concerning that marijuana-naive subjects dropped out of the study because they were unable to tolerate the psychiatric AEIs induced by marijuana. The authors suggest that future studies should examine whether different doses can result in similar beneficial effects with less cognitive impact. However, the current study produced positive results suggesting that marijuana should be studied further as an adjunct treatment for spasticity in MS patients.

3.4 Asthma

Tashkin et al. (1974) examined bronchodilation in 10 subjects with bronchial asthma in the study entitled, “Acute Effects of Smokeless Marijuana and Oral Δ9-Tetrahydrocannabinol on Specific Airway Conductance in Asthmatic Subjects”. The study was a double-blind, placebo-controlled, crossover design. All subjects were clinically stable at the time of the study; four subjects were symptom free, and six subjects had chronic symptoms of mild to moderate severity. Subjects were tested with 0.25ml of isoproterenol HCl prior to the study to ensure they responded to bronchodilator medications. Subjects were not allowed to take bronchodilator medication within 8 hours prior to the study. Previous experience with marijuana was not required for participation in the study, but 7 of the 10 subjects reported
previous use of marijuana at a rate of less than 1 marijuana cigarette per month. No subjects reported marijuana use within 7 days of the study.

The study consisted of four test sessions with an interval of at least 48 hours between sessions. On two test sessions subjects smoked 7 mg/kg of body weight of either marijuana, with 2% THC concentration by weight, or placebo marijuana. During the other two test sessions, subjects ingested capsules with either 15 mg of synthetic THC or placebo. Marijuana was administered using a uniform smoking technique: subjects inhaled deeply for 2–4 seconds, held smoke in lungs for 15 seconds, and resumed normal breathing for approximately 5 seconds. The author did not provide a description of the number of puffs taken at any smoking session. The authors state that the smoking procedure was repeated until the cigarette was consumed, which took approximately 10 minutes.

The outcome measure used was specific airway conductance (SGaw), as calculated using measurements of thoracic gas volume (TGV) and airway resistance (Raw) using a variable-pressure body plethysmograph.

Additionally, an assessment of degree of intoxication was administered only to those subjects reporting previous marijuana use. This assessment consisted of subjects rating “how high” they felt on a scale of 0–7, 7 representing “the highest they had ever felt after smoking marijuana”.

Marijuana produced a significant increase of 33–48% in average SGaw compared to both baseline and placebo (P < 0.05). This significant increase in SGaw lasted for at least 2 hours after administration. The average TGV significantly decreased by 4–13% compared to baseline and placebo (P < 0.05). The authors stated that all subjects reported feelings of intoxication after marijuana administration.

The authors conclude that marijuana produced bronchodilation in clinically stable asthmatic subjects with minimal to moderate bronchospasms. Study limitations include: inclusion of subjects with varying severity of asthmatic symptoms, use of SGaw to measure lung responses to marijuana administration, and administration of smoke to asthmatic subjects. Smoke delivers a number of harmful substances and is not an optimal delivery symptom, especially for asthmatic patients. FEV1 via spirometry is the gold standard to assess changes in lung function, pre and post asthma treatment, by pharmacy. SGaw has been shown to be a valid tool in bronchoconstriction lung assessment; however, since the FEV1 method was not utilized, it is unclear whether these results would correlate if the FEV1 method had been employed.

3.5 Glaucma

Two randomized, double-blind, placebo-controlled Phase 2 clinical studies examined smoked marijuana in glaucoma (Crawford and Merritt, 1979; Merritt et al., 1980). In both studies, intraocular pressure (IOP) was significantly reduced 30 minutes after smoking marijuana. Maximal effects occurred 60–90 minutes after smoking, with IOP returning to baseline within 3–4 hours. These two studies were included in the 1999 IOM report on the medical uses of marijuana. Because our independent analysis of these studies concurred with the conclusions from the 1999 IOM report, these studies will not be discussed in further detail in this review. No recent studies have been conducted examining the effect of inhaled marijuana on IOP in glaucoma patients. The lack of recent clinical studies may be attributed to the conclusions made in the 1999 IOM report that while cannabinoids can reduce intraocular pressure (IOP), the therapeutic effects require high doses that produce short-lasting responses, with a high degree of AEs. This high degree of AEs means that the potential harmful effects of chronic marijuana smoking may outweigh its modest benefits in the treatment of glaucoma.

3.6 Conclusions

Of the eleven randomized, double-blind, placebo-controlled Phase 2 clinical studies that met the criteria for review (see Sections 2.2 and 2.3), ten studies administered marijuana through smoking, while one study utilized marijuana vaporization. In these eleven studies, there were five different therapeutic indications: Five examined chronic neuropathic pain, two examined appetite stimulation in HIV patients, two examined glaucoma, one examined spasticity in MS, and one examined asthma.

There are limited conclusions that can be drawn from the data in these published studies evaluating marijuana for the treatment of different therapeutic indications. The analysis relied on published studies, thus information available about protocols, procedures, and results were limited to documents published and widely available in the public domain. The published studies on medical marijuana are effectively proof-of-concept studies. Proof-of-concept studies provide preliminary evidence on a proposed hypothesis regarding a drug’s effect. For drugs under development, the effect often relates to a short-term clinical outcome being investigated. Proof-of-concept studies serve as the link between preclinical studies and dose ranging clinical studies. Therefore, proof-of-concept studies are not sufficient to demonstrate efficacy of a drug because they provide only preliminary information about the effects of a drug. Although these studies do not provide evidence that marijuana is effective in treating a specific, recognized disorder, these studies do support future larger well-controlled studies to assess the safety and efficacy of marijuana for a specific medical indication. Overall, the conclusions below are preliminary, based on very limited evidence.

3.6.1 Conclusions for Chronic Neuropathic Pain

In subjects with chronic neuropathic pain who are refractory to other pain treatments, five proof-of-concept studies produced positive results regarding the use of smoked marijuana for analgesia. However, the subjects in these studies continued to use their current analgesic drug regime, and thus no conclusions can be made regarding the potential efficacy of marijuana for neuropathic pain in patients not taking other analgesic drugs. Subjects also had numerous forms of neuropathic pain, making it difficult to identify whether a specific set of symptoms might be more responsive to the effects of marijuana. It is especially concerning that some marijuana-naïve subjects had intolerable psychiatric responses to marijuana exposure at analgesic doses.

3.6.2 Conclusions for Appetite Stimulation in HIV

In subjects who were HIV-positive, two proof-of-concept studies produced positive results with the use of both dronabinol and smoked marijuana to increase caloric intake and produce weight gain in HIV-positive patients. However, the amount of THC in the marijuana tested in these studies is four times greater than the dose of dronabinol typically tested for appetite stimulation (10 mg vs. 2.5 mg: Haney et al., 2005). Thus, it is possible that the low degree of AEs reported in this study may reflect the development of tolerance to cannabinoids in this patient population, since all individuals had current histories of chronic marijuana use. Thus, individuals with little prior exposure to marijuana may not respond similarly and may not be able to tolerate sufficient marijuana to produce appetite stimulation.
3.6.3 Conclusions for Spasticity in MS

In subjects with MS, a proof of concept study produced positive results using smoked marijuana as a treatment for pain and symptoms associated with treatment-resistant spasticity. The subjects in this study continued to take their current medication regimen, and thus no conclusions can be made regarding the potential efficacy of marijuana when taken on its own. It is also concerning that marijuana-naive subjects dropped out of the study because they were unable to tolerate the psychiatric AEs induced by marijuana. The authors suggest that future studies should examine whether different doses can result in similar beneficial effects with less cognitive impact.

3.6.4 Conclusions for Asthma

In subjects with clinically stable asthma, a proof of concept study produced positive results of smoked marijuana producing bronchodilation. However, in this study marijuana was administered at rest and not while experiencing bronchospasms. Additionally, the administration of marijuana through smoking introduces harmful and irritating substances to the subject, which is undesirable especially in asthmatic patients. Thus the results suggest marijuana may have bronchodilator effects, but it may also have undesirable adverse effects in subjects with asthma.

3.6.5 Conclusions for Glaucoma

As noted in Sections 3.5, the two studies that evaluated smoked marijuana for glaucoma were conducted decades ago, and they have been thoroughly evaluated in the 1999 IOM report. The 1999 IOM report concludes that while the studies with marijuana showed positive results for reduction in IOP, the effect is short-lasting, requires a high dose, and is associated with many AEs. Thus, the potential harmful effects may outweigh any modest benefit of marijuana for this condition. We agree with the conclusions drawn in the 1999 IOM report.

3.7 Design Challenges for Future Studies

The positive results reported by the studies discussed in this review support the conduct of more rigorous studies in the future. This section discusses methodological challenges that have occurred in clinical studies with smoked marijuana. These design issues should be addressed when larger-scale clinical studies are conducted to ensure that valid scientific data are generated in studies evaluating marijuana’s safety and efficacy for a particular therapeutic use.

3.7.1 Sample Size

The ability for results from a clinical study to be generalized to a broader population is reliant on having a sufficiently large study sample size. However, as noted above, all of the 11 studies reviewed in this document were early Phase 2 proof of concept studies for efficacy and safety. Thus, the sample sizes used in these studies were inherently small, ranging from 10 subjects per treatment group (Tashkin et al., 1974; Haney et al., 2007) to 25 subjects per treatment group (Abrams et al., 2007). These sample sizes are statistically inadequate to support a showing of safety or efficacy. FDA’s recommendations about sample sizes for clinical trials can be found in the Guidance for Industry: E9 Statistical Principles for Clinical Trials (1998). For example, “the number of subjects in a clinical trial should always be large enough to provide a reliable answer to the questions addressed. This number is usually determined by the primary objective of the trial. The method by which the sample size is calculated should be given in the protocol, together with the estimates of any quantities used in the calculations (such as variances, mean values, response rates, event rates, difference to be detected).” (pg. 21). Other clinical FDA Guidance for Industry may also contain recommendations regarding the appropriate number of subjects that should be investigated for a specific medical indication.

3.7.2 Marijuana Dose Standardization

Dose standardization is critical for any clinical study in order to ensure that each subject receives a consistent exposure to the test drug. The Guidance for Industry: Botanical Drug Products (2004) provides specific information on the development of botanical drug products. Specifically, this guidance includes information about the need for well-characterized and consistent chemistry for the botanical plant product and for consistent and reliable dosing. Specifically for marijuana studies, dose standardization is important because if marijuana leads to plasma levels of cannabinoids that are significantly different between subjects, this variation may lead to differences in therapeutic responsibility or in the prevalence of psychiatric AEs.

In most marijuana studies discussed in this review, investigators use a standardized cued smoking procedure. In this procedure, a subject is instructed to inhale marijuana smoke for 5 seconds, hold the smoke in the lungs for 10 seconds, exhale and breathe normally for 40 seconds. This process is repeated to obtain the desired dose of the drug. However, this procedure may not lead to equivalent exposure to marijuana and its constituent cannabinoids, based on several factors:

- Intentional or unintentional differences in the depth of inhalation may change the amount of smoke in the subject’s lungs.
- Smoking results in loss from side stream smoke, such that the entire dose is not delivered to the subject.
- There may be differences in THC concentration along the length of a marijuana cigarette. According to Tashkin et al. (1991), the area of the cigarette closest to the mouth tends to accumulate a higher concentration of THC, but this section of the cigarette is not smoked during a study.

For example, Wilsey et al. (2008) used this standardized smoking procedure. The reported mean (range) of marijuana cigarettes consumed was 550 mg (200–830mg) for the low strength marijuana (3.5% THC) and 490 mg (270–870mg) for the high strength marijuana (7% THC). This wide range of amounts of marijuana cigarette smoked by the individual subjects, even with standardized smoking procedure and controlled number of puffs, supports the issues with delivering consistent doses with smoke in marijuana studies. In other marijuana studies that do not use a cued smoking procedure, subjects are simply told to smoke the marijuana cigarette over a specific amount of time (usually 10 minutes) without further instruction (Crawford and Merritt, 1979; Merritt et al., 1980; Ellis et al., 2009).

The use of a nonstandardized procedure may lead to non-equivalent exposures to marijuana and its constituent cannabinoids between subjects because of additional factors that are not listed above, such as:

- Differences in absorption and drug response if subjects (especially marijuana-naïve ones) are not instructed to hold marijuana smoke in their lungs for a certain period of time.

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36 Other Guidelines for Industry can be found at: www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064981.htm.
• Prolonged periods between puffs may increase loss to side stream smoke.
• Subjects may attempt to smoke the marijuana cigarette in the way they would smoke a tobacco cigarette, which relies primarily on short, shallow puffs.

In both standardized and non-standardized smoking procedures, subjects may seek to control the dose of THC through self-titration (Crawford and Merritt, 1979; Merritt et al., 1980; Tashkin et al., 1974; Abrams et al., 2007; Ellis et al., 2009). Self-titration involves an individual moderating the amount of marijuana smoke inhaled over time in order to obtain a preferred level of psychoactive or clinical response. The ability of an individual to self-titrate by smoking is one reason given by advocates of “medical marijuana” in support of smoking of marijuana rather than through its ingestion via edibles. However, for research purposes, self-titration interferes with the ability to maintain consistent dosing levels between subjects, and thus, valid comparisons between study groups.

All of these factors can make the exact dose of cannabinoids received by a subject in a marijuana study difficult to determine with accuracy. Testing whether plasma levels of THC or other cannabinoids are similar between subjects following the smoking procedure would establish whether the procedure is producing appropriate results. Additionally, studies could be conducted to determine if vaporization can be used to deliver consistent doses of cannabinoids from marijuana plant material. Specifically, vaporization devices that involve the collection of vapors in an enclosed bag or chamber may help with delivery of consistent doses of marijuana. Thus, more information could be collected on whether vaporization is comparable to or different than smoking in terms of producing similar plasma levels of THC in subjects using identical marijuana plant material.

3.7.3 Acute vs. Chronic Therapeutic Marijuana Use

The studies that were reviewed administered the drug for short durations lasting no longer than 5 days (Abrams et al., 2007; Ellis et al., 2009; Ware et al., 2010). Thus all studies examined the short-term effect of marijuana administration for therapeutic purposes. However, many of the medical conditions that have been studied are persistent or expected to last the rest of a patient’s life. Therefore, data on chronic exposure to smoked marijuana in clinical studies is needed. In this way, more information will be available regarding whether tolerance, physical dependence, or specific adverse events develop over the course of time with continuing use of therapeutic marijuana.

3.7.4 Smoking as a Route of Administration

As has been pointed out by the IOM and other groups, smoking is not an optimum route of administration for marijuana-derived therapeutic drug products, primarily because introducing the smoke from a burnt botanical substance into the lungs of individuals with a disease state is not recommended when their bodies may be physically compromised. The 1999 IOM report on medicinal uses of marijuana noted that alternative delivery methods offering the same ability of dose titration as smoking marijuana will be beneficial and may limit some of the possible long-term health consequences of smoking marijuana. The primary alternative to smoked marijuana is vaporization, which can reduce exposure to hazardous plant material containing cannabinoids. The only study to use vaporization as the delivery method was Wilsey et al. (2013). The results from Wilsey et al. (2013) showed a similar effect of decreased pain as seen in the other studies using smoking as the delivery method (Ware et al., 2010; Wilsey et al., 2008). This similar effect of decrease pain supports vaporization as a possibly viable route to administer marijuana in research, while potentially limiting the risks associated with smoking.

3.7.5 Difficulty in Blinding of Drug Conditions

An adequate and well-controlled clinical study involves double-blinding, where both the subjects and the investigators are unable to tell the difference between the test treatments (typically consisting of at least a test drug and placebo) when they are administered. All of the studies reviewed in this document administered treatments under double-blind conditions and thus were considered to have an appropriate study design.

However, even under the most rigorous experimental conditions, blinding can be difficult in studies with smoked marijuana because the rapid onset of psychoactive effects readily distinguishes active from placebo marijuana. The presence of psychoactive effects also occurs with other drugs. However, most other drugs have a similar psychoactive effect with substances with similar mechanisms of action; these substances can be used as positive controls to help maintain blinding to the active drug being tested.

Marijuana on the other hand, has a unique set of psychoactive effects which makes the use of appropriate positive controls difficult (Barrett et al., 1995). However, two studies did use Dronabinol as a positive control drug to help maintain blinding (Haney et al., 2005; Haney et al., 2007).

When blinding is done using only placebo marijuana, the ability to distinguish active from placebo marijuana may lead to expectation bias and an alteration in perceived responsiveness to the therapeutic outcome measures. With marijuana-experienced subjects, for example, there may be an early recognition of the more subtle cannabinoid effects that can serve as a harbinger of stronger effects, which is less likely to occur with marijuana-naïve subjects. To reduce this possibility, investigators have tested doses of marijuana other than the one they were interested in experimentally to maintain the blind (Ware et al., 2010).

Blinding can also be compromised by differences in the appearance of the marijuana plant material based on THC concentration. Marijuana with higher concentrations of THC tends to be heavier and seemingly darker, with more “tar-like” substance. Subjects who have experience with marijuana have reported being able to identify marijuana from placebo cigarettes by sight alone when the plant material in a cigarette was visible (Tashkin et al., 1974; Ware et al., 2010). Thus, to maintain a double-blind design, many studies obscure the appearance of plant material by closing both ends of the marijuana cigarette and placing it in an opaque plastic tube.

While none of these methods to secure blinding may be completely effective, it is important to reduce bias as much as possible to produce consistent results between subjects under the same experimental conditions.

3.7.6 Prior Marijuana Experience

Marijuana use histories in test subjects may influence outcomes, related to both therapeutic responsibility and psychiatric AEs. Marijuana-naïve subjects may also experience a marijuana drug product as so aversive that they would not want to use the drug product. Thus, subjects’ prior experience with marijuana may affect the conduct and results of studies.

Most of the studies reviewed in this document required that subjects have a history of marijuana use (see tables in Appendix that describe specific requirements for each study). However, in studies published in the scientific literature, the full inclusion criteria with
regard to specific amount of experience with marijuana may not be provided. For those studies that do provide inclusion criteria, acceptable experience with marijuana can range from once in a lifetime to use multiple times a day.

The varying histories of use might affect everything from scores on adverse event measures, safety measures, or efficacy measures. Additionally, varying amounts of experience can impact cognitive effects measures assessed during acute administration studies. For instance, Schreiner and Dunn (2012) contend cognitive deficits in heavy marijuana users continue for approximately 28 days after cessation of smoking. Studies requiring less than a month of abstinence prior to the study may still see residual effects of heavy use at baseline and after placebo marijuana administration, thus showing no significant effects on cognitive measures. However, these same measurements in occasional or naive marijuana users may demonstrate a significant effect after acute marijuana administration. Therefore, the amount of experience and the duration of abstinence of marijuana use are important to keep in mind when analyzing results for cognitive and other adverse event measures. Lastly, a study population with previous experience with marijuana may underreport the incidence and severity of adverse events. Because most studies used subjects with prior marijuana experience, we are limited in our ability to generalize the results, especially for safety measures, to marijuana naive populations.

Five of 11 studies reviewed in this document included both marijuana-naive and marijuana-experienced subjects (Corey-Bloom et al., 2012; Ellis et al., 2009; Ware et al., 2010; Merritt et al., 1980; Tashkin et al., 1974). Since the number of marijuana-naive subjects in these studies was low, it was not possible to conduct a separate analysis compared to experienced users. However, systematically evaluating the effect of marijuana experience on study outcomes is important, since many patients who might use a marijuana product for a therapeutic use will be marijuana-naive.

Research shows that marijuana-experienced subjects have a higher ability to tolerate stronger doses of oral dronabinol than marijuana-naive subjects (Haney et al., 2005). Possibly, this increased tolerance is also the case when subjects smoke or vaporize marijuana. Studies could be conducted to investigate the role of marijuana experience in determining tolerability of and responses to a variety of THC concentrations in marijuana.

3.7.7 Inclusion and Exclusion Criteria

For safety reasons, all clinical studies have inclusion and exclusion criteria that restrict the participation of individuals with certain medical conditions. For studies that test marijuana, these criteria may be based on risks associated with exposure to smoked material and the effects of THC. Thus, most studies investigating marijuana require that subjects qualify for the study based on restrictive symptom criteria such that individuals do not have other symptoms that may be known to interact poorly with cannabinoids.

Similarly, clinical studies with marijuana typically exclude individuals with cardiac or pulmonary problems, as well as psychiatric disorders. These exclusion criteria are based on the well-known effects of marijuana smoke to produce increases in heart rate and blood pressure, and the exacerbation of psychiatric disturbances in vulnerable individuals. Although these criteria are medically reasonable for research protocols, it is likely that future marijuana products will be used in patients who have cardiac, pulmonary or psychiatric conditions. Thus, individuals with these conditions should be evaluated, whenever possible.

Additionally, all studies reviewed in this document allowed the subjects to continue taking their current regimen of medications. Thus all results evaluated marijuana as an adjunct treatment for each therapeutic indication.

3.7.8 Number of Female Subjects

A common problem in clinical research is the limited number of females who participate in the studies. This problem is present in the 11 studies reviewed in this document, in which one study did not include any female subjects (Ellis et al., 2009), and three studies had a low percentage of female subjects (Abrams et al., 2007; Haney et al., 2005; Haney et al., 2007). However, each of these four studies investigated an HIV-positive patient population, where there may have been a larger male population pool from which to recruit compared to females.

Since there is some evidence that the density of CB1 receptors in the brain may vary between males and females (Crande et al., 2012), there may be differing therapeutic or subjective responsivity to marijuana. Studies using a study population that is equal parts male and female would show whether and how the effects of marijuana differ between male and female subjects.

4. References


### Appendix (Tables)

**Table 1: Randomized, controlled, double-blind trials examining smoked marijuana in treatment of neuropathic pain**

<table>
<thead>
<tr>
<th>Author &amp; Date Indication</th>
<th>Subjects (n) completed/randomized Subject characteristics</th>
<th>Drugs Admin. Methods</th>
<th>Study Type Duration</th>
<th>Primary Outcome Measure</th>
<th>Primary Outcome Measure Results</th>
<th>Adverse events/AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abrams et al. (2007)</td>
<td>Marijuana Group: 25/27 22 males 5 females</td>
<td>NIDA marijuana, smoked 0%, 3.65% THC</td>
<td>Parallel Group 5-day treatment period</td>
<td>VAS daily pain score</td>
<td>-52% of the marijuana group showed &gt;30% decrease in pain score compared to 24% of placebo group. -Marijuana group had significantly greater reduction in daily pain score than placebo group. -NNT=3.6</td>
<td>-Rating for adverse events of anxiety, sedation, disorientation, confusion, and dizziness were significantly higher in the marijuana group compared to placebo group. -Marijuana and placebo groups showed a reduction in total mood disturbance on POMS. AEs: -1 grade 3 dizziness in marijuana group -2 grade 3 anxiety, 1 in each group.</td>
</tr>
<tr>
<td><em>HIV-Sensory Neuropathy; Neuropathic Pain</em></td>
<td>Placebo Group: 25/28 26 males 2 females</td>
<td>Smoking Procedure: 1) 5s inhale smoke, 2) 10s hold smoke in lungs 3) 40s exhale and breath normally 4) repeat procedure for desired number of puffs # of puffs not specified, only specified that subjects smoked the entire marijuana/placebo cigarette</td>
<td>On 1st and last day of intervention period BID. For all other days TID</td>
<td></td>
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<tr>
<td>Previous Marijuana Experience: -marijuana group: 21 current users -placebo group: 19 current users</td>
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<tr>
<td>Exclusion Criteria: -substance abuse (including tobacco) -family history of neuropathy due to causes not HIV related -use of isoniazid, dapsone, or metronidazole within 8 weeks of enrollment</td>
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</tr>
<tr>
<td>Ellis et al. (2009)</td>
<td>28/34 28 males</td>
<td>NIDA marijuana, smoked 0%, 1%, 2%, 4%, 6%, 8% THC</td>
<td>Crossover Dose-titation (on 1st day)</td>
<td>Pain magnitude on DDS</td>
<td>-Pain reduction was significantly greater after marijuana compared to placebo.</td>
<td>-Mood disturbance, quality of life, and psychical disability improved for both marijuana and placebo. -Moderate to severe adverse events were more common with marijuana than placebo.</td>
</tr>
<tr>
<td><em>HIV Sensory Neuropathy; Neuropathic</em></td>
<td>Inclusion Criteria: -documented HIV -documented neuropathic</td>
<td>Smoking Procedures:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Author &amp; Date</td>
<td>Subjects (n) completed/randomized Subject characteristics</td>
<td>Drugs Admin. Methods</td>
<td>Study Type Duration</td>
<td>Primary Outcome Measure</td>
<td>Primary Outcome Measure Results</td>
<td>Adverse events/AEs</td>
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</tr>
</tbody>
</table>
| Wilsey et al. (2008) | Pain | pain refractory to ≥2 analgesics  
- pain score ≥5 on pain intensity subscale of DDS Previous Marijuana Experience:  
- 27 subjects had previous experience  
- 63% of subjects had no exposure for >1 year before study  
Exclusion Criteria:  
- current DSM-IV substance abuse disorder  
- lifetime history of dependence on marijuana  
- previous psychosis with or intolerance to cannabinoids  
- concurrent use of approved cannabinoid medications  
- positive UDS for cannabinoids during wash-in week  
- serious medical conditions that affect safety  
- alcohol or drug dependence within 12 months of study | - Verbally cued smoking of marijuana cigarette with each puff consisting of:  
1) 5s inhale smoke,  
2) 10s hold smoke in lungs  
3) 40s exhale and breath normally  
4) repeat procedure for desired number of puffs  
- unknown number of puffs QID | 2, 5-day treatment phase, with 2-week washout period | - NNT = 3.5 | - HIV disease parameters did not differ for marijuana or placebo.  
- Adverse events included: concentration difficulties, fatigue, sleepiness or sedation, increased duration of sleep, reduced salivation, and thirst. These adverse events were more frequent in marijuana compared to placebo.  
Withdrawals for drug related reasons:  
1 cannabis-naïve subject had acute cannabis-induced psychosis  
1 subjects developed an intractable smoking-related cough during marijuana administration |

| Neuropathic pain; Various Causes | 32/38  
20 males  
18 females | Inclusion Criteria:  
- CRPS type I, spinal cord | NIDA marijuana, smoked  
0%, 3.55%, 7% THC  
Smoking Procedure: Verbally cued | Crossover  
3, 6-hour sessions, with 3-day between | VAS spontaneous pain intensity | - A significant decrease in pain intensity for both strengths of marijuana compared to placebo  
- 7% THC marijuana significantly decreased functioning on neurocognitive measures compared to placebo.  
- Subjective effects were greater for 7% THC marijuana than 3.55% |
<table>
<thead>
<tr>
<th>Author &amp; Date Indication</th>
<th>Subjects (n) completed/randomized Subject characteristics</th>
<th>Drugs Admin. Methods</th>
<th>Study Type</th>
<th>Primary Outcome Measure</th>
<th>Primary Outcome Measure Results</th>
<th>Adverse events/AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>injury, peripheral neuropathy, or nerve damage - previous marijuana use</td>
<td>smoking of marijuana cigarette with each puff consisting of: 1) 5s inhale smoke, 2) 40s hold smoke in lungs 3) 40s exhale and breath normally 4) repeat procedure for desired number of puffs</td>
<td>sessions</td>
<td>TID</td>
<td>THC marijuana with significantly more ratings of good drug effect, bad drug effect, feeling high, feeling stoned, impaired, sedation, confusion, and hunger compared to placebo.</td>
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<tr>
<td>Previous Marijuana Experience: - median (range) time from previous exposure: 1.7 years (31 days to 30 years) - median (range) exposure duration: 2 years (1 day to 22 years).</td>
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<tr>
<td>Exclusion Criteria: - no marijuana or cannabinoid medication use for 30 days prior to study; confirmed by UDS - severe depression - history of schizophrenia or bipolar depression - uncontrolled hypertension, cardiovascular disease, and pulmonary disease - active substance abuse</td>
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</tr>
<tr>
<td>Ware et al. (2010) Post-traumatic or postsurgical neuropathic pain</td>
<td>21/23 11 males 12 females</td>
<td>NIDA placebo; Prairie Plant System Inc. (Canada) marijuana, smoked 0%, 2.5%, 6%, 9.4% THC (25 mg of marijuana/placebo plant material was placed in opaque)</td>
<td>Crossover 4, 5-day out-patient treatment phase, with 9-day washout periods</td>
<td>Pain intensity on 11-item NRS</td>
<td>- Average daily pain intensity was significantly lower after 9.4% THC compared to placebo.</td>
<td>- Anxiety and depression were significantly improved with 9.4% THC compared to placebo. - No significant difference between placebo and 9.4% THC for subjective effects.</td>
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<td></td>
<td>AEs:</td>
<td>- 248 mild AEs were reported - 6 moderate AEs were reported: 2 fall, 1 increased pain, 1 numbness,</td>
</tr>
<tr>
<td>Author &amp; Date</td>
<td>Subjects (n) completed/randomized</td>
<td>Drugs Admin. Methods</td>
<td>Study Type Duration</td>
<td>Primary Outcome Measure</td>
<td>Primary Outcome Measure Results</td>
<td>Adverse events/AEs</td>
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</tr>
<tr>
<td>Wilsey et al. (2013)</td>
<td>Neurpathic Pain: Various Causes</td>
<td>36/39</td>
<td>NIDA marijuana, vaporized 0%, 1.29%, 3.53% THC</td>
<td>Crossover 3, 6-hour sessions, with at least 3 days between sessions</td>
<td>VAS spontaneous pain intensity</td>
<td>-Number of subjects that showed a 30% reduction in pain intensity was significantly greater for both strengths of marijuana compared to placebo. -Both strengths of marijuana showed a similar significant decrease in pain compared to placebo. -NNT=3.2 for 1.29% THC marijuana vs. -Scores for feeling stoned, feeling high, like the drug effect, feeling sedated, and feeling confused were significantly greater for 3.53% THC marijuana compared to 1.29% THC marijuana, and for both strengths of marijuana compared to placebo. -Scores for feeling drunk and feeling impaired are significantly greater in both strengths of marijuana compared to placebo. -Scores for desired more of the drug were significantly greater for 1.29% THC marijuana compared to placebo, with no significant</td>
</tr>
<tr>
<td></td>
<td>Previous Marijuana Experience:</td>
<td>- median (range) time from last exposure prior to</td>
<td></td>
<td></td>
<td></td>
<td>1 drowsiness, 1 pneumonia</td>
</tr>
<tr>
<td></td>
<td>-18 subjects had used marijuana before</td>
<td></td>
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<td></td>
<td>Withdrawals for drug related reason:</td>
</tr>
<tr>
<td></td>
<td>Exclusion Criteria:</td>
<td>-pain due to cancer or nociceptive causes</td>
<td></td>
<td>smoking procedures:</td>
<td>1 puff burned all 25 mg of plant material</td>
<td>-1 subject had increased pain after 6% THC administration</td>
</tr>
<tr>
<td></td>
<td>-significant cardiac or pulmonary disease</td>
<td>-current substance abuse or dependence (including marijuana)</td>
<td>-history of psychotic disorders</td>
<td>-current suicidal ideations</td>
<td>TID</td>
<td>-1 subject tested positive for cannabinoids in urine test during placebo treatment</td>
</tr>
<tr>
<td></td>
<td>-Peripheral neuropathy, radiculopathy, or nerve injury</td>
<td>-previous marijuana use</td>
<td></td>
<td></td>
<td>Intermediate doses were used to help maintain blinding</td>
<td></td>
</tr>
<tr>
<td>Author &amp; Date Indication</td>
<td>Subjects (n) completed/randomized Subject characteristics</td>
<td>Drugs Admin. Methods</td>
<td>Study Type Duration</td>
<td>Primary Outcome Measure</td>
<td>Primary Outcome Measure Results</td>
<td>Adverse events/AEs</td>
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<tr>
<td>screening: 9.6 years (1 day to 45 years) -16 current marijuana users and 23 past users -# smoked daily: 6 current users, 5 past users -# used approx. once every 2 weeks: 8 current users, 6 past users -# used once every 4 weeks or less: 2 current users, 12 past users</td>
<td>4) repeat procedure for desired number of puffs -BID</td>
<td>Cumulative &amp; Flexible Dosing: -1st drug admin. consisted of 4 puffs from balloon. -Followed 2 hours later by 2nd drug admin.</td>
<td>2nd drug admin. consisted of 4 to 8 puffs from balloon; number of puffs taken was left up to the subject so they could self-titrate to their target does, which balanced desired response and tolerance levels.</td>
<td>placebo. -NNT=2.9 for 3.53% THC marijuana vs. placebo.</td>
<td>difference seen for 3.53% THC marijuana. -3.53% THC marijuana had significantly worse performance than 1.29% THC marijuana for learning and memory. -Both strengths of marijuana significantly reduced scores on attention compared to placebo.</td>
<td></td>
</tr>
</tbody>
</table>

*Out-patient: subjects were given enough doses of marijuana/placebo to last the 5-day treatment phase, and then were sent home for the remainder of the treatment phase. AE=Adverse Event; BID=drug administered two times per day; CRPS=complex regional pain syndrome; DDS=Descriptor Differential Scale; NIDA=National Institute of Drug Abuse; NNT=Number Needed to Treat; NRS=Numeric Rating Scale; QID=drug administered four times per day; THC=delta-9-tetrahydrocannabinol; TID=drug administered three times per day; UDS=urine drug screen; VAS=Visual Analog Scale.
Table 2: Randomized, controlled, double-blind trials examining smoked marijuana in treatment of appetite stimulation in HIV/AIDS

<table>
<thead>
<tr>
<th>Author &amp; Date Indication</th>
<th>Subjects (n) completed/randomized Subject characteristics</th>
<th>Drugs Admin. Methods</th>
<th>Study Type Duration</th>
<th>Primary Outcome Measure</th>
<th>Results (summary)</th>
<th>Adverse events/AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haney et al. (2005)</td>
<td>Low-BIA: 15/17, 12 males, 3 females</td>
<td>NIDA marijuana, smoked 0%, 1.8%, 2.8%, 3.9% THC</td>
<td>Crossover 8, 7-hour session, with at least 1 day between sessions</td>
<td>No primary outcome measure is specified</td>
<td>-In Low-BIA all dronabinol doses and 1.8% and 3.9% THC marijuana significantly increased caloric intake compared with placebo.</td>
<td>-Ratings of high and good drug effect were significantly increased for all strengths of marijuana and all doses of dronabinol except 10mg dronabinol. -3.9% THC significantly increased ratings of dry mouth and thirsty compared to placebo. -Low-BIA group showed no significant adverse event ratings, and in the normal-BIA group the only significant adverse events in response to marijuana included diarrhea after 3.9% THC marijuana. -Dronabinol had more incidences of adverse events at all doses compared to marijuana.</td>
</tr>
<tr>
<td>HIV-+ with either normal muscle mass (Normal-BIA) or clinically significant loss of muscle mass (Low-BIA)</td>
<td>Inclusion Criteria: -21-50 years of age -prescribed at least 2 antiretroviral medications -currently under the care of a physician for HIV management -medically and psychiatrically stable -smoke marijuana ≥ 2x/week for past 4 weeks</td>
<td>Dronabinol, oral 0, 10, 20, 30mg</td>
<td>Double-dummy drug admin Procedures: -only 1 active dose per session -one dronabinol/placebo capsule followed 1 hour later by marijuana/placebo smoking</td>
<td>Related outcome measure was caloric intake</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Author &amp; Date</td>
<td>Subjects (n) completed/randomized Subject characteristics</td>
<td>Drugs Admin. Methods</td>
<td>Study Type</td>
<td>Primary Outcome Measure</td>
<td>Results (summary)</td>
<td>Adverse events/AEs</td>
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</tr>
<tr>
<td>Haney et al. (2007)</td>
<td>malabsorption, major depression, dementia, chronic diarrhea, weakness, fever, significant pulmonary disease -an opportunistic infection within past 3 months -obesity -use of steroids within past 3 weeks -drug dependence (excluding marijuana or nicotine)</td>
<td>QD</td>
<td>Crossover 2, 16-day treatment phases, with 5-10 days between phases</td>
<td>No primary outcome measure is specified</td>
<td>-Both strengths of marijuana significantly increased caloric intake compared to placebo. -3.9% THC marijuana significantly increased body weight compared to placebo.</td>
<td>-Both strengths of marijuana significantly increased ratings of: good drug effect, high, mellow, stimulate, friendly, and self-confident. Only 2% THC marijuana significantly increased ratings of anxious. -Both strengths of marijuana significantly increased subjective measures for satisfied sleep and estimated time of sleep.</td>
</tr>
</tbody>
</table>

<p>| NIDA marijuana, smoked 0%, 2%, 3.9% THC | Dronabinol, oral 0, 5, 10mg | Double-dummy drug admin. Procedures: -only 1 active dose per session -one dronabinol/placebo capsule followed 1 hour later by marijuana/placebo smoking | Smoking Procedures: |</p>
<table>
<thead>
<tr>
<th>Author &amp; Date</th>
<th>Subjects (n) completed/randomized Subject characteristics</th>
<th>Drugs Admin. Methods</th>
<th>Study Type Duration</th>
<th>Primary Outcome Measure</th>
<th>Results (summary)</th>
<th>Adverse events/AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-mean (SD) # marijuana cigarettes/day: 3.2 (0.8)</td>
<td>Light cued smoking of marijuana cigarette with each puff consisting of: 1) 5s inhale smoke, 2) 10s hold smoke in lungs 3) 40s exhale and breath normally 4) repeat for 3 puffs per smoking session QID</td>
<td></td>
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<tr>
<td></td>
<td>-mean (SD) years of marijuana use: 18.6 (3.3)</td>
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</tbody>
</table>

Exclusion Criteria:
- Diagnosis of nutritional malabsorption, major depression, dementia, chronic diarrhea, weakness, fever, significant pulmonary disease
- An opportunistic infection within past 3 months
- Obesity
- Use of steroids within past 3 weeks
- Drug dependence (excluding marijuana or nicotine)

AE=Adverse Event; BIA=Bioelectric Impedance Analysis; NIDA=National Institute of Drug Abuse; QD=drug administered one time per day; QID=drug administered four times per day; THC=delta-9-tetrahydrocannabinol
<table>
<thead>
<tr>
<th>Author &amp; Date</th>
<th>Subjects (n) completed/randomized</th>
<th>Study Type</th>
<th>Primary Outcome Measure</th>
<th>Adverse events/AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corey-Bloom et al. (2012)</td>
<td>30/37 males 19 females</td>
<td>Crossover</td>
<td>Smoking marijuana on the Modified Ashworth Scale</td>
<td>-Marijuana reduced scores on cognitive measure compared to placebo.</td>
</tr>
<tr>
<td>Multiple Sclerosis; Spasticity</td>
<td>Inclusion Criteria: -documented MS -spasticity -moderate increase in tone (score ≥ 3 on modified Ashworth scale</td>
<td></td>
<td>-Smoking marijuana significantly reduced spasticity scores compared to placebo</td>
<td>-Marijuana significantly increased perceptions of &quot;highness&quot; compared to placebo</td>
</tr>
<tr>
<td>Previous Marijuana Experience:</td>
<td>-24 subjects had previous exposure to marijuana -10 subjects used marijuana within the year</td>
<td></td>
<td></td>
<td>Withdrawals for drug-related reasons:</td>
</tr>
<tr>
<td>Exclusion Criteria:</td>
<td>-no marijuana smoking for ≤1 month prior to screening -psychiatric disorder (other than depression) -history of substance use -substantial neurological disease other than MS -severe or unstable medical illnesses -known pulmonary disorders -using high dose narcotic medication for pain -using benzodiazepines to control spasticity</td>
<td>QD</td>
<td></td>
<td>-2 subjects felt uncomfortably high</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-2 dizziness</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-1 fatigue</td>
</tr>
</tbody>
</table>

AE=Adverse Event; MS=Multiple Sclerosis; NIDA=National Institute of Drug Abuse; QD=drug administered one time per day; THC=delta-9-tetrahydrocannabinol
### Table 4: Randomized, controlled, double-blind trails examining smoked marijuana in treatment of intraocular pressure in Glaucoma

<table>
<thead>
<tr>
<th>Author &amp; Date Indication</th>
<th>Subjects (n) completed/randomized Subject characteristics</th>
<th>Drugs Admin. Methods</th>
<th>Study Type Duration</th>
<th>Primary Outcome Measure</th>
<th>Results (summary)</th>
<th>Adverse events/AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crawford &amp; Merritt (1979) Hypertensive and Normotensive Glaucoma</td>
<td>HT group: 8 males 4 females NT group: 8 males 4 females</td>
<td>NIDA marijuana, smoked 0%, 2.8% THC</td>
<td>Crossover 4, 1-day sessions, no time between sessions</td>
<td>No primary outcome measure is specified</td>
<td>Marijuana decreased IOP by 37-44% from baseline. The maximal decrease in IOP was significantly greater in HT (-14mmHg) than NT (-9mmHg) after marijuana.</td>
<td>-Placebo marijuana increased heart rate for 10 minutes in both groups. -The maximal increase in heart rate was significantly greater in NT than HT after marijuana. -The maximal decrease in blood pressure was significantly greater in HT than NT after marijuana.</td>
</tr>
<tr>
<td></td>
<td>Inclusion Criteria: documented glaucoma</td>
<td>Smoking Procedure: -instructed to inhale 20 times deeply and retain smoke in lungs -smoke marijuana/placebo cigarette in 5 minutes</td>
<td></td>
<td>Related outcome measure was IOP</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Previous Marijuana Experience: -all were marijuana naïve</td>
<td>QD</td>
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</tr>
<tr>
<td></td>
<td>Exclusion Criteria: -coronary artery disease</td>
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</tr>
<tr>
<td>Merritt et al. (1980) Glaucoma</td>
<td>18 (12 males 6 females (31 glaucoma eyes, analyzed results for each eye))</td>
<td>NIDA marijuana, smoked 0%, 2% THC</td>
<td>Crossover 2, 1-day sessions</td>
<td>No primary outcome measure is specified</td>
<td>Marijuana significantly decreased IOP compared to placebo</td>
<td>-Marijuana significantly increased heart rate compared to placebo -Blood pressure significantly decreased after marijuana -All subjects experienced hunger, thirst, euphoria, drowsy, and feeling cold -Observed adverse events were greater in marijuana naïve subjects than in subjects with prior marijuana experience.</td>
</tr>
<tr>
<td></td>
<td>Inclusion Criteria: documented glaucoma</td>
<td>Smoking Procedure: -None described -smoked 1 marijuana/placebo cigarette over 10-20 minutes</td>
<td></td>
<td>Related outcome measure was IOP</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Previous Marijuana Experience: -9 subjects had used marijuana at least once</td>
<td>QD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Exclusion Criteria: -cardiac, neurological,</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**AEs:**
- 5 subjects postural hypotension
- 8 subjects anxiety with
<table>
<thead>
<tr>
<th>Author &amp; Date</th>
<th>Subjects (n) completed/randomized</th>
<th>Drugs Admin. Methods</th>
<th>Study Type Duration</th>
<th>Primary Outcome Measure</th>
<th>Results (summary)</th>
<th>Adverse events/AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>and psychiatric dysfunction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>tachycardia and palpitations</td>
</tr>
</tbody>
</table>

AE=Adverse Event; HT=Hypertensive; IOP=Intraocular pressure; NIDA=National Institute of Drug Abuse; NT=Normotensive; QD=drug administered one time per day; THC=delta-9-tetrahydrocannabinol
<table>
<thead>
<tr>
<th>Author &amp; Date Indication</th>
<th>Subjects (n) completed/randomized Subject characteristics</th>
<th>Drugs Admin. Methods</th>
<th>Study Design Duration</th>
<th>Primary Outcome Measure</th>
<th>Results (summary)</th>
<th>Adverse events/AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tashkin et al. (1974)</td>
<td>10 5 males 5 females</td>
<td>NIMH (NIDA) marijuana, smoked 0%, 2% THC  Dronabinol, oral 0, 15mg  Dosing is 7mg/kg of body weight of plant material</td>
<td>Crossover 4, 1-day sessions, with at least 48 hours between sessions</td>
<td>No primary outcome measure is specified  Related outcome measure was sGaw</td>
<td>-Marijuana significantly increased sGaw (33-48%) compared to placebo and baseline  -Marijuana initially significantly increased pulse rate compared to placebo, and then at 90 minutes pulse rate was significantly decreased compared to baseline.  -All subjects felt intoxicated after marijuana.</td>
<td></td>
</tr>
</tbody>
</table>

AE=Adverse Event; NIDA=National Institute of Drug Abuse; QD=drug administered one time per day; sGaw=Specific Airway Conductance; THC=delta-9-tetrahydrocannabinol
U.S. Department of Justice—Drug Enforcement Administration

Schedule of Controlled Substances: Maintaining Marijuana in Schedule I of the Controlled Substances Act

Background, Data, and Analysis: Eight Factors Determinative of Control and Findings Pursuant to 21 U.S.C. 812(b)

Prepared by: Office of Diversion Control, Drug and Chemical Evaluation Section, Washington, DC 20537

July 2016

Background

On November 30, 2011, Governors Lincoln D. Chafee of Rhode Island and Christine O. Gregoire of Washington submitted a petition to the Drug Enforcement Administration (DEA) to initiate proceedings for a repeal of the rules or regulations that place marijuana in schedule I of the Controlled Substances Act (CSA). The petition requests that marijuana and “related items” be rescheduled in schedule II of the CSA. The petitioners claim that:

1. Cannabis has accepted medical use in the United States;
2. Cannabis is safe for use under medical supervision;
3. Cannabis for medical purposes has a relatively low potential for abuse, especially in comparison with other schedule II drugs.

The DEA accepted this petition for filing on January 30, 2012.

The Attorney General may by rule transfer a drug or other substance between schedules of the CSA if she finds that such drug or other substance has a potential for abuse, and makes the findings prescribed by 21 U.S.C. 812(b) for the schedule to which such drug is to be placed. 21 U.S.C. 811(a)(1). The Attorney General has delegated this responsibility to the Acting Administrator of the DEA. 28 CFR 0.100(b).

In accordance with 21 U.S.C. 811(b), after gathering the necessary data, the DEA submitted the petition and necessary data to the Department of Health and Human Services (HHS) on June 11, 2013, and requested that HHS provide a scientific and medical evaluation and scheduling recommendation for marijuana. In documents dated June 3 and June 25, 2015, the acting Assistant Secretary for Health of the HHS recommended to the DEA that marijuana continue to be controlled in Schedule I of the CSA, and provided to the DEA its scientific and medical evaluation titled “Basis for the Recommendation for Maintaining Marijuana in Schedule I of the Controlled Substances Act.” The HHS’s recommendations are binding on the DEA as to scientific and medical matters. 21 U.S.C. 811(b).

Before initiating proceedings to reschedule a substance, the CSA requires the Acting Administrator to determine whether the HHS scheduling recommendation, scientific and medical evaluation, and “all other relevant data” constitute substantial evidence that the drug should be rescheduled as proposed. 21 U.S.C. 811(b). The Acting Administrator must determine whether there is substantial evidence to conclude that the drug meets the criteria for placement in another schedule based on the criteria set forth in 21 U.S.C. 812(b). The CSA requires that both the DEA and the HHS consider the eight factors specified by Congress in 21 U.S.C. 811(c). This document lays out those considerations and is organized according to the eight factors. As DEA sets forth in detail below, the evidence shows:

1. Actual or relative potential for abuse. Marijuana has a high potential for abuse. Preclinical and clinical data show that it has reinforcing effects characteristic of drugs of abuse. National databases on actual abuse show marijuana is the most widely abused drug, including significant numbers of substance abuse treatment admissions. Data on marijuana seizures show widespread availability and trafficking.

2. Scientific evidence of its pharmacological effect. The scientific understanding of marijuana, cannabinoid receptors, and the endocannabinoid system continues to be studied and elucidated. Marijuana produces various pharmacological effects, including subjective (e.g., euphoria, dizziness, disinhibition), cardiovascular, acute and chronic respiratory, immune system, and prenatal exposure effects, as well as behavioral and cognitive impairment.

3. Current scientific knowledge. There is no currently accepted medical use for marijuana in the United States. Marijuana sources are derived from numerous cultivated strains and may have different levels of Δ9-THC and other cannabinoids. Under the five-element test for currently accepted medical use discussed in more detail below and upheld by the Court of Appeals for the District of Columbia in Alliance for Cannabis Therapeutics v. DEA, 15 F. 3d 1131, 1135 (D.C. Cir. 1994) (hereinafter “ACT”), there is no complete scientific analysis of marijuana’s chemical components; there are not adequate safety studies; there are not adequate and well-controlled efficacy studies; there is not a consensus of medical opinion that marijuana is useful in the medical applications of marijuana; and the scientific evidence regarding marijuana’s safety and efficacy is not widely available. To date, scientific and medical research has not progressed to the point that marijuana has a currently accepted medical use, even under conditions where its use is severely restricted.

4. History and current pattern of abuse. Marijuana continues to be the most widely used illicit drug. In 2014, there were 22.2 million current users. There were also 2.6 million new users, most of whom were less than 18 years of age. During the same period, marijuana was the most frequently identified drug exhibit in federal, state, and local forensic laboratories.

5. Scope, duration, and significance of abuse. Abuse of marijuana is widespread and significant. In 2014, for example, an estimated 6.5 million people aged 12 or older used marijuana on a daily or almost daily basis over a 12-month period. In addition, a significant proportion of all admissions for substance abuse treatment are for marijuana/hashish as their primary drug of abuse. In 2013, 16.8% of all such admissions—281,991 over the course of the year—were for primary marijuana/hashish abuse.

6. Risk, if any, to public health. Together with the health risks outlined in terms of pharmacological effects above, public health risks from acute use of marijuana include impaired psychomotor performance, impaired driving, and impaired performance on tests of learning and associative...
processes. Chronic use of marijuana poses a number of other risks to the public health including physical as well as psychological dependence.

7. Psychic or physiological dependence liability. Long-term, heavy use of marijuana can lead to physical dependence and withdrawal following discontinuation, as well as psychic or psychological dependence. In addition, a significant proportion of all admissions for treatment for substance abuse are for primary marijuana abuse; in 2013, 16.8% of all admissions were for primary marijuana/hashish abuse, representing 281,991 individuals.

8. Immediate precursor. Marijuana is not an immediate precursor of any controlled substance.

As specified in 21 U.S.C. 812(b)(1), in order for a substance to be placed in schedule I, the Acting Administrator must find that:

A. The drug or other substance has a high potential for abuse.

B. The drug or other substance has no currently accepted medical use in treatment in the United States.

C. There is a lack of accepted safety for use of the drug or other substance under medical supervision.

To be classified in another schedule under the CSA (e.g., II, III, IV, or V), a substance must have a “currently accepted medical use in treatment in the United States.” 21 U.S.C. 812(b)(2)–(5). A substance also may be placed in schedule II if it is found to have “a currently accepted medical use with severe restrictions.” 21 U.S.C. 812(b)(2).

If a controlled substance has no such currently accepted medical use, it must be placed in schedule I. See Notice of Denial of Petition, 66 FR 20038 (Apr. 18, 2001) (“Congress established only one schedule—schedule I—for drugs of abuse with ‘no currently accepted medical use in treatment in the United States’ and ‘lack of accepted safety for use . . . under medical supervision.’”).

A drug that is the subject of an approved new drug application (NDA) or abbreviated new drug application (ANDA) under Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355), is considered to have a currently accepted medical use in treatment in the United States for purposes of the CSA. The HHS stated in its review, however, that FDA has not approved any NDA for marijuana for any indication.

In the absence of NDA or ANDA approval, DEA has established a five-element test for determining whether the drug has a currently accepted medical use in the United States. Under this test, a drug will be considered to have a currently accepted medical use only if the following five elements are satisfied:

1. The drug’s chemistry is known and reproducible;
2. There are adequate safety studies;
3. There are adequate and well-controlled studies proving efficacy;
4. The drug is accepted by qualified experts; and
5. The scientific evidence is widely available.

(57 FR 10499, 10506 (March 26, 1992)). See also ACT, 15 F.3d at 1135. As discussed in Factor 3, below, HHS concluded, and DEA agrees, that the scientific evidence is insufficient to demonstrate that marijuana has a currently accepted medical use under the five-element test. The evidence was insufficient in this regard also when the DEA considered petitions to reschedule marijuana in 1992 (57 FR 10499),41 in 2001 (66 FR 20038), and in 2011 (76 FR 40552).42 Little has changed since 2011 with respect to the lack of clinical evidence necessary to establish that marijuana has a currently accepted medical use. No studies have scientifically assessed the efficacy and full safety profile of marijuana for any specific medical condition.

The limited existing clinical evidence is not adequate to warrant rescheduling of marijuana under the CSA. To the contrary, the data in this scheduling review document show that marijuana continues to meet the criteria for schedule I control under the CSA for the following reasons:

1. Marijuana has a high potential for abuse.
2. Marijuana has no currently accepted medical use in treatment in the United States.
3. Marijuana lacks accepted safety for use under medical supervision.

Factor 1: The Drug’s Actual or Relative Potential for Abuse

Marijuana is the most commonly abused illegal drug in the United States. It is also the most commonly used illicit drug by high school students in the United States. Further, marijuana is the most frequently identified drug by state, local and federal forensic laboratories. Marijuana’s main psychoactive ingredient, Δ⁹-tetrahydrocannabinol (Δ⁹-THC),43 is an effective reinforcer in laboratory animals, including primates and rodents. These animal studies both predict and support the observations that marijuana produces reinforcing effects in humans. Such reinforcing effects can account for the repeated abuse of marijuana.

A. Indicators of Abuse Potential

The HHS has concluded in its document, “Basis for the Recommendation for Maintaining Marijuana in Schedule I of the Controlled Substances Act,” that marijuana has a high potential for abuse. The finding of “abuse potential” is critical for control under the Controlled Substances Act (CSA). Although the term is not defined in the CSA, guidance in determining abuse potential is provided in the legislative history of the Act (Comprehensive Drug Abuse Prevention and Control Act of 1970, H.R. Rep. No. 91–1444, 91st Cong., Sess. 2 (1970), reprinted in 1970 U.S.C.C.A.N. 4566, 4603). Accordingly, the following items are indicators that a drug or other substance has potential for abuse:

• There is evidence that individuals are taking the drug or drugs containing such a substance in amounts sufficient to create a hazard to their health or to the safety of other individuals or of the community; or
• There is significant diversion of the drug or drugs containing such a substance from legitimate drug channels; or
• Individuals are taking the drug or drugs containing such a substance on their own initiative rather than on the basis of medical advice from a practitioner licensed by law to administer such drugs in the course of his professional practice; or
• The drug or drugs containing such a substance are new drugs so related in their action to a drug or drugs already listed as having a potential for abuse to make it likely that the drug will have the same potentiality for abuse as such drugs, thus making it reasonable to assume that there may be significant diversions from legitimate channels, significant use contrary to or without medical advice, or that it has a substantial capability of creating hazards to the health of the user or to the safety of the community.

Of course, evidence of actual abuse of a substance is indicative that a drug has a potential for abuse.

In its recommendation, the HHS analyzed and evaluated data on marijuana as applied to each of the above four criteria. The analysis presented in the recommendation (HHS, 2015) is discussed below:

1. There is evidence that individuals are taking the drug or drugs containing such a substance in amounts sufficient to create a hazard to their health or to...
the safety of other individuals or of the community.

The HHS stated that some individuals are taking marijuana in amounts sufficient to create a hazard to their health and to the safety of other individuals and the community. Data from national databases on actual abuse of marijuana support the idea that a large number of individuals use marijuana. In its recommendation (HHS, 2015), the HHS presented data from the National Survey on Drug and Health (NSDUH) of the Substance Abuse and Mental Health Services Administration (SAMHSA) and the Monitoring the Future (MTF) survey of the National Institute on Drug Abuse (NIDA), and the DEA has since updated this information. The most recent data from SAMHSA’s NSDUH in 2014 reported that marijuana was the most used illicit drug. Among Americans aged 12 years and older, an estimated 22.2 million Americans used marijuana within the past month according to the 2014 NSDUH. In 2004, an estimated 14.6 million individuals reported using marijuana within the month prior to the study. The estimated rates in 2014 thus reflect an increase of approximately 7.6 million individuals over a 10-year period. According to the 2013 NSDUH report, an estimated 19.8 million individuals reported using marijuana. Thus, over a period of one year (2013 NSDUH–2014 NSDUH), there was an estimated increase of 2.4 million individuals in the United States using marijuana.

The results from the 2015 Monitoring the Future survey of 8th, 10th, and 12th grade students indicate that marijuana was the most widely used illicit drug in these age groups. Current monthly use was 6.5% of 8th graders, 14.8% of 10th graders, and 21.3% of 12th graders. The Treatment Episode Data Set (TEDS) in 2013 reported that marijuana abuse was the primary factor in 16.8 percent of non-private substance-abuse treatment facility admissions. In 2011, SAMHSA’s Drug Abuse Warning Network (DAWN) reported that marijuana was mentioned in 36.4% (455,668 out of approximately 1.25 million) of illicit drug-related Emergency Department (ED) visits.

Data on the extent and scope of marijuana abuse are presented under Factors 4 and 5 of this analysis. Discussion of the health effects of marijuana is presented under Factor 2, and the assessment of risk to the public health posed by acute and chronic marijuana abuse is presented under Factor 6 of this analysis.

2. There is significant diversion of the drug drugs containing such a substance from legitimate drug channels.

In accordance with the CSA, the only lawful source of marijuana in the United States is that produced and distributed for research purposes under the oversight of NIDA and in conformity with United States obligations under the Single Convention on Narcotic Drugs. The HHS stated that there is a lack of significant diversion from legitimate drug sources, but that this is likely due to high availability of marijuana from illicit sources. Marijuana is not an FDA-approved drug product. Neither a New Drug Application (NDA) nor a Biologics License Application (BLA) has been approved by the FDA to market in the United States. However, the marijuana used for nonclinical and clinical research represents a very small amount of the total amount of marijuana available in the United States and therefore information about marijuana diversion from legitimate sources is limited or not available.

The DEA notes that the magnitude of the demand for illicit marijuana is evidenced by information from a number of databases presented under Factor 4. Briefly, marijuana is the most commonly used illegal drug in the United States. It is also the most commonly used illicit drug by American high schoolers. Marijuana is the most frequently identified drug in state, local, and federal forensic laboratories, with increasing amounts of both domestically grown and of illicitly smuggled marijuana.

Given that marijuana has long been the most widely trafficked and abused controlled substance in the United States, and that all aspects of such illicit activity are entirely outside of the closed system of distribution mandated by the CSA, it may well be the case that there is little thought given to diverting marijuana from the small supplies produced for legitimate research purposes. Thus, the lack of data indicating diversion of marijuana from legitimate channels to the illicit market is not indicative of a lack of potential for abuse of the drug.

3. Individuals are taking the drug or drugs containing such a substance on their own initiative rather than on the basis of medical advice from a practitioner licensed by law to administer such drugs in the course of his professional practice.

The HHS stated that the FDA has not evaluated or approved an NDA or BLA for marijuana for any therapeutic indication. Consistent with federal law, therefore, an individual legitimately can take marijuana based on medical advice from a practitioner only by participating in research that is being conducted under an Investigational New Drug (IND) application. The HHS noted that there are several states as well as the District of Columbia which have passed laws allowing for individuals to use marijuana for purported “medical” use under certain circumstances, but data are not available yet to determine the number of individuals using marijuana under these state laws. Nonetheless, according to 2014 NSDUH data, 22.2 million American adults currently use marijuana (SAMHSA, 2015a). Based on the large number of individuals who use marijuana and the lack of an FDA-approved drug product, the HHS concluded that the majority of individuals using marijuana do so on their own initiative rather than by following medical advice from a licensed practitioner.

4. The drug or drugs containing such a substance are new drugs so related in their action to a drug or drugs already listed as having a potential for abuse to make it likely that the drug will have the same potential for abuse as such drugs, thus making it reasonable to assume that there may be significant divergences from legitimate channels, significant use contrary to or without medical advice, or that it has a substantial capability of creating hazards to the health of the user or to the safety of the community.

Marijuana and its primary psychoactive ingredient, Δ⁹-THC, are controlled substances in schedule I under the CSA.

The HHS stated that one approved, marketed drug product contains synthetic Δ⁹-THC, also known as dronabinol, and another approved, marketed drug product contains a cannabinoid-like synthetic compound that is structurally related to Δ⁹-THC, the main active component in marijuana. Both products are controlled under the CSA.

Marinol is a schedule III drug product containing synthetic Δ⁹-THC (dronabinol) formulated in sesame oil in soft gelatin capsules. Marinol was approved by the FDA in 1985 for the treatment of nausea and vomiting associated with cancer chemotherapy in patients who did not respond to conventional anti-emetic treatments. In 1992, FDA approved Marinol for the treatment of anorexia associated with weight loss in patients with acquired immunodeficiency syndrome (AIDS). Marinol was originally placed in schedule II and later rescheduled to schedule III under the CSA due to the

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4 See 76 FR 51403, 51409–51410 (2011) (discussing cannabis controls required under the Single Convention).
low reports of abuse relative to marijuana.

Cesamet is a drug product containing the schedule II substance nabilone, a synthetic substance structurally related to Δ⁹-THC. Cesamet was approved for marketing by the FDA in 1985 for the treatment of nausea and vomiting associated with cancer chemotherapy. All other naturally occurring cannabinoids in marijuana and their synthetic equivalents with similar chemical structure and pharmacological activity are already included as schedule I drugs under the CSA.

B. Abuse Liability Studies

In addition to the indicators suggested by the CSA’s legislative history, data as to preclinical and clinical abuse liability studies, as well as actual abuse, including clandestine manufacture, trafficking, and diversion from legitimate sources, are considered in this factor.

Abuse liability evaluations are obtained from studies in the scientific and medical literature. There are many preclinical measures of a drug’s effects that when taken together provide an accurate prediction of the human abuse liability. Clinical studies of the subjective and reinforcing effects in humans and epidemiological studies provide quantitative data on abuse liability in humans and some indication of actual abuse trends. Both preclinical and clinical studies have clearly demonstrated that marijuana and Δ⁹-THC possess the attributes associated with drugs of abuse: They function as a positive reinforcer to maintain drug-seeking behavior, they function as a discriminative stimulus, and they have dependence potential.

Preclinical and most clinical abuse liability studies have been conducted with the psychoactive constituents of marijuana, primarily Δ⁹-THC and its metabolite, 11-hydroxy-Δ⁹-THC. Δ⁹-THC’s subjective effects are considered to be the basis for marijuana’s abuse liability. The following studies provide a summary of that data.

1. Preclinical Studies

Δ⁹-THC, the primary psychoactive component in marijuana, is an effective reinforcer in laboratory animals, including primates and rodents, as these animals will self-administer Δ⁹-THC. These animal studies both predict and support the observations that Δ⁹-THC, whether smoked as marijuana or administered by other routes, produces reinforcing effects in humans. Such reinforcing effects can account for the repeated abuse of marijuana.

a. Drug Discrimination Studies

The drug discrimination paradigm is used as an animal model of human subjective effects (Solinas et al., 2006) and is a method where animals are able to indicate whether a test drug is able to produce physical or psychological changes similar to a known drug of abuse. Animals are trained to press one bar (in an operant chamber) when they receive a known drug of abuse and another bar when they receive a placebo. When a trained animal receives a test drug, if the drug is similar to the known drug of abuse, it will press the bar associated with the drug.

Discriminative stimulus effects of Δ⁹-THC have specificity for the pharmacological effects of cannabinoids found in marijuana (Balster and Prescott, 1992; Browne and Weissman, 1981; 1993; Wiley et al., 1995). As mentioned by the HHS, the discriminative stimulus effects of cannabinoids appear to be unique because abused drugs of other classes including stimulants, hallucinogens, opioid, benzodiazepines, barbiturates, NMDA antagonists, and antipsychotics do not fully substitute for Δ⁹-THC.

Laboratory animals including monkeys (McMahon et al., 2009), mice (McMahon et al., 2008), and rats (Gold et al., 1992) are able to discriminate cannabinoids from other drugs and placebo. The major active metabolite of Δ⁹-THC, 11-hydroxy-Δ⁹-THC, generalizes to Δ⁹-THC (Browne and Weissman, 1981). In addition, according to the HHS, twenty-two other cannabinoids found in marijuana also substitute for Δ⁹-THC. At least one cannabinoid, CBD, does not substitute for Δ⁹-THC in rats (Vann et al., 2008).

b. Self-Administration Studies

Animal self-administration behavior associated with a drug is a commonly used method for evaluating if the drug produces rewarding effects and for predicting abuse potential (Balster, 1991; Balster and Bigelow, 2003). Drugs that are self-administered by animals are likely to produce rewarding effects in humans. As mentioned in the HHS review document, earlier attempts to demonstrate self-administration of Δ⁹-THC were unsuccessful and confounded by diet restrictions, animal restraint, and known analgesic activity of Δ⁹-THC at testing doses (Tanda and Goldberg, 2003; Justinova et al., 2003). Self-administration of Δ⁹-THC was first demonstrated by Tanda et al. (2000).

Tanda et al. (2000) showed that squirrel monkeys that were initially trained to self-administer cocaine (30 μg/kg, i.v.) self-administered 2 μg/kg Δ⁹-THC (i.v.) and at a rate of 30 injections per one hour session. Tanda et al. (2000) used a lower dose of Δ⁹-THC that was rapidly delivered (0.2 ml injection over 200 ms) than in previous self-administration studies such that analgesic activity of Δ⁹-THC was not a confounding factor. The authors also stated that the doses were comparable to those doses used by humans who smoke marijuana. A CB1 receptor antagonist (SR141716) blocked this rewarding effect of THC.

Justinova et al. (2003) were able to demonstrate self-administration of Δ⁹-THC in drug-naïve squirrel monkeys (no previous exposure to other drugs). The authors tested the monkeys with several doses of Δ⁹-THC (1, 2, 4, 8, and 16 μg/kg, i.v.) and found that the maximal rates of self-administration were observed with the 4 μg/kg infusion. Subsequently, Braida et al. (2004) reported that rats will self-administer Δ⁹-THC when delivered intracerebroventricularly (i.c.v.), but only at the lowest doses tested (0.01–0.02 μg/infusion, i.c.v.).

Self-administration behavior with Δ⁹-THC was found to be antagonized in rats and squirrel monkeys by rimonabant (SR141716A, CB1 antagonist) and the opioid antagonists (naloxone and naltrexone) (Tanda et al., 2000; Braida et al., 2004; Justinova et al., 2004).

c. Conditioned Place Preference Studies

Conditioned place preference (CPP) is a behavioral assay where animals are given the opportunity to spend time in two distinct environments: one where they previously received drug and one where they received a placebo. If the drug is reinforcing, animals in a drug-free state will choose to spend more time in the environment paired with the drug when both environments are presented simultaneously.

CPP has been demonstrated with Δ⁹-THC in rats but only at low doses (0.075–1.0 mg/kg, i.p.; Braida et al., 2004). Rimonabant (0.25–1.0 mg/kg, i.p.) and naltroxone (0.5–2.0 mg/kg, i.p.) antagonized Δ⁹-THC-mediated CPP (Braida et al., 2004). However, in another study with rats, rimonabant was demonstrated to induce CPP at doses ranging from 0.25–3.0 mg/kg (Cheer et al., 2000). Mice without μ-opioid receptors did not exhibit CPP to Δ⁹-THC (paired with 1 mg/kg Δ⁹-THC, i.p.) (Ghoshland et al., 2002).
following moderate and heavy use. As discussed further in Factor 7, the DEA notes that the American Psychiatric Association’s (APA) Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM–5) included a list of withdrawal symptoms following marijuana [cannabis] use (DSM–5, 2013).

C. Actual Abuse of Marijuana—National Databases Related to Marijuana Abuse and Trafficking

Marijuana continues to be the most widely used illicit drug. Evidence of actual abuse can be defined by episodes/mentions in databases indicative of abuse/dependence. The HHS provided in its recommendation (HHS, 2015) information relevant to actual abuse of marijuana including data results from the National Survey on Drug Use and Health (NSDUH), a Monitoring the Future (MTF) survey, the Drug Abuse Warning Network (DAWN), and the Treatment Episode Data Set (TEDS). These data sources provide quantitative information on many factors related to abuse of a particular substance, including incidence and patterns of use, and profile of the abuser of specific substances. The DEA is providing updated information from these databases in this discussion. The DEA also includes data on trafficking and illicit availability of marijuana from DEA databases including the National Forensic Laboratory Information System (NFLIS) and the National Seizure System (NSS), formerly the Federal-wide Drug Seizure System (FDSS), as well as other sources of data specific to marijuana, including the Potency Monitoring Project and the Domestic Cannabis Eradication and Suppression Program (DCE/SP).

1. National Survey on Drug Use and Health (NSDUH)

The National Survey on Drug Use and Health (NSDUH) is conducted annually by the Department of Health and Human Service’s Substance Abuse and Mental Health Services Administration (SAMHSA). SAMHSA is the primary source of estimates of the prevalence and incidence of pharmaceutical drugs, illicit drugs, alcohol, and tobacco use in the United States. The survey is based on a nationally representative sample of the civilian, non-institutionalized population 12 years of age and older. The survey excludes homeless people who do not use shelters, active military personnel, and residents of institutional group quarters such as jails and hospitals.

According to the 2014 NSDUH report, marijuana was the most commonly used and abused illicit drug. That data showed that there were 22.2 million people who were past month users (8.4%) among those aged 12 and older in the United States. (Note: NSDUH figures on marijuana use include hashish use; the relative proportion of hashish use to marijuana use is very low.) Marijuana had the highest rate of past-year dependence or abuse in 2014. The NSDUH report estimates that 3.0 million people aged 12 or older used an illicit drug for the first time in 2014; a majority (70.3%) of these past year initiates reported that their first drug used was marijuana. Among those who began using illicit drugs in the past year, 65.6%, 70.3%, and 67.6% reported marijuana as the first illicit drug initiated in 2012, 2013, and 2014 respectively. In 2014, the average age of marijuana initiates among 12- to 49-year-olds was 18.5 years. These usage rates and demographics are relevant in light of the risks presented.

Marijuana had the highest rate of past year dependence or abuse of any illicit drug in 2014. The 2014 NSDUH report stated that 4.2 million persons were classified with substance dependence or abuse of marijuana in the past year (representing 1.6% of the total population aged 12 or older, and 59.0% of those classified with illicit drug dependence or abuse) based on criteria specified in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM–IV).

Among past year marijuana users age 12 or older, 18.5% used marijuana on 300 or more days within the previous 12 months in 2014. This translates into 6.5 million people using marijuana on a daily or almost daily basis over a 12-month period, significantly more than the estimated 5.7 million daily or almost daily users in just the year before. Among past month marijuana users, 41.6% (9.2 million) used the drug on 20 or more days in the past month, a significant increase from the 8.1 million who used marijuana 20 days or more in 2013.

2. Monitoring the Future (MTF)

Monitoring the Future (MTF) is an ongoing study which is funded under a series of investigator-initiated competing research grants from the National Institute on Drug Abuse (NIDA). MTF tracks drug use trends among American adolescents in the 8th, 10th, and 12th grades. According to its 2015 survey results, marijuana was the most commonly used illicit drug, as was the case in previous years. Approximately 6.5% of 8th graders,
14.8% of 10th graders, and 21.3% of 12th graders surveyed in 2015 reported marijuana use during the past month prior to the survey. A number of high school students in 2015 also reported daily use in the past month, including 1.1%, 3.0%, and 6.0% of 8th, 10th, and 12th graders, respectively.

3. Drug Abuse Warning Network (DAWN), Emergency Department (ED) Visits

The Drug Abuse Warning Network (DAWN) is a public health surveillance system that monitors drug-related hospital emergency department (ED) visits to track the impact of drug use, misuse, and abuse in the United States. For the purposes of DAWN, the term “drug abuse” applies if the following conditions are met: (1) The case involved at least one of the following: use of an illegal drug, use of a legal drug contrary to directions, or inhalation of a non-pharmaceutical substance; and (2) the substance was used for one of the following reasons: Because of drug dependence, to commit suicide (or attempt to commit suicide), for recreational purposes, or to achieve other psychic effects. Importantly, many factors can influence the estimates of ED visits, including trends in overall use of a substance as well as trends in the reasons for ED usage. For instance, some drug users may visit EDs for life-threatening issues while others may visit to seek care for detoxification because they needed certification before entering treatment. Additionally, DAWN data do not distinguish the drug responsible for the ED visit from other drugs that may have been used concomitantly. As stated in a DAWN report, “Since marijuana/hashish is frequently present in combination with other drugs, the reason for the ED visit may be more relevant to the other drug(s) involved in the episode.”

In 2011, marijuana was involved in 455,668 ED visits out of 2,462,948 total ED visits involving all abuse or misuse in the United States and out of 1.25 million visits involving abuse or misuse of illicit drugs (excluding alcohol-related visits), as estimated by DAWN. This is lower than the number of ED visits involving cocaine (505,224) and higher than the number of ED visits involving heroin (258,482) and stimulants (e.g., amphetamine, methamphetamine) (159,840). Visits involving the other major illicit drugs, such as MDMA, GHB, LSD and other hallucinogens, PCP, and inhalants, were much less frequent, comparatively.

In young patients, marijuana is the illicit drug most frequently involved in ED visits, according to DAWN estimates, with 240.2 marijuana-related ED visits per 100,000 population ages 12 to 17, 443.8 per 100,000 population ages 18 to 20, and 446.9 per 100,000 population ages 21 to 24.

4. Treatment Episode Data Set (TEDS) System

The Treatment Episode Data Set (TEDS) system is part of the SAMHSA Drug and Alcohol Services Information System and is a national census of annual admissions to state licensed or certified, or administratively tracked, substance abuse treatment facilities. The TEDS system contains information on patient demographics and substance abuse problems of admissions to treatment for abuse of alcohol and/or drugs in facilities that report to state administrative data systems. For this database, the primary substance of abuse is defined as the main substance of abuse reported at the time of admission. TEDS also allows for the recording of two other substances of abuse (secondary and tertiary).

In 2011, the TEDS system included 1,928,792 admissions to substance abuse treatment; in 2012 there were 1,801,385 admissions; and in 2013 there were 1,683,451 admissions. Marijuana/hashish was the primary substance of abuse for 18.3% (352,397) of admissions in 2011; 17.5% (315,200) in 2012; and 16.8% (281,991) in 2013. Of the 281,991 admissions for marijuana/hashish treatment in 2013, 24.3% used marijuana/hashish daily. Among those treated for marijuana/hashish as the primary substance in 2013, 27.4% were ages 12 to 17 years and 29.7% were ages 18 to 24 years. Those admitted for marijuana/hashish were mostly male (72.6%) and non-Hispanic (82.2%). Non-Hispanic whites (43.2%) represented the largest ethnic group of marijuana admissions.

5. Forensic Laboratory Data

Data on marijuana seizures from federal, state, and local forensic laboratories have indicated that there is significant trafficking of marijuana. The National Forensic Laboratory System (NFLIS) is a program sponsored by the Drug Enforcement Administration’s Office of Diversion Control. NFLIS systematically collects drug identification results and associated information from drug exhibits encountered by law enforcement and analyzed in federal, state, and local forensic laboratories. NFLIS is a comprehensive information system that includes data from 278 individual forensic laboratories that report more than 91% of the drug caseload in the U.S. NFLIS captures data for all drugs and chemicals identified and reported by forensic laboratories. More than 1,700 unique substances are represented in the NFLIS database.

Data from NFLIS showed that marijuana was the most frequently identified drug in federal, state, and local laboratories from January 2004 through December 2014. Marijuana accounted for between 29.47% and 34.64% of all drug exhibits analyzed annually during that time frame (Table 1).
Table 1. NFLIS Federal, State and Local Forensic Laboratory Data of Marijuana Reports (other than hashish)

<table>
<thead>
<tr>
<th>Year</th>
<th>Reports</th>
<th>Percent of Total Reports</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>454,582</td>
<td>34.42%</td>
</tr>
<tr>
<td>2005</td>
<td>483,134</td>
<td>32.53%</td>
</tr>
<tr>
<td>2006</td>
<td>520,060</td>
<td>32.55%</td>
</tr>
<tr>
<td>2007</td>
<td>525,668</td>
<td>33.66%</td>
</tr>
<tr>
<td>2008</td>
<td>526,420</td>
<td>34.07%</td>
</tr>
<tr>
<td>2009</td>
<td>536,888</td>
<td>34.30%</td>
</tr>
<tr>
<td>2010</td>
<td>544,418</td>
<td>34.91%</td>
</tr>
<tr>
<td>2011</td>
<td>495,937</td>
<td>33.42%</td>
</tr>
<tr>
<td>2012</td>
<td>485,591</td>
<td>32.02%</td>
</tr>
<tr>
<td>2013</td>
<td>452,839</td>
<td>30.70%</td>
</tr>
<tr>
<td>2014</td>
<td>432,989</td>
<td>29.27%</td>
</tr>
<tr>
<td>2015*</td>
<td>341,162</td>
<td>26.73%</td>
</tr>
</tbody>
</table>

NFLIS database queried 03-23-2016, by date of submission, all drugs reported *2015 data are still being reported to NFLIS due to normal lag time.

Since 2004, the total number of reports of marijuana and the amount of marijuana encountered federally has remained high (see data from Federal-wide Drug Seizure System and Domestic Cannabis Eradication and Suppression Program below).

6. Federal-Wide Drug Seizure System

The Federal-wide Drug Seizure System (FDSS) contains information about drug seizures made within the jurisdiction of the United States by the Drug Enforcement Administration, the Federal Bureau of Investigation, United States Customs and Border Protection, and United States Immigration and Customs Enforcement. It also records maritime seizures made by the United States Coast Guard. Drug seizures made by other Federal agencies are included in the FDSS database when drug evidence custody is transferred to one of the agencies identified above. FDSS is now incorporated into the National Seizure System (NSS), which is a repository for information on clandestine laboratory and contraband (chemicals and precursors, currency, drugs, equipment and weapons). FDSS reports total federal drug seizures [in kilograms (kg)] of substances such as cocaine, heroin, MDMA, methamphetamine, and cannabis (marijuana and hashish). The yearly volume of cannabis seized (Table 2), consistently exceeding a thousand metric tons per year, shows that cannabis is very widely trafficked in the United States.

Table 2. Total Federal Seizures of Cannabis (Expressed in Kg)
(Source: NSS, U.S. Seizures, EPIC System Portal, queried 08-05-2015)

<table>
<thead>
<tr>
<th></th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cannabis</td>
<td>4,071,328</td>
<td>3,622,256</td>
<td>2,756,439</td>
<td>2,622,494</td>
<td>1,768,277</td>
</tr>
<tr>
<td>Marijuana</td>
<td>4,070,850</td>
<td>3,621,322</td>
<td>2,754,457</td>
<td>2,618,340</td>
<td>1,767,741</td>
</tr>
<tr>
<td>Hashish</td>
<td>478</td>
<td>934</td>
<td>1,982</td>
<td>4,154</td>
<td>536</td>
</tr>
</tbody>
</table>

7. Potency Monitoring Project

The University of Mississippi’s Potency Monitoring Project (PMP), through a contract with the National Institute on Drug Abuse (NIDA), analyzes and compiles data on the Δ9-

THC concentrations of marijuana, hashish and hash oil samples provided by DEA regional laboratories and by state and local police agencies. After 2010, PMP has analyzed only marijuana samples provided by DEA regional laboratories. As indicated in Figure 1, the percentage of Δ9-THC increased from 1995 to 2010 with an average THC content of 3.75% in 1995 and 9.53% in 2010. In examining marijuana samples only provided by DEA laboratories, the average Δ9-THC content was 3.96% in 1995 in comparison to 11.16% in 2015.
8. The Domestic Cannabis Eradication and Suppression Program

The Domestic Cannabis Eradication and Suppression Program (DCE/SP) was established in 1979 to reduce the supply of domestically cultivated marijuana in the United States. The program was designed to serve as a partnership between federal, state, and local agencies. Only California and Hawaii were active participants in the program at its inception. However, by 1982 the program had expanded to 25 states and by 1985 all 50 states were participants. Cannabis is cultivated in remote locations and frequently on public lands and illicitly grown in all states. Data provided by the DCE/SP (Table 3) show that in the United States in 2014, there were 3,904,213 plants eradicated in outdoor cannabis cultivation areas compared to 2,597,798 plants in 2000. Significant quantities of marijuana were also eradicated from indoor cultivation operations. There were 396,620 indoor plants eradicated in 2014 compared to 217,105 eradicated in 2000.
Table 3. Domestic Cannabis Eradication, Outdoor and Indoor Plants Seized, 2000–2014 (Source: Domestic Cannabis Eradication/Suppression Program)

<table>
<thead>
<tr>
<th></th>
<th>2000</th>
<th>2001</th>
<th>2002</th>
<th>2003</th>
<th>2004</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outdoor</td>
<td>2,597,798</td>
<td>3,068,632</td>
<td>3,128,800</td>
<td>3,427,923</td>
<td>2,996,144</td>
</tr>
<tr>
<td>Indoor</td>
<td>217,105</td>
<td>236,128</td>
<td>213,040</td>
<td>223,183</td>
<td>203,896</td>
</tr>
<tr>
<td>Total</td>
<td>2,814,903</td>
<td>3,304,760</td>
<td>3,341,840</td>
<td>3,651,106</td>
<td>3,200,040</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outdoor</td>
<td>3,938,151</td>
<td>4,830,766</td>
<td>6,599,599</td>
<td>7,562,322</td>
<td>9,980,038</td>
</tr>
<tr>
<td>Indoor</td>
<td>270,935</td>
<td>400,892</td>
<td>434,728</td>
<td>450,986</td>
<td>414,604</td>
</tr>
<tr>
<td>Total</td>
<td>4,209,086</td>
<td>5,231,658</td>
<td>7,034,327</td>
<td>8,013,308</td>
<td>10,394,642</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outdoor</td>
<td>9,866,766</td>
<td>6,226,288</td>
<td>3,631,582</td>
<td>4,033,513</td>
<td>3,904,213</td>
</tr>
<tr>
<td>Indoor</td>
<td>462,419</td>
<td>509,231</td>
<td>302,377</td>
<td>361,727</td>
<td>396,620</td>
</tr>
<tr>
<td>Total</td>
<td>10,329,185</td>
<td>6,735,519</td>
<td>3,933,959</td>
<td>4,395,240</td>
<td>4,300,833</td>
</tr>
</tbody>
</table>

The recent statistics from these various surveys and databases show that marijuana continues to be the most commonly used illicit drug, with considerable rates of heavy abuse and dependence. They also show that marijuana is the most readily available illicit drug in the United States.

Petitioners’ Major Comments in Relation to Factor 1 and the Government’s Responses

1 In Exhibit B, the petitioners compared the effects of marijuana to currently controlled schedule II substances and made repeated claims about the comparative effects.

The HHS noted that comparisons between marijuana and schedule II substances are difficult because of differences in the actions of different pharmacological classes of schedule II drugs in the CSA. The HHS notes that schedule II substances include stimulant-like drugs (e.g., cocaine, amphetamine), opioids (e.g., fentanyl), oxycodone), depressant drugs (e.g., pentobarbital), dissociative anesthetics (e.g., phencyclidine), and naturally occurring plant components (e.g., coca leaves and poppy straw). The mechanism of action of Δ⁹-THC and marijuana, which act primarily through the cannabinoid receptors (discussed further in Factor 2) are completely different from the above-mentioned classes of schedule II substances. The HHS concludes that the differences in the mechanisms of action in the various classes of schedule II substances make it inappropriate to compare the range of those substances with marijuana.

Furthermore, as noted by the HHS, many substances scheduled under the CSA are evaluated within the context of drug development using data submitted under a New Drug Application (NDA). However, the petitioners have not identified a specific indication for use of marijuana and therefore the HHS notes that an appropriate comparator based on indication cannot be identified.

2 The petitioners indicated that the actual or relative potential of abuse of marijuana is low. The petitioners state, “Some researchers claim that cannabis is not particularly addictive. Experts assert that cannabis’s addictive potential parallels caffeine’s.” [Exhibit B, page 19, lines 20–21]. Furthermore, petitioners stated that, “Cannabis use indicates a lower likelihood of addiction and abuse potential as compared to other substances.” [Exhibit B, page 22, lines 12–13].

Under the CSA, for a substance to be placed in schedule II, III, IV, or V, it must have a currently accepted medical use in treatment in the United States. As DEA has previously stated, Congress established only one schedule, schedule I, for drugs of abuse with “no currently accepted medical use in treatment in the United States.” 76 FR 40552 (2011). Thus, any attempt to compare the relative abuse potential of schedule I substance to that of a substance in another schedule is inconsequential since a schedule I substance must remain in schedule I until it has been found to have a currently accepted medical use in treatment in the United States.

Moreover, the petitioners failed to review the indicators of abuse potential, as discussed in the legislative history of the CSA. The petitioners did not use data on marijuana usage, diversion, psychoactive properties, and dependence in their evaluation of marijuana abuse potential. The HHS and the DEA discuss those indicators above in this factor. HHS’s evaluation of the full range of data led HHS and DEA to conclude that marijuana has a high potential for abuse.

The petitioners, based on their review of a survey by Gore and Earleywine (2007), concluded that marijuana has a low abuse potential. Gore and Earleywine surveyed 746 mental health professionals and asked them to rate the addictiveness (based on a seven-point scale) of several drugs (heroin, nicotine, cocaine/crack, oxycodone, methamphetamine, amphetamine, caffeine, alcohol, and marijuana). The petitioners stated that the health professionals rated marijuana as least addictive of the drugs surveyed. The DEA notes that the survey cited by the petitioners is based on subjective opinions from health professionals.

3 The petitioners mentioned that many of the cannabinoids in marijuana decrease the psychoactive effects of Δ⁹-THC, and therefore marijuana lacks sufficient abuse potential for placement into schedule I. Further, the petitioners mentioned on page 4 in Exhibit B (lines 11–13), “While the DEA considers cannabis a schedule I drug, it classifies dronabinol (Marinol) as schedule III. Dronabinol is 100 percent THC and is
potentially very psychoactive. Natural cannabis typically would be no more than 15 percent THC by weight. Thus it is inconsistent that cannabis, with 15 percent weight THC, remains a [schedule I drug, while dronabinol, at 100 percent THC, is schedule III.”

The HHS addressed this issue by indicating that the modulating effects of the other cannabinoids in marijuana on Δ^9-THC have not been demonstrated in controlled studies. The HHS and the DEA also note that the determination of the abuse potential of a substance considers not only psychoactive effects but also chemistry, pharmacology, pharmacokinetics, usage patterns, and diversion history among other measures.

Marinol (dronabinol in sesame oil) was rescheduled from schedule II to schedule III on July 2, 1999 (64 FR 35928, DEA 1999). In assessing Marinol, HHS compared Marinol to marijuana on several aspects of abuse potential and found that major differences between the two, such as formulation, availability, and usage, contribute to differences in abuse potential. The psychoactive effects from smoking are generally more rapid and intense than those that occur through oral administration (HHS, 2015; Wesson and Washburn, 1990; Hollister and Gillespie, 1973). Therefore, as concluded by both the HHS and the DEA, the delayed onset of action and longer duration of action from an oral dose of Marinol may contribute in limiting the abuse potential of Marinol relative to marijuana, which is most often smoked. The HHS also stated that the extraction and purification of dronabinol from the encapsulated sesame oil mixture of Marinol is highly complex and difficult, and that the presence of sesame oil mixture may preclude the smoking of Marinol-laced cigarettes.

Furthermore, marijuana and Marinol show significant differences in actual abuse and illicit trafficking. There have been no reports of abuse, diversion, or public health risks due to Marinol. In contrast, 22.2 million American adults report currently using marijuana (SAMHSA, 2015a). The DEA database, NFlIS, showed that marijuana was the most frequently identified drug in state and local forensic laboratories from January 2001 to December 2014 and indicates the high availability of marijuana. The differences in composition, actual abuse, and diversion contribute to the differences in scheduling between marijuana and Marinol.

Additionally, the FDA approved a New Drug Application (NDA) for Marinol, indicating a legitimate medical use for Marinol in the United States and allowing for Marinol to be rescheduled into schedule II and subsequently into schedule III of the CSA. The HHS mentioned that marijuana and Marinol differ on a wide variety of factors and these differences are major reasons for differential scheduling of marijuana and Marinol. Marijuana, as discussed more fully in Factors 3 and 6, does not have a currently accepted medical use in the United States, is highly abused, and has a lack of accepted safety.

**Factor 2: Scientific Evidence of the Drug Pharmacological Effects, if Known**

The HHS stated that there are large amounts of scientific data on the neurochemistry, mechanistic effects, toxicology, and pharmacology of marijuana. A scientific evaluation, as conducted by the HHS and the DEA, of marijuana’s neurochemistry, human and animal behavioral pharmacology, central nervous system effects, and other pharmacological effects (e.g., cardiovascular, immunological effects) is presented below.

**Neurochemistry**

Marijuana contains numerous constituents such as cannabinoids that have a variety of pharmacological actions. The petition defined marijuana as including all cannabis cultivated strains. The HHS stated that different marijuana samples derived from various cultivated strains may differ in their chemical constituents including Δ^9-THC and other cannabinoids. Therefore marijuana products from different strains will have different biological and pharmacological effects. The chemical constituents of marijuana are discussed further in Factor 3.

The primary site of action for cannabinoids such as Δ^9-THC is at the cannabinoid receptor. Two cannabinoid receptors, CB1 and CB2, have been identified and characterized (Battista et al., 2012; Piomelli, 2005) and are G-protein-coupled receptors. Activation of these inhibitory G-protein-coupled receptors inhibits adenylate cyclase activity, which prevents conversion of ATP to cyclic AMP. Cannabinoid receptor activation also results in inhibition of N- and P/Q-type calcium channels and activates inwardly rectifying potassium channels (Mackie et al., 1995; Twitchell et al., 1997). The HHS mentioned that inhibition of N-type calcium channels decreases neurotransmitter release and this may be the underlying mechanism in the ability of cannabinoids to inhibit acetylcholine, norepinephrine and glutamate from specific areas of the brain. These cellular actions may underlie the antinociceptive and psychoactive effects of cannabinoids.

Δ^9-THC acts as an agonist at cannabinoid receptors.

CB1 receptors are primarily found in the central nervous system and are located mainly in the basal ganglia, hippocampus and cerebellum of the brain (Howlett et al., 2004). CB1 receptors are also located in peripheral tissues such as the immune system (De Petrocellis and Di Marzo, 2009), but the concentration of CB1 receptors there is considerably lower than in the central nervous system (Herkenham et al., 1990; 1992). CB2 receptors are found primarily in the immune system and predominantly in B lymphocytes and natural killer cells (Bouaboula et al., 1993). CB2 receptors are also found in the central nervous system, primarily in the cerebellum and hippocampus (Gong et al., 2006).

Two endogenous ligands to the cannabinoid receptors, anandamide and arachidonyl glycerol (2–AG), were identified in 1992 (Devane et al., 1992) and 1995 (Mechoulam et al., 1995), respectively. Anandamide is a low-efficacy agonist (Brievogel and Childers, 2000) and 2–AG is a high efficacy agonist (Gonsiorek et al., 2000) to the cannabinoid receptors. These endogenous ligands are present in both the central nervous system and in the periphery (HHS, 2015).

Δ^9-THC and cannabidiol (CBD) are two of the major cannabinoids in marijuana. Δ^9-THC is the major psychoactive cannabinoid (Wachtel et al., 2002). Δ^9-THC has similar affinity for CB1 and CB2 receptors and acts as a weak agonist at CB2 receptors. The HHS indicated that activation of CB1 receptors mediates psychotropic effects of cannabinoids. CBD has low affinity for both CB1 and CB2 receptors. CBD has antagonistic effects at CB1 receptors, and some inverse agonistic properties at CB2 receptors.

**Animal Behavioral Effects**

Animal abuse potential studies (drug discrimination, self-administration, conditioned place preference) are discussed more fully in Factor 1. Briefly, it was consistently demonstrated that Δ^9-THC, the primary psychoactive component in marijuana, and other cannabinoids in marijuana have a distinct drug discriminative profile. In addition, animals self-administer Δ^9-THC, and Δ^9-THC in low doses produces conditioned place preference.
Central Nervous System Effects

Psychoactive Effects

The clinical psychoactive effects of marijuana are discussed more fully in Factor 1. Briefly, the psychoactive effects from marijuana use are considered pleasurable and associated with drug-seeking or drug-taking (HHS, 2015; Maldonado, 2002). Further, it was noted by HHS that marijuana users prefer higher concentrations of the principal psychoactive component (Δ⁴-THC) over lower concentrations (HHS, 2015).

Studies have evaluated psychoactive effects of THC in the presence of high CBD, CBC, or CBN ratios. Even though some studies suggest that CBD may decrease some of Δ⁴-THC’s psychoactive effects, the HHS found that the ratios of CBD to Δ⁴-THC administered in the studies were not comparable to the amounts found in marijuana used by most people (Dalton et al., 1976; Karniol et al., 1974; 1992). In fact, the CBD ratios in these studies are significantly higher than the CBD found in most marijuana currently found on the streets (Mehmedic et al., 2010). HHS indicated that most of the marijuana available on the street has a high THC and low CBD content and therefore any lessening of THC’s psychoactive effects by CBD will not occur for most marijuana users (HHS, 2015). Dalton et al. (1976) reported that when volunteers smoked cigarettes with a ratio of 7 CBD to 1 Δ⁴-THC (0.15 mg/kg CBD and 0.025 mg/kg Δ⁴-THC), there was a significant decrease in ratings of acute subjective effects and achieving a “high” in comparison to smoking Δ⁴-THC alone.

In oral administration studies, the subjective effects and anxiety produced by combination of CBD and THC in a ratio of at least 1:2 CBD to Δ⁴-THC (15, 30, 60 mg CBD to 30 mg Δ⁴-THC; Karniol et al., 1974) or a ratio of 2:1 CBD to Δ⁴-THC (1 mg/kg CBD to 0.5 mg/kg Δ⁴-THC; Zuardi et al., 1982) are less than those produced by Δ⁴-THC administered alone.

In one study (Ilan et al., 2005), the authors calculated the naturally occurring concentrations of CBC and CBD in marijuana cigarettes with either 1.8 or 3.6% Δ⁴-THC by weight. The authors varied the concentrations of CBC and CBD for each concentration of Δ⁴-THC in the marijuana cigarettes. Administrations in healthy marijuana users (n=23) consisted of either: (1) Low CBC (0.1% by weight) and low CBD (0.2% by weight); (2) high CBC (0.5% by weight) and low CBD; (3) low CBC and high CBD (0.5% by weight); or (4) high CBC and high CBD and the users were divided into low Δ⁴-THC (1.8% by weight) and high Δ⁴-THC (3.6% by weight) groups. Subjective psychoactive effects were significantly greater for all groups in comparison to placebo and there were no significant differences in effects among the treatments (Ilan et al., 2005).

The HHS also referred to a study with Δ⁴-THC and cannabinol (CBN) (Karniol et al., 1975). In this study, oral administration of either 12.5, 25, or 50 mg CBN combined with 25 mg Δ⁴-THC (ratio of at least 1:2 CBN to Δ⁴-THC) significantly increased subjective psychoactive ratings of Δ⁴-THC compared to Δ⁴-THC alone (Karniol et al., 1975).

Behavioral Impairment

Several factors may influence marijuana’s behavioral effects including the duration (chronic or short term), frequency (daily, weekly, or occasionally), and amount of use (heavy or moderate). Researchers have examined how long behavioral impairments persist following chronic marijuana use. These studies used self-reported histories of exposure duration, frequency, and amount of marijuana use, and administered several performance and cognitive tests at different time points following marijuana abstinence. According to HHS, behavioral impairments may persist for up to 28 days of abstinence in chronic marijuana users.

Psychoactive effects of marijuana can lead to behavioral impairment including cognitive decrements and decreased ability to operate motor vehicles (HHS, 2015). Block et al. (1992) evaluated cognitive measures in 48 healthy male subjects following smoking a marijuana cigarette that contained 2.57% or 19 mg Δ⁴-THC by weight or placebo. Each subject participated in eight sessions (four sessions with marijuana; four sessions with placebo) and several cognitive and psychomotor tests were administered (e.g. verbal recall, facial recognition, test learning, reaction time). Marijuana significantly impaired performances in most of these cognitive and psychomotor tests (Block et al., 1992).

Ramaekers et al. (2006) reported that in 20 recreational users of marijuana, acute administration of 250 μg/kg and 500 μg/kg Δ⁴-THC in smoked marijuana resulted in dose-dependent impairments in cognition, motor impulsivity, motor control (tracking impairments), and risk taking. In another study (Kurzthaler et al., 1999), when 290 μg/kg Δ⁴-THC was administered via a smoked marijuana cigarette to 13 subjects with no history of substance abuse there were significant impairments of motor speed and accuracy. Furthermore, administration of 3.95% Δ⁴-THC in a smoked marijuana cigarette increased the latency in a task of simulated braking in a vehicle (Ligouri et al., 1998). The HHS noted that the motor impairments reported in these studies (Kurzthaler et al., 1999; Ligouri et al., 1998) are critical skills needed for operating a vehicle.

As mentioned in the HHS document, some studies examined the persistence of the behavioral impairments immediately after marijuana administration. Some of marijuana’s acute effects may still be present for at least 24 hours after the acute psychoactive effects have subsided. In a brief communication, Heishmann et al. (1990) reported that there were cognitive impairments (digit recall and arithmetic tasks) in two out of three experienced marijuana smokers for 24 hours after smoking marijuana cigarettes containing 2.57% Δ⁴-THC. However, Fant et al. (1998) evaluated subjective effects and performance measures for up to 5 hours in 10 healthy males after exposure to either 1.8% or 3.6% Δ⁴-THC in marijuana cigarettes. Peak decrements in subjective and performance measures were noted within 2 hours of marijuana exposure but there were minimal residual alterations in subjective or performance measures at 23–25 hours after exposure.

Persistence of behavioral impairments following repeated and chronic use of marijuana has also been investigated and was reviewed in the HHS document (HHS, 2015). In particular, researchers examined how long behavioral impairments last following chronic marijuana use. In studies examining persistence of effects in chronic and heavy marijuana users, there were significant decrements in cognitive and motor function tasks in all studies of up to 27 days, and in most studies at 28 days (Solowij et al., 2002; Messinis et al., 2006; Lisdahl and Price, 2012; Pope et al., 2002; Bolla et al., 2002; Bolla et al., 2005). In studies that followed heavy marijuana users for longer than 28 days and up to 20 years of marijuana abstinence, cognitive and psychomotor impairments were no longer detected (Fried et al., 2005; Lyons et al., 2004; Tait et al., 2011). For example, Fried et al. (2005) reported that after 3 months of abstinence from marijuana, any deficits in intelligence (IQ), memory, and processing speeds following heavy marijuana use were no longer observed (Fried et al., 2005). In a meta-analysis that examined non-acute and long-lasting effects of marijuana on cognitive deficits in neurocognitive performance that were observed within the first month.
were no longer apparent after approximately one month of abstinence (Schreiner and Dunn, 2012). HHS further notes that in moderate marijuana users deficits in decision-making skills were not observed after 25 days of abstinence and additionally IQ, immediate memory and delayed memory skills were not significantly impacted as observed with heavy and chronic marijuana users (Fried et al., 2005; HHS, 2015).

As mentioned in the HHS document (HHS, 2015), the intensity and persistence of neurological impairment from chronic marijuana use also may be dependent on the age of first use. In two separate smaller scale studies (less than 100 participants per exposure group), Fontes et al. (2011) and Gruber et al. (2012) compared neurological function in early onset (chronic marijuana use prior to age 15 or 16) and late onset (chronic marijuana use after age 15 or 16) heavy marijuana users and found that there were significant deficits in executive neurological function in early onset users which were not observed or were less apparent in late onset users. In a prospective longitudinal birth cohort study following 1,037 individuals (Meier et al., 2012), a significant decrease in IQ and neuropsychological performance was observed in adolescent-onset users and persisted even after abstinence from marijuana for at least one year. However, Meier et al. (2012) reported in there was no significant change in IQ in adult-onset users.

The HHS noted that there is some evidence that the severity of the persistent neurological impairments may also be due in part to the amount of marijuana usage. In the study mentioned above, Gruber et al. (2012) found that the early onset users consumed three times as much marijuana per week and used it twice as often as late onset users. Meier et al. (2012) reported in their study, mentioned above, that there was a correlation between IQ deficits in adolescent onset users and the increased amount of marijuana used.

Behavioral Effects of Prenatal Exposure

In studies that examined effects of prenatal marijuana exposure, many of the pregnant women also used alcohol and tobacco in addition to marijuana. Even though other drugs were used in conjunction with marijuana, there is evidence of an association between heavy prenatal marijuana exposure and deficits in some cognitive function. There have been two prospective longitudinal birth cohort studies following individuals prenatally exposed to marijuana from birth until adulthood: The Ottawa Prenatal Prospective Study (OPPS; Fried et al., 1980), and the Maternal Health Practices and Child Development Project (MHPCD; Day et al., 1985). Both longitudinal studies report that heavy prenatal marijuana use is associated with decreased performance on tasks assessing memory, verbal and quantitative reasoning in 4-year-olds (Fried and Watkinson, 1990) and in 6 year olds (Goldschmidt et al., 2008). In subsequent studies with the OPPS cohort, deficits in sustained attention were reported in children ages 6 and 13–16 years (Fried et al., 1992; Fried, 2002) and deficits in executive neurological function were observed in 9- and 12-year-old children (Fried et al., 1998). DEA further notes that with the MHPCD cohort, follow-up studies reported an increased rate of delinquent behavior (Day et al., 2011) and decreased achievement test scores (Goldschmidt et al., 2012) at age 14. When the MHPCD cohort was followed to age 22, there was a marginal (p = 0.06) increase in psychosis with prenatal marijuana exposure and early onset of marijuana use (Day et al., 2015). Association of Marijuana Use With Psychosis

There has been extensive research to determine whether marijuana usage is associated with development of schizophrenia or other psychoses, and the HHS indicated that the available data do not suggest a causative link between marijuana and the development of psychosis (HHS, 2015; Minozzi et al., 2010). As mentioned in the HHS review (HHS, 2015), numerous large scale longitudinal studies demonstrated that subjects who used marijuana do not have a greater incidence of psychotic diagnoses compared to non-marijuana users (van Os et al., 2002; Fergusson et al., 2005; Kuepper et al., 2011). Further, the HHS commented that when analyzing the available data examining the association between marijuana and psychosis, it is critical to differentiate whether the patients in a study are already diagnosed with psychosis or if the individuals have a limited number of symptoms associated with psychosis without qualifying for a diagnosis of the disorder.

As mentioned by the HHS, some of the studies examining the association between marijuana and psychosis utilized non-standard methods to categorize psychosis and these methods did not meet criteria in the Diagnostic and Statistical Manual (DSM–5) or the International Classification of Diseases (ICD–10) and would not be appropriate for use in evaluating the association between marijuana use and psychosis. For example, researchers characterized psychosis as “schizophrenic cluster” (Maremmani et al., 2004), “subclinical psychotic symptoms” (van Castel et al., 2012), “pre-psychotic clinical high risk” (van der Meer et al., 2012), and symptoms related to “psychosis vulnerability” (Griffith-Lendering et al., 2012).

The HHS discussed an early epidemiological study conducted by Andreasson et al. (1987), which examined the link between psychosis and marijuana use. In this study, about 45,000 15- and 19-year-old male Swedish subjects provided detailed information on their drug-taking history and 274 of these subjects were diagnosed with schizophrenia over a 14-year period (1969–1983). Out of the 274 subjects diagnosed with psychosis, 21 individuals (7.7%) had used marijuana more than 50 times, while 197 individuals (72%) never used marijuana. As presented by the authors (Andreasson et al., 1987), individuals who claimed to take marijuana on more than 50 occasions were 6 times more likely to be diagnosed with schizophrenia than those who had never consumed the drug. The authors concluded that marijuana users who are vulnerable to developing psychoses are at the greatest risk for schizophrenia. In a 35 year follow up to the subjects evaluated in Andreasson et al. (1987), Manrique-Garcia et al. (2012) reported similar findings. In the follow up study, 354 individuals developed schizophrenia. Of those, 32 individuals (9%) had used marijuana more than 50 times and were 6.3 times more likely to develop schizophrenia. 255 of the 354 individuals (72%) never used marijuana.

The HHS also noted that many studies support the assertion that psychosis from marijuana usage may manifest only in individuals already predisposed to development of psychotic disorders. Marijuana use may precede diagnosis of psychosis (Schimmelmann et al., 2011), but most reports indicate that prodromal symptoms of schizophrenia are observed prior to marijuana use (Schiffman et al., 2005). In a review examining gene-environmental interaction between marijuana exposure and the development of psychosis, it was concluded that there is some evidence to support that marijuana use may influence the development of psychosis but only for susceptible individuals (Pelayo-Teran et al., 2012).
Degenhardt et al. (2003) modeled the prevalence of schizophrenia against marijuana use across eight birth cohorts in individuals born during 1940 to 1979 in Australia. Even though there was an increase in marijuana use in the adult subjects over this time period, there was not an increase in diagnoses of psychosis for these same subjects. The authors concluded that use of marijuana may increase schizophrenia only in persons vulnerable to developing psychosis.

Cardiovascular and Autonomic Effects

The HHS stated that acute use of marijuana causes an increase in heart rate (tachycardia) and may increase blood pressure (Caprioni et al., 1988; Benowitz and Jones, 1975). There is some evidence that associates the increased heart rate from Δ⁹-THC exposure with excitation of the sympathetic and depression of the parasympathetic nervous systems (Malinowska et al., 2012). Tolerance to tachycardia develops with chronic exposure to marijuana (Jones, 2002; Sidney, 2002).

Prolonged exposure to Δ⁹-THC results in a decrease in heart rate (bradycardia) and hypotension (Benowitz and Jones, 1975). These effects are thought to be mediated through peripherally located, presynaptic CB1 receptor inhibition of norepinephrine release with possible direct activation of vascular cannabinoid receptors (Wagner et al., 1998; Pacher et al., 2006).

As stated in the HHS recommendation (HHS, 2015), marijuana exposure causes orthostatic hypotension (fainting-like feeling; sudden drop in blood pressure upon standing up) and tolerance can develop to this effect upon repeated, chronic exposure (Jones, 2002). Tolerance to orthostatic hypotension is potentially related to plasma volume expansion, but tolerance does not develop to supine hypotensive effects (Benowitz and Jones, 1975).

Marijuana smoking, particularly by those with some degree of coronary artery or cerebrovascular disease, poses risks such as increased cardiac work, increased catecholamines and carboxyhemoglobin, myocardial infarction and postural hypotension (Benowitz and Jones, 1981; Hollister, 1988; Mittleman et al., 2001; Malinowska et al., 2012). However, electrocardiographic changes were minimal after administration of large cumulative doses of Δ⁹-THC (Benowitz and Jones, 1975).

The DEA noted two recent reports that reviewed several case studies on marijuana and cardiovascular complications (Panayiutides, 2015; Hackam, 2015). Panayiutides (2015) reported that approximately 25.6% of the cardiovascular cases from marijuana use resulted in death from data provided by the French Addictovigilance Network during the period of 2006–2010. Several case studies on marijuana usage and cardiovascular events were discussed and it was concluded that although a causal link cannot be established due to not knowing exact amounts of marijuana used in the cases and confounding variables, the available evidence supports a link between marijuana and cardiotoxicity. Hackam (2015) reviewed 34 case reports or case series reports of marijuana and stroke/ischemia in 64 stroke patients and reported that in 81% of the cases there was a temporal relationship between marijuana usage and stroke or ischemic event. The author concluded that collective analysis of the case reports supports a causal link between marijuana use and stroke.

Respiratory Effects

The HHS stated that transient bronchodilation is the most typical respiratory effect of acute exposure to marijuana (Gong et al., 1984). In a recent longitudinal study, information on marijuana use and pulmonary data function were collected from 5,115 individuals over 20 years from 4 communities in the United States (Oakland, CA; Chicago, IL; Minneapolis, MN; Birmingham, AL) (Pletcher et al., 2012). Of the 5,115 individuals, 795 individuals reported use of only marijuana (without tobacco). The authors reported that occasional use of marijuana (7 joint-years for lifetime or 1 joint/day for 7 years or 1 joint/week for 49 years) does not adversely affect pulmonary function. Pletcher et al. (2012) further concluded that there is some preliminary evidence suggesting that heavy marijuana use may have a detrimental effect on pulmonary function, but the sample size of heavy marijuana users in the study was too small. Further, as mentioned in the HHS recommendation document (HHS, 2015), long-term use of marijuana may lead to chronic cough, increased sputum, as well as increased frequency of chronic bronchitis and pharyngitis (Adams and Martin, 1996; Hollister, 1986).

The HHS stated that the evidence that marijuana may lead to cancer of the respiratory system is inconsistent, with some studies suggesting a positive correlation while others do not (Lee and Hancox, 2005). The HHS noted a case series that reported lung cancer occurrences in three marijuana smokers (age range 31–37 years) with no history of tobacco smoking (Fung et al., 1999). Furthermore, in a case-control study (n = 173 individuals with squamous cell carcinoma of the head and neck; n = 176 controls; Zhang et al., 1999), prevalence of marijuana use was 9.7% in controls and 13.9% in cases and the authors reported that marijuana use may dose-dependently interact with mutagenic sensitivity, cigarette smoking, and alcohol use to increase risk associated with head and neck cancers (Zhang et al., 1999). However, in a large clinical study with 1,650 subjects, no positive correlation was found between marijuana use and lung cancer (Tashkin et al., 2006). This finding held true regardless of the extent of marijuana use when both tobacco use and other potential confounding factors were controlled. The HHS concluded that new evidence suggests that the effects of smoking marijuana on respiratory function and cancer are different from the effects of smoking tobacco (Lee and Hancox, 2011).

The DEA further notes the publication of recent review articles critically evaluating the association between marijuana and lung cancer. Most of the reviews agree that the association is weak or inconsistent (Huang et al., 2015; Zhang et al., 2015; Gates et al., 2014; Hall and Degenhardt, 2014). Huang et al. (2015) identified and reviewed six studies evaluating the association between marijuana use and lung cancer and the authors concluded that an association is not supported most likely due to the small amounts of marijuana smoked in comparison to tobacco. Zhang et al. (2015) examined six case control studies from the US, UK, New Zealand, and Canada within the International Lung Cancer Consortium and found that there was a weak association between smoking marijuana and lung cancer in individuals who never smoked tobacco, but precision of the association was low at high marijuana exposure levels. Hall and Degenhardt (2014) noted that even though marijuana smoke contains several of the same carcinogens and co-carcinogens as tobacco smoke (Roth et al., 1998) and has been found to be mutagenic and carcinogenic in the mouse skin test, epidemiological studies have been inconsistent, but more consistent positive associations have been reported in case control studies. Finally Gates et al. (2014), reviewed the studies evaluating marijuana use and lung cancer and concluded that there is evidence that marijuana produces changes in the respiratory system (precursors to cancer) that could lead to
lung cancer, but overall association is weak between marijuana use and lung cancer especially when controlling for tobacco use.

Endocrine System

Reproductive Hormones

The HHS stated that administration of marijuana to humans does not consistently alter the endocrine system. In a controlled human exposure study (n = 4 males), subjects were acutely administered smoked marijuana containing 2.8% Δ⁹-THC or placebo and an immediate significant decrease in luteinizing hormone and an increase in cortisol was reported in the subjects that smoked marijuana (Cone et al., 1986). Furthermore, as cited by the HHS, two later studies (Dax et al., 1989; Block et al., 1991) reported no changes in hormone levels. Dax et al. (1989) recruited male volunteers (n = 17) that were occasional or heavy users of marijuana. Following exposure to smoked Δ⁹-THC (10 mg/cigarette) or oral Δ⁹-THC (10 mg three times per day for three days and on the morning of the fourth day), the subjects in that study showed no changes in plasma adrenocorticotrophic hormone (ACTH), cortisol, prolactin, luteinizing hormone, or testosterone levels. Additionally, Block et al. (1991) compared plasma hormone levels amongst non-users as well as infrequent, moderate, and frequent users of marijuana (n = 93 men and 56 women) and found that chronic use of marijuana (infrequent, moderate, and frequent users) did not significantly alter concentrations of testosterone, luteinizing hormone, follicle stimulating hormone, prolactin, or cortisol.

The HHS noted that there is a discrepancy in the effect of marijuana on female reproductive system functionality between animals and humans (HHS, 2015). Female rhesus monkeys that were administered 2.5 mg/kg Δ⁹-THC, i.m., during days 1–18 of the menstrual cycle had reduced progesterone levels and ovulation was suppressed (Asch et al., 1981). However, women who smoked marijuana (1 gram marijuana cigarette with 1.8% Δ⁹-THC) during the periovulatory period (24–36 hours prior to ovulation) did not exhibit changes in reproductive hormone levels or their menstrual cycles (Mendelson and Mello, 1984). In a review article by Brown and Dobs (2002), the authors state that endocrine changes observed with marijuana are no longer observed with chronic administration and this may be due to drug tolerance.

Reproductive Cancers

The HHS stated that recent studies support a possible association between frequent, long-term marijuana use and increased risk of testicular germ cell tumors. In a hospital-based case-control study, the frequency of marijuana use was compared between testicular germ cell tumor (TGCT) patients (n = 187) and controls (n = 146) (Trabert et al., 2011).

TGCT patients were more likely to be frequent marijuana users than controls with an odds ratio (OR) of 2.2 (95% confidence limits of 1.0–5.1) and were less likely to be infrequent or short-term users with odds ratios of 0.5 and 0.6, respectively in comparison to controls (Trabert et al., 2011). The DEA further notes that in two population-based case-control studies (Dalig et al., 2009; Lacson et al., 2012), marijuana use was compared between patients diagnosed with TGCT and matched controls in Washington State or Los Angeles County. In both studies, it was reported that TGCT patients were twice as likely as controls to use marijuana. Authors of both studies concluded that marijuana use is associated with an elevated risk of TGCT (Dalig et al., 2009; Lacson et al., 2012).

The HHS cited a study (Sarfaraz et al., 2005) demonstrating that WIN 55,212–2 (a mixed CB1/CB2 agonist) induces apoptosis (one form of cell death) in prostate cancer cells and decreases expression of androgen receptors and prostate specific antigens, suggesting a potential therapeutic value for cannabinoid agonists in the treatment of prostate cancer, an androgen-stimulated type of carcinoma.

Other Hormones (e.g. Thyroid, Appetite)

In more recent studies, as cited by the HHS, chronic marijuana use by subjects (n = 39) characterized as dependent on marijuana according to the ICD–10 criteria did not affect serum levels of thyroid hormones: TSH (thyrotrpin), T₄ (thyroxine), and T₃ (triiodothyronine) (Bonnet, 2013). With respect to appetite hormones, in a pilot study with HIV-positive males, smoking marijuana dose-dependently increased plasma levels of ghrelin and leptin and decreased plasma levels of peptide YY (Riggs et al., 2012).

The HHS stated that Δ⁹-THC reduces binding of the corticosteroid dexamethasone in hippocampal tissue from adrenalectomized rats and acute Δ⁹-THC releases corticosterone, with tolerance developing to this effect with chronic administration (Eldridge et al., 1991). These data suggest that Δ⁹-THC may interact with the glucocorticoid receptor system.

Immune System

The HHS stated that cannabinoids alter immune function but that there can be differences between the effects of synthetic, natural, and endogenous cannabinoids (Croxford and Yamamura, 2005; Tanasecu and Constantinescu, 2010).

The HHS noted that there are conflicting results in animal and human studies with respect to cannabinoid effects on immune functioning in subjects with compromised immune systems. Abrams et al. (2003) examined the effects of marijuana and Δ⁹-THC in 62 HIV–1-infected patients. Subjects received one of three treatments, three times a day: smoked marijuana cigarette containing 3.95% Δ⁹-THC, oral tablet containing Δ⁹-THC (2.5 mg oral dronabinol), or oral placebo. There were no changes in CD4+ and CD8+ cell counts, HIV RNA levels, or protease inhibitor levels in any of the treatment groups (Abrams et al., 2003). Therefore, use of cannabinoids showed no short-term adverse virologic effects in individuals with compromised immune systems. Conversely, Roth et al. (2005) reported that in immunodeficient mice implanted with human blood cells infected with HIV, exposure to Δ⁹-THC in vivo suppresses immune function, increases HIV co-receptor expression, and acts as a cofactor to enhance HIV replication.

The DEA notes two recent clinical studies reporting a decrease in cytokine and interleukin levels following marijuana use. Keen et al. (2014) compared the differences in the levels of IL-6 (interleukin-6), a proinflammatory cytokine, amongst non-drug users (n = 78), marijuana only users (n = 46) and marijuana plus other drug users (n = 45) in a community-based sample of middle-aged African Americans (Keen et al., 2014). After adjusting for confounders, analyses revealed that lifetime marijuana only users had significantly lower IL–6 levels than the nonuser group. Further, Sexton et al. (2014) compared several immune parameters in healthy individuals and subjects with multiple sclerosis (MS) and found that the chronic use of marijuana resulted in reduced monocyte migration, and decreased levels of CCL2 and IL–17 in both healthy and MS groups.

The DEA also notes a review suggesting that Δ⁹-THC suppresses the immune responses in experimental animal models and in vitro and that these changes may be primarily
mediated through the CB2 cannabinoid receptor (Eisenstein and Meissner, 2015).

Petitioners’ Major Comments in Relation to Factor 2 and the Government’s Responses

(1) The petitioners state that “medical use of cannabis is considered safe.” (Exhibit B, page 7); and that “[t]here are adequate and well-controlled studies proving the medical efficacy of cannabis.” (Exhibit B, page 10). The petitioners also allege that “Cannabis is safer than current, legal Schedule II opiate drugs” and that it presents milder side effects (Exhibit B, page 9–10).

As detailed in the HHS review and as discussed later in this document (see Factor 3), there are neither adequate safety studies nor adequate, well-controlled studies proving marijuana’s efficacy. The DEA notes that neither the CSA nor established scheduling criteria suggest that the HHS and DEA should consider the relative safety profiles of drugs when determining the proper schedule. To the extent that the petitioners were referring to abuse and dependence liability, this document discusses those effects in factors 1, 4, and 7.

(2) The petitioners state that “scientific evidence regarding the safety and efficacy of cannabis is readily available directly from the National Library of Medicine.” (Exhibit B, page 14).

The government agrees that many articles discuss marijuana and its constituents. Yet, these articles in no way demonstrate that marijuana is safe and effective for the treatment of any disease or condition. As mentioned in the HHS review and as discussed later in this document (see Factor 3), the current research does not provide adequate detailed scientific evidence regarding chemistry, pharmacology, toxicology, and effectiveness derived from well-controlled clinical investigations to permit a conclusion that marijuana is safe and effective for treating a specific, recognized disorder.

(3) The petitioners mentioned on page 9 of exhibit B that “[t]here has never been a lethal overdose of marijuana reported in humans” and that “[t]here is no known LD50 for any form of cannabis.”

As more fully discussed in Factor 3 below, the HHS and DEA conclude that there are not adequate studies to determine the safety of marijuana. As discussed in the HHS document and below, the determination of safety is more complex than a mere determination of the rate or likelihood of death. Moreover, the lack of overdose deaths attributed to a drug is not evidence that the drug is safe for medical use.

Factor 3: The State of the Current Scientific Knowledge Regarding the Drug or Substance

Chemistry

The HHS stated that marijuana, also known as Cannabis sativa L., is part of the Cannabaceae plant family and is one of the oldest cultivated crops. The term “marijuana” is generally used to refer to a mixture of the dried flowering tops and leaves from Cannabis. Marijuana users primarily smoke the marijuana leaves, but individuals also ingest marijuana through food infused with marijuana and its extracts. Cannabis sativa is the primary species of Cannabis that is legally marketed in the United States. Marijuana is one of three major derivatives sold as separate illicit products, the other two being hashish and hash oil. Hashish is composed of the dried and compressed cannabinoid-rich resinous material of Cannabis and is found as balls and cakes as well as other forms. Individuals may break off pieces and place them into a pipe to smoke. Hash oil, a viscous brown or amber colored liquid, is produced by solvent extraction of cannabinoids from Cannabis and contains approximately 50% cannabinoids. One to two drops of hash oil on a cigarette has been reported to produce the equivalent of a single marijuana cigarette (DEA, 2015).

The HHS indicated in its evaluation that the petitioners defined marijuana as including all Cannabis cultivated strains. However, different marijuana samples are derived from numerous cultivated strains and may have different chemical compositions including levels of Δ9-THC and other cannabinoids (Appendino et al., 2011). A consequence of having different chemical compositions in the various marijuana samples is that there will be significant differences in safety, biological, pharmacological, and toxicological profiles and therefore, according to the HHS, all Cannabis strains cannot be considered collectively because of the variations in chemical composition. Furthermore, the concentration of Δ9-THC and other cannabinoids present in marijuana may vary due to growing conditions and processing of the plant after harvesting. For example, the plant parts collected such as flowers, leaves and stems can influence marijuana’s potency, quality, and purity (Adams and Martin, 1996; Agrawell et al., 1984; Mechoulan, 1973). Variations in marijuana harvesting have resulted in potencies ranging from a low of 1 to 2% up to a high of 17% as indicated by cannabinoid content. The concentration of Δ9-THC averages approximately 12% by weight in a typical marijuana mixture of leaves and stems. However, some specifically grown and selected marijuana samples can contain 15% or greater Δ9-THC (Appendino et al., 2011). As a result, the Δ9-THC content in a 1 gram marijuana cigarette can range from as little as 3 milligrams to 150 milligrams or more. In a systematic review conducted by Cascini et al. (2012), it was reported that marijuana’s Δ9-THC content has increased significantly from 1979–2009.

Since there is considerable variability in the cannabinoid concentrations and chemical constituency among marijuana samples, the interpretation of clinical data with marijuana is complicated. A primary issue is the lack of consistent concentrations of Δ9-THC and other substances in marijuana which complicates the interpretation of the effects of different marijuana constituents. An additional issue is that the non-cannabinoid components in marijuana may potentially modify the overall pharmacological and toxicological properties of various marijuana strains and products. Various Cannabis strains contain more than 525 identified natural constituents including cannabinoids, 21 (or 22) carbon terpenoids found in the plant, as well as their carboxylic acids, analogues, and transformation products (Agrawell et al., 1984; 1986; Mechoulan, 1973; Appendino et al., 2011). To date, more than 100 cannabinoids have been characterized (ElSohly and Slade, 2005; Radwan et al., 2009; Appendino et al., 2011), and most major cannabinoid compounds occurring naturally have been identified. There are still new and comparably more minor cannabinoids being characterized (Pollastro et al., 2011). The majority of the cannabinoids are found in Cannabis. One study reported accumulation of two cannabinoids, cannabigerol and its corresponding acid, in Helichrysum (H. umbroculigerum) which is a non- Cannabis source (Appendino et al., 2011).

Of the cannabinoids found in marijuana, Δ9-THC (previously known as Δ-THC) and delta-8-tetrahydrocannabinol (Δ8-THC, Δ8-THC) have been demonstrated to produce marijuana’s psychoactive effects. Psychoactive effects from marijuana usage have been mainly attributed to Δ9-THC because Δ9-THC is present in significantly more quantities than Δ8-THC in most marijuana varieties. There are only a few marijuana strains that
contain Δ⁹-THC in significant amounts (HivELY et al., 1966). Δ⁹-THC is an optically active resinous substance that is extremely lipophilic. The chemical name for Δ⁹-THC is (6aR-trans)-6a,7,8,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol, or (−)-delta9-(trans)-tetrahydrocannabinol. The (−)-trans Δ⁹-THC isomer is pharmacologically 6 to 100 times more potent than the (+)-trans isomer (Dewey et al., 1984).

Other relatively well-characterized cannabinoids present in marijuana include cannabidiol (CBD), cannabichromene (CBC), and cannabinol (CBN). CBD and CBN are major cannabinoids in marijuana and are both lipophilic. The chemical name for CBD is 2-[(1R,6R)-3-methyl-6-prop-1-en-2-ylcyclohex-2-en-1-yl]-5-pentylbenzene-1,3-diol and the chemical name for CBN is 2-methyl-2-(4-methylpent-3-enyl)-7-pentyl-5-chromenol. CBN is a minor naturally-occurring cannabinoid with weak psychoactivity and is also a major metabolite of Δ⁹-THC. The chemical name for CBN is 6a-(3-methyl-3-pentylbenzo[c]chromen-1-ol.

In summary, marijuana has several strains with high variability in the concentrations of Δ⁹-THC, the main psychoactive component, as well as other cannabinoids and compounds. Marijuana is not a single chemical and does not have a consistent and reproducible chemical profile with predictable or consistent clinical effects. In the HHS recommendation for marijuana scheduling (HHS, 2015), it was recommended that investigators consult a guidance for industry entitled, Botanical Drug Products,* which provides information on the approval of botanical drug products. Specifically, in order to investigate marijuana in support of a New Drug Application (NDA), clinical studies under an Investigational New Drug (IND) application should include “consistent batches of a particular marijuana product for a particular disease.” (HHS, 2015). Furthermore, the HHS noted that investigators must provide data meeting the requirements for new drug approval as stipulated in 21 CFR 314.50 (HHS, 2015).

**Human Pharmacokinetics**

Pharmacokinetics of marijuana in humans is dependent on the route of administration and formulation (Adams and Martin, 1996; Agurell et al., 1984; Agurell et al., 1986). Individuals primarily smoke marijuana as a cigarette (weighing between 0.5 and 1 gram) or in a pipe. More recently, vaporizers have been used as another means for individuals to inhale marijuana. Marijuana may also be ingested orally in foods or as an extract in ethanol or other solvents. Pharmacokinetic studies with marijuana focused on evaluating the absorption, metabolism, and elimination profile of Δ⁹-THC and other cannabinoids (Adams and Martin, 1996; Agurell et al., 1984; Agurell et al., 1986).

**Absorption and Distribution of Inhaled Marijuana Smoke**

There is high variability in the pharmacokinetics of Δ⁹-THC and other cannabinoids from smoked marijuana due to differences in individual smoking behavior even under controlled experimental conditions (Agurell et al., 1986; Herning et al., 1986; Huestis et al., 1992a). Experienced marijuana users can titrate and regulate the dose by holding marijuana smoke in their lungs for an extended period of time resulting in increased psychoactive effects by prolonging absorption of the smoke. This property may also help explain why there is a poor correlation between venous levels of Δ⁹-THC and the intensity of effects and intoxication (Agurell et al., 1986; Barnett et al., 1985; Huestis et al., 1992a). The HHS recommended that puff and inhalation volumes should be tracked in experimental studies because the concentration of cannabinoids can vary at different stages of smoking.

Δ⁹-THC from smoked marijuana is rapidly absorbed within seconds. Psychoactive effects are observed immediately following absorption with measurable neurological and behavioral changes for up to 6 hours (Gronethern, 2003; Hollister, 1986; Hollister, 1988). Δ⁹-THC is distributed to the brain in a rapid and efficient manner. Bioavailability of Δ⁹-THC from marijuana (from a cigarette or pipe) ranges from 1 to 24% with the fraction absorbed rarely exceeding 10% to 20% (Agurell et al., 1986; Hollister, 1988). The low and variable bioavailability of Δ⁹-THC is due to loss in side-stream smoke, variation in individual smoking behaviors and experience, incomplete absorption of inhaled smoke, and metabolism in lungs (Herning et al., 1986; Johansson et al., 1989). After cessation of smoking, Δ⁹-THC venous levels decline within minutes and continue to decline to about 5% to 10% of the peak level within an hour (Agurell et al., 1986; Huestis et al., 1992a; Huestis et al., 1992b). Absorption and Distribution of Orally Administered Marijuana

Following oral administration of Δ⁹-THC or marijuana, onset of effects start within 30 to 90 minutes, peak after 2 to 3 hours and effects remain for 4 to 12 hours (Gronethern, 2003; Adams and Martin, 1996; Agurell et al., 1984; Agurell et al., 1986). Dose titration of Δ⁹-THC from orally ingested marijuana is difficult for users in comparison to smoked or inhaled marijuana due to the delay in the onset of effects. Oral bioavailability of Δ⁹-THC, either in its pure form or in marijuana, is low and variable with a range from 5% to 20% (Agurell et al., 1984; Agurell et al., 1986). There is also inter- and intra-subject variability of orally administered Δ⁹-THC under experimental conditions and even under repeated dosing experiments (HHS, 2015). The HHS noted that in bioavailability studies using radiolabeled Δ⁹-THC, Δ⁹-THC plasma levels following oral administration of Δ⁹-THC were low relative to plasma levels after inhaled or intravenously administered Δ⁹-THC. The low and variable bioavailability of orally administered Δ⁹-THC is due to first pass hepatic elimination from blood and erratic absorption from stomach and bowel (HHS, 2015).

**Metabolism and Excretion of Cannabinoids From Marijuana**

Studies evaluating cannabinoid metabolism and excretion focused on Δ⁹-THC because it is the primary psychoactive component in marijuana. Δ⁹-THC is metabolized via microsomal hydroxylation and oxidation to both active and inactive metabolites (Lemberger et al., 1970; Lemberger et al., 1972a; Lemberger et al., 1972b; Agurell et al., 1986; Hollister, 1988). Metabolism of Δ⁹-THC is consistent among frequent and infrequent marijuana users (Agurell et al., 1986). The primary active metabolite of Δ⁹-THC following oral ingestion is 11-hydroxy-Δ⁹-THC which is equipotent to Δ⁹-THC in producing marijuana-like subjective effects (Agurell et al., 1986; Lemberger and Rubin, 1975). Metabolite levels following oral administration may be greater than that of Δ⁹-THC and may contribute greatly to the pharmacological effects of oral Δ⁹-THC or marijuana.

Plasma clearance of Δ⁹-THC approximates hepatic blood flow at a rate of approximately 950 ml/min or greater. Rapid clearance of Δ⁹-THC from blood is primarily due to redistribution to other tissues in the body rather than to metabolism (Agurell et al., 1984; Agurell et al., 1986). Outside of the

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*Available at [http://www.fda.gov/Drugs/default.htm](http://www.fda.gov/Drugs/default.htm) under Guidance (Drugs).
liver, metabolism in most tissues is considerably slow or does not occur. The elimination half-life of Δ⁹-THC ranges from 20 hours to between 10 and 13 days [Hunt and Jones, 1980]. Lemberger et al. (1970) reported that the half-life of Δ⁹-THC ranged from 23–28 hours in heavy marijuana users and up to 60 to 70 hours in naïve users. The long elimination half-life of Δ⁹-THC is due to slow release of Δ⁹-THC and other cannabinoids from tissues and subsequent metabolism. Inactive carboxy metabolites of Δ⁹-THC have terminal half-lives of 50 hours to 6 days or more and serve as long-term markers in urine tests for marijuana use.

Most of the absorbed Δ⁹-THC dose is eliminated in the feces and about 33% in urine. The glucuronide metabolite of Δ⁹-THC is excreted as the major urinary metabolite along with 18 non-conjugated metabolites [Agurell et al., 1986].

Research Status and Test of Currently Accepted Medical Use for Marijuana

According to the HHS, there are numerous human clinical studies with marijuana in the United States under FDA-regulated IND applications. Results of small clinical exploratory studies have been published in the medical literature. Approval of a human drug for marketing, however, is contingent upon FDA approval of a New Drug Application (NDA) or a Biologics License Application (BLA). According to the HHS, the FDA has not approved any drug product containing marijuana for marketing.

The HHS noted that a drug may be found to have a medical use in treatment in the United States for purposes of the CSA if the drug meets the five elements described by the DEA in 1992. Those five elements “are both necessary and sufficient to establish a prima facie case of currently accepted medical use” in treatment in the United States.” (57 FR 10499, 10504 [March 26, 1992]). This five-element test, which the HHS and DEA have utilized in all such analyses for more than two decades, has been upheld by the Court of Appeals. ACT, 15 F.3d at 1135. The five elements that characterize “currently accepted medical use” for a drug are summarized here and expanded upon in the discussion below:

1. The drug’s chemistry must be known and reproducible;
2. There must be adequate safety studies;
3. There must be adequate and well-controlled studies proving efficacy;
4. The drug must be accepted by qualified experts; and
5. Scientific evidence must be widely available.

In its review (HHS, 2015), the HHS evaluated the five elements with respect to the currently available research for marijuana. The HHS concluded that marijuana does not meet any of the five elements—all of which must be demonstrated to find that a drug has a “currently accepted medical use.” A brief summary of the HHS’s evaluation is provided below.

Element #1: The drug’s chemistry must be known and reproducible.

“The substance’s chemistry must be scientifically established to permit it to be reproduced into dosages which can be standardized. The listing of the substance in a current edition of one of the official compendia, as defined by section 201[j] of the Food, Drug and Cosmetic Act, 21 U.S.C. 321[j], is sufficient generally to meet this requirement.” 57 FR 10499, 10506 (March 26, 1992).

Marijuana, as defined in the petition, includes all Cannabis strains. (For purposes of the CSA, marijuana includes all species of the genus Cannabis, including all strains therein 47). Based on the definition of marijuana in the petition, the chemistry of marijuana is not reproducible such that a standardized dose can be created. Chemical constituents including Δ⁹-THC and other cannabinoids vary significantly in marijuana samples derived from different strains (Appendino et al., 2011). As a result, there will be significant differences in safety, biological, pharmacological, and toxicological parameters amongst the various marijuana samples. Due to the variation of the chemical composition in marijuana samples, it is not possible to reproduce a standardized dose when considering all strains together. The HHS does advise that if a specific Cannabis strain is cultivated and processed under controlled conditions, the plant chemistry may be consistent enough to derive reproducible and standardized doses.

Element #2: There must be adequate safety studies.

“There must be adequate pharmacological and toxicological studies, done by all methods reasonably applicable, on the basis of which it could fairly and responsibly be concluded, by experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, that the substance is safe for treating a specific, recognized disorder.” 57 FR 10499, 10506 (March 26, 1992).

The HHS stated that there are no adequate safety studies on marijuana. As indicated in their evaluation of Element #1, the considerable variation in the chemistry of marijuana complicates the safety evaluation. The HHS concluded that marijuana does not satisfy Element #2 for having adequate safety studies such that medical and scientific experts may conclude that it is safe for treating a specific ailment.

Element #3: There must be adequate and well-controlled studies of efficacy.

“There must be adequate, well-controlled, well-designed, well-conducted and well-documented studies, including clinical investigations, by experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, on the basis of which it could be fairly and responsibly concluded by such experts that the substance will have the intended effect in treating a specific, recognized disorder.” 57 FR 10499, 10506 (March 26, 1992).

As indicated in the HHS’s review of marijuana (HHS, 2015), there are no adequate or well-controlled studies that prove marijuana’s efficacy. The FDA independently reviewed (FDA, 2015) publicly available clinical studies on marijuana published prior to February 2013 to determine if there were appropriate studies to determine marijuana’s efficacy (please refer to FDA, 2015 and HHS, 2015 for more details). After review, the FDA determined that out of the identified articles, including those identified through a search of bibliographic references and 566 abstracts located on PubMed, 11 studies met the a priori selection criteria, including placebo control and double-blinding. FDA and HHS critically reviewed each of the 11 studies to determine if the studies met accepted scientific standards. FDA and HHS concluded that these studies do not “currently prove efficacy of marijuana” for any therapeutic indication due to limitations in the study designs. The HHS indicated that these studies could be used as proof of

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47 Although the CSA definition of marijuana refers only to the species “Cannabis sativa L.”, federal courts have consistently ruled that all species of the genus cannabis are included in this definition. See United States v. Kelly, 527 F.2d 961, 963–964 (9th Cir. 1976) (collecting and examining cases). The Single Convention (article 1, par. 1c) likewise defines the “cannabis plant” to mean “any plant of the genus Cannabis.” As explained above in the attachment titled “Preliminary Note Regarding Treaty Considerations,” 21 U.S.C. 811(d)(1) provides that, where a drug is subject to control under the Single Convention, the DEA Administrator must control the drug under the schedule he deems most appropriate to carry out such treaty obligations, without regard to the findings required by 21 U.S.C. 811(a) or 812(b) and without regard to the procedures prescribed by 21 U.S.C. 811(a) and (b).
concept studies, providing preliminary evidence on a proposed hypothesis involving a drug's effect.

Element #4: The drug must be accepted by qualified experts.

“[A] consensus of the national community of experts, qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, accepts the safety and effectiveness of the substance for use in treating a specific, recognized disorder. A material conflict of opinion among experts precludes a finding of consensus.” 57 FR 10499, 10506 (March 26, 1992).

The HHS concluded that there is currently no evidence of a consensus among qualified experts that marijuana is safe and effective in treating a specific and recognized disorder. The HHS indicated that medical practitioners who are not experts in evaluating drugs cannot be considered qualified experts (HHS, 2015; 57 FR 10499, 10505).

Further, the HHS noted that the 2009 American Medical Association (AMA) report entitled, “Use of Cannabis for Medicinal Purposes” does not conclude that there is a currently accepted medical use for marijuana. HHS also pointed out that state-level “medical marijuana” laws do not provide evidence of such a consensus among qualified experts.

Element #5: The scientific evidence must be widely available.

“In the absence of NDA approval, information concerning the chemistry, pharmacology, toxicology, and effectiveness of the substance must be reported, published, or otherwise widely available, in sufficient detail to permit experts, qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, to fairly and responsibly conclude the substance is safe and effective for use in treating a specific, recognized disorder.” 57 FR 10499, 10506 (March 26, 1992).

The HHS concluded that the currently available data and information on marijuana is not sufficient to allow scientific scrutiny of the chemistry, pharmacology, toxicology, and effectiveness. In particular, scientific evidence demonstrating the chemistry of a specific Cannabis strain that could provide standardized and reproducible doses is not available.

Petitioners’ Major Comments in Relation to Factor 3 and the Government’s Responses

(1) The petitioners indicate that there is medical support and acceptance for the medical use of marijuana and stated that “[c]annabis has been accepted by the medical community as meeting the current, modern accepted standards for what constitutes medicine.” (Exhibit B, page 13). On page 3 of the cover letter of the petition, the petitioners stated, “The American medical community supports rescheduling, and there are safe pharmacy-based methods to dispense medicinal cannabis.”

Furthermore, they stated that “[i]n 2009, the American Medical Association (AMA) reversed its earlier position that supported [s]chedule I classification of cannabis. The AMA now supports investigation and clinical research of cannabis for medicinal use, and urged the federal government to reassess the [s]chedule I classification. The American College of Physicians [ACP] recently expressed similar support.”

In addition, they note that the Institute of Medicine (IOM) also documented the scientific basis and therapeutic effects of cannabis (Exhibit B, page 13).

The DEA notes that the statements by the cited organizations (AMA, ACP, IOM) support more research into the potential medical uses associated with marijuana. The HHS did not find that the statements by these organizations provide evidence supporting a conclusion that adequate safety studies and adequate, well-controlled efficacy studies demonstrate the safety and efficacy of marijuana (HHS, 2015). The AMA’s official policy on medicinal use of marijuana is as follows: “Our AMA urges that marijuana’s status as a federal [s]chedule I controlled substance be reviewed with the goal of facilitating the conduct of clinical research and development of cannabinoid-based medicines, and alternative delivery methods. This should not be viewed as an endorsement of state-based medical cannabis programs, the legalization of marijuana, or that scientific evidence on the therapeutic use of cannabis meets the current standards for a prescription drug product.” (AMA, 2009).

The DEA further notes that the 2013 AMA House of Delegates report states that, “cannabis is a dangerous drug and as such is a public health concern.” (AMA, 2013). In 2008, the ACP indicated that “[f]urther research is needed to compare cannabinoids’ efficacy and safety with current treatments.” (ACP, 2008). The ACP stated that, “ACP urges an evidence-based review of marijuana’s status as a [s]chedule I controlled substance to determine whether it should be reclassified to a different schedule. This review should consider the scientific findings regarding marijuana’s safety and efficacy and medical conditions as well as evidence on the health risks associated with marijuana consumption, particularly in its crude smoked form.” (ACP, 2008). The IOM, consistent with others in the medical community, endorses further studies into the potential therapeutic uses of marijuana, but did not advocate for medicinal use without further testing (IOM, 2009).

As detailed in the HHS review, in order for a drug to be found to have a “currently accepted medical use,” it must be accepted by qualified experts. There is no evidence that there is a consensus among qualified experts that marijuana is safe and effective for use in treating a specific, recognized disorder.

(2) The petitioners claim that, “The chemistry of cannabis is known and reproducible” (Exhibit B, page 6) and “newer medicinal strains of cannabis are lower in THC and higher in the non-psychoactive, more therapeutic cannabinoids, such as CBD, and CBN. These compounds further improved the efficacy of cannabis.” (Exhibit B, page 10).

As indicated by the HHS, the petitioners defined marijuana to include all Cannabis strains. As such, the chemistry of marijuana is not reproducible such that a standardized dose can be created. Chemical constituents including Δ^8-THC and other cannabinoids vary significantly in different marijuana samples (Appendino et al., 2011). Furthermore, the HHS cited a published report that indicates that new substances in marijuana are continually being characterized (Pollastro et al., 2011). If there is significant variance in the chemical composition of marijuana between samples, it is not possible for the chemistry to be reproducible.

Because the petition defines marijuana as including all cultivated strains, the DEA believes that the THC and CBD level of specific strains is not relevant to this consideration. In fact, the average Δ^8-THC content in marijuana has steadily risen from 1995 to 2014 as reported by the University of Mississippi Potency Monitoring Project, as presented in Factor 1. In 1995, the Δ^8-THC content was 4% on average and by 2015, the average content of THC had risen to 11.2% over a 20 year period. In the same time period, CBD and CBN percentages have ranged from 0.15% to 0.60% on average.

The DEA also notes statements in the petitioners’ document that support the conclusion reached by DEA and HHS that the chemistry of marijuana as broadly defined by the petitioners is not reproducible or well-defined. For example, the petitioners acknowledge that “Cannabis is a complex plant, with several subtypes of cannabis.” (Exhibit...
B, page 6). The petitioners also acknowledge that “the ratios of the various cannabinoid oils differ according to the plant strain, and, to some extent, how the plant is grown.” (Exhibit B, page 12).

(3) The petitioners stated in Exhibit B, page 8, that “[o]verall, the 33 completed and published American controlled clinical trials with cannabis have studied its safety, routes of administration, and use in comparison with placebos, standard drugs, and in some cases dronabinol . . . .” and further cited a systematic review by Wang et al. (2008), that evaluated 23 randomized controlled trials and 8 observational studies, stating that, “[o]f all the adverse events reported, 97 percent were considered ‘not serious,’ with the most commonly reported dizziness.”

The petitioners also cited in Exhibit B, page 8, “There has been a long-term, prospective, federally funded cannabis clinical study jointly administered by National Institute on Drug Abuse (NIDA) and FDA. This study has been running for over 30 years without any demonstrable adverse outcomes related to chronic medicinal cannabis use.”

As cited in the HHS recommendation document (HHS, 2015), the FDA conducted its own evaluation of the published clinical studies on the medical application of marijuana prior to February 2013 (FDA, 2015). Further details on the FDA review can be found in the published report (FDA, 2015). Based on the analysis, 11 studies were evaluated further and the FDA concluded that none of these studies “meet the criteria required by the FDA to determine if marijuana is safe and effective in specific therapeutic areas.” (page 6; FDA, 2015).

The DEA has reviewed the systematic review by Wang et al. (2008) and notes that most of the studies included in the review were synthetic cannabinoid medicines (e.g., dronabinol) or cannabinoid extracts (e.g., Sativex®); these types of studies were excluded in the FDA review as the analysis focused solely on natural forms of marijuana (FDA, 2015). Wang et al. (2008) concluded that “good safety and efficacy data on smoked cannabis are urgently needed.”

With respect to the 30-year study cited by the petitioners (Russo et al., 2001) on page 8 of Exhibit B, it should be clarified that the referenced study was not jointly administered by NIDA and the FDA. As with other clinical studies, an IND application was approved for the study and marijuana was supplied by NIDA. The authors evaluated only 8 patients over this period, of which one patient died. While the findings cited by the petitioners and authors (e.g., no adverse outcomes with long-term marijuana use) are informative, conclusions on long-term use of marijuana cannot be applied to the general population.

**Factor 4: Its History and Current Pattern of Abuse**

Marijuana continues to be the most widely used illicit drug. In 2013, an estimated 24.6 million Americans age 12 or older were current (past month) illicit drug users. Of those, 19.8 million were current (past month) marijuana users. As of 2013, an estimated 114.7 million Americans age 12 and older had used marijuana or hashish in their lifetime and 33.0 million had used it in the past year.

According to the NSDUH estimates, 3.0 million people age 12 or older used an illicit drug for the first time in 2014. Marijuana initiates totaled 2.6 million in 2014. Nearly all (96.8%) of the 2.6 million new users were less than 18 years of age. In 2014, marijuana was used by 82.2% of current (past month) illicit drug users. In 2014, among past year marijuana users age 12 or older, 18.5% used marijuana on 300 or more days within the previous 12 months. This translates into 6.5 million people using marijuana on a daily or almost daily basis over a 12-month period, a significant increase from the 3.1 million daily or almost daily users in 2006 and from the 5.7 million in just the previous year. In 2014, among past month marijuana users, 41.6% (9.2 million people) used the drug on 20 or more days in the past month, a significant increase from the 8.1 million in 2013.

Marijuana is also the illicit drug with the highest numbers of past year dependence or abuse in the U.S. population. According to the 2014 NSDUH report, of the 7.1 million persons aged 12 or older who were classified with illicit drug dependence or abuse, 4.2 million of them abused or were dependent on marijuana (representing 59.0% of all those classified with illicit drug dependence or abuse and 1.6% of the total U.S. non-institutionalized population aged 12 or older).

According to the 2015 Monitoring the Future (MTF) survey, marijuana is used by a large percentage of American youths, and is the most commonly used illicit drug among American youth. Among students surveyed in 2015, 13.5% of 8th graders, 31.1% of 10th graders, and 44.7% of 12th graders reported they had used marijuana in their lifetime. In addition, 11.8%, 25.4%, and 34.9% of 8th, 10th, and 12th graders, respectively, reported using marijuana in the past year. A number of high school students reported daily use in the past month, including 1.1%, 3.0%, and 6.0% of 8th, 10th, and 12th graders, respectively.

The prevalence of marijuana use and abuse is also indicated by criminal investigations for which drug evidence was analyzed in federal, state, and local forensic laboratories, as discussed above in Factor 1. The National Forensic Laboratory System (NFLIS), a DEA program, systematically collects drug identification results and associated information from drug cases submitted to and analyzed by federal, state, and local forensic laboratories. NFLIS data shows that marijuana was the most frequently identified drug from January 2001 through December 2014. In 2014, marijuana accounted for 29.3% (432,989) of all drug exhibits in NFLIS.

The high consumption of marijuana is being fueled by increasing amounts of domestically grown marijuana as well as increasing amounts of marijuana being illicitly smuggled into the United States. In 2014, the Domestic Cannabis Eradication and Suppression Program (DCE/SP) reported that 3,904,213 plants were eradicated in outdoor cannabis cultivation areas compared to 2,597,798 in 2000, as shown above in Table 3. Significant quantities of marijuana were also eradicated from indoor cultivation operations. There were 396,620 indoor plants eradicated in 2014 compared to 217,105 eradicated in 2000. As shown in Table 2 above, in 2014, the National Seizure System (NSS) reported seizures of 1,767,741 kg of marijuana.

**Petitioners’ Major Comments in Relation to Factor 4 and the Government’s Responses**

(1) The petitioners indicated that the history and current pattern of abuse is difficult to estimate since “a large percentage of United States citizens” have used marijuana at least once in their lifetime and some estimates have indicated that “over 40 percent of the nation has tried the plant.” Further, the petitioners stated that “trying marijuana once should not be confused with a health problem, let alone a diagnosis of dependence or abuse.” (Exhibit B, page 26).

Marijuana usage numbers mentioned in both the HHS Recommendation and this DEA document include surveys from NSDUH and MTF. These surveys measure extent of use of marijuana. As mentioned in this Factor, according to the results of the 2013 NSDUH survey, 17.4% of past year marijuana users age 12 or older used marijuana on 300 or
more days within the previous 12 months. This indicates that 5.7 million people used marijuana on a daily or almost daily basis over this 12-month period, which is a 1.8-fold increase from the 3.1 million daily or almost daily users in 2006. Furthermore, 6% of all twelfth graders in the United States reported daily use of marijuana in the 2015 MTF survey. These data strongly indicate that there is a significant portion of the U.S. population using marijuana on a daily basis.

(2) As stated in Exhibit B on page 26, subpart A, “Rates of dependence or abuse are remarkably low” and further suggest that “[i]nterviews for the National Longitudinal Alcohol Epidemiological Survey ([INLAEs] [sic] and National Epidemiological Survey on Alcohol and Related Conditions ([NESARC] [sic]) each confirm that rates of dependence or abuse of cannabis have never exceed (sic) two percent in a given year.”

The authors of study cited by the petitioners (Compton et al., 2004) concluded that a higher percentage of American adults had a marijuana use disorder in 2001–2002 (1.5%) than in 1991–1992 (1.2%). Compton et al. (2004) noted that the marijuana use disorder increase of 0.3% over the 10 year period would equate to an increase from 2.2 million people to 3 million people in the United States. The petitioners failed to explain the impact of 1.5% (or less than 2 percent) of the U.S. population having a marijuana use disorder. In order to put these numbers into perspective, the DEA reviewed the literature and found that non-medical prescription drug use and abuse rates were examined in the same NLAES and NESARC (1991–1992 and 2001–2002) populations (Blanco et al., 2007). Blanco et al. (2007) examined non-medical prescription drug use and abuse rates from the periods of 1991–1992 and 2001–2002. In 1991 through 1992, the prevalence of non-medical prescription drug (opioid, stimulant, and tranquilizer) abuse and dependence was 0.1%. Non-medical prescription drug (primarily opioid-based drugs) abuse and dependence increased to 0.3% in 2001 through 2002. Therefore, in the same 2001–2002 NLAES and NESARC populations, the percentage of people with a marijuana use disorder was approximately five-fold higher (1.5% versus 0.3%) than those with opioid abuse and dependence resulting from non-medical prescription drug use.

Further, Volkow et al. (2014) reported that in long-term or heavy marijuana users, 9% of users become addicted to marijuana. This percentage increases to 17% when marijuana use starts in adolescence and it increases to 25 to 50% of those who are daily users.

**Factor 5: The Scope, Duration, and Significance of Abuse**

 Abuse of marijuana is widespread and significant. As previously noted, according to the NSDUH, in 2014, an estimated 117.2 million Americans (44.2%) age 12 or older had used marijuana or hashish in their lifetime, 35.1 million (13.2%) had used it in the past year, and 22.2 million (6.4%) had used it in the past month. Past year and past month marijuana use has increased significantly since 2013. Past month marijuana use is highest among 18–21 year olds and it declines among those 22 years of age and older. In 2014, an estimated 18.5% of past year marijuana users age 12 or older used marijuana on 300 or more days within the past 12 months. This translates into 6.5 million persons using marijuana on a daily or almost daily basis over a 12-month period. In 2014, an estimated 41.6% (9.2 million) of adult marijuana users age 12 or older used the drug on 20 or more days in the past month (SAMHSA, NSDUH). Chronic use of marijuana is associated with a number of health risks (see Factors 2 and 6).

Furthermore, the average percentage of Δ⁹-THC in seized marijuana has increased over the past two decades (The University of Mississippi Potency Monitoring Project). Additional studies are needed to clarify the impact of greater potency, but one study shows that higher levels of Δ⁹-THC in the body are associated with greater psychoactive effects (Harder and Rietbrock, 1997), which can be correlated with higher abuse potential (Chait and Burke, 1994).

TEDS data show that in 2013, marijuana/hashish was the primary substance of abuse in 16.8% of all admissions to substance abuse treatment among patients age 12 and older. TEDS data also show that marijuana/hashish was the primary substance of abuse for 77.0% of all 12- to 14-year-olds admitted for drug treatment and 75.5% of all 15- to 17-year-olds admitted for drug treatment in 2013. Among the 281,991 admissions to drug treatment in 2013 in which marijuana/hashish was the primary drug, the average age at admission was 25 years and the peak age cohort was 15 to 17 years (22.5%). Thirty-nine percent of the 281,991 primary marijuana/hashish admissions (35.9%) were under the age of 20.

In summary, the recent statistics from these various surveys and databases (see Factor 1 for more details) demonstrate that marijuana continues to be the most commonly used illicit drug, with large incidences of heavy use and dependence in teenagers and young adults.

**Petitioners’ Major Comment in Relation to Factor 5 and DEA’s Response**

(1) Petitioners’ contend that, “The prevalence and significance of potential abuse are limited for cannabis, especially in relation to other [sic] substances.” The petitioners cited results from the 1990 NIDA Household Survey on Drug Abuse and indicated that, “more than four out of five people who had used cannabis in the previous year reported no problems related to the drug.” (Exhibit B, page 26). The prevalence of marijuana usage and marijuana dependence is significant in the United States. The 2014 NSDUH findings indicate that there are approximately 6.5 million Americans using marijuana on a daily or almost daily basis. Further, Volkow et al. (2014) reported that in long-term or heavy marijuana users, 9% of users become addicted to marijuana. Among those who began using marijuana in adolescence, marijuana dependence increases to 17%, and it further increases to 25 to 50% of daily users that started using marijuana during adolescence. These collective findings indicate that there is considerable significance associated with marijuana use and abuse since 9% of users become addicted to marijuana, 25 to 50% of daily marijuana users started during adolescence, and prevalence of usage is significantly high based on the data presented from Volkow et al (2014) and the 2014 NSDUH survey.

**Factor 6: What, if any, Risk There is to the Public Health**

In its recommendation, the HHS discussed public health risks associated with acute and chronic marijuana use in Factor 6. Public health risks as measured by emergency department visits and drug treatment admissions are discussed by HHS and DEA in Factors 1, 4, and 5. Similarly, Factor 2 discusses marijuana’s pharmacology and presents some of the adverse health effects and associated with use. Marijuana use may affect the physical and/or psychological functioning of an individual user, but may also have broader public impacts including driving impairments and fatalities from car accidents.

**Risks From Acute Use of Marijuana**

As discussed in the HHS review document (HHS, 2015), acute usage of marijuana impairs psychomotor performance including motor control and impulsivity, risk taking and executive function (Rameakers et al., 2004; Rameakers et al., 2006). In a
minority of individuals using marijuana, dysphoria, prolonged anxiety, and psychological distress may be observed (Haney et al., 1999). The DEA further notes a recent review of acute marijuana effects (Wilkinson et al., 2014) that reported impaired neurological function including altered perception, paranoia, delayed response time, and memory deficits.

In its recommendation, HHS references a meta-analysis conducted by Li et al. (2012) where the authors concluded that psychomotor impairments associated with acute marijuana usage have also been associated with increased risk of car accidents with individuals experiencing acute marijuana intoxication (Li et al., 2012; HHS, 2015). The DEA further notes more recent studies examining the risk associated with marijuana use and driving. Younger drivers (under 21) have been characterized as the highest risk group associated with marijuana use and driving (Whitehill et al., 2014). Furthermore, in 2015, marijuana was found in 13% of the drivers involved in automobile-related fatal accidents (McCart, 2015). The potential risk of automobile accidents associated with marijuana use appears to be increasing since there has been a steady increase in individuals intoxicated with marijuana over the past 20 years (Wilson et al., 2014). However, a recent study commissioned by the National Highway Traffic Safety Administration (NHTSA) reported that when adjusted for confounders (e.g., alcohol use, age, gender, ethnicity), there was not a significant increase in crash risk (fatal and nonfatal, n = 2,682) associated with marijuana use (Compton and Berning, 2015).

The DEA also notes recent studies examining unintentional exposures of children to marijuana (Wang et al., 2013; 2014). Wang et al. (2013) reviewed emergency department (ED) visits at a children’s hospital in Colorado from January 1, 2005 to December 31, 2011. As stated by the authors, in 2000 Colorado passed Amendment 20 which allowed for the use of marijuana. Following the passage of “a new Justice Department policy” instructing “federal prosecutors not to seek arrest of medical marijuana users and suppliers as long as they conform to state laws” (as stated in Wang et al., 2013), 14 patients in Colorado under the age of 12 were admitted to the ED for the unintended use of marijuana over a 27 month period. Prior to the passage of this policy, from January 1, 2005 to September 30, 2009 (57 months), there were no pediatric ED visits due to unintentional marijuana exposure (Wang et al., 2013). The DEA also notes a larger scale evaluation of pediatric exposures using the National Poison Data System (Wang et al., 2014). That study reported that there were 985 unintentional marijuana exposures in children (9 years and younger) between January 1, 2005 to December 31, 2011. The authors stratified the ED visits by states with laws allowing medical use of marijuana, states transitioning to legalization for medical use, and states with no such laws. Out of the 985 exposures, 495 were in non-legal states (n = 33 states), 93 in transitional states (n = 8 states), and 396 in “legal” states (n = 9 states). The authors reported that there was a twofold increase (OR = 2.1) in moderate or major effects in children with unintentional marijuana use and a threefold increase (OR = 3.4) in admissions to critical care units in states allowing medical use of marijuana, in comparison to non-legal states.

**Risks Associated With Chronic Use of Marijuana**

The HHS noted that a major risk from chronic marijuana use is a distinctive withdrawal syndrome, as described in the 2013 DSM–5. The HHS analysis also quoted the following description of risks associated with marijuana [cannabis] abuse from the DSM–5:

> Individuals with cannabis use disorder may use cannabis throughout the day over a period of months or years, and thus may spend many hours a day under the influence. Others may use less frequently, but their use causes recurrent problems related to family, school, work, or other important activities (e.g., repeated absences at work; neglect of family obligations). Periodic cannabis use and intoxication can negatively affect behavioral and cognitive functioning and thus interfere with optimal performance at work or school, or bring an individual to increased physical risk when performing activities that could be physically hazardous (e.g., driving a car; playing certain sports; performing manual work activities, including operating machinery). Arguments with spouses or parents over the use of cannabis in the home, or its use in the presence of children, can adversely impact family functioning and are common features of those with cannabis use disorder. Last, individuals with cannabis use disorder may continue using marijuana despite knowledge of physical problems (e.g. chronic cough related to smoking) or psychological problems (e.g. excessive sedation or exacerbation of other mental health problems) associated with its use. (HHS 2015, page 34).

The HHS stated that chronic marijuana use produces acute and chronic adverse effects on the respiratory system, memory and learning. Regular marijuana smoking can produce a number of long-term pulmonary consequences, including chronic cough and increased sputum (Adams and Martin, 1996), and histopathologic abnormalities in bronchial epithelium (Adams and Martin, 1996).

**Marijuana as a “Gateway Drug”**

The HHS reviewed the clinical studies evaluating the gateway hypothesis in marijuana and found them to be limited. The primary reasons were: (1) Recruited participants were influenced by social, biological, and economic factors that contribute to extensive drug abuse (Hall and Lynskey, 2005), and (2) most studies testing the gateway drug hypothesis for marijuana use the determinative measure any use of an illicit drug rather than applying DSM–5 criteria for drug abuse or dependence (DSM–5, 2013).

The HHS cited several studies where marijuana use did not lead to other illicit drug use (Kandel and Chen, 2000; von Sydow et al., 2002; Nace et al., 1975). Two separate longitudinal studies with adolescents using marijuana did not demonstrate an association with use of other illicit drugs (Kandel and Chen, 2000; von Sydow et al., 2002).

It was noted by the HHS that, when evaluating the gateway hypothesis, differences appear when examining use versus abuse or dependence of other illicit drugs. Van Gundy and Rebello (2010) reported that there was a correlation between marijuana use in adolescence and other illicit drug use in early adulthood, but when examined in terms of drug abuse of other illicit drugs, age-linked stressors and social roles were confounders in the association. Degenhardt et al. (2009) reported that marijuana use often precedes use of other illicit drugs, but dependence involving drugs other than marijuana frequently correlated with higher levels of illicit drug abuse. Furthermore, Degenhardt et al. (2010) reported that in countries with lower prevalence of marijuana usage, use of other illicit drugs before marijuana was often documented.

**Based on these studies among others,** the HHS concluded that although many individuals with a drug abuse disorder may have used marijuana as one of their first illicit drugs, this does not mean that individuals initiated with marijuana inherently will go on to become regular users of other illicit drugs.
Petitioners’ Major Comment in Relation to Factor 6 and the Government’s Responses

(1) The petitioners commented that marijuana does not significantly impact social behaviors such as motivation, driving, aggression, or hostility (Exhibit B, pages 30-41).

The HHS concluded that “Marijuana’s acute effects can significantly interfere with a person’s ability... to operate motor vehicles.” (HHS, 2015) As mentioned in this factor, there is a significant risk with marijuana use and driving. Marijuana was found in 13% of drivers involved in automobile fatal accidents (McCartt, 2015). Furthermore, in a meta-analysis conducted by Li et al. (2011), an association was identified between marijuana use by the driver and an increased risk of getting into a car accident.

The DEA notes that the petitioners only considered whether marijuana creates social problems, and did not consider physiological changes and impacts that also should be evaluated in determining the risk to public health. The HHS and DEA considered the public health impacts of such physiological effects, as discussed in this factor and others above. Marijuana may result in cardiovascular toxicity as indicated by recent reviews examining these associations (Hackham, 2015; Panayiotides, 2015). There is a possible association between frequent, long-term marijuana use and increased risk of testicular germ cell cancers and some evidence that chronic marijuana use may lead to lung cancer although the evidence is inconsistent.

Furthermore, a more recent risk is the increase in ED visits of children unintentionally exposed to marijuana with increased risk factors for major adverse effects or admission to critical care units in states that have legalized marijuana for medical purposes (Wang et al., 2014).

Factor 7: Its Psychiatric or Physiological Dependence Liability

Physiological (Physical) Dependence in Humans

The HHS stated that heavy and chronic use of marijuana can lead to physical dependence (DSM-5, 2013; Budney and Hughes, 2006; Haney et al., 1999). Tolerance is developed following repeated administration of marijuana and withdrawal symptoms are observed as following discontinuation of marijuana usage (HHS, 2015).

The HHS mentioned that tolerance can develop to marijuana’s effects, but does not appear to develop with respect to the psychoactive effects.

It is believed that lack of tolerance to psychoactive effects may relate to electrophysiological data demonstrating that chronic Δ9-THC administration does not affect increased neuronal firing in the ventral tegmental area, a brain region that plays a critical role in drug reinforcement and reward (Wu and French, 2000). Humans can develop tolerance to marijuana’s cardiovascular, autonomic, and behavioral effects (Jones et al., 1981). Tolerance to some behavioral effects appears to develop with heavy and chronic use, but not with occasional usage. Ramaekers et al. (2009) reported that following acute administration of marijuana, occasional marijuana users still exhibited impairments in tracking and attention tasks whereas performance of heavy users on the tests was not affected. In a follow-up study with the same subjects that participated in the study by Ramaekers et al. (2009), a neurophysiological assessment was conducted where event-related potentials (ERPs) were measured using electroencephalography (EEG) (Theunissen et al., 2012). Similar to the earlier results, the heavy marijuana users (n = 11; average of 340 marijuana uses per year) had no changes in their ERPs with the acute marijuana exposure. However, occasional users (n = 10; average of 55 marijuana uses per year) had significant decreases in the amplitude of an ERP component (categorized as P100) on tracking and attention tasks and ERP amplitude change is indicative of a change in brain activity (Theunissen et al., 2012).

The HHS indicated that down-regulation of cannabinoid receptors may be a possible mechanism for tolerance to marijuana’s effects (Hirvonen et al., 2012; Gonzalez et al., 2005; Rodriguez de Fonseca et al., 1994; Oviedo et al., 1993).

As indicated by the HHS, the most common withdrawal symptoms in heavy, chronic marijuana users are sleep difficulties, decreased appetite or weight loss, irritability, anger, anxiety or nervousness, and restlessness (Budney and Hughes, 2006; Haney et al., 1999). As reported by HHS, most marijuana withdrawal symptoms begin within 24–48 hours of discontinuation, peak within 4–6 days, and last for 1–3 weeks. The HHS pointed out that the American Psychiatric Association’s (APA’s) Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) included a list of withdrawal symptoms following marijuana [cannabis] use (DSM-5, 2013). The DEA notes that a DSM-5 work group report indicated that marijuana withdrawal symptoms were added to DSM-5 (they were not previously included in DSM-IV) because marijuana withdrawal has now been reliably presented in several studies (Hasin et al., 2013). In short, marijuana withdrawal signs are reported in up to one-third of regular users and between 50% and 90% of heavy users (Hasin et al., 2013). According to DSM–5 criteria, in order to be characterized as having marijuana withdrawal, an individual must develop at least three of the seven symptoms within one week of decreasing or stopping the heavy and prolonged use (DSM–5, 2013). These seven symptoms are: (1) Irritability; anger or aggression, (2) nervousness or anxiety, (3) sleep difficulty, (4) decreased appetite or weight loss, (5) restlessness, (6) decreased mood, (7) somatic symptoms causing significant discomfort (DSM–5, 2013).

Psychological (Psychic) Dependence in Humans

High levels of psychoactive effects such as positive reinforcement correlate with increased marijuana abuse and dependence (Scherrer et al., 2009; Zeiger et al., 2010). Epidemiological marijuana use data reported by NSDUH, MTF, and TEDS support this assertion as presented in the HHS 2015 review of marijuana and updated by the DEA. According to the findings in the 2014 NSDUH survey, an estimated 9.2 million individuals 12 years and older used marijuana daily or almost daily (20 or more days within the past month). In the 2015 MTF report, daily marijuana use (20 or more days within the past 30 days) in 6th, 10th, and 12th graders is 1.1%, 3.0%, and 6.8%, respectively.

The 2014 NSDUH report stated that 4.2 million persons were classified with dependence on or abuse of marijuana in the past year (representing 1.6% of the total population age 12 or older, and 59.0% of those classified with illicit drug dependence or abuse) based on criteria specified in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM–IV). Furthermore, of the admissions to licensed substance abuse facilities, as presented in TEDS, marijuana/hashish was the primary substance of abuse for; 18.3% (352,297) of 2011 admissions; 17.5% (315,200) of 2012 admissions; and 16.8% (281,991) of 2013 admissions. Of the 281,991 admissions in 2013 for marijuana/hashish as the primary substance, 24.3% used marijuana/hashish daily. Among admissions to treatment for marijuana/hashish as the primary substance in 2013, 27.4% were ages 12 to 17 years and 29.7% were ages 20 to 24 years.
Petitioners’ Major Comment in Relation to Factor 7 and the Government’s Response

(1) The petitioners stated, “There is no severe physical withdrawal syndrome associated with cannabis. Cannabis addiction is amenable to treatment.” (Exhibit B, page 10). The petitioners further indicated that marijuana “may be psychologically addictive, but much less so than other Scheduled [sic] II drugs.” (Exhibit B, page 10) and that there is a low risk of dependence associated with marijuana use. Petitioners further stated in Exhibit B, page 23, “Cannabis has low relative dependence risk and does not reach the severity associated with other drugs.”

The HHS states that marijuana withdrawal syndrome “appears to be mild compared to classical alcohol and barbiturate withdrawal syndromes” and is similar in magnitude and time course to tobacco withdrawal syndrome.

DSM–5 now recognizes and describes a marijuana [cannabis] withdrawal syndrome. The lifetime risk of dependence to marijuana is approximately 9% among heavy or long-term users [Volkow et al., 2014]. Marijuana results in tolerance and withdrawal as described earlier in this Factor 7. The data from NSDUH indicate that there is constant desire for marijuana as noted by the consistently high numbers of current daily users in adults and adolescents. Marijuana use also persists despite problems associated with the drug. Changes in IQ have been noted in adolescent-onset, chronic or dependent marijuana users, in addition to withdrawal symptoms. However, marijuana use has not declined in the time that usage of this drug has been monitored. Additionally, there has been an increase in content of the primary psychoactive chemical, Δ⁹-THC, in marijuana samples analyzed by the University of Mississippi’s Potency Monitoring Project, suggesting preference for marijuana strains with higher levels of Δ⁹-THC.

Factor 8: Whether the Substance is an Immediate Precursor of a Substance Already Controlled Under the CSA

Marijuana is not an immediate precursor of another controlled substance.

Determination

After consideration of the eight factors discussed above and of the HHS’s Recommendation, the DEA finds that marijuana meets the three criteria for placing a substance in schedule I of the CSA under 21 U.S.C. 812(b)(1):

1. Marijuana has a high potential for abuse.

The HHS concluded that marijuana has a high potential for abuse based on a large number of people regularly using marijuana, its widespread use, and the vast amount of marijuana that is available through illicit channels. Marijuana is the most abused and trafficked illicit substance in the United States. Approximately 22.2 million individuals in the United States (6.4% of the United States population) were past month users of marijuana according to the 2014 NSDUH survey. A 2015 national survey (Monitoring the Future) that tracks drug use trends among high school students showed that, by 12th grade, 21.3% of students reported using marijuana in the past month, and 6.0% reported having used it daily in the past month. In 2011, SAMHSA’s Drug Abuse Warning Network (DAWN) reported that marijuana was mentioned in 36.4% of illicit drug-related emergency department (ED) visits, corresponding to 455,668 out of approximately 1.25 million visits. The Treatment Episode Data Set (TEDS) showed that 16.8% of non-private substance-abuse treatment facility admissions in 2013 were for marijuana as the primary drug.

Marijuana has dose-dependent reinforcing effects that encourage its abuse. Both clinical and preclinical studies have demonstrated that marijuana and its principle psychoactive constituent, Δ⁹-THC, possess the pharmacological attributes associated with drugs of abuse. They function as discriminative stimuli and as positive reinforcers to maintain drug use and drug-seeking behavior. Additionally, use of marijuana can result in psychological dependence.

2. Marijuana has no currently accepted medical use in treatment in the United States.

The HHS stated that the FDA has not approved an NDA for marijuana. The HHS noted that there are opportunities for scientists to conduct clinical research with marijuana and there are active INDs for marijuana, but marijuana does not have a currently accepted medical use in the United States, nor does it have an accepted medical use with severe restrictions.

FDA approval of an NDA is not the sole means through which a drug can be determined to have a “currently accepted medical use” under the CSA. Applying the five-part test summarized below, a drug has a currently accepted medical use if all of the following five elements have been satisfied. As detailed in the HHS evaluation and as set forth below, none of these elements has been fulfilled for marijuana:

i. The drug’s chemistry must be known and reproducible.

Chemical constituents including Δ⁹-THC and other cannabinoids in marijuana vary significantly in different marijuana strains. In addition, the concentration of Δ⁹-THC and other cannabinoids may vary between strains. Therefore the chemical composition among different marijuana samples is not reproducible. Due to the variation of the chemical composition in marijuana strains, it is not possible to derive a standardized dose. The HHS does advise that if a specific Cannabis strain is cultivated and processed under controlled conditions, the plant chemistry may be consistent enough to derive standardized doses.

ii. There must be adequate safety studies.

There are not adequate safety studies on marijuana for use in any specific, recognized medical condition. The considerable variation in the chemistry of marijuana results in differences in safety, biological, pharmacological, and toxicological parameters amongst the various marijuana samples.

iii. There must be adequate and well-controlled studies proving efficacy.

There are not adequate and well-controlled studies that determine marijuana’s efficacy. In an independent review performed by the FDA of publicly available clinical studies on marijuana (FDA, 2015), FDA concluded that the HHS studies do not have enough information to “currently prove efficacy of marijuana” for any therapeutic indication.

iv. The drug must be accepted by the medical community.

At this time, there is no consensus of opinion among experts concerning the medical utility of marijuana for use in treating specific recognized disorders.

v. The scientific evidence must be widely available.

The currently available data and information on marijuana is not sufficient to address the chemistry, pharmacology, toxicology, and effectiveness. The scientific evidence regarding marijuana’s chemistry with regard to a specific cannabis strain that could be formulated into standardized and reproducible doses is not currently available.

3. There is a lack of accepted safety for use of marijuana under medical supervision.

Currently, there are no FDA-approved marijuana products. The HHS also concluded that marijuana does not have a currently accepted medical use in treatment in the United States or a currently accepted medical use with severe restrictions. According to the HHS, the FDA is unable to conclude that marijuana has an acceptable level of
safety in relation to its effectiveness in treating a specific and recognized disorder due to lack of evidence with respect to a consistent and reproducible dose that is contamination free. The HHS indicated that marijuana research investigating potential medical use should include information on the chemistry, manufacturing, and specifications of marijuana. The HHS further indicated that a procedure for delivering a consistent dose of marijuana should also be developed. Therefore, the HHS concluded that marijuana does not have an acceptable level of safety for use under medical supervision.

References


174. Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality (2015a). Results from the 2014 National Survey on Drug Use and Health: Detailed Tables. Rockville, MD.


[IFDoc 2016–17954 Filed 8–11–16; 8:45 am]
Enclosure B: “The DEA’s Denial of Existing Medical Cannabis Research” (August 2016)
The DEA’s Denial of Existing Medical Cannabis Research

A Peer-Reviewed Comparative Analysis of DEA’s
“Denial of Petition to Initiate Proceedings to Reschedule Marijuana”


Reviewed by Jahan Marcu, Ph.D., Ethan Russo, MD, Jason Schechter, Ph.D., and Steph Sherer
The research and analysis in this report was conducted by Americans for Safe Access Foundation, a 501(c)(3) non-profit organization. With over 100,000 active members in all 50 states, Americans for Safe Access (ASA) is the largest national member-based organization of patients, medical professionals, scientists and concerned citizens promoting safe and legal access to cannabis for therapeutic use and research. ASA works to overcome political and legal barriers by creating policies that improve access to medical cannabis for patients and researchers through legislation, education, litigation, grassroots actions, advocacy and services for patients and their caregivers, the medical cannabis industry, and governments.

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I. Foreword

Today over 300 million Americans live in states with medical cannabis laws, and over 2 million individuals are legally using medical cannabis under these state programs. However, all of these patients and programs are in violation of federal laws. According to the Department of Justice (DOJ), this is due to the fact that Congress determined that cannabis belongs in Schedule I of the Controlled Substances Act (CSA).

However, the scheduling of cannabis has been a political – rather than scientific – establishment from the very beginning. In 1970, cannabis was placed in Schedule I under the CSA as a placeholder, pending evaluation by a government-appointed commission known as the National Commission on Marihuana and Drug Abuse – since known as the Shafer Commission after the Commission’s chairman, Raymond P. Shafer. Even though the Shafer Commission recommended decriminalization of cannabis and medical availability, these policies were rejected by President Nixon before the report could be published. Despite numerous advances in science and research in the medical value of cannabis, due to political forces, as well as Drug Enforcement Administration (DEA) and U.S. Food and Drug Administration (FDA) policies that were designed for prescription drugs, cannabis has been stuck in Schedule I ever since.

Under these circumstances, the current rescheduling process will never allow cannabis to be rescheduled. This is made clear in the DEA’s most recent “Denial of Petition to Initiate Proceedings to Reschedule Marijuana,” which focuses on the fact that cannabis does not fit with current federal regulations for a FDA approved drug, i.e. the medical value assigned to cannabis does not meet their definition of “medicine,” not that cannabis has no medical value.

This is the 4th time in just over 4 decades that the DEA has denied a petition to reschedule cannabis. Not only has the DEA taken several years to respond to each petition, but special rules for cannabis are created and applied whenever there is data that does not support their policy. In the 1990s, the DEA established a “5-element test” to determine if there was accepted medical use for a drug. However, the consequences of not satisfying this test to fulfill the DEA’s definition of medicine have only been applied to cannabis. Applying prescription drug standards – such as those required for FDA approval – to a botanical drug is a case in point of special rules being applied where they wouldn’t be otherwise. Rather than using the FDA guidelines for botanical drugs, cannabis is criticized as though it were a purified pharmaceutical agent, and not a botanical medicine.

The rescheduling process has been designed for prescription drugs to move between the schedules, and not for a Schedule I substance to enter into less restrictive schedules. This unworkable process for botanical medicines, including but not limited to cannabis, has led 42 states plus the District of Columbia to create their own definitions of medicine and distribution.

The DEA’s recent decision shows that the war against medical cannabis will unfortunately continue unabated, and unaffected by either reason or scientific evidence. Until these policies can be changed, the only viable solutions will require action by Congress.
II. Introduction

In April 2011, the Department of Justice (DOJ) sent letters to governors of 9 medical cannabis states “clarifying” that medical cannabis programs – and specifically regulated distribution programs – were in violation of federal law, due to the Schedule I status of marijuana. In response, in November of the same year, Governors Lincoln D. Chafee (RI) and Christine O. Gregoire (WA), petitioned the DEA to initiate rulemaking proceedings under the rescheduling provisions of the CSA – to remove marijuana and “related items” from Schedule I of the CSA and to reschedule as “medical cannabis” in Schedule II. After nearly five years of review, on August 10, 2016 the DEA responded to the petition with a document entitled Denial of Petition to Initiate Proceedings to Reschedule Marijuana (herein referred to as the "DEA report").

The DEA concluded that “marijuana” (cannabis) should not be removed from the Schedule I status due to the below 3 factors:

1) Marijuana has a high potential for abuse;

2) Marijuana has no currently accepted medical use in treatment in the United States; and

3) Marijuana lacks accepted safety for use under medical supervision.

DEA chief Chuck Rosenberg stated that this decision was based heavily on the FDA’s determination if marijuana is “a safe and effective medicine.” This determination was based upon input from the Department of Health and Human Services (HHS), which was conducted in consultation with the National Institute on Drug Abuse (NIDA).

The DEA report cited the following in making their determination:


2. While not listed in their cover letter as a submitted document, a review article added at the end of the bibliography of the HHS report, entitled The Medical Application of Marijuana: A Review of Published Clinical Studies prepared by the U.S. Food and Drug Administration (page 66).


While we do not agree with the DEA’s final determination that marijuana is not a safe and effective medicine, we do appreciate the time and resources the DEA put into making this decision. We are pleased to see a few areas of agreement between their report and the available scientific data on cannabis. Generally, our analysis found that the DEA admits that cannabis satisfies several criteria regarding the 8-Factor analysis.

However, the DEA report included both inaccurate and unclear background materials pertaining to the scheduling process of cannabis, conjoined to misinterpretations of the CSA in general. In one clear
example of this, the report states there are *no known* standardized cannabis products. The DEA chose to use a misinterpretation of the CSA to exclude any clinical research conducted with standardized cannabis extracts from the HHS report. The report defines cannabis/marijuana in the CSA as including derivatives and extracts of cannabis/marijuana such as purified THC, CBD, and nabiximols. However, in the DEA’s *political* view, these resinous hash oils do not count as standardized cannabis products, nor do the cannabis cigarettes that NIDA themselves produce according to DEA (and FDA) guidelines and mandate. Clinical studies with resinous hash oil extractions were systematically excluded in the DEA’s denial of rescheduling report.

Actual standardized “cannabis medicines” include purified THC, purified CBD, THC/CBD mixtures, and nabiximols (commonly known as Sativex®). Purified CBD and Sativex® are FDA approved under IND for pediatric epilepsy, and in Phase III clinical trials in the U.S., respectively. Marinol® is an FDA approved cannabis product known as dronabinol. There exists no evidence of significant abuse, nor black market or diversion issues, with currently available standardized medicinal cannabis products – including dronabinol, nabiximols, or NIDA’s cannabis products. Such persistent misinterpretation of existing law – coupled to apparent lack of knowledge of prevailing scientific investigations concerning both general safety and medicinal usefulness – suggests that an uninformed and unbalanced opinion of cannabinoid-based medicine is being advanced.

In anticipation of the DEA’s pending decision on the scheduling of medical cannabis, Americans for Safe Access (ASA) coordinated world experts on cannabis to draft an independent 8-Factor Analysis based on all available data that concluded that cannabis does not meet the requirements for a Schedule I substance under the CSA. The following memo is a comparative analysis of the research and findings used by the DEA to make their determination that cannabis remain a Schedule I drug. The references in this memo refer to DEA materials and ASA’s 8-Factor analysis.

**III. Common Ground**

The DEA report claims that cannabis satisfies some sections of the 8-factor analysis. This means there are sections where we all agree that cannabis meets the criteria for rescheduling. In short, we agree with the DEA that cannabis satisfies Factors 1b, 1d, 2, 3, 6, and 8 (of the 8-factor analysis). For example, the DEA cites research demonstrating that there is no evidence for long term harms associated from the chronic use of cannabis to satisfy Factors 2 and 3.

Below are the Factors and the statements from the DEA to which we agree regarding cannabis as a medicine and its rescheduling.

**Factor 1b:** There is no significant diversion of the substance from legitimate drug channels.

**Factor 1b definition:** *“There is significant diversion of the substance from legitimate drug channels.”*

On page 11, the DEA states, *“There is a lack of evidence of significant diversion of marijuana from legitimate drug channels.”*
We agree with the FDA and DEA that legal cannabis products have not suffered from significant diversion and additionally that cannabis is not a precursor for another schedule drug. Pure THC has been FDA approved since the 1980s and no significant black market for Marinol is known to exist.

Factor 1d: Cannabis is related to other approved drugs with acceptable safety profiles.

Factor 1d definition: “The substance is not so related in its action to a substance already listed as having a potential for abuse to make it likely that it will have the same potential for abuse as such substance, thus it is not reasonable to assume that there may be significant diversions from legitimate channels, significant use contrary to or without medical advice, or that it has a substantial capability of creating hazards to the health of the user or to the safety of the community.”

On page 12 the DEA states, “FDA has approved two drug products containing cannabinoid compounds that are structurally related to the active components in marijuana. These two marketed products are controlled under the CSA.” Furthermore, the DEA goes on, “FDA approved Marinol in 1985 for the treatment of nausea and vomiting associated with cancer chemotherapy in patients who failed to respond adequately to conventional anti-emetic treatments. In 1992, FDA approved Marional [sic] for anorexia associated with weight loss in patients with acquired immunodeficiency syndrome (AIDS). Secondly, in 1985, FDA approved Cesamet, a drug product containing the Schedule II substance nabilone, for the treatment of nausea and vomiting associated with cancer chemotherapy.”

We agree with the DEA and FDA that cannabis is a substance related in action to Marinol and Cesamet. THC (Marinol) and Cesamet are two FDA approved drugs with acceptable safety profiles (i.e., low abuse potential) and no evidence of any significant diversion. Factors 2 and 3: Scientific Evidence for the Pharmacological Effects and the State of Current Scientific Knowledge Regarding the Drug or Other Substance.

On page 12, the DEA report states, “Abundant scientific data are available on the neurochemistry, toxicology, and pharmacology of marijuana.”

On page 20, the DEA report states, “cannabis-associated cognitive deficits are reversible and related to recent cannabis exposure, rather than irreversible and related to lifetime use.”

On page 22, the DEA report states, “At present, the available data do not suggest a causative link between marijuana use and the development of psychosis.”

We agree with the DEA that the effects of cannabis are non-toxic and have no long-term consequences on the human brain. Available data show that the chemistry of cannabis is well understood and does not cause significant harm to the adult brain.

Factor 6: That the “gateway” hypothesis is not supported by scientific evidence.

Factor 6 definition: “What, if any, risk there is to public health.”

On page 43, the DEA report states, “Overall, research does not support a direct causal relationship between regular marijuana use and other illicit drug use.”
On page 44, the DEA report states, “the gateway hypothesis only addresses the order of drug use initiation, the gateway hypothesis does not specify any mechanistic connections between drug "stages" following exposure to marijuana and does not extend to the risks for addiction.”

On page 162, the DEA report states, “The HHS reviewed the clinical studies evaluating the gateway hypothesis in marijuana and found them to be limited.” The DEA goes on to say, “The HHS cited several studies where marijuana use did not lead to other illicit drug use.”

On page 162, the DEA report states, “Based on these studies among others, the HHS concluded that although many individuals with a drug abuse disorder may have used marijuana as one of their first illicit drugs, this does not mean that individuals initiated with marijuana inherently will go on to become regular users of other illicit drugs.”

Over 40 years ago the “gateway” hypothesis of cannabis was proposed. The report concludes predictably, that the gateway theory of cannabis is not supported by the evidence. We agree that the hypothesis attempted but failed to predict that cannabis use leads to the addiction of other drugs. Furthermore, no clinically significant adverse public health effects related to rescheduling cannabis were provided to by the DEA.

Factor 8: Cannabis is not an immediate precursor to a controlled substance.

Factor 8 definition: “Whether the substance is immediate precursor of a substance already controlled under the article.”

On page 46, the DEA report states, “Marijuana is not an immediate precursor of another controlled substance.”

We agree that cannabis is not an immediate precursor of another controlled substance.

While not sufficient for the DEA to reschedule, these statements show an evolution in the DEA’s opinions on cannabis. All federal conversations about cannabis should begin with the above information.

IV. Comparative Analysis of Available Data vs HHS Report

The 2016 HHS evaluation and the additional data gathered by the DEA constitute a document, entitled “Basis for the Recommendation for Maintaining Marijuana in Schedule I of the Controlled Substances Act.” This document supporting the basis of the DEA recommendation was preliminarily scrutinized by ASA through use of a comparative reference analysis, in which we categorized and characterized each reference in the DEA’s basis article according to multiple criteria (each references can have more than one category selected). Our goal in doing this was to compare the proportion and type of research article utilized in forming the DEA decision with that of the current available data that ASA used to write their 8-Factor Analysis.

Criteria/categories are as follows:

- Peer Reviewed (Peer reviewed research articles of any type)
• Non-Peer Reviewed (Agency and policy documents, journalistic pieces, no independent 3rd party analysis)
• Clinical Research (Clinical research with controlled dosing looking for therapeutic effect)
• Safety Studies (may or may not have controlled dosing, not investigating therapeutic effects but safety)
• Animal (Animal based research, rats, mice and their brains)
• Surveys (Sociology and epidemiology research, survey based research articles)
• Human Brain (Research pertaining to the human brain, disease, and toxicology to neuronal tissue)
• Reviews (Review type article and reference manuals)
• Original Publication (Original research article cited, opposite of review article)
• <2000 (published during the year 2000 or earlier)
• >2001 (Published in the year 2001 or later)
• Product Safety Related (Research on medical cannabis programs, product safety, traffic and fatality research in states with medical cannabis programs)

![Figure 1 Proportion and Type of References Used in Reporting](image-url)
Table 1. Number, Type and Percentage of Citations Used

<table>
<thead>
<tr>
<th>Title</th>
<th>ASA (558 Citations)</th>
<th>HHS Report (207 Citations)</th>
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<td>Proportion of Research Meeting Criteria</td>
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<td>93.55%</td>
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<td>Non-Peer reviewed</td>
<td>5.56%</td>
<td>31</td>
</tr>
<tr>
<td>Clinical Research</td>
<td>7.17%</td>
<td>40</td>
</tr>
<tr>
<td>Safety Studies</td>
<td>15.59%</td>
<td>87</td>
</tr>
<tr>
<td>Animal</td>
<td>10.04%</td>
<td>56</td>
</tr>
<tr>
<td>Surveys</td>
<td>18.10%</td>
<td>101</td>
</tr>
<tr>
<td>Human Brain</td>
<td>11.11%</td>
<td>62</td>
</tr>
<tr>
<td>Reviews</td>
<td>36.92%</td>
<td>206</td>
</tr>
<tr>
<td>Original Publication</td>
<td>56.63%</td>
<td>315</td>
</tr>
<tr>
<td>&lt;2000</td>
<td>29.21%</td>
<td>163</td>
</tr>
<tr>
<td>&gt;2001</td>
<td>67.56%</td>
<td>377</td>
</tr>
<tr>
<td>Product Safety Related</td>
<td>12.54%</td>
<td>70</td>
</tr>
</tbody>
</table>

Data was generated by adding together all qualifying studies listed in each criterion, then dividing the total number of articles to generate a percentage or proportion.

In comparison, ASA’s 8-Factor analysis utilized a significantly higher proportion and number of clinical research references and product safety related publications in its determinations. The DEA devoted less than 1% of their referenced work to addressing clinical cannabinoid trials, and consists of almost 10% non-peer reviewed publications, as compared to ASA’s 5%.

Fully, one-third of the DEA’s report is based only on surveys, regarding sociology and epidemiology. These types of studies largely lack any clear clinical applications or scientific relevance. For example, the DEA repeatedly cites surveys about cannabis use and suggested associations with psychosis, while completely disregarding clinical correlations such as research from the last 10 years demonstrating that suicide risks are not significantly increased with use.

The discrepancy between pre- and post-2001 literature in the analysis requires additional emphasis. Almost 40% of the DEA report relies primarily on outdated research articles, many of which have not been reproduced by the scientific community. In contrast, the ASA 8-Factor analysis uses almost 70% of research citations that have been published within this century, conducted with modern scientific instrumentation and controls. Several of the research articles used in the DEA report are so dated, that they do not provide any practical information to address current issues. Research studies primarily
published in the last 15 years, focus more on clinical studies using standardized cannabis products and biomedical breakthroughs in multiple sclerosis, cancer, regenerative and personalized medicine.

Pertaining to safety, the DEA report does not include any research regarding more recent standards of safety. For instance, there is no mention of the volume of product safety research that exists on cannabis and botanical medicine regulations today. Nor does it mention any relevant medical cannabis research on edible products from John Hopkins University, which was prominently published in the Journal of the American Medical Association (JAMA) and covered by well over 200 media outlets upon its publication. The DEA report also ignores the book on the quality control and quality assurances of medical cannabis products published by the Research Triangle Institute (RTI).

This analysis provides a characterization of the DEA’s basis report.

In summation:

- DEA’s basis report had only 207 citations, as compared to ASA’s 558.
- ASA’s report was submitted for peer-review to external third parties; there is no evidence that the DEA basis report was peer reviewed, there are no listed authors, and thus no accountability at the either the FDA, DEA, or HHS.
- DEA’s basis report is deficient in addressing clinically relevant harms associated with cannabis.
- DEA’s basis report is deficient in addressing clinical trials with existing standardized cannabis-based medicines (2 citations; representing <1% of the citations).
- Nearly 1/10th of the DEA basis report comes from non-peer reviewed sources.
- Fully 1/3rd of the DEA’s basis comes from epidemiologic and survey based research, many of which do not bare clinical significance or do not demonstrate long term harm.
- The DEA’s report was deficient in its analysis and reporting of medical cannabis products, i.e., 9,000 patient/years of placebo-controlled clinical research with nabiximols (i.e., cannabis extracts) was not even mentioned.
- While the DEA devoted a higher proportion of citations to the human brain (19%), it represents only 40 citations. While ASA cited 62 studies on the subject, which represents about 11% of ASA’s 558 citations.

V. Evaluating the DEA’s Rationale for 1) Marijuana has a high potential for abuse.

DEA’s Evidence

“The HHS evaluation and the additional data gathered by the DEA show that marijuana has a high potential for abuse.”
Available Scientific Data

If medical cannabis and related products had a high potential for abuse, there would exist a significant black market for both FDA and non-FDA approved medical cannabis products, such as FDA approved Marinol (pure THC), and the IND approved cannabis products Sativex®, Epidiolex®, and NIDA’s catalogue of cannabis products for research (i.e., cannabis cigarettes). However, despite decades of availability, there is virtually no identifiable black market for NIDA’s cannabis products, FDA approved Marinol, or the cannabis extracts Epidiolex and Sativex.

Marinol is pure THC, and can legally be created as a generic drug from the THC isolated from cannabis plants. Epidiolex and Sativex are standardized resinous extracts from cannabis plants. According to GW Pharmaceuticals’ website and their widely available peer-reviewed clinical publications, their cannabis extract Sativex has already been utilized in Phase II and III clinical trials in the U.S. for almost 10 years, and without any abuse or diversion. Furthermore, biochemical fingerprinting of this standardized cannabis extract has been adequate for FDA CMC (Chemistry, Manufacturing, and Control) approval.

Another cannabis extract, marketed under the name Epidiolex, is part of a national clinical study in the U.S., investigating the role of this standardized product as frontline treatment in pediatric epilepsy. The University of Mississippi has been producing whole plant cannabis products for decades, and shipping about 300 cannabis cigarettes a month to IND patients since 1970, yet no report exists of finding these on the black market. GW Pharmaceuticals has produced more tonnage of cannabis than any other organization, legal or illegal, yet their cannabis extracts are simply not found on the black market. There exists no case whereupon either a user or abuser has arrived to a clinic for treatment of addiction related to the abuse of NIDA cannabis cigarettes, despite decades of use by IND patients. Further, neither Europe nor the UK have reported any significant development of a black market for medical cannabis products such as Sativex, Marinol, or pharmaceutical grade cannabis produced by Bedrocan®.

The DEA provides substantial evidence from surveys, that a great number of people report having used cannabis at some point within the last year. However, these surveys cited by the HHS report do not point to any relevant or significant negative public health outcome from these patterns of mass use. Indeed, cannabis is physiologically non-toxic (there is no known LD50 for cannabis) and is not associated with causing any long-term negative health consequences.

VI. Evaluating the DEA’s Statement 2) Marijuana has no currently accepted medical use in treatment in the Unites States.

“Based on the established five-part test for making such determination, marijuana has no currently accepted medical use,” because:

1 For Available Scientific Data references (i.e., [553]) please refer to the bibliography of ASA’s peer reviewed 8-Factor analysis, available at: http://www.safeaccessnow.org/8_factor_analysis_on_cannabis.
As detailed in the HHS evaluation, the drug’s chemistry is not known and reproducible; there are no adequate safety studies; there are no adequate and well-controlled studies proving efficacy; the drug is not accepted by qualified experts; and the scientific evidence is not widely available...This five-element test, which the HHS and DEA have utilized in all such analyses for more than two decades, has been upheld by the Court of Appeals. ACT, 15 F.3d at 1135."

- Drug Enforcement Administration, August 12, 2016, Denial of Petition to Initiate Proceedings to Reschedule Marijuana

The above statement from the DEA defines that a drug has a "currently accepted medical use" if all of the following five elements have been satisfied:

1. the drug’s chemistry is known and reproducible;
2. there are adequate safety studies;
3. there are adequate and well-controlled studies proving efficacy;
4. the drug is accepted by qualified experts; and
5. the scientific evidence is widely available.

In the absence of a New Drug Application (NDA) or Abbreviated New Drug Application (ANDA) approval, DEA has established a “five-element test” for determining whether the drug has a currently accepted medical use in treatment in the United States. Under this test, a drug will be considered to have a currently accepted medical use only if all five elements are satisfied.

The following are intact and unaltered quotes from the FDA’s submitted report regarding cannabis and the five elements. While FDA maintains that cannabis does not meet the 5-element test, we think the evidence points to the contrary.

Element (1) The drug’s chemistry is known and reproducible.

Definition: “The substance’s chemistry must be scientifically established to permit it to be reproduced into dosages which can be standardized. The listing of the substance in a current edition of one of the official compendia, as defined by section 201(j) of the Food, Drug and Cosmetic Act, 21 U.S.C. 321(j), is sufficient generally to meet this requirement.” 57 Fed. Reg. 10499, 10506 (March 26, 1992).

DEA/FDA Evidence for Element 1

“Marijuana, as defined in the petition, includes all Cannabis strains. (For purposes of the CSA, marijuana includes all species of the genus Cannabis, including all strains therein). Based on the definition of marijuana in the petition, the chemistry of marijuana is not reproducible such that a standardized dose can be created. Chemical constituents including Δ9-THC and other cannabinoids vary significantly in marijuana samples derived from different strains (Appendino et al., 2011). As a result, there will be significant differences in safety, biological, pharmacological, and toxicological parameters amongst the various marijuana samples. Due to the variation of the chemical composition in marijuana samples, it is not possible to reproduce a standardized dose when considering all strains together. The HHS does advise that if a specific Cannabis
strain is cultivated and processed under controlled conditions, the plant chemistry may be consistent enough to derive reproducible and standardized doses."

Available Scientific Data for Element 1

There are two blatant issues with the DEA’s statement on element 1. First, “strains,” as listed by the DEA report, is not a technical or botanical term, it is a vague term and not appropriate. The terms that are appropriate to use are chemovar or chemotype (i.e., chemical variety). A chemovar is often defined as a particular species of plants, the chemical composition of which varies from the average because of different environmental growing conditions.

Second, the DEA report states above, “Due to the variation of the chemical composition in marijuana samples, it is not possible to reproduce a standardized dose when considering all strains together.” This statement is scientifically indefensible. No product or company is responsible for the scientific, nor manufacturing shortcomings of their predecessors. The fact that confiscated drug samples vary widely in potency across the nation, should bear no weight when discussing the products produced by licensed and pharmaceutical manufacturers. The DEA is implying that cannabis cannot be standardized based solely on data from their confiscated drug samples, which of course are not uniform in content. Illicit street cannabis varies widely in content but this has no relevance to developing standardized medical products and again it must be stressed that this is a scientifically indefensible statement from DEA.

The chemistry of cannabis is both known and reproducible. Complete cannabis monographs have been published, including one by the American Herbal Pharmacopoeia (AHP), setting clear, peer-reviewed guidance for standards of identity, analysis, quality control, administration, and dosing of cannabinoid-based medicine. The AHP monographs themselves are based on FDA and the United States Pharmacopeia (USP) guidelines for all botanical medicines. Additionally, standardized cannabis products are available from the NIDA-funded University of Mississippi marijuana farm for the FDA’s IND program – a program that has provided standardized cannabis cigarettes to the same participants, every month, for decades. Furthermore, the Research Triangle Institute (A NIDA-funded, DEA-compliant organization) has also released a quality control manual for cannabis, entitled The Analytical Chemistry of Cannabis – Quality Assessment, Assurance, and Regulation of Medicinal Marijuana and Cannabinoid Preparations.

Internationally, private companies have completed controlled clinical studies and successfully marketed standardized cannabis products (flowers, extracts, and nabiximols) in 27 countries. In the last decade, the U.S. has approved over 550 studies of marijuana or cannabis, 144 with dronabinol or tetrahydrocannabinol (THC), and 96 with pure CBD or a CBD-rich cannabis extract, according to clinicaltrials.gov.

While cannabis is dispensed in pharmacies throughout Europe and at state-regulated dispensaries in the U.S., many conform to standards that would qualify cannabis products as botanical medicines, based on existing safety guidelines from the FDA, AHP, and the U.S. Department of Agriculture (USDA). The quality and safety of medical cannabis and its derivatives are adequately addressed by extant national and local standards. These standards also address best-practices for cannabis operations – such as manufacturers, cultivation sites, laboratories, and dispensaries.

Botanical medicines and herbal products are regulated. A diverse set of local, national and international botanical safety standards are directly applied to medical cannabis and cannabis products. Several
countries have made significant regulatory efforts to enact the existing national and local level standards for cannabis production and distribution [57, 214, 543]. Various countries have published monographs (i.e., Czech Republic, Holland, U.S., and Canada) to specifically address quality control of cannabis, including methodology. Trade associations, internationally, have published best practices for cultivation, dispensing, manufacturing, and laboratory practices [544]. Furthermore, an abundance of national and international guidance documents provide quality control standards that address nearly every aspect of quality control and product safety for botanical substances, such as cannabis and its derivatives.

One hurdle to quality control of medical cannabis products is the existing control status of cannabis in countries such as the U.S., as well as controls under the conventions. National and international controls prevent adequate product testing in U.S. cannabis programs, and may therefore inadvertently jeopardize public health. To date, there has only been a single study that examined labeling accuracy (i.e., potency) of those cannabis products’ accessed through three state programs in the U.S. – A study that demonstrated that medical cannabis product labels can be inaccurate [545]. However, this U.S. study also demonstrated that the current national controls for cannabis serve to impair the ability to address public health concerns concerning medical cannabis and its derivatives.

It is difficult to address public health issues regarding medical cannabis products while it remains in Schedule I status. As the DEA tightly controls the release of analytical-quality standards for calibrating scientific instruments, cannabinoid compounds can only be purchased in necessary amounts if the operation has received a Schedule I license from the DEA. However, the DEA will not grant a Schedule I license to a state sponsored medical cannabis laboratory, because the laboratory would receive medical cannabis samples for analysis from non-DEA licensed sources (such as state licensed manufacturers, distribution centers, cultivation sites, patients, or doctors that recommend cannabis to patients). Therefore, the Schedule I status of Cannabis blocks most laboratories from determining the precise potency of a product. In contrast, testing for clinically relevant contaminants – such as heavy metals, bacteria, and fungus – can proceed without requiring DEA licensure, but this product safety testing is just as vulnerable to DEA or federal interference due to the scheduling status.

A potential normalizing factor for a medicine like cannabis in the U.S. could be for the USP to create a cannabis monograph; these standards could then be adopted to regulate cannabis as a medicinal product nationally [546]. However, such an action would grant pharmacists in the U.S. the ability to work with cannabis, which is forbidden by the DEA. Hence, the USP cannot create a cannabis monograph and still maintain compliance with the DEA. Presently, the USP defers to the AHP monograph as the current standard for cannabis products in the U.S. [7]. A recent meeting of the USP suggested that drafting of the document will not begin until cannabis is rescheduled – at least to a status that recognizes its medicinal use and outstanding safety profile. This lack of a permitted monograph (i.e., from the USP) is one of the issues that is directly responsible for the horrendous dereliction of responsibility in the industry to produce well-characterized, non-toxic products. A terrible public health threat has resulted from this policy. The best illustration is the pesticide contamination of legal cannabis in the Washington State market, that many patients now have no option but to utilize.

The standards issued by the AHP monograph and American Herbal Products Association (AHPA) have been adopted by 16 U.S. states to regulate product safety for their respective medical cannabis programs. Furthermore, AHPA – the trade association for the herbal products industry – has issued its medical cannabis manufacturing guidelines, completing its series of recommendations for state regulators in the areas of manufacturing, packaging and labeling, cultivation, dispensary operations, and laboratory
practices. Another example of medicinal cannabinoid production with outstanding quality assurances/controls exists in the Dutch program for medicinal cannabis. Produced under responsibility of the Ministry of Health, the program meets a number of quality requirements including, but not limited to: consistent strength on THC and composition of secondary cannabinoids, absence of microbiological contamination, pesticides and heavy metals, and humidity. Where there is a norm provided in the European Pharmacopoeia, this norm is followed [547].

The next sections below briefly discuss published resources and guidance documents being utilized by world governments to provide proper quality control and product safety for agricultural products and botanical medicines, including cannabis.

Good Agricultural and Collection Practices

The quality of raw material for botanical medicine can be safeguarded by using Good Agricultural and Collection Practices (GACP, aka GAP) to the extent possible in all aspect of growing, harvesting, and storage [548]. Specific guidelines for regulators regarding cannabis cultivation practices in the U.S. have been published by the AHPA. These standards include requirements for standard operating procedure documentation, employee safety training, security, and batch tracking [544]. Similarly, the American Herbal Pharmacopoeia has also released standards of quality control for cannabis cultivation.

In the Netherlands, Czech Republic, and Italy, medicinal cannabis must be produced under GMP-like conditions. All products must to be fully tested (by an independent laboratory) for cannabinoid content, absence of heavy metals, aflatoxins, pesticides (residue), and microbes to a level of <10 cfu. Standardization of cannabis and cannabis derivatives – according to the monograph of herbal medicines of the European Medicine Agency (EMA) – is mandatory and must be proven for each batch produced.

In Austria (AGES) and the UK (GW Pharmaceuticals, Ltd), cannabis is required to be produced under GAP, but any derivatives of this cannabis must be produced under GMP. Finished products must be standardized according to regular pharmaceutical products.

Good Manufacturing Practice for Cannabis

Many guidance documents are available for reference and use in the manufacturing of plant medicines and products, and any facility manufacturing products for human consumption should follow GMP. The World Health Organization has published guidelines on manufacturing botanical and herbal medicines, and the U.S. FDA has published guidance documents as well [549-552]. The AHPA manufacturing guidelines have a specific procedure for the recall of medical cannabis products, in the case of cannabis materials that do not meet “appropriate standards of identity, purity, strength, and composition and their freedom from contamination or adulteration.” The AHP cannabis monograph also sets limits for residues such as solvents and pesticides, heavy metals, bacteria, and fungi [214].

Good Laboratory Practices

Methods used to determine potency should be scientifically validated by laboratories for several criteria including, but not limited to: specificity, linearity, accuracy, precision, and ruggedness. The FDA and other organizations (i.e., AHPA, USP, and AHP) have provided extensive guidance documents that represent the current thinking on method validation and other aspects of good laboratory practices. There are further
international standards for analyzing medical cannabis products, which have been issued, for example, by the UN’s Office of Drugs and Crime in their document, entitled *Recommended Methods for the Identification and Analysis of cannabis and cannabis products* [553].

Below are a few examples of applicable guidance from a regulatory perspective, for analytical method validation for new methods, or methods not outlined in existing international and national regulatory documents:

- **American Herbal Pharmacopoeia Cannabis Inflorescence. Standards of Identity, Analysis, and Quality Control (2013).**

Quality control and quality standards for medicinal cannabis have been developed and adopted by 16 U.S. states and many countries, including Canada, Israel, the Netherlands, and the Czech Republic. Current standards are presently being appropriately applied or implemented through third party licensed certification bodies, for regulating cannabis and cannabis-related products for human consumption.

Both the AHP and AHPA documents point to Patient Focused Certification (PFC) for implementation of these standards. PFC has offices in Washington, DC and the Czech Republic. PFC is the only international program that can verify that a country, state, or region’s cannabis standards are being followed.² PFC conducts both physical (i.e. site or facility) and documentation audits of the operation, to generate an audit report that is submitted to a review board. PFC’s review board features experts that have served in regulatory and scientific roles in U.S. presidential administrations, at the USDA, in quality control laboratories, and related disciplines. PFC audited its first cannabis operations in the U.S. in 2013 and in Europe in 2015, and is now an option for regulators in every country, state, or region with medical cannabis access programs.

An undeniably successful public health outcome of product safety regulations has been demonstrated through numerous successful product recalls in Canada and the U.S. Recalls required the cooperation of government, manufacturers, and 3rd party certifying bodies, resulting in consumer protection [554-560].

To address public health concerns regarding the increasing availability of medical cannabis products, the scheduling status of cannabis needs to be thoughtfully and deliberately rescheduled (or descheduled), in order for producers, cultivators, manufacturers, laboratories, clinicians, researchers, and regulators to fully implement quality control standards for medical cannabis products.

**Element (2) There are adequate safety studies.**

Definition: “There must be adequate pharmacological and toxicological studies, done by all methods reasonably applicable, on the basis of which it could fairly and responsibly be concluded, by experts

² For more information about the PFC program, see: [www.patientfocusedcertification.org](http://www.patientfocusedcertification.org)
qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, that the substance is safe for treating a specific, recognized disorder.” 57 Fed. Reg. 10499, 10506 (March 26, 1992).

DEA/FDA Evidence for Element 2

“The HHS stated that there are no adequate safety studies on marijuana. As indicated in their evaluation of Element #1, the considerable variation in the chemistry of marijuana complicates the safety evaluation. The HHS concluded that marijuana does not satisfy Element #2 for having adequate safety studies such that medical and scientific experts may conclude that it is safe for treating a specific ailment.”

Available Scientific Data for Element 2

Cannabis products have been on the market for decades, and have shown clearly acceptable safety standards for use under medical supervision. Smoked, vaporized, or ingested cannabinoid medicine can deliver consistent amounts of active constituents, while toxic and/or lethal overdose of cannabis is not achievable and remains undocumented in either scientific or medical literature.

Sixteen states have adopted the national standards and guidance provided by the AHPA Cannabis Best Practices documents and the American Herbal Pharmacopoeia Cannabis Inflorescence Standards of Identity, Analysis, and Quality Control monograph. Federal standards are not available for cannabis and will not be produced by the USP while the plant is Schedule I, because the USP would thusly fall out of compliance with Drug Enforcement Administration (DEA) standards. Meanwhile, the FDA has approved several cannabis studies and a new IND program with a cannabis extract (marketed as Epidiolex), currently being administered to children in hospitals across the U.S with positive results.

While street marijuana arguably has a higher potential for abuse, standardized cannabis products accessed through a regulated program do not appear to have such high societal potential of abuse. Standardized cannabis-based medicines have been on the market for decades in the U.S. (Marinol and Nabilone), and whole-plant cannabis medicines are now available in 27 other countries (Bedrocan and nabiximols) [60]. Common sense dictates that self-administration of unstandardized, untested street drugs possesses a high potential for abuse, but the data addressing cannabis does not report, document, nor support the notion of significant abuse or divergence with standardized cannabis products. Cannabis should therefore be rescheduled because standardized preparations show very low potential for abuse and, therefore, possess minimal street value or resale value.

Based on current understanding of basic toxicity research – sedation, cytotoxicity, genotoxicity, etc. – cannabis and its components have a uniquely wide safety margin [36-39]. To date, there has never been a single well-documented case of human fatality attributable to an overdose of cannabis or its components, and no experimental or non-extrapolated LD<sub>50</sub> can be attributed to a toxic or lethal overdose of cannabis or a preparation thereof. No scientifically significant negative neuropsychological sequelae have yet been attributable to cannabis usage. The meta-analytical study of long-term cannabis use on neurocognitive functioning, results failed to find any substantial, systematic effect on users who were not concurrently intoxicated. Claims of brain damage and cerebral atrophy are not supported by current evidence. When controlling for pertinent variables such as age, gender, and history of alcohol use, research has not been able to show any association between the use of cannabis and changes in brain structures [59].
Short-term use of existing standardized medical cannabis and cannabis products appear to increase the risk of non-serious adverse events. Risks associated with long-term cannabis use are poorly characterized in published clinical trials and observational studies; however, the cognitive effects observed in long-term users do not appear to be permanent in nature [40]. With the exception of very limited studies on synthetic endocannabinoid system modulators, cannabis medicines do not appear to cause significant serious adverse events.

Arguably, some prior studies remain limited by a number of factors that need to be controlled in future investigations. Primarily, cannabis use and dosing needs to be confirmed in users with biological and chemical tests, as issues of dosing and patterns of use are confounding factors when not adjusted for.

Element (3) There are adequate and well-controlled studies proving efficacy.

“There must be adequate, well-controlled, well-designed, well-conducted and well-documented studies, including clinical investigations, by experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, on the basis of which it could be fairly and responsibly concluded by such experts that the substance will have the intended effect in treating a specific, recognized disorder.”


DEA/FDA Evidence for Element 3

“As indicated in the HHS’s review of marijuana (HHS, 2015), there are no adequate or well-controlled studies that prove marijuana’s efficacy. The FDA independently reviewed (FDA, 2015) publicly available clinical studies on marijuana published prior to February 2013 to determine if there were appropriate studies to determine marijuana’s efficacy (please refer to FDA, 2015 and HHS, 2015 for more details). After review, the FDA determined that out of the identified articles, including those identified through a search of bibliographic references and 566 abstracts located on PubMed, 11 studies met the a priori selection criteria, including placebo control and double-blinding. FDA and HHS critically reviewed each of the 11 studies to determine if the studies met accepted scientific standards. FDA and HHS concluded that these studies do not “currently prove efficacy of marijuana” for any therapeutic indication due to limitations in the study designs. The HHS indicated that these studies could be used as proof of concept studies, providing preliminary evidence on a proposed hypothesis involving a drug’s effect.”

Available Scientific Data for Element 3

To date, more than 30,000 modern peer-reviewed scientific articles on the chemistry and pharmacology of cannabis and the cannabinoids have been published. More than 1,500 articles investigating the body’s naturally-occurring endocannabinoids are published every year. In recent years, modern gold-standard placebo-controlled human trials have also been conducted.

At the time of writing this document, according to clinicaltrials.gov, there are hundreds of approved human research studies utilizing cannabinoids – A total of 144 are approved for THC, 96 are approved for CBD, and 559 are approved for cannabis. These studies are currently either completed, recruiting, approved, or in process. Due to the Schedule I status, however, medical cannabis preparations such as nabiximols and CBD-rich extracts are imported and cannot be manufactured in the U.S., even though they are licensed pharmaceutical products.
A 2009 review of clinical studies conducted over a 38-year period found that “nearly all of the 33 published controlled clinical trials conducted in the U.S. have shown significant and measurable benefits in subjects receiving the treatment,” [148]. The review’s authors made particular effort to note that cannabinoids have the capacity for analgesia through neuromodulation in ascending and descending pain pathways, neuroprotection, and by anti-inflammatory mechanisms – all of which indicate that the cannabinoids found in cannabis have applications in significantly managing chronic pain, muscle spasticity, cachexia, and other variously debilitating conditions.

There is a wealth of clinical information available on the uses of standardized medical cannabis products. The FDA has approved new drug applications for cannabis products. For example, a CBD-rich extract (marketed as Epidiolex) is an imported, purified cannabis extract that has been approved for clinical use in children and is currently in clinical practice across several institutions in the U.S. Additionally, an inhaled cannabis study has recently been approved for investigating therapeutic effects in PTSD.

Cannabis currently has accepted medical uses in 42 states and the District of Columbia and, appropriately, its products have mandatory testing requirements. A cannabis nabiximols (Sativex), a whole-plant ethanolic extract, has generated more than 9,000 patient/years of modern clinical data for the treatment of chronic pain [126].

Currently, cannabis is most often recommended as a complementary or adjunctive medicine. However, there exists a substantial consensus amongst experts in the relevant disciplines – including the American College of Physicians – that cannabis and cannabinoid-based medicines have undeniable therapeutic properties that could potentially treat a wide spectrum of serious and chronic illnesses.

Element (4) The drug is accepted by qualified experts.


DEA/FDA Evidence for Element 4

“The HHS concluded that there is currently no evidence of a consensus among qualified experts that marijuana is safe and effective in treating a specific and recognized disorder. The HHS indicated that medical practitioners who are not experts in evaluating drugs cannot be considered qualified experts (HHS, 2015; 57 FR 10499, 10505). Further, the HHS noted that the 2009 American Medical Association (AMA) report entitled, “Use of Cannabis for Medicinal Purposes” does not conclude that there is a currently accepted medical use for marijuana. HHS also pointed out that state-level “medical marijuana” laws do not provide evidence of such a consensus among qualified experts.”

Available Scientific Data for Element 4

In ASA’s 8-Factor analysis, under the section entitled “List of Medical and Scientific Organizations that have Issued Letter of Support for Medical Cannabis,” there are over 200 medical, scientific, health professionals, religious and community organizations who accept cannabis as a medicine and have issued letters in support of this medicine.
In April 2016, the Federation of State Medical Boards (FSMB) adopted “Model Guidelines for the Recommendation of Marijuana in Patient Care.”

The National Cancer Institute – one of 11 federal agencies under the National Institutes of Health – changed its website to include cannabis as a Complementary Alternative Medicine, with possible benefits for people living with cancer.

Statements from Qualified Experts and Medical Organizations

“Based on much evidence, from patients and doctors alike, on the superior effectiveness and safety of whole Cannabis (marijuana) compared to other medicines for many patients — suffering from the nausea associated with chemotherapy, the wasting syndrome of AIDS, and the symptoms of other illnesses … we hereby petition the Executive Branch and the Congress to facilitate and expedite the research necessary to determine whether this substance should be licensed for medical use by seriously ill persons.” - American Academy of Family Physicians

The American Medical Association “urges that marijuana’s status as a federal Schedule I substance be reviewed with the goal of facilitating the conduct of clinical research and development of cannabinoid-based medicines.”

The American College of Physicians “urges an evidence-based review of marijuana’s status as a Schedule I controlled substance to determine whether it should be reclassified to a different schedule.”

The American Public Health Association “adopted a resolution [...] which urged federal and state drugs laws to exclude Marijuana as a narcotic drug,” and “conclude[d] that Cannabis was wrongfully placed in Schedule I of Controlled Substances, depriving patients of its therapeutic potential.”

“Marijuana should be available for appropriate medicinal purposes, when such use is in accordance with state law, and that physicians who recommend and prescribe marijuana for medicinal purposes in states where such use is legal, should not be censured, harassed, prosecuted or otherwise penalized by the federal government.” - American Preventive Medical Association

“The Texas Medical Association supports (1) the physician’s right to discuss with his/her patients any and all possible treatment options related to the patients’ health and clinical care, including the use of marijuana, without the threat to the physician or patient of regulatory, disciplinary, or criminal sanctions; and (2) further well-controlled studies of the use of marijuana with seriously ill patients who may benefit from such alternative treatment.” - Texas Medical Association

The Rhode Island Medical Society has stated that “[T]here is sufficient evidence for us to support any physician-patient relationship that believes the use of marijuana will be beneficial to the patient.”

“The definitive review of scientific studies ... found medical benefits related to pain relief, control of nausea and vomiting, and appetite stimulation ... While there are a variety of ways of supplying marijuana for

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3 See www.medicalCannabis.com/about/health-care-professionals/supporting-organizations.
medical use, serious consideration should be given to the 1997 recommendation ... that the FDA reclassify marijuana from Schedule I and provide a consistent, safe supply.” - New York County Medical Society

“The American Medical Student Association strongly urges the United States Government ... to meet the treatment needs of currently ill Americans by restoring the Compassionate (Investigational New Drug) program for medical marijuana, and ... reschedule marijuana to Schedule II of the Controlled Substances Act, and ... end the medical prohibition against marijuana.” - American Medical Student Association

“The National Nurses Society on Addictions urges the federal government to remove marijuana from the Schedule I category immediately, and make it available for physicians to prescribe. NNSA urges the American Nurses’ Association and other health care professional organizations to support patient access to this medicine.” - National Nurses Society on Addictions

“The American Cancer Society supports the need for more scientific research on cannabinoids for cancer patients, and recognizes the need for better and more effective therapies that can overcome the often debilitating side effects of cancer and its treatment. The Society also believes that the classification of marijuana as a Schedule I controlled substance by the US Drug Enforcement Administration imposes numerous conditions on researchers and deters scientific study of cannabinoids. Federal officials should examine options consistent with federal law for enabling more scientific study on marijuana.” - American Cancer Society

“The Society supports the rights of people with MS to work with their MS health care providers to access marijuana for medical purposes in accordance with legal regulations in those states where such use has been approved. In addition, the Society supports advancing research to better understand the benefits and potential risks of marijuana and its derivatives as a treatment for MS.” - National Multiple Sclerosis Society

“The Epilepsy Foundation supports the rights of patients and families living with seizures and epilepsy to access physician directed care, including medical marijuana. Nothing should stand in the way of patients gaining access to potentially life-saving treatment. If a patient and their healthcare professionals feel that the potential benefits of medical marijuana for uncontrolled epilepsy outweigh the risks, then families need to have that legal option now — not in five years or ten years. For people living with severe uncontrolled epilepsy, time is not on their side. This is a very important, difficult, and personal decision that should be made by a patient and family working with their healthcare team.” - Epilepsy Foundation

“(T)he Leukemia & Lymphoma Society supports legislation to remove criminal and civil sanctions for the doctor-advised, medical use of marijuana by patients with serious physical medical conditions.” - Leukemia & Lymphoma Society

Medical schools are teaching required coursework which includes the endocannabinoid system and the therapeutic applications of cannabis. One example, theanswerpage.org, a Harvard University based CME, is educating physicians about the benefits of the medical uses of cannabis. This has led to the creation of
clinical cannabis certification for physicians; an educational program that is required for physicians to recommended medical cannabis in states such programs.⁵

Element (5) The scientific evidence is widely available.

“In the absence of NDA approval, information concerning the chemistry, pharmacology, toxicology, and effectiveness of the substance must be reported, published, or otherwise widely available, in sufficient detail to permit experts, qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, to fairly and responsibly conclude the substance is safe and effective for use in treating a specific, recognized disorder.” 57 Fed. Reg. 10499, 10506 (March 26, 1992).

DEA/FDA Evidence for Element 5

“The HHS concluded that the currently available data and information on marijuana is not sufficient to allow scientific scrutiny of the chemistry, pharmacology, toxicology, and effectiveness. In particular, scientific evidence demonstrating the chemistry of a specific Cannabis strain that could provide standardized and reproducible doses is not available.”

Available Scientific Data for Element 5

One of the criteria preventing the rescheduling of cannabis is the notion that information about this medicine is not widely available. There are tens of thousands of peer reviewed articles available through online portals, journal websites, and other resources for health professionals to access clinical information about cannabis, including but not limited to: Springer, Wiley, Pubmed, Public Libraries, medical and graduate school libraries, and websites of expert groups such as Americans for Safe Access, theAnswerpage.org, and the International Cannabis and Cannabinoid Institute.

The Internet has also revolutionized cannabinoid research and science, by allowing the generation of, and access to, large amounts of information that would have previously been nearly impossible to obtain. People across the globe can now access innumerable sources (a search for ‘cannabis research’ through web of science alone yields 120,000 separate articles) of previously unavailable scientific and clinical information.

Furthermore, the nabiximol Sativex is extracted from two fully-characterized, standardized cannabis chemovars, one of which is called Skunk No.1. It is odd, therefore, that the FDA would claim, “scientific evidence demonstrating the chemistry of a specific cannabis strain that could provide standardized and reproducible doses is not available.” While according to NIDA, DEA, FDA, and RTI, University of Mississippi researchers have grown several types of cannabis strains for decades, which are allegedly turned into standardized products for clinical research under the supervision and participation of NIDA, DEA, FDA and RTI⁶.

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⁵ For more information about Cannabis Care Certification, see http://cannabiscarecertification.org.

It is simply disingenuous for an organization to state that no standardized cannabis product exists, while simultaneously licensing both the production and distribution of such products.

VII. Evaluating the DEA’s Statement 3) Marijuana lacks accepted safety for use under medical supervision.

DEA’s Evidence Regarding Safety

“At present, there are no marijuana products approved by the U.S. Food and Drug Administration (FDA), nor is marijuana under a New Drug Application (NDA) evaluation at the FDA for any indication. The HHS evaluation states that marijuana does not have a currently accepted medical use in treatment in the United States or a currently accepted medical use with severe restrictions. At this time, the known risks of marijuana use have not been shown to be outweighed by specific benefits in well-controlled clinical trials that scientifically evaluate safety and efficacy.”

Available Scientific Data Regarding Safety

According to the CSA statute, as cited by the DEA in their evaluation:

“The CSA defines marijuana as the following:

All parts of the plant Cannabis Sativa L., whether growing or not; the seeds thereof; the resin extracted from any part of such plant; and every compound, manufacture, salt, derivative, mixture, or preparation of such plant, its seeds or resin. Such term does not include the mature stalks of such plant, fiber produced from such stalks, oil or cake made from the seeds of such plant, any other compound, manufacture, salt, derivative, mixture, or preparation of such mature stalks (except the resin extracted therefrom), fiber, oil, or cake, or the sterilized seed of such plant which is incapable of germination (21 U.S.C. 802(16)).”

This definition means that THC and CBD isolated from the plant are “resins”. Yet, the DEA states clearly under item 3:

“At present, there are no marijuana products approved by the U.S. Food and Drug Administration (FDA), nor is marijuana under a New Drug Application (NDA) evaluation at the FDA for any indication.”

This statement is incorrect. Marinol, an FDA approved form of pure THC, can now be generically made from THC isolated from cannabis plants, such as those from the University of Mississippi. Marinol started out as synthetic THC, but can now be plant-derived, however the DEA report is implying that cannot occur. No companies have admitted to pursuing this path, but it is an approved generic form of Marinol by the FDA. As defined by the CSA, both Epidiolex® and Sativex® are resinous cannabis extracts, and are presently undergoing clinical studies in the United States. According to GW Pharmaceutical’s website, Phase III trials got underway in 2015, utilizing the cannabis extract Sativex® with FDA approval. Both standardized cannabis extracts marketed by GW Pharmaceutical (Epidolex® and Sativex®) continue to be imported and are undergoing clinical study in the United States.

This arbitrary interpretation of the CSA is used to simultaneously and systematically prevent any discussion of the nearly 100 clinical trials completed with cannabis products while, at the same time,
THC, CBD, Sativex, and NIDA-generated cannabis cigarettes are considered “marijuana” if the user is prosecuted.

This is another example of how the DEA report seems to follow a more politically-driven agenda, rather than one of modern science and medicine. By attempting to redefine the CSA as meaning only whole plant cannabis, when it was intended to include derivatives and extracts thereof, the DEA is allowed to generate reports and statements that are not based on scientific research. The systematic use of biased methods to generate reports on scientific data leaves large swathes of modern cannabinoid research unheeded. Hence, the clinical references in the HHS 8-factor analysis consists of less than 1% of the discussed research. If the DEA report had included more than two clinical studies in their HHS 8-factor analysis, this would be a different conversation.

VIII. Conclusion

The goal of this comparative analysis is to objectively examine the data used in the DEA’s determination of their denial to allow a petition to reschedule cannabis, and to compare it to the prevailing scientific data on the medical value of cannabis. While we agree with portions of the DEA report – such as the lack of evidence to support either diversion or black market sales or the “gateway” hypothesis, we do not agree with either the process or the evidence upon which their denial was based. By applying politics and ideology, while excluding current scientific information, the DEA can only further the passage of truly inaccurate statements, which might then then be used to establish inaccurate laws regarding health and medicine.

Ideology and politics should never be allowed to eclipse the available scientific and clinical truth in matters of medicine or the health of our citizenry. This DEA report highlights how the use of engrained, historically inaccurate political beliefs to arbitrarily interpret the CSA has been exploited at the expense of public health. This stems from the fact that the DEA alone, inexplicably, has been allowed to determine how “medicine” is defined in this country, with little to no accountability.

Unfortunately, cannabis will never be rescheduled under these Catch-22-like circumstances. The CSA is arbitrarily used, on one hand, to exclude all medical research on derivatives of cannabis from their report...while, on the other hand, it is used to prosecute anyone in possession of those derivatives. Persistent misinterpretation of existing laws, coupled to lack of scientific knowledge, results in a very dangerous and socially destructive policy for a government enforcement agency.

The documents submitted in the report for the denial of the petitions are contradictory, and would appear to have little or no relevance to either contemporary cannabinoid science or medicine. Even so, as there were no clear negative public health implications relating to moving cannabis out of Schedule I status presented therein, it would appear that the DEA has chosen a disingenuous, overtly biased response to legitimate medicinal cannabinoid progress.

This type of response is responsible for the pitfalls of the current cannabis market by preventing the implementation of suitable controls. Such as addressing the pesticide contamination in the legal adult use
markets as a key case in point. Interference with product safety that results directly from ideological policies, is a dereliction of responsibility that supports a major public health threat.

Recommendations

Pass CARERS

Congress should pass The Compassionate Access, Research Expansion, and Respect for States (CARERS) Act (S. 683, H.R. 1538) as introduced in 2015 which, in addition to rescheduling cannabis and removing cannabidiol (CBD) from the schedule entirely, allows states to establish medical cannabis access laws and product safety regulations without interference by the federal government, and removes current obstacles to research. The CARERS Act is currently stalled in the Senate Judiciary Committee, with Chairman Chuck Grassley (IA) refusing to hold a vote.

Update Information on DEA Website and Educational Materials

We also recommend that the DEA update the following on their website and in education materials provided online. The updates should be made to reflect the information from the current DEA report.

1. DEA statements regarding adverse health effects related to cannabis

- “[According to an Australian study,] there is now conclusive evidence that smoking cannabis hastens the appearance of psychotic illnesses by up to three years.”

- “Marijuana’s effects on these abilities may last a long time or even be permanent.”

Requested change to reflect current information from the DEA’s report:

On page 12, the DEA report states, “Abundant scientific data are available on the neurochemistry, toxicology, and pharmacology of marijuana.”

On page 20, the DEA report states, “cannabis-associated cognitive deficits are reversible and related to recent cannabis exposure, rather than irreversible and related to lifetime use.”

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8 And from “DrugFacts: Marijuana.” Link available through DEA website/a DEA resource site: https://www.drugabuse.gov/publications/drugfacts/marijuana

9 Link to paragraph: https://www.federalregister.gov/articles/2016/08/12/2016-17954/denial-of-petition-to-initiate-proceedings-to-reschedule-marijuana#p-81

10 Link to paragraph: https://www.federalregister.gov/articles/2016/08/12/2016-17954/denial-of-petition-to-initiate-proceedings-to-reschedule-marijuana#p-123
On page 22, the DEA report states, “At present, the available data do not suggest a causative link between marijuana use and the development of psychosis.”

2. Statements from DEA regarding the “gateway theory”

- “Teens who experiment with marijuana may be making themselves more vulnerable to heroin addiction later in life, if the findings from experiments with rats are any indication. Cannabis has very long-term, enduring effects on the brain…” (pg. 37)

- “Marijuana use in early adolescence is particularly ominous. Adults who were early marijuana users were found to be five times more likely to become dependent on any drug, eight times more likely to use cocaine in the future, and fifteen times more likely to use heroin later in life.” (pg. 38)

- “Marijuana is a frequent precursor to the use of more dangerous drugs and signals a significantly enhanced likelihood of drug problems in adult life.” (pg. 37)

Below are the requested changes to reflect the current information from the DEA report:

On page 43, the DEA report states, “Overall, research does not support a direct causal relationship between regular marijuana use and other illicit drug use.”

On page 44, the DEA report states, “the gateway hypothesis only addresses the order of drug use initiation, the gateway hypothesis does not specify any mechanistic connections between drug "stages" following exposure to marijuana and does not extend to the risks for addiction.”

On page 162, the DEA report states, “The HHS reviewed the clinical studies evaluating the gateway hypothesis in marijuana and found them to be limited.” The DEA goes on to say, “The HHS cited several studies where marijuana use did not lead to other illicit drug use.”

On page 162, the DEA report states, “Based on these studies among others, the HHS concluded that although many individuals with a drug abuse disorder may have used marijuana as one of their first illicit drug use experiences, the majority of these individuals did not transition into the use of other illicit drugs.”

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drugs, this does not mean that individuals initiated with marijuana inherently will go on to become regular users of other illicit drugs.”

Over 40 years ago the “gateway” hypothesis of cannabis was proposed. The report concludes predictably, that the gateway theory of cannabis is not supported by the evidence. We agree that the hypothesis attempted but failed to predict that cannabis use leads to the addiction of other drugs.

3. Statements from the DEA regarding cannabis and cancer

“Marijuana smoking has been implicated as a causative factor in tumors of the head and neck and of the lung.” (pg.34)

“Marijuana takes the risks of tobacco and raises them. Marijuana smoke contains more than 400 chemicals and increases the risk of serious health consequences, including lung damage.” (pg 36)

Below are the requested changes to reflect the current information from the DEA report:

“However, in a large clinical study with 1,650 subjects, no positive correlation was found between marijuana use and lung cancer (Tashkin et al., 2006). This finding held true regardless of the extent of marijuana use when both tobacco use and other potential confounding factors were controlled. The HHS concluded that new evidence suggests that the effects of smoking marijuana on respiratory function and cancer are different from the effects of smoking tobacco (Lee and Hancox, 2011).”

“The DEA further notes the publication of recent review articles critically evaluating the association between marijuana and lung cancer. Most of the reviews agree that the association is weak or inconsistent (Huang et al., 2015; Zhang et al., 2015; Gates et al., 2014; Hall and Degenhardt, 2014). Huang et al. (2015) identified and reviewed six studies evaluating the association between marijuana use and lung cancer and the authors concluded that an association is not supported most likely due to the small amounts of marijuana smoked in comparison to tobacco. Zhang et al. (2015) examined six case control studies from the US, UK, New Zealand, and Canada within the International Lung Cancer Consortium and found that there was a weak association between smoking marijuana and lung cancer in individuals who never smoked tobacco, but precision of the association was low at high marijuana exposure levels...overall association is weak between marijuana use and lung cancer especially when controlling for tobacco use.”

16 Link to paragraph: https://www.federalregister.gov/articles/2016/08/12/2016-17954/denial-of-petition-to-initiate-proceedings-to-reschedule-marijuana#p-959


18 Link to paragraph: https://www.federalregister.gov/articles/2016/08/12/2016-17954/denial-of-petition-to-initiate-proceedings-to-reschedule-marijuana#p-860

Enclosure C: “IQA Request for Correction of Information Disseminated by DEA Regarding Marijuana (Cannabis)”
RE: DEA’s “The Dangers and Consequences of Marijuana Abuse” and “Drugs of Abuse"

REQUEST FOR CORRECTION OF INFORMATION DISSEMINATED BY DEA REGARDING MARIJUANA (CANNABIS)

INFORMATION QUALITY ACT REQUEST FOR CORRECTION

DATE: DECEMBER 5, 2016

SUBMITTED BY: AMERICANS FOR SAFE ACCESS FOUNDATION

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Request for Correction Pursuant to the DOJ’s Information Quality Guidelines

ISSUE

The Drug Enforcement Agency’s (“DEA”) website (dea.gov) contains inaccurate statements that do not meet the standards of quality required by the Department of Justice (“DOJ”) and Office of Management and Budget (“OMB”) under the Information Quality Act (“IQA”). In particular, the DEA continues to disseminate certain statements about the health risks of medical cannabis use that have been incontrovertibly refuted by the DEA itself in its recent “Denial of Petition to Initiate Proceedings to Reschedule Marijuana” (the “DPR”), issued August 12, 2016. In fact, the DEA’s recent statements confirm scientific facts about medical cannabis that have long been accepted by a majority of the scientific community. Accordingly, Americans for Safe Access (“ASA”) requests that the DEA correct or remove from the dea.gov website the inaccurate statements described below in Section II (a)-(d). At minimum, the corrections should comport with the DEA’s statements in the DPR.

PETITIONER

Americans for Safe Access Foundation (“ASA”), a non-profit advocacy group that represents the interests of medical cannabis patients and caregivers, files this Request for Correction of inaccurate information, disseminated by the DEA, relating to certain purported health effects of cannabis use. ASA brings this action on behalf of patients, their families, medical providers, scientists, and veterans across the United States who are deeply and immediately affected by the DEA’s controverted statements. The seriously ill patients that ASA represents suffer variably from cancer and the side-effects of its treatments, multiple sclerosis, HIV/AIDS, spinal injury, chronic seizures, and other medical conditions that produce chronic pain, nausea, loss of appetite and spasticity. Many of these persons who use medical cannabis to treat these symptoms do not respond to conventional treatment options, cannot tolerate certain medications, or have serious health needs not treatable by pharmaceutical medicine. If patients, who currently have access to medical cannabis under state programs, were to lose access, they would be irreparably harmed. And, patients in need of medical cannabis, but without access, are already being seriously harmed.

The DEA’s misinformation informs the opinions and actions of Congress. As a result of this misinformation, there is a substantial risk that Congress will fail to reauthorize the Rohrabacher-Farr Medical Cannabis Amendment (“the Amendment”) (discussed below)—failure to reauthorize would encourage the DOJ to dismantle state medical cannabis systems and prosecute medical cannabis users and providers throughout the nation. Furthermore, the CARERS Act (discussed below) has yet to receive a vote, due in part to the dissemination of DEA misinformation. ASA’s members reside in every United States Congressional District—they have been negatively affected by Congress’ continuing refusal to hold a vote on the CARERS Act, and they will be negatively affected by Congress’ failure to reauthorize the Amendment.
RELIEF REQUESTED

ASA requests corrections to DEA disseminated information as described in Section II (a)-(d).


FACTUAL BACKGROUND

For years, the DEA has published scientifically inaccurate information about the health effects of medical cannabis, directly influencing the action – and inaction – of Congress. The Compassionate Access, Research Expansion, and Respect States Act (“CARERS”) is a prime example. Three senators introduced CARERS in March 2015 and an identical bill was introduced in the House later that month. The legislation seeks to protect patient access to medical cannabis in states with existing medical cannabis programs from federal intervention, thereby codifying the collection of DOJ memoranda that currently govern federal policy of medical cannabis enforcement against the states.1 Notably, CARERS would also reschedule cannabis from Schedule I to Schedule II status, thus easing current restrictions on medical and scientific research of the substance.2 Furthermore, the Act would exclude cannabidiols (cannabis derivatives with less than 0.3% THC content) from the definition of cannabis entirely,3 permit businesses acting in conformity with state cannabis laws to access banking services,4 mandate the issuance of additional licenses to cultivate cannabis for FDA approved research,5 and grant VA dependent veterans access to state medical cannabis programs.6

Since the CARERS Act was introduced in March of 2015, it has received additional support in the Senate and House, but it seems unlikely that there will be a formal vote on the bill before the new administration commences in January 2017. Proponents of the Act believe that it is less likely to pass once the new Congress is sworn in and the new administration takes control. The House bill is sitting in four committees and subcommittees; the Senate analog sits in the Senate Judiciary Committee.7 Committee leadership in both chambers have denied the respective bills a

1 https://www.congress.gov/bill/114th-congress/senate-bill/683/text, at Section 2 (The Controlled Substances Act, “shall not apply to any person acting in compliance with State law relating to the production, possession, distribution, dispensation, administration, laboratory testing, or delivery of medical marihuana.”).
2 Id. at Section 3.
3 Id. at Section 4.
4 Id. at Section 6.
5 Id. at Section 7.
6 Id. at Section 8.
7 H.R. 1538 has been assigned to the (1) House Energy and Commerce Subcommittee on Health; (2) House Judiciary Subcommittee on Crime, Terrorism, Homeland Security, and Investigations; (3) House Financial Services
hearing. House leadership has been hostile to medical cannabis legislation with the surreptitious removal of a medical cannabis amendment to the Military Construction and Veterans Affairs Appropriations Act in June 2016, after being approved by votes from the Senate Appropriations Committee and House Floor. Changes in the Senate Judiciary Committee for the 115th Congress include the ascension of CARERS opponent Dianne Feinstein to Ranking Member of the Senate Judiciary Committee, while fellow CARERS opponent Chuck Grassley remains committee chair. Representatives and senators that have commented unfavorably on the bills have cited, implicitly and explicitly, the inaccurate DEA information on the supposed dangers of medical cannabis.

The CARERS Act is not the only attempt to protect medical cannabis patients. In 2014, Congress included the Amendment in the Commerce, Justice, and Science Appropriations Bill. The Amendment prevents the DOJ from spending federal funds to inhibit the implementation of state medical cannabis laws. Without the Amendment, the DOJ could restrict or eliminate patients’ access to medicine legally available to them under their states’ laws. The Amendment was reauthorized in 2015, and a functionally identical amendment was introduced in April 2016 as part of the 2017 Commerce, Justice, Science, and Related Appropriations Act. While the Amendment was approved by the Senate Appropriations Committee in May 2016 by a vote of 21-8, it has yet to receive a vote in the House for Fiscal Year 2017. Congress’ failure to pass the CARERS Act or to reauthorize the Amendment, could destroy patients’ access to vital medicine in states where medical cannabis is currently legal and available. Also, even if patients are not the direct target of federal enforcement actions, they can be caught in harm’s way during a raid. And, even if they are not present at the raid, losing access to their dispensary means a disruption in their supply of medicine that may not be restored through access to another dispensing facility. As a result, patients are terrified of losing access to essential medicine and providers live in constant fear of federal criminal prosecution.

Elected representatives in Congress are using inaccurate DEA published information to inform their votes on the CARERS Act and the Amendment. In the Denial of Petition to Initiate Proceedings to Reschedule Marijuana (“DPR”), the DEA directly contradicted a multitude of previously disseminated statements, which are currently available on the dea.gov website. The following sections detail (1) the inaccurate information and requested changes, (2) how the inaccurate information adversely impacts affected persons (i.e. ASA’s members), and (3) how the requested changes will benefit affected persons.

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ARGUMENT

I. LEGAL STANDARDS

Passed as an amendment to the Paperwork Reduction Act, 44 U.S.C. § 3501, the Information Quality Act requires administrative agencies to devise guidelines to ensure the “quality, objectivity, utility, and integrity of information” they disseminate and to “[e]stablish administrative mechanisms allowing affected persons to seek and obtain correction of information maintained and disseminated by the agency that does not comply with the guidelines.”12

The DOJ Guidelines quote the OMB Guidelines, which define “quality” as “an encompassing term comprising utility, objectivity, and integrity.”13 The term “utility” refers to the “usefulness of the information to be disseminated to the public,” achieved by “continuously monitoring information needs and developing new information sources or by revising existing methods, models, and information products where appropriate.”14 “Objectivity” assures that, as a “matter of substance and presentation,” disseminated information is “accurate, reliable, and unbiased.”15 In short, the agency is required, prior to dissemination of information, to ensure “compliance with the OMB and DOJ Guidelines” and “that the information fulfills the intentions stated and that the conclusions are consistent with the evidence.”16

Additionally, where the agency is responsible for disseminating “influential” scientific or statistical information, the DEA has heightened responsibilities under the Act to ensure that such disseminated information is reproducible and accurate. Indeed, the accuracy of this information is “significant due to the critical nature of these decisions.”17 “Influential information” is that which is “expected to have a genuinely clear and substantial impact at the national level, or on major public and private policy decisions as they relate to federal justice issues.”18 To determine that there is a clear and substantial impact, the agency must “have greater certainty than would be the case for many ordinary factual determinations that the impact is occurring or will occur.”19

Furthermore, the DOJ Guidelines require that statistical information disseminated by the agency be based on the promotion of sound statistical methods. “Sound” scientific methods “produce information (data and analysis results) that is accurate, reliable, and unbiased. Guidelines to promote sound statistical methods would cover the planning of statistical data

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14 Id. at “Utility.”
15 Id. at “Objectivity.”
16 Supra Note 11.
17 Id. at “For Influential Information.”
18 Id.
19 Id.
systems, the collection of statistical data, and the processing of statistical data (including analysis).”

II. THE DEA’S STATEMENTS ABOUT MEDICAL CANNABIS IN THE DPR DIRECTLY CONTRADICT STATEMENTS CURRENTLY BEING MADE BY THE DEA ELSEWHERE

Each of the DEA’s statements about medical cannabis set forth below have been directly refuted by the DEA’s own statements in the DPR. Given its own recent contradiction of these statements, the DEA cannot credibly maintain that they are “accurate,” “reliable,” “unbiased,” or “reproducible.” Moreover, the statements are based on scientifically inaccurate data and result in denying patients access to vital medicine. Accordingly, each of these statements violate the IQA’s utility and objectivity standards and should be corrected.

ASA requests that the DEA replace the following scientifically inaccurate statements – currently disseminated by the DEA on its website in publications entitled “The Dangers and Consequences of Marijuana Abuse” and “Drugs of Abuse” – with the DEA’s own scientifically accurate statements made in the DPR.

a. The DEA’s statements in the DPR directly contradict its scientifically inaccurate statements about cannabis’ alleged capacity to induce psychosis

The DEA is disseminating information about cannabis use and psychosis that lacks both objectivity and utility. At the time the inaccurate statements were originally made, they may have been supported by some evidence. But, the DEA recently admitted that the only association between cannabis use and psychotic illness is in cannabis’ potential to increase the risk for psychosis among individuals already predisposed to develop a psychotic disorder. Thus, in light of numerous statements made by the DEA in the DPR, information suggesting that cannabis use causes psychosis no longer satisfies the objectivity and utility standards required by the DOJ and OMB Guidelines.

The DEA is making the following inaccurate statements regarding cannabis’ alleged capacity to induce psychosis and psychotic illness:

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20 Id. at “Sound Statistical Methods.”
23 Supra Note 9, at 53696-97 (citing Andreasson et al., Curr Med Chem. 18(7): 1085-99 (2011); Schimmelmann et al., Schizophr Res 129(1): 52-56 (2011); Schifffman et al., Psychiatry Res.134(1): 37-42 (2005); Pelayo et al., Curr Pharm Des 18(32): 5024-35 (2012); Degenhardt et al., Drug and Alcohol Depend 71(1): 37-48 (2003)) (“The authors concluded that marijuana use increased the risk for psychosis only among individuals predisposed to develop the disorder […] Additionally, the conclusion that the impact of marijuana may manifest only in individuals likely to develop psychotic disorders has been shown in many other studies.”) (emphasis added).
1. “According to an Australian study, there is now conclusive evidence that smoking cannabis hastens the appearance of psychotic illnesses by up to three years […] it makes it very clear that cannabis is playing a significant role in psychosis.”

2. “Evidence of the damage to mental health caused by cannabis use—from loss of concentration to paranoia, aggressiveness and outright psychosis—is mounting and cannot be ignored.”

3. “Marijuana use can worsen depression and lead to more serious mental illness such as schizophrenia, anxiety, and even suicide.”

4. “[T]eenage cannabis users are more likely to suffer psychotic symptoms and have a greater risk of developing schizophrenia in later life.”

5. “Dr. John MacLeod, a prominent British psychiatrist states: ‘If you assume such a link (to schizophrenia with cannabis) then the number of cases of schizophrenia will increase significantly in line with increased use of the drug.’ He predicts that cannabis use may account for a quarter of all new cases of schizophrenia in three years’ time.”

6. “Compared with those who had never used cannabis, young adults who had six or more years since first use of cannabis were twice as likely to develop a non-affective psychosis (such as schizophrenia) […] They were also four times as likely to have high scores in clinical tests of delusion.”

7. “Researchers have also found an association between marijuana use and increased risk of depression, an increased risk and earlier onset of schizophrenia, and other psychotic disorders, especially for teens that have a genetic predisposition.”

The following statements, taken directly from the DPR, contradict the aforementioned statements. Thus, in order to maintain the objectivity and utility standards, ASA requests that the DEA replace the aforementioned inaccurate statements with the following accurate statements, or in the alternative, delete the inaccurate statements in their entirety:

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24 Supra Note 21, at 12 (quotations omitted).
25 Id. at 8.
26 Id. at 10.
27 Id.
28 Id. at 12.
29 Id.
30 Supra Note 22, at 73.
1. “At present, the available data do not suggest a causative link between marijuana use and the development of psychosis.”

2. “Numerous large, longitudinal studies show that subjects who used marijuana do not have a greater incidence of psychotic diagnoses compared to those who do not use marijuana.”

3. “[M]arijuana per se does not appear to induce schizophrenia in the majority of individuals who have tried or continue to use marijuana. However, in individuals with a genetic vulnerability for psychosis, marijuana use may influence the development of psychosis.”

b. The DEA’s statements in the DPR directly contradict its scientifically inaccurate statements about cannabis’ alleged capacity to induce lung cancer and cause damage comparable to that caused by tobacco use

The DEA is disseminating information about cannabis use and lung cancer that lacks both objectivity and utility. At the time the inaccurate statements were originally made, they may have been supported by some evidence. But, the DEA recently admitted that the worst possible respiratory effects associated with long-term cannabis use are “chronic cough, increased sputum, as well as increased frequency of chronic bronchitis and pharyngitis.” Thus, in light of numerous statements made by the DEA in the DPR, information suggesting that cannabis use causes lung cancer and tobacco-like respiratory damage no longer satisfies the objectivity and utility standards required by the DOJ and OMB Guidelines.

The DEA is making the following inaccurate statements regarding cannabis’s alleged capacity to induce lung cancer and cause damage comparable to that caused by tobacco use:

1. “Marijuana smoking has been implicated as a causative factor in tumors of the head and neck and of the lung.”

2. “Marijuana takes the risks of tobacco and raises them. Marijuana smoke contains more than 400 chemicals and increases the risk of serious health consequences, including lung damage.”

31 Supra Note 11, at 53696.

32 Id.

33 Id. at 53696-97.

34 Id. at 53751 (citing HHS 2015; Adams and Martin, Addiction 91(11): 1585-1614 (1996); Hollister, Pharmacological Rev 38, 1-20 (1986)).

35 Supra Note 21, at 16.

36 Id.
3. “A study from New Zealand reports that cannabis smoking may cause five percent of lung cancer cases in that country.”  

4. “According to researchers at the Tale School of Medicine, long-term exposure to marijuana smoke is linked to many of the same kinds of health problems as those experienced by long-term cigarette smokers.”

5. “Smoking marijuana can cause changes in lung tissue that may promote cancer growth, according to a review of decades of research on marijuana smoking and lung cancer.”

6. “Nevertheless, researchers indicate […] that smoking pot could indeed boost lung cancer risk.”

7. “The Foundation warned that smoking one cannabis cigarette increase the chances of developing lung cancer by as much as an entire packet of 20 cigarettes.”

8. “Like tobacco smokers, marijuana smokers experience serious health problems such as bronchitis, emphysema, and bronchial asthma. Extended use may cause suppression of the immune system. Because marijuana contains toxins and carcinogens, marijuana smokers increase their risk of cancer of the head, neck, lungs, and respiratory tract.”

The following statements, taken directly from the DPR, contradict the aforementioned statements. Thus, in order to maintain the objectivity and utility standards, ASA requests that the DEA replace the aforementioned inaccurate statements with the following accurate statements, or in the alternative, delete the inaccurate statements in their entirety:

1. “The DEA further notes the publication of recent review articles critically evaluating the association between marijuana and lung cancer. Most of the reviews agree that the association is weak or inconsistent.”

2. “The HHS concluded that new evidence suggests that the effects of smoking marijuana on respiratory function and cancer are different from the effects of smoking tobacco.”

37 Id. at 14.

38 Id. at 15.

39 Id.

40 Id.

41 Id. at 18.

42 Supra Note 22, at 73.

43 Supra Note 11, at 53751 (internal citation omitted).

44 Id. (internal citation omitted).
3. “[O]verall association is weak between marijuana use and lung cancer especially when controlling for tobacco use.” 45

4. “[I]n a large clinical study with 1,650 subjects, no positive correlation was found between marijuana use and lung cancer. This finding held true regardless of the extent of marijuana use when both tobacco use and other potential confounding factors were controlled.” 46

5. “The authors reported that occasional use of marijuana (7 joint-years for lifetime or 1 joint/day for 7 years or 1 joint/week for 49 years) does not adversely affect pulmonary function.” 47

c. The DEA’s statements in the DPR directly contradict its scientifically inaccurate statements regarding the “gateway theory” and cannabis

The DEA is disseminating information about cannabis use and the gateway theory that lacks both objectivity and utility. The “gateway theory” – that cannabis use causes users to abuse more serious drugs in the future – was never supported by epidemiological scientific evidence. 48 And, in light of numerous statements made by the DEA in the DPR, information suggesting that cannabis is a “gateway drug,” no longer satisfies the objectivity and utility standards required by the DOJ and OMB Guidelines.

The DEA is making the following inaccurate statements regarding cannabis and the gateway theory:

1. “Legalization of marijuana, no matter how it begins, will come at the expense of our children and public safety. It will create dependency and treatment issues, and open the door to use of other drugs, impaired health, delinquent behavior, and drugged drivers.” 49

2. “Teens who experiment with marijuana may be making themselves more vulnerable to heroin addiction later in life, if the findings from experiments with rats are any indication.” 50

3. “Marijuana is a frequent precursor to the use of more dangerous drugs and signals a significantly enhanced likelihood of drug problems in adult life.” 51

45 Id. (internal citation omitted).
46 Id. (internal citation omitted).
47 Id.
48 Id. at 53705.
49 Supra Note 21, at 6.
50 Id. at 22.
51 Id.
4. “[T]eens who used marijuana at least once in the last month are 13 times likelier than other teens to use another drug like cocaine, heroin, or methamphetamine and almost 26 times likelier than those teens who have never used marijuana to use another drug.”

5. “Marijuana use in early adolescence is particularly ominous. Adults who were early marijuana users were found to be five times more likely to become dependent on any drug, eight times more likely to use cocaine in the future, and fifteen times more likely to use heroin later in life.”

6. “Healthcare workers, legal counsel, police and judges indicate that marijuana is a typical precursor to methamphetamine.”

7. “Teens past month heavy marijuana users [sic] are significantly more likely than teens that have not used marijuana in the past to: use cocaine/crack (30 times more likely); use Ecstasy (20 times more likely); abuse prescription pain relievers (15 times more likely); and abuse over the counter medications (14 times more likely).”

The following statements, taken directly from the DPR, contradict the aforementioned statements. Thus, in order to maintain the objectivity and utility standards, ASA requests that the DEA replace the aforementioned inaccurate statements with the following accurate statements, or in the alternative, delete the inaccurate statements in their entirety:

1. “Overall, research does not support a direct causal relationship between regular marijuana use and other illicit drug use.”

2. “The HHS cited several studies where marijuana use did not lead to other illicit drug use. Two separate longitudinal studies with adolescents using marijuana did not demonstrate an association with use of other illicit drugs.”

3. “Little evidence supports the hypothesis that initiation of marijuana use leads to an abuse disorder with other illicit substances. For example, one longitudinal study of 708 adolescents demonstrated that early onset marijuana use did not lead to problematic drug use.”

4. “Although many individuals with a drug abuse disorder may have used marijuana as one of their first illicit drugs, this fact does not correctly lead to the reverse inference

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52 Id.
53 Id. at 22-23.
54 Id. at 23.
55 Id.
56 Supra Note 11, at 53705.
57 Id. (internal citations omitted).
58 Id.
that most individuals who used marijuana will inherently go on to try or become regular users of other illicit drugs.”

5. “[B]ecause the gateway hypothesis only addresses the order of drug use initiation, the gateway hypothesis does not specify any mechanistic connection between drug ‘stages’ following exposure to marijuana and does not extend to the risks for addiction.”

6. “Degenhardt et al. (2009) examined the development of drug dependence and found an association that did not support the gateway hypothesis. Specifically, drug dependence was significantly associated with the use of other illicit drugs prior to marijuana use.”

d. The DEA’s statements in the DPR directly contradict its scientifically inaccurate statements regarding the alleged permanency of cannabis-associated cognitive deficits

The DEA is disseminating information about the alleged permanency of cannabis-associated cognitive deficits that lacks both objectivity and utility. At the time the inaccurate statements were originally made, they may have been supported by some evidence. But, the DEA recently noted that cannabis associated cognitive deficits are not apparent in those who initiate use after the age of 15 years. Thus, in light of numerous statements made by the DEA in the DPR, information suggesting that cannabis use causes permanent cognitive deficits no longer satisfies the objectivity and utility standards required by the DOJ and OMB Guidelines.

The DEA is making the following inaccurate statements regarding the alleged permanency of cannabis-associated cognitive deficits:


2. “Memory, speed of thinking, and other cognitive abilities get worse over time with marijuana use.”

59 Id.
60 Id.
61 Id.
62 Id. at 53695 (citing Fontes, et al., Br. J Psychiatry 198(6): 442-7 (2011)) (“Individuals with a diagnosis of marijuana misuse or dependence who were seeking treatment for substance use, who initiated marijuana use before the age of 15 years, showed deficits in performance on tasks assessing sustained attention, impulse control, and general executive functioning compared to non-using controls. These deficits were not seen in individuals who initiated marijuana use after the age of 15 years.”) (emphasis added).
63 Supra Note 21, at 8.
64 Id. at 11.
3. “This study is the first to show that long-term cannabis use can adversely affect all users, not just those in the high-risk categories such as the young, or those susceptible to mental illness, as previously thought.”\textsuperscript{65}

The following statements, taken directly from the DPR, contradict the aforementioned statements. Thus, in order to maintain the objectivity and utility standards, ASA requests that the DEA replace the aforementioned inaccurate statements with the following accurate statements, or in the alternative, delete the inaccurate statements in their entirety:

1. “[T]he adult-onset chronic marijuana users showed no significant changes in IQ compared to pre-exposure levels whether they were current users or abstinent for at least 1 year.”\textsuperscript{66}

2. “[C]annabis-associated cognitive deficits are reversible and related to recent cannabis exposure, rather than irreversible and related to cumulative lifetime use.”\textsuperscript{67}

3. “The effects of chronic marijuana use do not seem to persist after more than 1 to 3 months of abstinence. After 3 months of abstinence, any deficits observed in IQ, immediate memory, delayed memory, and information processing speeds following heavy marijuana use compared to pre-drug use scores were no longer apparent.”\textsuperscript{68}

4. “Similarly, following abstinence for a year or more, both light and heavy adult marijuana users did not show deficits on score of verbal memory compared to non-using controls.”\textsuperscript{69}

5. “According to a recent meta-analysis looking at non-acute and long-lasting effect of marijuana use on neurocognitive performance, any deficits seen within the first month following abstinence are generally not present after about 1 month of abstinence.”\textsuperscript{70}

III. THE INACCURATE DEA INFORMATION LACKS BOTH OBJECTIVITY AND UTILITY MAKING IT THE PROPER SUBJECT OF A REQUEST FOR CORRECTION UNDER THE IQA

The overwhelming majority of the objective scientific studies – including studies cited by the DEA in the DPR\textsuperscript{71} – disprove the inaccurate DEA statements described in Section II (a)-(d).

\textsuperscript{65} Id.
\textsuperscript{66} Supra Note 11, at 53695.
\textsuperscript{67} Id.
\textsuperscript{68} Id. (internal citation omitted).
\textsuperscript{69} Id.
\textsuperscript{70} Id.
\textsuperscript{71} Minozzi et al., \textit{Drug Alcohol Rev} 29(3): 304-317 (2010); Fergusson et al., \textit{Addiction} 100(3): 354-366 (2005); Kuepper et al., \textit{Psychol Med} 41(10): 2121-2129 (2011); Van Os et al., \textit{Am J Epidemiol} 156(4): 319-327 (2002); American Medical Association, \textit{AMA Policy: Medical Marijuana} H-95-952 (2009); Degenhardt et al., \textit{Drug Alcohol Depend} 71(1): 37-48 (2003); Department of Health and Human Services, \textit{Basis for the recommendation for maintaining marijuana in Schedule I of the Controlled Substances Act} (2015); Huang et al., \textit{Cancer Epidemiol
Because the DEA itself made statements in the DPR that directly contradict information in “The Dangers and Consequences of Marijuana Abuse” and “Drugs of Abuse,” it is undeniable that the DEA information at issue lacks utility and objectivity.72

The DEA information lacks utility. Utility requires that information disseminated by the DEA be useful to the public. Information that is admittedly incorrect – such as the DEA’s statements regarding the gateway hypothesis and that marijuana causes psychosis, lung cancer and permanent cognitive deficits – inherently lacks usefulness. While there may be some demonstrable negative effects associated with cannabis abuse, the presentation of scientifically unfounded information alongside scientifically accurate information obscures and diminishes the utility of the accurate information and can jeopardize public health. Furthermore, the disingenuous presentation of the inaccurate information described above makes it difficult for public officials and medical providers to make informed decisions regarding the viability of medical cannabis treatment options.

Utility also requires continuous monitoring of information and the correction and updating of information where appropriate. The statements made by the DEA in the DPR described above, as well as the studies cited by the DEA, demonstrate that the DEAs statements on its website regarding the gateway theory, psychosis, lung cancer and permanent cognitive deficits need to be corrected and updated.

The DEA information lacks objectivity. The information described in Section II (a)-(d) is neither accurate, reliable, nor unbiased, as evidenced by the DEA’s contradictory statements in the DPR. For example, as demonstrated above, the DEA makes numerous inaccurate, unreliable and biased statements regarding the gateway theory and the health risks of marijuana use, including that it causes psychosis, lung cancer and permanent cognitive deficits. The DEA itself has disproven each of these statements in the DPR as described above. The contradictory statements made in “The Dangers and Consequences of Marijuana Abuse” and in “Drugs of Abuse,” evince a strong bias against medical cannabis and represent a dereliction of responsibility. The documents cite outdated and unreliable studies, and fail to discuss contrary authorities or the documented benefits of medical cannabis.

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72 See https://www.justice.gov/oirpr/information-quality (“Utility: DOJ components will assess the usefulness of the information to be disseminated to the public. Utility is achieved by continuously monitoring information needs and developing new information sources or by revising existing methods, models, and information products where appropriate. Objectivity: DOJ components will ensure disseminated information, as a matter of substance and presentation, is accurate, reliable, and unbiased. Objectivity is achieved by using reliable data sources, sound analytical techniques, and documenting methods and data sources.”).
Moreover, as discussed in the next section, the DEA has a heightened burden of ensuring the accuracy of its statements regarding the risk of marijuana use because the information is highly influential and affects national public policy. The DEA’s failure to update and correct admittedly outdated and incorrect information does not meet this heightened burden. Moreover, because of the need for greater certainty for influential information, the results of any studies and information relied on by the DEA must be reproducible. The DPR demonstrates that the studies and information relied on by the DEA for each of the categories discussed above is not reproducible.

Because the inaccurate information is neither useful nor objective, it must be changed to more accurately reflect the current scientific consensus surrounding medical cannabis. At the very least, the DEA should update its public information to comport with the statements it made in the DPR—namely, that (1) the gateway drug hypothesis is invalid; (2) cannabis use does not cause irreversible cognitive decline in adults; and cannabis use does not cause (3) psychosis or (4) lung cancer.

IV. THE INACCURATE DEA STATEMENTS REQUIRE A HIGHER LEVEL OF SCRUTINY BECAUSE THEY ARE “INFLUENTIAL INFORMATION” AFFECTING NATIONAL PUBLIC POLICY

The DOJ Guidelines require an “added level of scrutiny” for information deemed “influential.”73 The responsibility for determining whether information is influential lies with the component of the DOJ responsible for disseminating the information.74 Here, because the relevant DOJ component (the DEA) has not designated medical cannabis information as a “class” of information that is “influential,” the DEA must determine whether information is influential on a case-by-case basis.75 As stated above, the Guidelines define “influential” information as that which has a “genuinely clear and substantial impact at the national level, or on major public and private policy decisions as they relate to federal justice issues.”76 The DEA should find that the inaccurate information described in Section II has a “clear and substantial impact” if it is firmly convinced that the information has a high probability of impacting public or private “policy, economic, or other decisions.”77

The incorrect information on medical cannabis published by the DEA clearly meets this standard. The DEA is one of the most respected and influential federal agencies providing information on drug use, drug abuse, and the health risks surrounding drug use. Unsurprisingly, many elected officials rely on DEA information in making policy decisions and in educating their colleagues regarding the risks and rewards of medical cannabis. In fact, members of the House of Representatives have repeatedly cited to “The Dangers and Consequences of Marijuana Abuse,” which is the primary subject of this request for correction. As such, the maintenance of the inaccurate DEA information described in Section II has a genuinely clear and substantial

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73 Supra Note 13, at “For Influential Information.”

74 Id.

75 Id.

76 Id.

77 Id.
impact at the national level and on important public policy decisions related to federal justice issues.

Indeed, the “high probability” of impact has already materialized – via Congress’ continuing failure to pass the 2015 CARERS Act – and is likely to continue occurring given the incoming administration’s stance on medical cannabis. Recent statements made on the floor of the House of Representatives indicate that elected officials are being directly influenced to vote against the interests of medical cannabis patients as a result of the DEA’s inaccurate statements. During a May 28, 2014 House discussion regarding the “Commerce, Justice, Science and Related Agencies Appropriation Act of 2015,” Representatives John Fleming (R-LA) and Frank Wolf (R-VA)78 directly cited to the DEA’s document “The Dangers and Consequences of cannabis Abuse,” to support inaccurate propositions regarding the gateway theory and cannabis’ health effects:

“I would like to close by reading the following statement from the Drug Enforcement Agency's DEA May 2014 booklet on the ugly truth about marijuana: ‘Legalization of marijuana, no matter how it begins, will come at the expense of our children and public safety. It will create dependency and treatment issues and opens the door to use of other drugs, impaired health, delinquent behavior, and drugged drivers.’ I think the DEA got it right. It is time for the rest of the Justice Department to do their job and enforce current U.S. law that recognizes marijuana's devastating impact on our children and society. I am hopeful that my amendment will encourage DOJ to take steps necessary to correct any misunderstanding regarding the Federal enforcement of the CSA and the BSA. I now urge my colleagues to join me in supporting this amendment.” 79

…

“[M]arijuana is highly addictive, is closely linked to altered brain development; schizophrenia; mental illness […]” 80

…

“I was just reading the dangers and consequences of marijuana abuse. What is happening to our country? […] I strongly support the amendment.” 81

78 Frank Wolf retired in January 2015.

79 https://www.congress.gov/congressional-record/2014/5/28/house-section/article/h4868-1?q=%7B%22search%22%3A%5B%22marijuana%22%5D%7D&resultIndex=4, at H4907.

80 Id.

81 Id.
“And trust me, my friend, I will tell the gentleman that whether it is marijuana or heroin or methamphetamines, as a drug addict once told me: All addicting substances are gateways to other addicting substances.”  

**These opinions were directly influenced by the inaccurate statements in the “Dangers and Consequences of Marijuana Abuse,” discussed in Section II above.**  

The Congressmen were speaking in support of Rep. Fleming’s proposed amendment to H.R. 4660, which would have reduced the DOJ’s general legal account by $866,000 until the Attorney General enforced the Controlled Substances Act (“CSA”) by prosecuting medical cannabis providers and patients operating under State laws.  

Because outspoken and active members of the House use the aforementioned DEA statements in support of federal criminal justice legislation, the subject information is highly influential and can be expected to have a genuinely clear and substantial impact at the national level on important public policy decisions related to federal justice issues. While this particular amendment did not pass, Congress could pass a similar amendment or simply refuse to reauthorize the Rohrabacher-Farr Medical Cannabis Amendment—an amendment that prohibits the DOJ from using funds under the Act to interfere with providers and patients acting in accordance with state medical cannabis laws. This injury could occur as soon as December 2016 when Congress passes 2017 appropriations acts. It is highly likely that Congress will (1) refuse to reauthorize the Amendment; and/or (2) refuse to pass the CARERS Act.

Similar statements made by other US representatives demonstrate the pervasiveness of inaccurate beliefs regarding medical cannabis that are being perpetuated by DEA misinformation.

In a July 2016 Hearing, the House Subcommittee on Crime and Terrorism discussed researching the potential medical benefits and risks of cannabis. Representative Lindsey Graham, the Chairman of the subcommittee, made statements about the refuted gateway drug theory:

“I also hear about how marijuana is a gateway drug that gets people going down the wrong road.”

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82 *Id.*

83 See generally supra Note 21.

84 *Supra* Note 79, at H4906.


“I have also been a prosecutor and I understand that this has been a gateway drug.” 87

While these statements do not explicitly reference DEA documents, they mirror DEA misinformation and strongly suggest that Sen. Graham believes that the gateway theory surrounding cannabis remains scientifically accurate. As a former prosecutor, it is likely that Sen. Graham was influenced by inaccurate DEA information in forming his opinions about the gateway theory. Yet, as a CARERS Act cosponsor, Sen. Graham believed he was presenting a balanced view regarding the potential benefits and harms of medical cannabis. This hearing took place approximately one month prior to the DEA’s August 2016 acknowledgement that the gateway theory is not supported by science. Had Sen. Graham been aware of the invalidity of the gateway theory, it is likely that he would have presented more nuanced and fact-based evaluation of the risks and benefits associated with medical cannabis and the CARERS Act.

Additionally, Sen. Graham has a major influence on public policy and on other representatives (especially republicans). And, while he seems willing to consider the medical potential of cannabis and cannabis derivatives, his willingness to support (1) research using federal funds, (2) institutional access to cannabis for research, or (3) medicinal access for patients in need is stymied by his belief in the gateway theory. Declining to allow or fund medical research at a national level certainly qualifies as a major public policy decision. As such, Rep. Graham’s statements suggest that inaccurate DEA information about the gateway theory has a genuinely clear and substantial impact at the national level on important public policy decisions.

In a June 24, 2015 Senate Drug Caucus Hearing on Barriers to Cannabidiol Research, Senator Dianne Feinstein (D-CA) stated:

“It concerns me greatly because young people use it … it is also a gateway drug … they go onto other things … and it’s problematic.” 88

Sen. Feinstein is the Co-Chair of the Senate Drug Caucus, and she is under the impression that cannabis is a gateway drug that leads users to abuse more serious drugs. Again, while the Senator did not directly reference DEA materials, it is likely that the DEA’s dissemination of inaccurate information regarding cannabis and the gateway theory contributed to her incorrect views. And, it is highly likely that she would reconsider her beliefs about the gateway theory if she were exposed to correct information from a nationally trusted source like the DEA. As the Co-Chair on the Senate Drug Caucus, Sen. Feinstein is in a unique position to influence federal drug policy and national research efforts; thus, her statements suggest that inaccurate DEA information about the gateway theory has a genuinely clear and substantial impact at the national level on important public policy decisions related to federal justice issues.

Senator Chuck Grassley’s (R-IA) views further demonstrate the “high probability” of impact posed by DEA misinformation. For example, Sen. Grassley’s spokeswoman noted specific

87 Id. at 01:05:21.
88 http://www.drugcaucus.senate.gov/content/drug-caucus-hearing-barriers-cannabidiol-research-0, at 02:00:51.
reasons that Sen. Grassley did not support the CARERS Act, stating that he believes “marijuana users [are] much more likely to take up heroin and other serious drugs than non-users.” The impact of Sen. Grassley’s belief in the gateway theory is particularly acute – as the Chairman of the Senate Judiciary Committee, Sen. Grassley is the proverbial gatekeeper to any Senate hearing on the CARERS Act. And, given his general support for research into cannabidiol medicines, Sen. Grassley’s belief in the gateway theory is likely a primary impediment preventing him from facilitating a vote on the CARERS Act.

At the April 5, 2016 Drug Caucus hearing, Senator Jeff Sessions (R-AL) made several references to the gateway theory without specifically mentioning the theory by name. In a conversation with hearing witness Benjamin B. Wagner, U.S. Attorney for the Eastern District of California, Sen. Sessions asserted that “good people do not smoke marijuana” and described the damage that could ensue if more people use cannabis:

“You can see that it is in fact a very real danger, you can see the accidents traffic deaths related to marijuana jumped by 20%. These are the kind of things we’re going to see throughout the country and you’ll see cocaine and heroin increase more than it would have I think had we not talked about it […]”

“Lives will be impacted, families will be broken up, children will be damaged because of the difficulties their parents have, and people may be psychologically impacted the rest of their lives with marijuana. And if they go on to more serious drugs which tends to happen, and you can deny it if you want to, but it tends to happen […]”

As the probable incoming attorney general, Sen. Sessions will dictate whether the DOJ does or does not interfere with state medical cannabis systems. He clearly harbors a strong hatred for cannabis generally; nevertheless, his erroneous views on the gateway theory and the alleged permanency of cannabis associated cognitive deficits are likely informed by DEA misinformation, as Sen. Sessions has displayed a sense of trust in the opinions of “the Drug Czar and the DEA leadership.” Notably, Sen. Sessions’ comments were made approximately four months before the DEA formally acknowledged that the gateway theory is not supported by science. Because Sen. Sessions – the apparent incoming attorney general – likely draws his opinions about the gateway theory from DEA misinformation, the maintenance of such

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91 https://www.youtube.com/watch?v=gg0bZvIS0K8&feature=youtu.be&t=38m47s, at 39:48.
92 Id. at 42:13.
93 Id. at 42:35.
inaccurate information has a genuinely clear and substantial impact at the national level on important public policy decisions related to federal justice issues.

During a May 29, 2014 House discussion regarding the “Commerce, Justice, Science and Related Agencies Appropriation Act of 2015,” Representative Andy Harris (R-MD) stated:

“This is dangerous for [children]. How do we know this? The health risks: brain development, schizophrenia, increased risk of stroke.”

As part of the House Committee on Appropriations, Representative Harris is charged with allocating dollars to federal agencies. As such, he has power to influence DOJ enforcement of federal cannabis laws by withholding DOJ funds. Rep. Harris believes that cannabis causes schizophrenia, an admittedly false fact currently being promulgated by DEA literature. Moreover, Rep. Harris believes in the gateway theory, as demonstrated by his statements at a National Rx Drug Abuse Summit on April 8, 2015:

“That's not the way we should deal with such a dangerous drug […] marijuana is pretty clearly a gateway drug that has not been shown to be safe or medically effective.”

Because of his belief in the psychosis and gateway theories, Rep. Harris opposed the Amendment. Rep. Harris’ statements suggest that currently accessible DEA information continues to promote the unfounded psychosis and gateway theories, thus creating a genuinely clear and substantial impact at the national level on important public policy decisions related to federal justice issues.

During a June 2, 2015 House discussion regarding the “Commerce, Justice, Science and Related Agencies Appropriation Act of 2016,” Representative John Fleming (R-LA) stated:

“It [marijuana] is known to have brain development alterations; schizophrenia and other forms of mental illness, psychosis; heart complications; and an increased risk of stroke.”

94 https://www.congress.gov/congressional-record/2014/5/29/house-section/article/h4968-2?q=%7B%22search%22%3A%5B%22marijuana%22%5D%7D&resultIndex=3, at H4983.
95 See e.g., supra Note 79, at H4906.
96 See supra Note 11, at 53696.
98 “I rise to oppose the amendment.” Supra Note 94.
99 https://www.congress.gov/congressional-record/2015/6/2/house-section/article/h3700-2?q=%7B%22search%22%3A%5B%22marijuana%22%5D%7D&resultIndex=2, at H3746.
“It means the younger a child is exposed to it, the more likely that child will later become an addict to something else, like methamphetamine, prescription drugs, heroin.” 100

As the Co-Chair of the Addiction, Treatment, and Recovery Caucus, Rep. Fleming is charged with raising awareness and increasing education regarding substance abuse and addiction treatment. As such, he is in a unique position to educate other members of Congress and the public about the dangers and benefits of medical cannabis. As illustrated by his statements in the May 28, 2014 and June 2, 2015 House discussions, 101 he is directly influenced by inaccurate DEA information and promulgates this shoddy information in support of strict anti-medical cannabis laws and stronger enforcement of the CSA amongst the states. It is clear that inaccurate DEA information regarding the gateway theory and cannabis’ alleged ability to cause psychosis has a genuinely clear and substantial impact at the national level on important public policy decisions related to federal justice issues.

Representative Frank Wolf (R-VA) opposed the Amendment in a floor speech on May 9, 2012 discussing the Commerce, Justice, Science, and Related Agencies Appropriations Act of 2013.102 Representative Jerrold Nadler (D-NY) pointed out why this was the case:

“I heard [Rep. Wolf] say that the DEA says there is no medical use for marijuana. That’s true that they’ve said it. The DEA has no credibility with people who have looked at [medical cannabis] . . . We know that, for people suffering pain, for people suffering nausea from AIDS and cancer, marijuana is the only thing that produces relief and enables them to eat and get sustenance and to regain weight and to, perhaps, regain health. . . . The DEA doesn’t know [this] because it refuses to see it and refuses to allow systematic research.” 103

Rep. Wolf’s opposition to the Amendment is directly influenced by DEA misinformation, as he has directly cited104 to the DEA’s faulty document: “The Dangers and Consequences of Marijuana Abuse.” The statement above lends further credence to the fact that DEA misinformation has a genuinely clear and substantial impact at the national level on important public policy decisions related to federal justice issues.

Due to the widespread acceptance of inaccurate DEA information amongst the United States Congress, the information at issue has a genuinely clear and substantial influential impact on federal public policy decisions. This is especially true when considering DEA statements which

100 Id. at H3747.

101 See Supra Notes 79-80 & 99-100.

102 https://www.congress.gov/congressional-record/2012/5/9/house-section/article/h2515-3?q=%7B%22search%22%3A%5B%22marijuana%22%5D%7D&resultIndex=1, at H2525.

103 Id. at H2526.

104 Supra Note 81.
perpetuate the false notions that cannabis use causes psychosis and acts as a gateway drug to more serious drug abuse. Affected persons (i.e. ASA members) have already been affected by Congress’ continuing refusal to hold a vote on the CARERS Act, and they will be further affected if the Amendment is not reauthorized. Because the information at issue is “influential information” within the meaning of the Guidelines, the DEA should review the inaccurate DEA information with an added level of scrutiny, to ensure that it is reproducible.

V. ASA REPRESENTS SERIOUSLY ILL “AFFECTED PERSONS” WHO ARE DEEPLY AND IMMEDIATELY AFFECTED BY THE DEA’S INCORRECT AND CONTROVERTED STATEMENTS

a. ASA’s members are “affected persons” within the meaning of the DOJ’s Information Quality Guidelines

According to the DOJ and OMB Guidelines, affected persons are allowed to “seek and obtain, where appropriate, timely correction of information maintained and disseminated by the agency that does not comply with OMB or agency guidelines.”105 And, an “affected person” is an “individual or entity that may use, benefit, or be harmed by the disseminated information at issue.”106 ASA is composed of the following affected persons: (1) patients who are unable to access medical cannabis or are at risk of losing access; (2) doctors who are unable to recommend medical cannabis or are at risk of losing their ability to recommend it; (3) patients and providers who have been criminally prosecuted or are at risk of prosecution; and (4) scientists who are unable to obtain cannabis for research or are at risk of losing access.107 On behalf of these affected persons, ASA seeks to obtain correction of DEA information that fails to comply with the Guidelines. ASA and its individual members are currently being harmed by – and are at risk of future harm from – the DEA’s dissemination of inaccurate information regarding medical cannabis. Specifically, the DEA’s aforementioned statements regarding the gateway theory, cannabis’ supposed tendency to induce psychosis and lung cancer, and the alleged permanency of cannabis associated cognitive deficits have harmed and continue to harm ASA and its members. The harm results because the inaccurate information obfuscates legitimate medical cannabis research, which would otherwise inform our elected official’s opinions and actions.

As described in Section III, elected officials across the nation rely on DEA information when forming opinions about the safety and efficacy of medical cannabis. These officials have made public policy decisions based, at least in part, on inaccurate DEA information. These policy decisions include failing to reschedule cannabis via passage of the CARERS Act, which has the effect of denying patients access to medical cannabis, preventing doctors from prescribing medical cannabis, and criminally prosecuting medical cannabis users/providers. And, while there are many states that have implemented their own medical cannabis systems, medical cannabis remains federally illegal, in part due to elected officials’ inaccurate perceptions that

105 Supra Note 13, at “Introduction and Purpose.”
106 Id. at “Process for Citizen Complaint.”
107 ASA has members residing in every United States Congressional District.
cannabis is a gateway drug and that it causes psychosis, lung cancer, and permanent cognitive deficits. The federal status of medical cannabis has prevented multiple states from allowing healthcare providers to recommend medical cannabis in those states. Furthermore, there is a substantial risk that a misinformed Congress will either repeal or refuse to reauthorize the Amendment, thereby urging the DOJ to enforce the CSA in states with legal medical cannabis systems.

The inaccurate perceptions of at least several outspoken United States Congressmen originate from DEA information lacking both objectivity and utility. These representatives often push for stricter enforcement of the CSA in the states and maintenance of cannabis as a Schedule I drug. A correction of the erroneous DEA information would benefit ASA, its members, and millions of medical cannabis patients by shifting US representatives’ perceptions of the true risks of medical cannabis. Such a shift could result in many benefits, including but not limited to: (1) patients’ continued access to medical cannabis in states that currently permit its use;108 (2) patients’ access to medical cannabis in states which currently prohibit its use;109 (3) elimination of criminal penalties for medical cannabis physicians and patients;110 and (4) more federal funding and access to cannabis for medical research.111

108 There were approximately 2,045,888 registered medical cannabis patients as of Dec. 2015, based on available patient registry statistics compiled by ASA. Available at https://american-safe-access.s3.amazonaws.com/documents/EstimatedNumberOfMMJPatientsDec2015.pdf.

109 There are currently 6 states with no medical cannabis and an additional 15 states with limited CBD-focused laws. Only one of the CBD-focused laws allows for patients to obtain the medical cannabis-derived products from a dispensary in the state, all other CBD-focused laws only protect patients from arrest if they obtain and possess products acquired from a state with licensed distribution and reciprocity access.

110 According to the FBI, there were 643,121 cannabis arrests in 2015, over 89% of which were for possession alone – this is the crime patients are most likely to violate. However, the FBI does not provide any information on how many of those arrests involved a defendant claiming medical necessity. While medical cannabis physicians are rarely targeted for arrest, the chilling effect of its Schedule I status creates stigma that suppresses the number of physicians who are willing to recommend medical cannabis under state law. Available at https://ucr.fbi.gov/crime-in-the-u.s/2015/crime-in-the-u.s.-2015/home.

111 Researchers have commented on the lack of federal funding available for medical cannabis research. University of Pennsylvania professor Marcel Bonn-Miller said, “[f]rom the National Institutes of Health to the VA to whatever, there was nothing,” referring to the available funding for medical cannabis research. Ethan Russo, Former GW Pharmaceuticals researcher and current medical director at the Los Angeles biotechnology firm Phytecs, elaborated on the problem facing medical cannabis researchers: “Traditionally, if you had a compelling reason to do research, you could get funding … Now nothing is getting funded unless you have something really sexy. And marijuana is like kryptonite.” Between 1999 and 2012, the number of studies approved for funding dropped from 34% to 19%. Available at http://www.ibtimes.com/marijuana-news-2016-scientists-frustrated-funding-shortfalls-launch-institute-2379921.
VI. CONCLUSION

ASA makes this narrow request for correction with the goal of educating our elected officials and the public at large about the verifiable health effects associated with cannabis use. ASA does not claim that cannabis is entirely harmless and devoid of risk. However, medical cannabis provides relief to a substantial portion of our population and it provides hope to many who live with chronic and incurable ailments. ASA merely requests that the DEA change its public information to better comport with its own expressed views in the DPR, so that Congress has access to the tools to make informed decisions about public health. In the alternative, ASA requests that the DEA simply remove the inaccurate statements or the documents in their entirety.

Dated: December 5, 2016

Respectfully submitted,

[Signatures]

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REQUEST FOR CORRECTION OF INFORMATION DISSEMINATED BY DEA REGARDING MARIJUANA (CANNABIS)

INFORMATION QUALITY ACT REQUEST FOR CORRECTION

DATE: DECEMBER 5, 2016

SUBMITTED BY: AMERICANS FOR SAFE ACCESS FOUNDATION

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Request for Correction Pursuant to the DOJ’s Information Quality Guidelines

ISSUE

The Drug Enforcement Agency’s (“DEA”) website (dea.gov) contains inaccurate statements that do not meet the standards of quality required by the Department of Justice (“DOJ”) and Office of Management and Budget (“OMB”) under the Information Quality Act (“IQA”). In particular, the DEA continues to disseminate certain statements about the health risks of medical cannabis use that have been incontrovertibly refuted by the DEA itself in its recent “Denial of Petition to Initiate Proceedings to Reschedule Marijuana” (the “DPR”), issued August 12, 2016. In fact, the DEA’s recent statements confirm scientific facts about medical cannabis that have long been accepted by a majority of the scientific community. Accordingly, Americans for Safe Access (“ASA”) requests that the DEA correct or remove from the dea.gov website the inaccurate statements described below in Section II (a)-(d). At minimum, the corrections should comport with the DEA’s statements in the DPR.

PETITIONER

Americans for Safe Access Foundation (“ASA”), a non-profit advocacy group that represents the interests of medical cannabis patients and caregivers, files this Request for Correction of inaccurate information, disseminated by the DEA, relating to certain purported health effects of cannabis use. ASA brings this action on behalf of patients, their families, medical providers, scientists, and veterans across the United States who are deeply and immediately affected by the DEA’s controverted statements. The seriously ill patients that ASA represents suffer variously from cancer and the side-effects of its treatments, multiple sclerosis, HIV/AIDS, spinal injury, chronic seizures, and other medical conditions that produce chronic pain, nausea, loss of appetite and spasticity. Many of these persons who use medical cannabis to treat these symptoms do not respond to conventional treatment options, cannot tolerate certain medications, or have serious health needs not treatable by pharmaceutical medicine. If patients, who currently have access to medical cannabis under state programs, were to lose access, they would be irreparably harmed. And, patients in need of medical cannabis, but without access, are already being seriously harmed.

The DEA’s misinformation informs the opinions and actions of Congress. As a result of this misinformation, there is a substantial risk that Congress will fail to reauthorize the Rohrabacher-Farr Medical Cannabis Amendment (“the Amendment”) (discussed below)—failure to reauthorize would encourage the DOJ to dismantle state medical cannabis systems and prosecute medical cannabis users and providers throughout the nation. Furthermore, the CARERS Act (discussed below) has yet to receive a vote, due in part to the dissemination of DEA misinformation. ASA’s members reside in every United States Congressional District—they have been negatively affected by Congress’ continuing refusal to hold a vote on the CARERS Act, and they will be negatively affected by Congress’ failure to reauthorize the Amendment.
RELIEF REQUESTED

ASA requests corrections to DEA disseminated information as described in Section II (a)-(d).


FACTUAL BACKGROUND

For years, the DEA has published scientifically inaccurate information about the health effects of medical cannabis, directly influencing the action – and inaction – of Congress. The Compassionate Access, Research Expansion, and Respect States Act ("CARERS") is a prime example. Three senators introduced CARERS in March 2015 and an identical bill was introduced in the House later that month. The legislation seeks to protect patient access to medical cannabis in states with existing medical cannabis programs from federal intervention, thereby codifying the collection of DOJ memoranda that currently govern federal policy of medical cannabis enforcement against the states.\(^1\) Notably, CARERS would also reschedule cannabis from Schedule I to Schedule II status, thus easing current restrictions on medical and scientific research of the substance.\(^2\) Furthermore, the Act would exclude cannabidiols (cannabis derivatives with less than 0.3% THC content) from the definition of cannabis entirely,\(^3\) permit businesses acting in conformity with state cannabis laws to access banking services,\(^4\) mandate the issuance of additional licenses to cultivate cannabis for FDA approved research,\(^5\) and grant VA dependent veterans access to state medical cannabis programs.\(^6\)

Since the CARERS Act was introduced in March of 2015, it has received additional support in the Senate and House, but it seems unlikely that there will be a formal vote on the bill before the new administration commences in January 2017. Proponents of the Act believe that it is less likely to pass once the new Congress is sworn in and the new administration takes control. The House bill is sitting in four committees and subcommittees; the Senate analog sits in the Senate Judiciary Committee.\(^7\) Committee leadership in both chambers have denied the respective bills a

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\(^1\) https://www.congress.gov/bill/114th-congress/senate-bill/683/text, at Section 2 (The Controlled Substances Act, “shall not apply to any person acting in compliance with State law relating to the production, possession, distribution, dispensation, administration, laboratory testing, or delivery of medical marihuana.”).
\(^2\) Id. at Section 3.
\(^3\) Id. at Section 4.
\(^4\) Id. at Section 6.
\(^5\) Id. at Section 7.
\(^6\) Id. at Section 8.
\(^7\) H.R. 1538 has been assigned to the (1) House Energy and Commerce Subcommittee on Health; (2) House Judiciary Subcommittee on Crime, Terrorism, Homeland Security, and Investigations; (3) House Financial Services
hearing. House leadership has been hostile to medical cannabis legislation with the surreptitious removal of a medical cannabis amendment to the Military Construction and Veterans Affairs Appropriations Act in June 2016, after being approved by votes from the Senate Appropriations Committee and House Floor. Changes in the Senate Judiciary Committee for the 115th Congress include the ascension of CARERS opponent Dianne Feinstein to Ranking Member of the Senate Judiciary Committee, while fellow CARERS opponent Chuck Grassley remains committee chair. Representatives and senators that have commented unfavorably on the bills have cited, implicitly and explicitly, the inaccurate DEA information on the supposed dangers of medical cannabis.

The CARERS Act is not the only attempt to protect medical cannabis patients. In 2014, Congress included the Amendment in the Commerce, Justice, and Science Appropriations Bill. The Amendment prevents the DOJ from spending federal funds to inhibit the implementation of state medical cannabis laws. Without the Amendment, the DOJ could restrict or eliminate patients’ access to medicine legally available to them under their states’ laws. The Amendment was reauthorized in 2015, and a functionally identical amendment was introduced in April 2016 as part of the 2017 Commerce, Justice, Science, and Related Appropriations Act. While the Amendment was approved by the Senate Appropriations Committee in May 2016 by a vote of 21-8, it has yet to receive a vote in the House for Fiscal Year 2017. Congress’ failure to pass the CARERS Act or to reauthorize the Amendment, could destroy patients’ access to vital medicine in states where medical cannabis is currently legal and available. Also, even if patients are not the direct target of federal enforcement actions, they can be caught in harm’s way during a raid. And, even if they are not present at the raid, losing access to their dispensary means a disruption in their supply of medicine that may not be restored through access to another dispensing facility. As a result, patients are terrified of losing access to essential medicine and providers live in constant fear of federal criminal prosecution.

Elected representatives in Congress are using inaccurate DEA published information to inform their votes on the CARERS Act and the Amendment. In the Denial of Petition to Initiate Proceedings to Reschedule Marijuana (“DPR”), the DEA directly contradicted a multitude of previously disseminated statements, which are currently available on the dea.gov website. The following sections detail (1) the inaccurate information and requested changes, (2) how the inaccurate information adversely impacts affected persons (i.e. ASA’s members), and (3) how the requested changes will benefit affected persons.


ARGUMENT

I. LEGAL STANDARDS

Passed as an amendment to the Paperwork Reduction Act, 44 U.S.C. § 3501, the Information Quality Act requires administrative agencies to devise guidelines to ensure the “quality, objectivity, utility, and integrity of information” they disseminate and to “[e]stablish administrative mechanisms allowing affected persons to seek and obtain correction of information maintained and disseminated by the agency that does not comply with the guidelines.”

The DOJ Guidelines quote the OMB Guidelines, which define “quality” as “an encompassing term comprising utility, objectivity, and integrity.” The term “utility” refers to the “usefulness of the information to be disseminated to the public,” achieved by “continuously monitoring information needs and developing new information sources or by revising existing methods, models, and information products where appropriate.” “Objectivity” assures that, as a “matter of substance and presentation,” disseminated information is “accurate, reliable, and unbiased.” In short, the agency is required, prior to dissemination of information, to ensure “compliance with the OMB and DOJ Guidelines” and “that the information fulfills the intentions stated and that the conclusions are consistent with the evidence.”

Additionally, where the agency is responsible for disseminating “influential” scientific or statistical information, the DEA has heightened responsibilities under the Act to ensure that such disseminated information is reproducible and accurate. Indeed, the accuracy of this information is “significant due to the critical nature of these decisions.” “Influential information” is that which is “expected to have a genuinely clear and substantial impact at the national level, or on major public and private policy decisions as they relate to federal justice issues.” To determine that there is a clear and substantial impact, the agency must “have greater certainty than would be the case for many ordinary factual determinations that the impact is occurring or will occur.”

Furthermore, the DOJ Guidelines require that statistical information disseminated by the agency be based on the promotion of sound statistical methods. “Sound” scientific methods “produce information (data and analysis results) that is accurate, reliable, and unbiased. Guidelines to promote sound statistical methods would cover the planning of statistical data

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14 Id. at “Utility.”
15 Id. at “Objectivity.”
16 Supra Note 11.
17 Id. at “For Influential Information.”
18 Id.
19 Id.
II. THE DEA’S STATEMENTS ABOUT MEDICAL CANNABIS IN THE DPR DIRECTLY CONTRADICT STATEMENTS CURRENTLY BEING MADE BY THE DEA ELSEWHERE

Each of the DEA’s statements about medical cannabis set forth below have been directly refuted by the DEA’s own statements in the DPR. Given its own recent contradiction of these statements, the DEA cannot credibly maintain that they are “accurate,” “reliable,” “unbiased,” or “reproducible.” Moreover, the statements are based on scientifically inaccurate data and result in denying patients access to vital medicine. Accordingly, each of these statements violate the IQA’s utility and objectivity standards and should be corrected.

ASA requests that the DEA replace the following scientifically inaccurate statements – currently disseminated by the DEA on its website in publications entitled “The Dangers and Consequences of Marijuana Abuse”21 and “Drugs of Abuse”22 – with the DEA’s own scientifically accurate statements made in the DPR.

a. The DEA’s statements in the DPR directly contradict its scientifically inaccurate statements about cannabis’ alleged capacity to induce psychosis

The DEA is disseminating information about cannabis use and psychosis that lacks both objectivity and utility. At the time the inaccurate statements were originally made, they may have been supported by some evidence. But, the DEA recently admitted that the only association between cannabis use and psychotic illness is in cannabis’ potential to increase the risk for psychosis among individuals already predisposed to develop a psychotic disorder.23 Thus, in light of numerous statements made by the DEA in the DPR, information suggesting that cannabis use causes psychosis no longer satisfies the objectivity and utility standards required by the DOJ and OMB Guidelines.

The DEA is making the following inaccurate statements regarding cannabis’ alleged capacity to induce psychosis and psychotic illness:

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20 *Id.* at “Sound Statistical Methods.”


23 *Supra* Note 9, at 53696-97 (citing Andreasson et al., *Curr Med Chem.*, 18(7): 1085-99 (2011); Schimmelmann et al., *Schizophr Res* 129(1): 52-56 (2011); Schiffman et al., *Psychiatry Res.* 134(1): 37-42 (2005); Pelayo et al., *Curr Pharm Des* 18(32): 5024-35 (2012); Degenhardt et al., *Drug and Alcohol Depend* 71(1): 37-48 (2003)) (“The authors concluded that marijuana use increased the risk for psychosis only among individuals predisposed to develop the disorder […] Additionally, the conclusion that the impact of marijuana may manifest only in individuals likely to develop psychotic disorders has been shown in many other studies.”) (emphasis added).
1. “According to an Australian study, there is now conclusive evidence that smoking cannabis hastens the appearance of psychotic illnesses by up to three years […] it makes it very clear that cannabis is playing a significant role in psychosis.”

2. “Evidence of the damage to mental health caused by cannabis use—from loss of concentration to paranoia, aggressiveness and outright psychosis—is mounting and cannot be ignored.”

3. “Marijuana use can worsen depression and lead to more serious mental illness such as schizophrenia, anxiety, and even suicide.”

4. “[T]eenage cannabis users are more likely to suffer psychotic symptoms and have a greater risk of developing schizophrenia in later life.”

5. “Dr. John MacLeod, a prominent British psychiatrist states: ‘If you assume such a link (to schizophrenia with cannabis) then the number of cases of schizophrenia will increase significantly in line with increased use of the drug.’ He predicts that cannabis use may account for a quarter of all new cases of schizophrenia in three years’ time.”

6. “Compared with those who had never used cannabis, young adults who had six or more years since first use of cannabis were twice as likely to develop a non-affective psychosis (such as schizophrenia) […] They were also four times as likely to have high scores in clinical tests of delusion.”

7. “Researchers have also found an association between marijuana use and increased risk of depression, an increased risk and earlier onset of schizophrenia, and other psychotic disorders, especially for teens that have a genetic predisposition.”

The following statements, taken directly from the DPR, contradict the aforementioned statements. Thus, in order to maintain the objectivity and utility standards, ASA requests that the DEA replace the aforementioned inaccurate statements with the following accurate statements, or in the alternative, delete the inaccurate statements in their entirety:

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24 Supra Note 21, at 12 (quotations omitted).
25 Id. at 8.
26 Id. at 10.
27 Id.
28 Id. at 12.
29 Id.
30 Supra Note 22, at 73.
1. “At present, the available data do not suggest a causative link between marijuana use and the development of psychosis.”

2. “Numerous large, longitudinal studies show that subjects who used marijuana do not have a greater incidence of psychotic diagnoses compared to those who do not use marijuana.”

3. “[M]arijuana per se does not appear to induce schizophrenia in the majority of individuals who have tried or continue to use marijuana. However, in individuals with a genetic vulnerability for psychosis, marijuana use may influence the development of psychosis.”

b. The DEA’s statements in the DPR directly contradict its scientifically inaccurate statements about cannabis’ alleged capacity to induce lung cancer and cause damage comparable to that caused by tobacco use

The DEA is disseminating information about cannabis use and lung cancer that lacks both objectivity and utility. At the time the inaccurate statements were originally made, they may have been supported by some evidence. But, the DEA recently admitted that the worst possible respiratory effects associated with long-term cannabis use are “chronic cough, increased sputum, as well as increased frequency of chronic bronchitis and pharyngitis.”

Thus, in light of numerous statements made by the DEA in the DPR, information suggesting that cannabis use causes lung cancer and tobacco-like respiratory damage no longer satisfies the objectivity and utility standards required by the DOJ and OMB Guidelines.

The DEA is making the following inaccurate statements regarding cannabis’s alleged capacity to induce lung cancer and cause damage comparable to that caused by tobacco use:

1. “Marijuana smoking has been implicated as a causative factor in tumors of the head and neck and of the lung.”

2. “Marijuana takes the risks of tobacco and raises them. Marijuana smoke contains more than 400 chemicals and increases the risk of serious health consequences, including lung damage.”

31 Supra Note 11, at 53696.

32 Id.

33 Id. at 53696-97.

34 Id. at 53751 (citing HHS 2015; Adams and Martin, Addiction 91(11): 1585-1614 (1996); Hollister, Pharmacological Rev 38, 1-20 (1986)).

35 Supra Note 21, at 16.

36 Id.
3. “A study from New Zealand reports that cannabis smoking may cause five percent of lung cancer cases in that country.”

4. “According to researchers at the Tale School of Medicine, long-term exposure to marijuana smoke is linked to many of the same kinds of health problems as those experienced by long-term cigarette smokers.”

5. “Smoking marijuana can cause changes in lung tissue that may promote cancer growth, according to a review of decades of research on marijuana smoking and lung cancer.”

6. “Nevertheless, researchers indicate [...] that smoking pot could indeed boost lung cancer risk.”

7. “The Foundation warned that smoking one cannabis cigarette increase the chances of developing lung cancer by as much as an entire packet of 20 cigarettes.”

8. “Like tobacco smokers, marijuana smokers experience serious health problems such as bronchitis, emphysema, and bronchial asthma. Extended use may cause suppression of the immune system. Because marijuana contains toxins and carcinogens, marijuana smokers increase their risk of cancer of the head, neck, lungs, and respiratory tract.”

The following statements, taken directly from the DPR, contradict the aforementioned statements. Thus, in order to maintain the objectivity and utility standards, ASA requests that the DEA replace the aforementioned inaccurate statements with the following accurate statements, or in the alternative, delete the inaccurate statements in their entirety:

1. “The DEA further notes the publication of recent review articles critically evaluating the association between marijuana and lung cancer. Most of the reviews agree that the association is weak or inconsistent.”

2. “The HHS concluded that new evidence suggests that the effects of smoking marijuana on respiratory function and cancer are different from the effects of smoking tobacco.”

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37 *Id.* at 14.
38 *Id.* at 15.
39 *Id.*
40 *Id.*
41 *Id.* at 18.
42 *Supra* Note 22, at 73.
43 *Supra* Note 11, at 53751 (internal citation omitted).
44 *Id.* (internal citation omitted).
3. “[O]verall association is weak between marijuana use and lung cancer especially when controlling for tobacco use.” 45

4. “[I]n a large clinical study with 1,650 subjects, no positive correlation was found between marijuana use and lung cancer. This finding held true regardless of the extent of marijuana use when both tobacco use and other potential confounding factors were controlled.” 46

5. “The authors reported that occasional use of marijuana (7 joint-years for lifetime or 1 joint/day for 7 years or 1 joint/week for 49 years) does not adversely affect pulmonary function.” 47

c. **The DEA’s statements in the DPR directly contradict its scientifically inaccurate statements regarding the “gateway theory” and cannabis**

The DEA is disseminating information about cannabis use and the gateway theory that lacks both objectivity and utility. The “gateway theory” – that cannabis use causes users to abuse more serious drugs in the future – was never supported by epidemiological scientific evidence. 48 And, in light of numerous statements made by the DEA in the DPR, information suggesting that cannabis is a “gateway drug,” no longer satisfies the objectivity and utility standards required by the DOJ and OMB Guidelines.

The DEA is making the following inaccurate statements regarding cannabis and the gateway theory:

1. “Legalization of marijuana, no matter how it begins, will come at the expense of our children and public safety. It will create dependency and treatment issues, and open the door to use of other drugs, impaired health, delinquent behavior, and drugged drivers.” 49

2. “Teens who experiment with marijuana may be making themselves more vulnerable to heroin addiction later in life, if the findings from experiments with rats are any indication.” 50

3. “Marijuana is a frequent precursor to the use of more dangerous drugs and signals a significantly enhanced likelihood of drug problems in adult life.” 51

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45 *Id.* (internal citation omitted).

46 *Id.* (internal citation omitted).

47 *Id.*

48 *Id.* at 53705.

49 *Supra* Note 21, at 6.

50 *Id.* at 22.

51 *Id.*
4. “[T]eens who used marijuana at least once in the last month are 13 times likelier than other teens to use another drug like cocaine, heroin, or methamphetamine and almost 26 times likelier than those teens who have never used marijuana to use another drug.”

5. “Marijuana use in early adolescence is particularly ominous. Adults who were early marijuana users were found to be five times more likely to become dependent on any drug, eight times more likely to use cocaine in the future, and fifteen times more likely to use heroin later in life.”

6. “Healthcare workers, legal counsel, police and judges indicate that marijuana is a typical precursor to methamphetamine.”

7. “Teens past month heavy marijuana users [sic] are significantly more likely than teens that have not used marijuana in the past to: use cocaine/crack (30 times more likely); use Ecstasy (20 times more likely); abuse prescription pain relievers (15 times more likely); and abuse over the counter medications (14 times more likely).”

The following statements, taken directly from the DPR, contradict the aforementioned statements. Thus, in order to maintain the objectivity and utility standards, ASA requests that the DEA replace the aforementioned inaccurate statements with the following accurate statements, or in the alternative, delete the inaccurate statements in their entirety:

1. “Overall, research does not support a direct causal relationship between regular marijuana use and other illicit drug use.”

2. “The HHS cited several studies where marijuana use did not lead to other illicit drug use. Two separate longitudinal studies with adolescents using marijuana did not demonstrate an association with use of other illicit drugs.”

3. “Little evidence supports the hypothesis that initiation of marijuana use leads to an abuse disorder with other illicit substances. For example, one longitudinal study of 708 adolescents demonstrated that early onset marijuana use did not lead to problematic drug use.”

4. “Although many individuals with a drug abuse disorder may have used marijuana as one of their first illicit drugs, this fact does not correctly lead to the reverse inference

52 Id.
53 Id. at 22-23.
54 Id. at 23.
55 Id.
56 Supra Note 11, at 53705.
57 Id. (internal citations omitted).
58 Id.
that most individuals who used marijuana will inherently go on to try or become regular users of other illicit drugs.”59

5. “[B]ecause the gateway hypothesis only addresses the order of drug use initiation, the gateway hypothesis does not specify any mechanistic connection between drug ‘stages’ following exposure to marijuana and does not extend to the risks for addiction.”60

6. “Degenhardt et al. (2009) examined the development of drug dependence and found an association that did not support the gateway hypothesis. Specifically, drug dependence was significantly associated with the use of other illicit drugs prior to marijuana use.”61

d. The DEA’s statements in the DPR directly contradict its scientifically inaccurate statements regarding the alleged permanency of cannabis-associated cognitive deficits

The DEA is disseminating information about the alleged permanency of cannabis-associated cognitive deficits that lacks both objectivity and utility. At the time the inaccurate statements were originally made, they may have been supported by some evidence. But, the DEA recently noted that cannabis associated cognitive deficits are not apparent in those who initiate use after the age of 15 years.62 Thus, in light of numerous statements made by the DEA in the DPR, information suggesting that cannabis use causes permanent cognitive deficits no longer satisfies the objectivity and utility standards required by the DOJ and OMB Guidelines.

The DEA is making the following inaccurate statements regarding the alleged permanency of cannabis-associated cognitive deficits:

1. “Those who started using marijuana regularly after age 18 showed minor [cognitive] declines.”63

2. “Memory, speed of thinking, and other cognitive abilities get worse over time with marijuana use.”64

59 Id.
60 Id.
61 Id.
62 Id. at 53695 (citing Fontes, et al., Br. J Psychiatry 198(6): 442-7 (2011)) (“Individuals with a diagnosis of marijuana misuse or dependence who were seeking treatment for substance use, who initiated marijuana use before the age of 15 years, showed deficits in performance on tasks assessing sustained attention, impulse control, and general executive functioning compared to non-using controls. These deficits were not seen in individuals who initiated marijuana use after the age of 15 years.”) (emphasis added).
63 Supra Note 21, at 8.
64 Id. at 11.
3. “This study is the first to show that long-term cannabis use can adversely affect all users, not just those in the high-risk categories such as the young, or those susceptible to mental illness, as previously thought.”\textsuperscript{65}

The following statements, taken directly from the DPR, contradict the aforementioned statements. Thus, in order to maintain the objectivity and utility standards, ASA requests that the DEA replace the aforementioned inaccurate statements with the following accurate statements, or in the alternative, delete the inaccurate statements in their entirety:

1. “[T]he adult-onset chronic marijuana users showed no significant changes in IQ compared to pre-exposure levels whether they were current users or abstinent for at least 1 year.”\textsuperscript{66}

2. “[C]annabis-associated cognitive deficits are reversible and related to recent cannabis exposure, rather than irreversible and related to cumulative lifetime use.”\textsuperscript{67}

3. “The effects of chronic marijuana use do not seem to persist after more than 1 to 3 months of abstinence. After 3 months of abstinence, any deficits observed in IQ, immediate memory, delayed memory, and information processing speeds following heavy marijuana use compared to pre-drug use scores were no longer apparent.”\textsuperscript{68}

4. “Similarly, following abstinence for a year or more, both light and heavy adult marijuana users did not show deficits on score of verbal memory compared to non-using controls.”\textsuperscript{69}

5. “According to a recent meta-analysis looking at non-acute and long-lasting effect of marijuana use on neurocognitive performance, any deficits seen within the first month following abstinence are generally not present after about 1 month of abstinence.”\textsuperscript{70}

\section*{III. THE INACCURATE DEA INFORMATION LACKS BOTH OBJECTIVITY AND UTILITY MAKING IT THE PROPER SUBJECT OF A REQUEST FOR CORRECTION UNDER THE IQA}

The overwhelming majority of the objective scientific studies – \textit{including studies cited by the DEA in the DPR}\textsuperscript{71} – disprove the inaccurate DEA statements described in Section II (a)-(d).

\textsuperscript{65} Id.

\textsuperscript{66} Supra Note 11, at 53695.

\textsuperscript{67} Id.

\textsuperscript{68} Id. (internal citation omitted).

\textsuperscript{69} Id.

\textsuperscript{70} Id.

\textsuperscript{71} Minozzi et al., Drug Alcohol Rev 29(3): 304-317 (2010); Fergusson et al., Addiction 100(3): 354-366 (2005); Kuepper et al., Psychol Med 41(10): 2121-2129 (2011); Van Os et al., Am J Epidemiol 156(4): 319-327 (2002); American Medical Association, AMA Policy: Medical Marijuana H-95-952 (2009); Degenhardt et al., Drug Alcohol Depend 71(1): 37-48 (2003); Department of Health and Human Services, Basis for the recommendation for maintaining marijuana in Schedule I of the Controlled Substances Act (2015); Huang et al., Cancer Epidemiol...
Because the DEA itself made statements in the DPR that directly contradict information in “The Dangers and Consequences of Marijuana Abuse” and “Drugs of Abuse,” it is undeniable that the DEA information at issue lacks utility and objectivity.72

The DEA information lacks utility. Utility requires that information disseminated by the DEA be useful to the public. Information that is admittedly incorrect – such as the DEA’s statements regarding the gateway hypothesis and that marijuana causes psychosis, lung cancer and permanent cognitive deficits – inherently lacks usefulness. While there may be some demonstrable negative effects associated with cannabis abuse, the presentation of scientifically unfounded information alongside scientifically accurate information obscures and diminishes the utility of the accurate information and can jeopardize public health. Furthermore, the disingenuous presentation of the inaccurate information described above makes it difficult for public officials and medical providers to make informed decisions regarding the viability of medical cannabis treatment options.

Utility also requires continuous monitoring of information and the correction and updating of information where appropriate. The statements made by the DEA in the DPR described above, as well as the studies cited by the DEA, demonstrate that the DEAs statements on its website regarding the gateway theory, psychosis, lung cancer and permanent cognitive deficits need to be corrected and updated.

The DEA information lacks objectivity. The information described in Section II (a)-(d) is neither accurate, reliable, nor unbiased, as evidenced by the DEA’s contradictory statements in the DPR. For example, as demonstrated above, the DEA makes numerous inaccurate, unreliable and biased statements regarding the gateway theory and the health risks of marijuana use, including that it causes psychosis, lung cancer and permanent cognitive deficits. The DEA itself has disproven each of these statements in the DPR as described above. The contradictory statements made in “The Dangers and Consequences of Marijuana Abuse” and in “Drugs of Abuse,” evince a strong bias against medical cannabis and represent a dereliction of responsibility. The documents cite outdated and unreliable studies, and fail to discuss contrary authorities or the documented benefits of medical cannabis.

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72 See https://www.justice.gov/iqpr/information-quality (“Utility: DOJ components will assess the usefulness of the information to be disseminated to the public. Utility is achieved by continuously monitoring information needs and developing new information sources or by revising existing methods, models, and information products where appropriate. Objectivity: DOJ components will ensure disseminated information, as a matter of substance and presentation, is accurate, reliable, and unbiased. Objectivity is achieved by using reliable data sources, sound analytical techniques, and documenting methods and data sources.”).
Moreover, as discussed in the next section, the DEA has a heightened burden of ensuring the accuracy of its statements regarding the risk of marijuana use because the information is highly influential and affects national public policy. The DEAs failure to update and correct admittedly outdated and incorrect information does not meet this heightened burden. Moreover, because of the need for greater certainty for influential information, the results of any studies and information relied on by the DEA must be reproducible. The DPR demonstrates that the studies and information relied on by the DEA for each of the categories discussed above is not reproducible.

Because the inaccurate information is neither useful nor objective, it must be changed to more accurately reflect the current scientific consensus surrounding medical cannabis. At the very least, the DEA should update its public information to comport with the statements it made in the DPR—namely, that (1) the gateway drug hypothesis is invalid; (2) cannabis use does not cause irreversible cognitive decline in adults; and cannabis use does not cause (3) psychosis or (4) lung cancer.

IV. THE INACCURATE DEA STATEMENTS REQUIRE A HIGHER LEVEL OF SCRUTINY BECAUSE THEY ARE “INFLUENTIAL INFORMATION” AFFECTING NATIONAL PUBLIC POLICY

The DOJ Guidelines require an “added level of scrutiny” for information deemed “influential.”73 The responsibility for determining whether information is influential lies with the component of the DOJ responsible for disseminating the information.74 Here, because the relevant DOJ component (the DEA) has not designated medical cannabis information as a “class” of information that is “influential,” the DEA must determine whether information is influential on a case-by-case basis.75 As stated above, the Guidelines define “influential” information as that which has a “genuinely clear and substantial impact at the national level, or on major public and private policy decisions as they relate to federal justice issues.”76 The DEA should find that the inaccurate information described in Section II has a “clear and substantial impact” if it is firmly convinced that the information has a high probability of impacting public or private “policy, economic, or other decisions.”77

The incorrect information on medical cannabis published by the DEA clearly meets this standard. The DEA is one of the most respected and influential federal agencies providing information on drug use, drug abuse, and the health risks surrounding drug use. Unsurprisingly, many elected officials rely on DEA information in making policy decisions and in educating their colleagues regarding the risks and rewards of medical cannabis. In fact, members of the House of Representatives have repeatedly cited to “The Dangers and Consequences of Marijuana Abuse,” which is the primary subject of this request for correction. As such, the maintenance of the inaccurate DEA information described in Section II has a genuinely clear and substantial

73 Supra Note 13, at “For Influential Information.”
74 Id.
75 Id.
76 Id.
77 Id.
impact at the national level and on important public policy decisions related to federal justice issues.

Indeed, the “high probability” of impact has already materialized – via Congress’ continuing failure to pass the 2015 CARERS Act—and is likely to continue occurring given the incoming administration’s stance on medical cannabis. Recent statements made on the floor of the House of Representatives indicate that elected officials are being directly influenced to vote against the interests of medical cannabis patients as a result of the DEA’s inaccurate statements. During a May 28, 2014 House discussion regarding the “Commerce, Justice, Science and Related Agencies Appropriation Act of 2015,” Representatives John Fleming (R-LA) and Frank Wolf (R-VA) directly cited to the DEA’s document “The Dangers and Consequences of cannabis Abuse,” to support inaccurate propositions regarding the gateway theory and cannabis’ health effects:

“I would like to close by reading the following statement from the Drug Enforcement Agency's DEA May 2014 booklet on the ugly truth about marijuana: ‘Legalization of marijuana, no matter how it begins, will come at the expense of our children and public safety. It will create dependency and treatment issues and opens the door to use of other drugs, impaired health, delinquent behavior, and drugged drivers.’ I think the DEA got it right. It is time for the rest of the Justice Department to do their job and enforce current U.S. law that recognizes marijuana's devastating impact on our children and society. I am hopeful that my amendment will encourage DOJ to take steps necessary to correct any misunderstanding regarding the Federal enforcement of the CSA and the BSA. I now urge my colleagues to join me in supporting this amendment.”

…

“[M]arijuana is highly addictive, is closely linked to altered brain development; schizophrenia; mental illness […]”

…

“I was just reading the dangers and consequences of marijuana abuse. What is happening to our country? […] I strongly support the amendment.”

78 Frank Wolf retired in January 2015.
79 https://www.congress.gov/congressional-record/2014/5/28/house-section/article/h4868-1?q=%7B%22search%22%3A%5B%22marijuana%22%5D%7D&resultIndex=4, at H4907.
80 Id.
81 Id.
“And trust me, my friend, I will tell the gentleman that whether it is marijuana or heroin or methamphetamines, as a drug addict once told me: All addicting substances are gateways to other addicting substances.”

These opinions were directly influenced by the inaccurate statements in the “Dangers and Consequences of Marijuana Abuse,” discussed in Section II above. The Congressmen were speaking in support of Rep. Fleming’s proposed amendment to H.R. 4660, which would have reduced the DOJ’s general legal account by $866,000 until the Attorney General enforced the Controlled Substances Act (“CSA”) by prosecuting medical cannabis providers and patients operating under State laws. Because outspoken and active members of the House use the aforementioned DEA statements in support of federal criminal justice legislation, the subject information is highly influential and can be expected to have a genuinely clear and substantial impact at the national level on important public policy decisions related to federal justice issues. While this particular amendment did not pass, Congress could pass a similar amendment or simply refuse to reauthorize the Rohrabacher-Farr Medical Cannabis Amendment—an amendment that prohibits the DOJ from using funds under the Act to interfere with providers and patients acting in accordance with state medical cannabis laws. This injury could occur as soon as December 2016 when Congress passes 2017 appropriations acts. It is highly likely that Congress will (1) refuse to reauthorize the Amendment; and/or (2) refuse to pass the CARERS Act.

Similar statements made by other US representatives demonstrate the pervasiveness of inaccurate beliefs regarding medical cannabis that are being perpetuated by DEA misinformation.

In a July 2016 Hearing, the House Subcommittee on Crime and Terrorism discussed researching the potential medical benefits and risks of cannabis. Representative Lindsey Graham, the Chairman of the subcommittee, made statements about the refuted gateway drug theory:

“I also hear about how marijuana is a gateway drug that gets people going down the wrong road.”

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82 Id.
83 See generally supra Note 21.
84 Supra Note 79, at H4906.
"I have also been a prosecutor and I understand that this has been a gateway drug." 87

While these statements do not explicitly reference DEA documents, they mirror DEA misinformation and strongly suggest that Sen. Graham believes that the gateway theory surrounding cannabis remains scientifically accurate. As a former prosecutor, it is likely that Sen. Graham was influenced by inaccurate DEA information in forming his opinions about the gateway theory. Yet, as a CARERS Act cosponsor, Sen. Graham believed he was presenting a balanced view regarding the potential benefits and harms of medical cannabis. This hearing took place approximately one month prior to the DEA’s August 2016 acknowledgement that the gateway theory is not supported by science. Had Sen. Graham been aware of the invalidity of the gateway theory, it is likely that he would have presented more nuanced and fact-based evaluation of the risks and benefits associated with medical cannabis and the CARERS Act.

Additionally, Sen. Graham has a major influence on public policy and on other representatives (especially republicans). And, while he seems willing to consider the medical potential of cannabis and cannabis derivatives, his willingness to support (1) research using federal funds, (2) institutional access to cannabis for research, or (3) medicinal access for patients in need is stymied by his belief in the gateway theory. Declining to allow or fund medical research at a national level certainly qualifies as a major public policy decision. As such, Rep. Graham’s statements suggest that inaccurate DEA information about the gateway theory has a genuinely clear and substantial impact at the national level on important public policy decisions.

In a June 24, 2015 Senate Drug Caucus Hearing on Barriers to Cannabidiol Research, Senator Dianne Feinstein (D-CA) stated:

“It concerns me greatly because young people use it … it is also a gateway drug … they go onto other things … and it’s problematic.” 88

Sen. Feinstein is the Co-Chair of the Senate Drug Caucus, and she is under the impression that cannabis is a gateway drug that leads users to abuse more serious drugs. Again, while the Senator did not directly reference DEA materials, it is likely that the DEA’s dissemination of inaccurate information regarding cannabis and the gateway theory contributed to her incorrect views. And, it is highly likely that she would reconsider her beliefs about the gateway theory if she were exposed to correct information from a nationally trusted source like the DEA. As the Co-Chair on the Senate Drug Caucus, Sen. Feinstein is in a unique position to influence federal drug policy and national research efforts; thus, her statements suggest that inaccurate DEA information about the gateway theory has a genuinely clear and substantial impact at the national level on important public policy decisions related to federal justice issues.

Senator Chuck Grassley’s (R-IA) views further demonstrate the “high probability” of impact posed by DEA misinformation. For example, Sen. Grassley’s spokeswoman noted specific

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87 Id. at 01:05:21.
88 http://www.drugcaucus.senate.gov/content/drug-caucus-hearing-barriers-cannabidiol-research-0, at 02:00:51.
reasons that Sen. Grassley did not support the CARERS Act, stating that he believes “marijuana users [are] much more likely to take up heroin and other serious drugs than non-users.”89 The impact of Sen. Grassley’s belief in the gateway theory is particularly acute – as the Chairman of the Senate Judiciary Committee, Sen. Grassley is the proverbial gatekeeper to any Senate hearing on the CARERS Act. And, given his general support for research into cannabidiol medicines,90 Sen. Grassley’s belief in the gateway theory is likely a primary impediment preventing him from facilitating a vote on the CARERS Act.

At the April 5, 2016 Drug Caucus hearing, Senator Jeff Sessions (R-AL) made several references to the gateway theory without specifically mentioning the theory by name. In a conversation with hearing witness Benjamin B. Wagner, U.S. Attorney for the Eastern District of California, Sen. Sessions asserted that “good people do not smoke marijuana” and described the damage that could ensue if more people use cannabis:

“You can see that it is in fact a very real danger, you can see the accidents traffic deaths related to marijuana jumped by 20%. These are the kind of things we’re going to see throughout the country and you’ll see cocaine and heroin increase more than it would have I think had we not talked about it […]”91

…

“Lives will be impacted, families will be broken up, children will be damaged because of the difficulties their parents have, and people may be psychologically impacted the rest of their lives with marijuana. And if they go on to more serious drugs which tends to happen, and you can deny it if you want to, but it tends to happen […]”92

As the probable incoming attorney general, Sen. Sessions will dictate whether the DOJ does or does not interfere with state medical cannabis systems. He clearly harbors a strong hatred for cannabis generally; nevertheless, his erroneous views on the gateway theory and the alleged permanency of cannabis associated cognitive deficits are likely informed by DEA misinformation, as Sen. Sessions has displayed a sense of trust in the opinions of “the Drug Czar and the DEA leadership.”93 Notably, Sen. Sessions’ comments were made approximately four months before the DEA formally acknowledged that the gateway theory is not supported by science. Because Sen. Sessions – the apparent incoming attorney general – likely draws his opinions about the gateway theory from DEA misinformation, the maintenance of such

91 https://www.youtube.com/watch?v=gg0bZv1S0K8&feature=youtu.be&t=38m47s, at 39:48.
92 Id. at 42:13.
93 Id. at 42:35.
inaccurate information has a genuinely clear and substantial impact at the national level on important public policy decisions related to federal justice issues.

During a May 29, 2014 House discussion regarding the “Commerce, Justice, Science and Related Agencies Appropriation Act of 2015,” Representative Andy Harris (R-MD) stated:

“This is dangerous for [children]. How do we know this? The health risks: brain development, schizophrenia, increased risk of stroke.”

As part of the House Committee on Appropriations, Representative Harris is charged with allocating dollars to federal agencies. As such, he has power to influence DOJ enforcement of federal cannabis laws by withholding DOJ funds. Rep. Harris believes that cannabis causes schizophrenia, an admittedly false fact currently being promulgated by DEA literature. Moreover, Rep. Harris believes in the gateway theory, as demonstrated by his statements at a National Rx Drug Abuse Summit on April 8, 2015:

“That's not the way we should deal with such a dangerous drug […] marijuana is pretty clearly a gateway drug that has not been shown to be safe or medically effective.”

Because of his belief in the psychosis and gateway theories, Rep. Harris opposed the Amendment. Rep. Harris’ statements suggest that currently accessible DEA information continues to promote the unfounded psychosis and gateway theories, thus creating a genuinely clear and substantial impact at the national level on important public policy decisions related to federal justice issues.

During a June 2, 2015 House discussion regarding the “Commerce, Justice, Science and Related Agencies Appropriation Act of 2016,” Representative John Fleming (R-LA) stated:

“It [marijuana] is known to have brain development alterations; schizophrenia and other forms of mental illness, psychosis; heart complications; and an increased risk of stroke.”

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94 https://www.congress.gov/congressional-record/2014/5/29/house-section/article/h4968-2?q=%7B%22search%22%3A%5B%22marijuana%22%5D%7D&resultIndex=3, at H4983.

95 See e.g., supra Note 79, at H4906.

96 See supra Note 11, at 53696.


98 “I rise to oppose the amendment.” Supra Note 94.

99 https://www.congress.gov/congressional-record/2015/6/2/house-section/article/h3700-2?q=%7B%22search%22%3A%5B%22marijuana%22%5D%7D&resultIndex=2, at H3746.
“It means the younger a child is exposed to it, the more likely that child will later become an addict to something else, like methamphetamine, prescription drugs, heroin.”

As the Co-Chair of the Addiction, Treatment, and Recovery Caucus, Rep. Fleming is charged with raising awareness and increasing education regarding substance abuse and addiction treatment. As such, he is in a unique position to educate other members of Congress and the public about the dangers and benefits of medical cannabis. As illustrated by his statements in the May 28, 2014 and June 2, 2015 House discussions, he is directly influenced by inaccurate DEA information and promulgates this shoddy information in support of strict anti-medical cannabis laws and stronger enforcement of the CSA amongst the states. It is clear that inaccurate DEA information regarding the gateway theory and cannabis’ alleged ability to cause psychosis has a genuinely clear and substantial impact at the national level on important public policy decisions related to federal justice issues.

Representative Frank Wolf (R-VA) opposed the Amendment in a floor speech on May 9, 2012 discussing the Commerce, Justice, Science, and Related Agencies Appropriations Act of 2013. Representative Jerrold Nadler (D-NY) pointed out why this was the case:

“I heard [Rep. Wolf] say that the DEA says there is no medical use for marijuana. That’s true that they’ve said it. The DEA has no credibility with people who have looked at [medical cannabis] . . . We know that, for people suffering pain, for people suffering nausea from AIDS and cancer, marijuana is the only thing that produces relief and enables them to eat and get sustenance and to regain weight and to, perhaps, regain health. . . . The DEA doesn’t know [this] because it refuses to see it and refuses to allow systematic research.”

Rep. Wolf’s opposition to the Amendment is directly influenced by DEA misinformation, as he has directly cited to the DEA’s faulty document: “The Dangers and Consequences of Marijuana Abuse.” The statement above lends further credence to the fact that DEA misinformation has a genuinely clear and substantial impact at the national level on important public policy decisions related to federal justice issues.

Due to the widespread acceptance of inaccurate DEA information amongst the United States Congress, the information at issue has a genuinely clear and substantial influential impact on federal public policy decisions. This is especially true when considering DEA statements which

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100 Id. at H3747.

101 See Supra Notes 79-80 & 99-100.

102 https://www.congress.gov/congressional-record/2012/5/9/house-section/article/h2515-3?q=%7B%22search%22%3A%5B%22marijuana%22%5D%7D&resultIndex=1, at H2525.

103 Id. at H2526.

104 Supra Note 81.
perpetuate the false notions that cannabis use causes psychosis and acts as a gateway drug to more serious drug abuse. Affected persons (i.e. ASA members) have already been affected by Congress’ continuing refusal to hold a vote on the CARERS Act, and they will be further affected if the Amendment is not reauthorized. Because the information at issue is “influential information” within the meaning of the Guidelines, the DEA should review the inaccurate DEA information with an added level of scrutiny, to ensure that it is reproducible.

V. ASA REPRESENTS SERIOUSLY ILL “AFFECTED PERSONS” WHO ARE DEEPLY AND IMMEDIATELY AFFECTED BY THE DEA’S INCORRECT AND CONTROVERTED STATEMENTS

a. ASA’s members are “affected persons” within the meaning of the DOJ’s Information Quality Guidelines

According to the DOJ and OMB Guidelines, affected persons are allowed to “seek and obtain, where appropriate, timely correction of information maintained and disseminated by the agency that does not comply with OMB or agency guidelines.”105 And, an “affected person” is an “individual or entity that may use, benefit, or be harmed by the disseminated information at issue.”106 ASA is composed of the following affected persons: (1) patients who are unable to access medical cannabis or are at risk of losing access; (2) doctors who are unable to recommend medical cannabis or are at risk of losing their ability to recommend it; (3) patients and providers who have been criminally prosecuted or are at risk of prosecution; and (4) scientists who are unable to obtain cannabis for research or are at risk of losing access.107 On behalf of these affected persons, ASA seeks to obtain correction of DEA information that fails to comply with the Guidelines. ASA and its individual members are currently being harmed by – and are at risk of future harm from – the DEA’s dissemination of inaccurate information regarding medical cannabis. Specifically, the DEA’s aforementioned statements regarding the gateway theory, cannabis’ supposed tendency to induce psychosis and lung cancer, and the alleged permanency of cannabis associated cognitive deficits have harmed and continue to harm ASA and its members. The harm results because the inaccurate information obfuscates legitimate medical cannabis research, which would otherwise inform our elected official’s opinions and actions.

As described in Section III, elected officials across the nation rely on DEA information when forming opinions about the safety and efficacy of medical cannabis. These officials have made public policy decisions based, at least in part, on inaccurate DEA information. These policy decisions include failing to reschedule cannabis via passage of the CARERS Act, which has the effect of denying patients access to medical cannabis, preventing doctors from prescribing medical cannabis, and criminally prosecuting medical cannabis users/providers. And, while there are many states that have implemented their own medical cannabis systems, medical cannabis remains federally illegal, in part due to elected officials’ inaccurate perceptions that

105 Supra Note 13, at “Introduction and Purpose.”

106 Id. at “Process for Citizen Complaint.”

107 ASA has members residing in every United States Congressional District.
cannabis is a gateway drug and that it causes psychosis, lung cancer, and permanent cognitive deficits. The federal status of medical cannabis has prevented multiple states from allowing healthcare providers to recommend medical cannabis in those states. Furthermore, there is a substantial risk that a misinformed Congress will either repeal or refuse to reauthorize the Amendment, thereby urging the DOJ to enforce the CSA in states with legal medical cannabis systems.

The inaccurate perceptions of at least several outspoken United States Congressmen originate from DEA information lacking both objectivity and utility. These representatives often push for stricter enforcement of the CSA in the states and maintenance of cannabis as a Schedule I drug. A correction of the erroneous DEA information would benefit ASA, its members, and millions of medical cannabis patients by shifting US representatives’ perceptions of the true risks of medical cannabis. Such a shift could result in many benefits, including but not limited to: (1) patients’ continued access to medical cannabis in states that currently permit its use;108 (2) patients’ access to medical cannabis in states which currently prohibit its use;109 (3) elimination of criminal penalties for medical cannabis physicians and patients;110 and (4) more federal funding and access to cannabis for medical research.111

108 There were approximately 2,045,888 registered medical cannabis patients as of Dec. 2015, based on available patient registry statistics compiled by ASA. Available at https://american-safe-access.s3.amazonaws.com/documents/EstimatedNumberOfMMJPatientsDec2015.pdf.

109 There are currently 6 states with no medical cannabis and an additional 15 states with limited CBD-focused laws. Only one of the CBD-focused laws allows for patients to obtain the medical cannabis-derived products from a dispensary in the state, all other CBD-focused laws only protect patients from arrest if they obtain and possess products acquired from a state with licensed distribution and reciprocity access.

110 According to the FBI, there were 643,121 cannabis arrests in 2015, over 89% of which were for possession alone – this is the crime patients are most likely to violate. However, the FBI does not provide any information on how many of those arrests involved a defendant claiming medical necessity. While medical cannabis physicians are rarely targeted for arrest, the chilling effect of its Schedule I status creates stigma that suppresses the number of physicians who are willing to recommend medical cannabis under state law. Available at https://ucr.fbi.gov/crime-in-the-u.s/2015/crime-in-the-u.s.-2015/home.

111 Researchers have commented on the lack of federal funding available for medical cannabis research. University of Pennsylvania professor Marcel Bonn-Miller said, “[f]rom the National Institutes of Health to the VA to whatever, there was nothing,” referring to the available funding for medical cannabis research. Ethan Russo, Former GW Pharmaceuticals researcher and current medical director at the Los Angeles biotechnology firm Phytecs, elaborated on the problem facing medical cannabis researchers: “Traditionally, if you had a compelling reason to do research, you could get funding … Now nothing is getting funded unless you have something really sexy. And marijuana is like kryptonite.” Between 1999 and 2012, the number of studies approved for funding dropped from 34% to 19%. Available at http://www.ibtimes.com/marijuana-news-2016-scientists-frustrated-funding-shortfalls-launch-institute-2379921.
VI. CONCLUSION

ASA makes this narrow request for correction with the goal of educating our elected officials and the public at large about the verifiable health effects associated with cannabis use. ASA does not claim that cannabis is entirely harmless and devoid of risk. However, medical cannabis provides relief to a substantial portion of our population and it provides hope to many who live with chronic and incurable ailments. ASA merely requests that the DEA change its public information to better comport with its own expressed views in the DPR, so that Congress has access to the tools to make informed decisions about public health. In the alternative, ASA requests that the DEA simply remove the inaccurate statements or the documents in their entirety.

Dated: December 5, 2016

Respectfully submitted,

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Americans for Safe Access
Enclosure D: ASA's IQA Deadline Letter to DEA
February 13, 2017

Drug Enforcement Administration
800 K Street, N.W.
Suite 500
Washington D.C. 20001

Re: Failure to Respond to Information Quality Act Request For Correction

To Whom It May Concern:

On December 5, 2016, Americans for Safe Access ("ASA") submitted an Information Quality Act ("IQA") Request for Correction of Information Disseminated by Drug Enforcement Administration (DEA) Regarding Marijuana (Cannabis) (enclosed). ASA would like to thank the DEA for removing the document, "The Dangers and Consequences of Marijuana Abuse," which was formerly available at: www.dea.gov/doc/dangers-consequences-marijuana-abuse.pdf. This document contained the majority of the inaccurate statements described in ASA’s Request.

However, neither the DEA nor the Department of Justice (DOJ) has actually responded to ASA’s Request. Moreover, every single one of the inaccurate statements formerly present in the recently removed Dangers and Consequences document, are currently present in the document, "The DEA Position on Marijuana," available at:
https://www.dea.gov/docs/marijuana_position_2011.pdf. This document appears to be an earlier, almost identical draft of the "Dangers and Consequences of Marijuana Abuse." ASA is under the impression that the DEA made an honest oversight by failing to remove this document. Thus, ASA respectfully requests that the DEA remove "The DEA Position on Marijuana" from its website as well.

Unfortunately, the DEA has yet to update or remove the document, "Drugs of Abuse," available at: https://www.dea.gov/pr/multimedia-library/publications/drug_of_abuse.pdf#page=73. While
this document contains important information regarding a variety of drugs, certain statements\(^1\) in section “IX. Marijuana/Cannabis,” remain in violation of the objectivity and utility standards established by the IQA. These statements were discussed in ASA’s Request, yet have not been corrected or removed. Also, the DEA has recently disseminated another document, “Drug Fact Sheet Marijuana,” containing the very same aforementioned inaccurate statements present in “Drugs of Abuse.” “Drug Facts Sheet Marijuana” is available at: https://www.dea.gov/druginfo/drug_data_sheets/Marijuana.pdf.

Perhaps the inaccurate statements in these two documents also slipped through the cracks, or perhaps the DEA believes the statements contained in these documents do not violate the IQA objectivity and utility standards. But, without a substantive response from the DEA, ASA has no means of discovering which statements the DEA has determined are compliant with the IQA.

The DOJ Information Quality Guidelines allow the responsible DOJ component (i.e., the DEA) 60 calendar days to respond to a request for correction.\(^2\) ASA has waited 70 calendar days for a response, but to no avail. While ASA appreciates the DEA’s removal of “The Dangers and Consequences of Marijuana Abuse,” DEA misinformation regarding the health effects of cannabis remains publically available. It is crucial that the DEA correct its inaccurate statements, especially in light of Senator Jeff Session’s confirmation as Attorney General of the United States. Attorney General Sessions has made several statements demonstrating his beliefs that cannabis is a gateway drug and that its psychological effects are permanent. These beliefs are verifiably false, as confirmed by the DEA in its “Denial of Petition to Initiate Proceedings to

\(^1\) “Researchers have also found an association between marijuana use and an increased risk of depression; an increased risk and earlier onset of schizophrenia and other psychotic disorders, especially for teens that have a genetic predisposition […] Like tobacco smokers, marijuana smokers experience serious health problems such as bronchitis, emphysema, and bronchial asthma. Extended use may cause suppression of the immune system. Because marijuana contains toxins and carcinogens, marijuana smokers increase their risk of cancer of the head, neck, lungs and respiratory track.”

Reschedule Marijuana." As the top law enforcement official in the nation, Mr. Sessions must have access to accurate information based on current scientific data in order to make informed decisions regarding the enforcement (or non-enforcement) of federal drug laws. Allowing Mr. Sessions to make law enforcement decisions based on biased, out-of-date information does a tremendous disservice to ASA’s members and the American people at large.

Therefore, ASA respectfully requests that the DEA respond to its Request, and/or remove the remaining inaccurate statements from its website.

Dated: February 13, 2017

Respectfully,

Vickie L. Feeman
Attorney for Petitioner
Orrick, Herrington, and Sutcliffe LLP

Steph Sherer
Executive Director for Petitioner
Americans for Safe Access

Enclosure

Enclosures E: Relevant research studies from ‘Denial of Petition to Initiate Proceedings to Reschedule Marijuana’


Neuropsychological Performance in Long-term Cannabis Users

Harrison G. Pope, Jr, MD; Amanda J. Gruber, MD; James I. Hudson, MD, SM; Marilyn A. Huestis, PhD; Deborah Yurgelun-Todd, PhD

Background: Although cannabis is the most widely used illicit drug in the United States, its long-term cognitive effects remain inadequately studied.

Methods: We recruited individuals aged 30 to 55 years in 3 groups: (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. Subjects underwent a 28-day washout from cannabis use, monitored by observed urine samples. On days 0, 1, 7, and 28, we administered a neuropsychological test battery to assess general intellectual function, abstraction ability, sustained attention, verbal fluency, and ability to learn and recall new verbal and visuospatial information. Test results were analyzed by repeated-measures regression analysis, adjusting for potentially confounding variables.

Results: At days 0, 1, and 7, current heavy users scored significantly below control subjects on recall of word lists, and this deficit was associated with users' urinary 11-nor-9-carboxy-Δ9-tetrahydrocannabinol concentrations at study entry. By day 28, however, there were virtually no significant differences among the groups on any of the test results, and no significant associations between cumulative lifetime cannabis use and test scores.

Conclusion: 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.

Arch Gen Psychiatry. 2001;58:909-915

Does long-term heavy use of cannabis cause residual neuropsychological deficits? The literature has long been divided on this question. A recent investigation by our laboratory found deficits on memory of word lists and on mental flexibility among 65 heavy-smoking college students, compared with 64 infrequent smokers after 1 day of abstinence from cannabis. Fletcher et al found significant differences between 17 older heavy cannabis users and 30 matched nonusers on memory of word lists and on selective and divided attention tasks after 72 hours of abstinence from cannabis. Another group found electroencephalographic abnormalities in chronic cannabis users after 24 hours of abstinence, but found no significant alteration in auditory or visual P300 responses in another study of cannabis users, after controlling for potentially confounding variables. By contrast, Solowij found significant delays in auditory P300 responses in heavy cannabis users examined after at least 12 hours of abstinence. Cannabis users also displayed significantly slower reaction times and reduced accuracy on a selective attention task. However, it is difficult to determine whether such deficits, observed after only 12 to 72 hours of abstinence, are temporary (eg, due to a residue of cannabinoids in the brain or to acute withdrawal effects from cannabis) or long-lasting (due to a neurotoxic effect of long-term cannabis exposure). On this critical latter question, the data are meager and conflicting. Lyketsos and colleagues, examining 1318 participants younger than age 65 in the Epidemiologic Catchment Area Study, found no significant differences among heavy cannabis users, light users, and nonusers in the degree of cognitive decline on the Mini-Mental State Examination during the course of 12 years. By contrast, Struve and colleagues tentatively suggested that electroencephalographic abnormalities were more pronounced in longer-duration cannabis users, even when adjusting for the...
SUBJECTS AND METHODS

SUBJECTS

We recruited individuals aged 30 to 55 years in 3 groups: (1) current long-term heavy users reporting at least 5000 lifetime episodes of cannabis smoking (to be counted as separate, episodes had to be at least 1 hour apart), and currently smoking at least 7 times per week; (2) former long-term heavy users reporting at least 5000 episodes of smoking, but no more than 12 episodes during at least the last 3 months; and (3) control subjects reporting that they had smoked at least once, but no more than 50 times in their lives, and no more than once during the past year.

Our threshold of 5000 episodes for “heavy use” was equivalent to smoking at least once a day for at least 15 years. We considered recruiting controls who had never smoked cannabis, but elected to choose subjects who had tried the drug at least once, because individuals who had never tried cannabis might differ from individuals who had in ways that might be associated with cognitive performance. All subjects were studied at McLean Hospital, Belmont, Mass., and were required to sign informed consent for the study, which was approved by the McLean Hospital Institutional review board.

Subjects qualifying on telephone screening were evaluated by one of us (H.G.P. or A.J.G.) at a baseline (day 0) interview, which included demographic questions, detailed questions about frequency of use of cannabis and other drugs throughout the subject’s lifetime, the Structured Clinical Interview for DSM-IV,10 assessment for history of attention-deficit/hyperactivity disorder (ADHD) using the Wender Utah Rating Scale11 and a modified ADHD rating scale,12,13 semistructured questions regarding family history of DSM-IV Axis I psychiatric disorders,14 and laboratory tests for standard chemistries, hematology, and urinalysis. Ratings of ADHD were introduced only during the second year of the study and, hence, were limited to 109 of the 180 subjects (33 current users, 31 former users, and 45 controls). We calculated a conductor disorder score by adding the scores on 4 items on the Wender Utah Rating Scale: “ran away from home”; “get in fights”; “trouble with authorities, trouble with school, visits to the principal’s office”; and “trouble with the police, hooked, convicted.”

We excluded subjects who reported (1) use of any other class of drugs of abuse (such as hallucinogens, cocaine, stimulants, or opiates) more than 100 times in their lives; (2) a history of DSM-IV alcohol abuse or dependence; (3) a current DSM-IV Axis I disorder other than simple phobia or social phobia; (4) a history of a head injury with loss of consciousness requiring hospitalization; (5) current use of any psychoactive medication; or (6) a medical, psychiatric, or neurological condition that might affect cognitive function. We also screened urine by immunoassay (EMIT II; Behring Diagnostics, Cupertino, Calif) for 11-nor-9-carboxy-9-tetrahydrocannabinol (THCCOOH), creatinine, cocaine metabolites, benzodiazepines, barbiturates, phencyclidine hydrochloride, opioids, and amphetamines, and by enzymatic assay for ethanol. The immunoassay threshold for detection of cannabinoids was 20 ng/mL; ethanol detection was considered positive if it exceeded 0.02 g/dL. Samples positive for THCCOOH were then tested by gas chromatography-mass spectroscopy to obtain quantitative THCCOOH and creatinine concentrations. Samples showing evidence of ethanol levels above 0.02 g/dL, or evidence of any of the other 6 classes of drugs listed, were also confirmed by gas chromatography–mass spectroscopy.

ABSTINENCE PERIOD

Following the baseline evaluation, subjects were required to abstain from cannabis and other drugs of abuse for 28 days, monitored by observed urine samples daily (current users) or every other day (former users and controls). All subjects were permitted to consume caffeine and tobacco, and up to 2 alcoholic drinks (defined as 12 oz of beer, 4 oz of wine, or 1/2 oz of distilled liquor) per day. Subjects were withdrawn from the study if urine samples indicated noncompliance with these requirements. Current users, who by definition were smoking regularly up until day 0, were judged to be abstinence provided that their urinary THCCOOH concentrations, normalized to urinary creatinine concentrations, decreased in a manner consistent with residual drug excretion in the absence of any new cannabis use.15

NEUROPSYCHOLOGICAL TESTING

On days 0, 1, 7, and 28, an investigator, blinded to the subject’s group status, administered the neuropsychological tests described in this subsection. To maintain blindness, the tester worked in a separate building. Before testing, subjects were instructed not to reveal to the tester any information about their prior cannabis use or current frequency of urine samples.

Day 0

At baseline, subjects were administered the vocabulary subtest of the Wechsler Adult Intelligence Scale–Revised, a measure correlated with general intellectual ability16 and relatively insensitive to cortical insults.17

Days 0, 1, 7, and 28

On all 4 testing days, subjects were administered (1) a computerized Continuous Performance Test (Conners’...
control subjects and current users, in analyses with and without VIQ adjustment. On the final testing day, subjects were administered 6 additional tests: (1) the Wisconsin Card Sorting Test, (2) the Wechsler Memory Scale, (3) the block design subtest of the Wechsler Adult Intelligence Scale–Revised, (4) the Controlled Oral Word Association Test (often known as the “FAS” test), (5) the Stroop Test, and (6) the Raven Progressive Matrices. These measures of attentional and executive functions and verbal and visuospatial memory were chosen because of their known sensitivity to various forms of brain dysfunction and because they had demonstrated possible deficits in heavy cannabis users in previously published studies. Because these 6 tests were not available in multiple versions, they could be administered on only a single occasion and, thus, were reserved for day 28.

STATISTICAL ANALYSIS

For baseline demographic characteristics, we compared groups using the Fisher exact test for binary variables and the Wilcoxon rank sum test for continuous variables. For neuropsychological test scores, we compared current users and former users separately with controls via multivariate linear regression analysis. We used 2 sets of adjustments for possible confounding variables. Analysis 1 adjusted only for variables that could not have been affected by cannabis use: sex, age, ethnicity (white vs non-white), mother’s and father’s educational level, parents’ household income, presence of substance abuse or dependence in a first-degree relative, and presence of any other psychiatric disorder in a first-degree relative. Analysis 2 adjusted for verbal IQ (VIQ), as determined by the vocabulary subtest of the Wechsler Adult Intelligence Scale–Revised in addition to the other variables.

Because VIQ is generally well preserved despite cortical insults, analysis 2 was intended to adjust for the effects of premorbid intelligence. This adjustment is potentially important, because the heavy users displayed lower VIQs than did controls (see the “Results” section). However, we cannot exclude the possibility that the lower VIQs of heavy users might be partially a consequence, rather than an antecedent, of cannabis use. Therefore, the 2 analyses effectively provide upper and lower bounds for the neuropsychological effects of cannabis use: analysis 1 (VIQ-unadjusted) assumes that the lower VIQ of heavy users is entirely a consequence of cannabis use and entirely unrelated to premorbid differences in intelligence, while analysis 2 (VIQ-adjusted) assumes that lower VIQ is entirely a consequence of premorbid differences and entirely unrelated to cannabis use. If one assumes that the truth lies somewhere between these extremes, then the VIQ-unadjusted analysis would be expected to overestimate the true neuropsychological deficits associated with heavy cannabis use, whereas the VIQ-adjusted analysis would tend to underestimate such deficits.

For tests involving serial measures at different time points, we used the methods of longitudinal analysis with generalized estimating equations, with compound symmetry as a working covariance structure, to account for correlation of observations within individuals. We used appropriate transformations for variables in which there appeared to be a dependence of the variance on the mean.

We also tested the association between neuropsychological measures and lifetime use of cannabis in current and former users, and between these measures and baseline THCCOOH-creatinine ratio. For these analyses, we used multivariate linear regression as already described in this subsection, except that we restricted the analysis to a single group and entered as predictor variables lifetime use (modeled as log of the total number of lifetime episodes of use) and baseline THCCOOH-creatinine ratio. Using this ratio allowed us to correct for differences in the concentration of urine samples provided by subjects at day 0 and, thus, provided a rough approximation of the subject’s recent exposure to cannabinoids. We modeled this value as log (ratio + 1).

We had complete information on the most important covariates: age, sex, ethnicity, and VIQ. For the small number of missing observations for other covariates, we assigned the median value for the total sample for purposes of analysis.

We also fitted a model that included terms for scores on the ADHD rating scale and the conduct disorder scores calculated as described in the “Subjects” subsection of the “Subjects and Methods” section. This was a secondary analysis, because these data were limited to 109 subjects and because we could not exclude the possibility that some features of ADHD and conduct disorder represented effects of cannabis use.

All tests were 2-tailed. The large number of correlated outcome measures makes proper adjustment for multiple comparisons difficult. To control partially for the effects of multiple comparisons, we set the α level at .01.

We used commercially available statistical software (Stata 6.0) for all analyses.
from control subjects at days 0, 1, and 7, although generally not at day 28 (Table 2). The former users, by contrast, were not significantly different from controls on all measures of all 4 tests at all time points, in the VIQ-adjusted and VIQ-unadjusted analyses.

Scores on the 6 neuropsychological tests administered exclusively at day 28 appeared consistent with these findings. We found no significant differences between either the current or former users and the control subjects, using either the VIQ-adjusted or VIQ-unadjusted analy-

Table 1. Demographic Features of Current Users and Former Users vs Control Subjects*

<table>
<thead>
<tr>
<th>Demographic Feature</th>
<th>Current Users (n = 63)</th>
<th>Former Users (n = 46)</th>
<th>Controls (n = 72)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [range], y</td>
<td>36 [32-41]</td>
<td>41 [37-48]</td>
<td>39.5 [34-44]</td>
</tr>
<tr>
<td>Male</td>
<td>55 (87)</td>
<td>30 (67)</td>
<td>61 (85)</td>
</tr>
<tr>
<td>White</td>
<td>54 (86)</td>
<td>39 (87)</td>
<td>60 (83)</td>
</tr>
<tr>
<td>High school education or less</td>
<td>18 (29)*</td>
<td>6 (13)*</td>
<td>0</td>
</tr>
<tr>
<td>Annual household income &lt; $30,000</td>
<td>32 (51)**</td>
<td>23 (51)*</td>
<td>19 (26)</td>
</tr>
<tr>
<td>Mother’s education high school or less§</td>
<td>37 (61)</td>
<td>17 (40)</td>
<td>42 (58)</td>
</tr>
<tr>
<td>Father’s education high school or less</td>
<td>26 (46)</td>
<td>22 (50)</td>
<td>27 (38)</td>
</tr>
<tr>
<td>Parents’ annual household income &lt; $30,000</td>
<td>16 (25)</td>
<td>11 (25)</td>
<td>13 (18)</td>
</tr>
<tr>
<td>Family history of any Axis I disorder#</td>
<td>37 (60)</td>
<td>21 (50)</td>
<td>26 (37)</td>
</tr>
<tr>
<td>Lifetime episodes of cannabis use</td>
<td>18,720 [11,700-27,000]**</td>
<td>11,000 [8400-16,000]**</td>
<td>10 [5-25]</td>
</tr>
<tr>
<td>Years smoking cannabis ≥ 7 times per week</td>
<td>19 [15-24]**</td>
<td>15 [11-19]**</td>
<td>0</td>
</tr>
<tr>
<td>Lifetime alcoholic drinks</td>
<td>4700 [2100-7000]</td>
<td>3800 [1100-10,100]</td>
<td>2800 [1100-5500]</td>
</tr>
<tr>
<td>Lifetime packs of cigarettes</td>
<td>730 [0-5100]**</td>
<td>420 [0-4400]**</td>
<td>70</td>
</tr>
<tr>
<td>Lifetime caffeinated drinks</td>
<td>13,800 [3000-23,200]</td>
<td>15,300 [3200-26,100]</td>
<td>12,400 [3600-20,000]</td>
</tr>
<tr>
<td>Conduct disorder score‡</td>
<td>1 [1-3]††</td>
<td>1 [0-2]</td>
<td>0 [0-1]</td>
</tr>
<tr>
<td>Attention-deficit/hyperactivity disorder score‡‡</td>
<td>10 [4-14]</td>
<td>10 [7-13]</td>
<td>7.5 [5-15]</td>
</tr>
<tr>
<td>Verbal IQ</td>
<td>106 [95-118]**</td>
<td>115 [99-127]</td>
<td>115 [110-126]</td>
</tr>
</tbody>
</table>

*Data are given as number (percentage) for proportions and as median [interquartile range] for continuous variables. P values are significance of differences vs controls. All statistical tests were 2-tailed. Numbers of users and controls vary because of missing data.

†P < .001, Fisher exact test.
‡‡P < .01, Wilcoxon rank sum test.
§§Current users, 44 former users, and 71 controls.
###Data are given as number (percentage) for proportions and as median [interquartile range] for continuous variables. P values are significance of differences vs controls. All statistical tests were 2-tailed. Numbers of users and controls vary because of missing data.

†P < .001, Fisher exact test.
‡‡P < .01, Wilcoxon rank sum test.
§§Thirty-three current users, 31 former users, and 45 controls.

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Table 2. Scores of Study Groups on the Buschke Selective Reminding Test on Successive Testing Days

<table>
<thead>
<tr>
<th>Test Score</th>
<th>Mean (SD) Scores</th>
<th>Estimated Mean Differences (SE) Between Groups*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Current Users</td>
<td>Current Users vs Controls</td>
</tr>
<tr>
<td></td>
<td>(n = 63)</td>
<td>With VIQ Adjustment</td>
</tr>
<tr>
<td></td>
<td>Former Users</td>
<td>With VIQ Adjustment</td>
</tr>
<tr>
<td></td>
<td>(n = 45)</td>
<td>With VIQ Adjustment</td>
</tr>
<tr>
<td></td>
<td>Controls</td>
<td>With VIQ Adjustment</td>
</tr>
<tr>
<td></td>
<td>(n = 72)</td>
<td>With VIQ Adjustment</td>
</tr>
<tr>
<td>Total Recall</td>
<td>Day 0</td>
<td>104.5 (15.0)</td>
</tr>
<tr>
<td></td>
<td>Day 1</td>
<td>106.7 (17.0)</td>
</tr>
<tr>
<td></td>
<td>Day 7</td>
<td>111.7 (15.4)</td>
</tr>
<tr>
<td></td>
<td>Day 28</td>
<td>116.4 (12.9)</td>
</tr>
<tr>
<td>Long-term Storage</td>
<td>Day 0</td>
<td>96.5 (22.7)</td>
</tr>
<tr>
<td></td>
<td>Day 1</td>
<td>99.4 (22.5)</td>
</tr>
<tr>
<td></td>
<td>Day 7</td>
<td>105.7 (22.0)</td>
</tr>
<tr>
<td></td>
<td>Day 28</td>
<td>112.4 (18.6)</td>
</tr>
<tr>
<td>Consistent Long-term Retrieval</td>
<td>Day 0</td>
<td>58.0 (29.2)</td>
</tr>
<tr>
<td></td>
<td>Day 1</td>
<td>62.0 (33.4)</td>
</tr>
<tr>
<td></td>
<td>Day 7</td>
<td>70.8 (32.8)</td>
</tr>
<tr>
<td></td>
<td>Day 28</td>
<td>79.4 (31.2)</td>
</tr>
<tr>
<td>30-Minute Delayed Free Recall</td>
<td>Day 0</td>
<td>8.8 (2.3)</td>
</tr>
<tr>
<td></td>
<td>Day 1</td>
<td>8.3 (2.7)</td>
</tr>
<tr>
<td></td>
<td>Day 7</td>
<td>8.6 (2.6)</td>
</tr>
<tr>
<td></td>
<td>Day 28</td>
<td>9.1 (2.3)</td>
</tr>
</tbody>
</table>

*VIQ indicates verbal IQ. P values are significance of differences vs controls.
†P<.01.
‡P<.001.

Table 3. Scores of Study Groups at Day 28 on Representative Test Measures

<table>
<thead>
<tr>
<th>Test Score</th>
<th>Mean (SD) Scores</th>
<th>Estimated Mean Differences (SE) Between Groups*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Current Users</td>
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</tr>
<tr>
<td></td>
<td>(n = 63)</td>
<td>With VIQ Adjustment</td>
</tr>
<tr>
<td></td>
<td>Former Users</td>
<td>With VIQ Adjustment</td>
</tr>
<tr>
<td></td>
<td>(n = 45)</td>
<td>With VIQ Adjustment</td>
</tr>
<tr>
<td></td>
<td>Controls</td>
<td>With VIQ Adjustment</td>
</tr>
<tr>
<td></td>
<td>(n = 72)</td>
<td>With VIQ Adjustment</td>
</tr>
<tr>
<td>Total score on Wechsler Memory Scale</td>
<td>69.3 (8.4)</td>
<td>0.2 (1.3)</td>
</tr>
<tr>
<td>Raw score on Controlled Oral Word Association Test</td>
<td>47.1 (10.8)</td>
<td>-2.3 (2.3)</td>
</tr>
<tr>
<td>Total perseverations on Wisconsin Card Sorting Test†</td>
<td>2.4 (0.8)</td>
<td>0.1 (0.1)</td>
</tr>
<tr>
<td>Scaled score on block design substest of the Wechsler</td>
<td>11.7 (2.5)</td>
<td>0.1 (0.5)</td>
</tr>
<tr>
<td>Scale–Revised</td>
<td>105.5 (26.5)</td>
<td>0.0 (0.3)</td>
</tr>
<tr>
<td>Color interference time on Stroop Test, s</td>
<td>49.3 (6.5)</td>
<td>-0.5 (1.3)</td>
</tr>
</tbody>
</table>

*None of these differences achieved statistical significance. VIQ indicates verbal IQ.
†Shown and analyzed as logarithm of total perseverations because of right-skewed distribution.

Violations proved significant in either the VIQ-adjusted or VIQ-unadjusted analyses.

Turning to the issue of recent cannabis exposure, we also examined the association between baseline THCCOOH-creatinine ratios and the neuropsychological measures at each time point for the current users. This analysis, with VIQ adjustment, produced significant associations between baseline ratios and BSRT Total Recall at day 1 (estimated decrease in words recalled for every increase of 1 in log of ratio [SE], -5.7 [2.0], P = .005) and Consistent Long-term Retrieval on day 1 (-11.8 [4.3], P = .006). Without VIQ adjustment, we also found significant associations with BSRT Total Recall at day 1 (-6.6 [2.1], P = .002), Consistent Long-term Retrieval at day 1 (-13.3 [4.4], P = .002) and day 7 (-11.8 [4.2], P = .005), and 30-Minute Delayed Recall at day 28 (-0.9 [0.3],
In a study of cognitive function among long-term heavy cannabis users, we found deficits on memory of word lists, detectable at least 7 days after discontinuing the drug and related to initial urinary concentrations of THCCOOH. After 28 days of abstinence, however, users showed virtually no significant differences from control subjects on a battery of 10 neuropsychological tests. Former heavy users, who had consumed little or no cannabis in the 3 months before testing, showed no significant differences from control subjects on any of these tests on any of the testing days. The paucity of significant differences between the cannabis and control groups at day 28, together with the lack of significant associations between test scores and lifetime cannabis consumption, suggests that cannabis-associated cognitive deficits may be reversible phenomena associated with recent drug exposure, rather than irreversible phenomena associated with cumulative lifetime use.

Deficits on memory of word lists, persisting for days after discontinuing cannabis use, might be attributable to cannabinoids lingering in the central nervous system or to withdrawal from abruptly stopping use. Although we cannot clearly discriminate between these hypotheses, measures of aggression and subjective indices in the users suggest that withdrawal-associated agitation, often lasting at least 7 days, may have compromised their neuropsychological performance. A withdrawal hypothesis might explain why deficits on the BSRT in current users were at least as great on day 7 as on days 0 and 1 (Table 2).

Our findings are generally congruent with those of previous studies showing neuropsychological deficits within the first few days after cannabis use is stopped. Also, in agreement with another recent study, we failed to find an association between cumulative lifetime use of cannabis and cognitive deterioration. Only the findings by Solowij appear somewhat discrepant with ours, in that she found significant negative processing on digit-symbol substitution after 28 days of abstinence. Possibly, cannabis produces irreversible effects detectable on electroencephalographic measures, but too subtle to be detected on our neuropsychological test battery. Alternatively, the differences between the 2 studies may have been because of unmeasured or inadequately controlled confounding variables.

The cannabis users and controls in our study reported similar educational levels and income in their families of origin, whereas the users themselves exhibited significantly lower educational attainment, income, and estimated IQ than controls. We cannot determine whether these differences are because of premorbid attributes of the users or because of cannabis effects. Even if cannabis produces little or no irreversible cognitive deficit, chronic cannabis intoxication might still compromise educational ambitions, income potential, and the acquisition of new verbal information.

Several limitations of our study should be considered. The first is a possible selection bias caused by our study requirements. For example, users with severe neuropsychological deficits might have been less likely to enter the study, although a similar bias might also have affected the control group. In any event, we cannot exclude the possibility that we might have underestimated the cognitive deficits associated with cannabis use because severely impaired individuals were underrepresented.

A second limitation is the possibility of residual confounding, because of either unmeasured confounders or inadequate adjustment for measured confounders. However, it seems unlikely that such confounders could explain the lack of differences between users and controls at day 28, because the most plausible unmeasured confounding variables in the users—such as undetected psychopathologic conditions, unrecognized premorbid cognitive deficits, unreported prior use of other drugs, or undetected surreptitious use of cannabis during the study—would all be expected to militate against our finding, barring the remote possibility that nicotine from possible compensatory cigarette smoking among abstinent users might actually improve neuropsychological performance.

Third, subjects’ histories, including information on cannabis and other drug use, were obtained by self-report without external validation. However, as mentioned in the “Subjects and Methods” section, subjects were interviewed about their drug histories without knowledge of the answers necessary to gain acceptance into the study. Furthermore, previous studies have suggested that self-reports of use of cannabis and other drugs are fairly reliable. Finally, our principal positive findings—the initial cognitive deficit of the current users and its association with THCCOOH concentrations at study entry—were largely independent of self-report, because THCCOOH concentrations were measured on observed urine samples, using a sophisticated method likely to detect all but the most minimal levels of surreptitious cannabis use.

Fourth, it might be argued that we should have chosen control subjects who had never used cannabis, as opposed to individuals who had used the drug 1 to 50 times. However, we reasoned that “minimal-user” controls would more closely resemble the heavy users on possible confounding variables (measured and unmeasured) than would “never-used” controls, while still differing more...
than 1000-fold from the heavy users in their median level of exposure to cannabis (Table 1).

Fifth, our study design included only a limited assessment of premorbid intellectual functioning, based on the vocabulary subtest of the Wechsler Adult Intelligence Scale–Revised. Although this measure has been shown to provide reliable estimates of premorbid IQ in other populations, it is possible that lower VIQ is, at least partly, a consequence, rather than an antecedent, of long-term cannabis use. As discussed in the “Statistical Analysis” subsection of the “Subjects and Methods” section, we addressed this question by performing analyses with and without adjustment for VIQ, thus providing upper and lower bounds for our estimate of the neuropsychological deficits associated with cannabis use. However, in the non–VIQ-adjusted analysis, which would be expected to be the least favorable to cannabis users, we still found virtually no significant differences at day 28 between users and controls on the test measures.

Sixth, it is possible that long-term cannabis use might produce long-term cognitive deficits, but that our neuropsychological tests were not sufficiently sensitive to detect them. For example, practice effects on the BSRT, combined with a possible ceiling effect, might have reduced the ability of this instrument to detect differences between groups on the fourth administration, on day 28. The sensitivity of the study is also limited by its sample size. For example, in the VIQ-adjusted analysis for current users, the 99% confidence intervals for the day 28 test measures shown in Tables 2 and 3 do not exclude an effect of 0.4 to 0.8 (median, 0.6) SD units (the estimated difference between groups divided by the SD in the control group). Therefore, the possibility remains that more sophisticated neurocognitive assessment measures, such as electroencephalographic or functional magnetic resonance imaging measures, might reveal deficits in long-term cannabis users below the threshold detectable with our neuropsychological test battery.

In summary, our findings do not support the hypothesis that long-term heavy cannabis use causes irreversible cognitive deficits, at least at the level detectable with our test instruments and our sample size. However, in agreement with previous reports, we found evidence that heavy users exhibit some cognitive deficits lasting for many days, and possibly for weeks, after discontinuing cannabis use.

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REFERENCES


Does the ‘gateway’ matter? Associations between the order of drug use initiation and the development of drug dependence in the National Comorbidity Study Replication

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Background. The ‘gateway’ pattern of drug initiation describes a normative sequence, beginning with alcohol and tobacco use, followed by cannabis, then other illicit drugs. Previous work has suggested that ‘violations’ of this sequence may be predictors of later problems but other determinants were not considered. We have examined the role of pre-existing mental disorders and sociodemographics in explaining the predictive effects of violations using data from the US National Comorbidity Survey Replication (NCS-R).

Method. The NCS-R is a nationally representative face-to-face household survey of 9282 English-speaking respondents aged 18 years and older that used the World Health Organization (WHO) Composite International Diagnostic Interview (CIDI) to assess DSM-IV mental and substance disorders. Drug initiation was estimated using retrospective age-of-onset reports and ‘violations’ defined as inconsistent with the normative initiation order. Predictors of violations were examined using multivariable logistic regressions. Discrete-time survival analysis was used to see whether violations predicted progression to dependence.

Results. Gateway violations were largely unrelated to later dependence risk, with the exception of small increases in risk of alcohol and other illicit drug dependence for those who initiated use of other illicit drugs before cannabis. Early-onset internalizing disorders were predictors of gateway violations, and both internalizing and externalizing disorders increased the risks of dependence among users of all drugs.

Conclusions. Drug use initiation follows a strong normative pattern, deviations from which are not strongly predictive of later problems. By contrast, adolescents who have already developed mental health problems are at risk for deviations from the normative sequence of drug initiation and for the development of dependence.

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Key words: Alcohol, cannabis, dependence, gateway, illicit drugs, National Comorbidity Survey Replication, tobacco.
that the concept of gateway drugs has been applied to ecstasy (Reid et al. 2007) and oxycodone (Grau et al. 2007) in the USA, and that a ‘reverse gateway’ has been described for cannabis in Australia (where cannabis use has been linked to increased risk of subsequent initiation to tobacco use and dependence) (Patton et al. 2005).

There have been investigations of the extent and significance of violations of normative patterns. Studies in the USA of problematic drug users (Golub & Johnson, 1994a, b; 2002; Mackesy-Amiti et al. 1997) and homeless youths (Ginzler et al. 2003) have found that significant proportions had not progressed through the typical pattern of progression, with many beginning cannabis use before they had first used alcohol, and some starting other illicit drug use before using alcohol or cannabis. In those studies, individuals with ‘atypical’ patterns of progression were found to come from more disadvantaged backgrounds (Mackesy-Amiti et al. 1997), be from different birth cohorts (Golub & Johnson, 1994a, b; Mackesy-Amiti et al. 1997), and be heavier polydrug users (Mackesy-Amiti et al. 1997; Ginzler et al. 2003) than users who followed the normative progression.

This suggests that violations of normative patterns of progression may be important markers of subsequent risk of progression. The above studies provided interesting data, yet were in most cases limited to unrepresentative samples of heavy drug users; typically presented limited bivariate associations with other characteristics; did not adjust for pre-morbid mental health or demographic factors that might have been related to progression; and did not consider the impact of such atypical progressions for the later development of dependence. In this paper, we consider all of these possibilities using data from a representative sample of the US adult population, from the National Comorbidity Survey Replication (NCS-R).

Method

Participants and study procedures

As described in detail elsewhere (Kessler & Merikangas, 2004), the NCS-R is a nationally representative household survey of English speakers aged ≥18 years in the contiguous USA. Respondents were selected from a multistage clustered area probability sample of households and face-to-face interviews carried out from February 2001 to April 2003 by professional interviewers from the Institute for Social Research at the University of Michigan (U-M). The response rate was 71%.

The survey was administered in two parts. Part 1 included a core diagnostic assessment (n = 9282). Part 2 included assessed risk factors, consequences, correlates, and assessments of additional disorders that were administered to all Part 1 respondents who met lifetime criteria for any disorder plus a probability subsample of other respondents (n = 5692). Interviewers explained the study and obtained verbal informed consent prior to beginning the survey. Recruitment, consent and field procedures were approved by the Human Subjects Committees of Harvard Medical School and U-M.

Diagnostic assessment

Drug use modules

Drug use modules in the Part II sample were administered following a positive response to screening questions inquiring whether the respondent had ever used (1) tobacco (cigarettes, cigar or pipe); (2) alcohol; (3) cannabis, hashish; (4) cocaine; (5) tranquilizers, stimulants, painkillers or other prescription drugs; or (6) any other illicit drug including heroin, opium, glue, LSD or peyote. Detailed analyses of drug use and associations with demographic variables from this dataset have been reported previously (Degenhardt et al. 2007c).

Assessments of DSM-IV mental and substance use disorders were based on responses to the World Health Organization (WHO) Composite International Diagnostic Interview (CIDI; Kessler & Ustun, 2004), a fully structured lay-administered diagnostic interview used to generate DSM-IV diagnoses.

Drug use disorders

Any positive responses to drug use were followed with a detailed assessment of lifetime use of that drug, including age of onset of use, progression, and symptoms of abuse and dependence. Assessment of dependence was conducted separately for tobacco and alcohol. For other drugs, assessment of dependence was carried out with participants responding to dependence symptoms attributed to any of the drugs they reported having used. This is consistent with the DSM category for ‘dependence not otherwise specified’, whereby a person may meet criterion A1 for cannabis, A2 for cocaine and A3-4 for yet another drug, but does not meet full criteria for dependence on any single drug; they would nonetheless be classified as meeting criteria for ‘drug dependence’. Included here are people who meet full criteria for dependence, and where the symptoms are associated with the use of either one particular drug or multiple drugs.

This method of assessment of drug dependence was the same as that used in the Epidemiological Catchment Area (ECA) study and the National Comorbidity Survey (NCS). Good concordance has been reported in
an NCS-R clinical reappraisal subsample between diagnoses of substance use disorders based on the CIDI and diagnoses based on blinded clinical re-appraisal interviews (Kessler et al. 2004a) using the Structured Clinical Interview for DSM-IV (SCID; First et al. 1996).

**DSM-IV internalizing disorders**

These included specific phobia, social phobia, panic disorder, agoraphobia with panic disorder, generalized anxiety disorder with hierarchy, post-traumatic stress disorder, and major depressive disorder with hierarchy or dysthymia with hierarchy. They were aggregated into a summary variable reflecting the number of internalizing disorders that were reported to have occurred as of the age of 15 (range 0–7).

**DSM-IV externalizing disorders**

These included bipolar disorder, oppositional-defiant disorder with hierarchy, conduct disorder, attention deficit hyperactivity disorder, and intermittent explosive disorder with hierarchy. They were aggregated to reflect the number that had occurred as of the age of 15 (range 0–5). Assessment of the disorders requiring childhood onset of symptoms (separation anxiety disorder, oppositional-defiant disorder, conduct disorder, attention deficit hyperactivity disorder) was limited to those under 45 years at the time of interview to reduce recall bias.

**Order of onset and violations of the ‘typical’ gateway progression**

Different onset orders, as determined by retrospective age-of-onset reports, were evaluated separately. The violations were:

1. the use of cannabis prior to both alcohol and tobacco use;
2. other illicit drug use prior to both alcohol and tobacco use;
3. other illicit drug use prior to cannabis use.

Initiation of cannabis and/or other illicit drug use (a) prior to alcohol use (but not tobacco) and (b) prior to tobacco use (but not alcohol) was considered. These were post hoc and, given they are not ‘true’ violations of the gateway sequence, were not considered in further analyses.

**Statistical analyses**

Weights were used to adjust for variation in Part II probabilities described earlier, as well as within-household probability of selection, non-response, and differences between the sample and the 2000 Census on sociodemographic variables. Further detail has been provided in previous work (Kessler et al. 2004b).

Cumulative incidence proportions of gateway violations were estimated, with standard errors derived using the Taylor series linearization (TSL) methods implemented in SUDAAN version 9 (SAS Institute, Cary, NC, USA) to adjust for the effects of weighting and clustering on the precision of estimates. Regression coefficients were estimated and then exponentiated for interpretation as odds ratios (ORs). When p values are reported or indicated (by an asterisk), they are from Wald tests obtained from TSL design-based coefficient variance–covariance matrices ($\alpha = 0.05$, two-tailed).

Regression analysis was carried out to examine the association with age, sex and early-onset mental disorders with gateway ‘violations’ among users of each drug type. Predictors of gateway violations among users of each drug were examined using multivariable logistic regression models.

Discrete-time survival models among users of a drug examined predictors of dependence onset. Predictors included sex, age cohort (defined by age at interview: 18–29, 30–44, 45–59, $\geq 60$ years), number of externalizing and internalizing disorders by age 15, age of onset of use of the drug concerned, years since first onset of use (a time-varying covariate), a variable indicating whether there was a gateway violation (three dummy variables defined as outlined above), tobacco use (a time-varying covariate), alcohol use (a time-varying covariate), and the number of other drugs used (a time-varying covariate). The resulting ORs represent the estimates of risk of first-onset dependence in a given year.

**Results**

Overall, 5.2% of participants initiated substance use in an order that violated the gateway sequence (Table 1). The most common violation was initiation of other illicit drugs before cannabis (3.7%), followed by cannabis use before alcohol and tobacco use (1.6%). Prevalence differed significantly across birth cohorts. Respondents in the $\geq 60$ years group were extremely unlikely to report illicit drug use before alcohol and tobacco, whereas the three younger age groups were more likely to do so.

Table 2 specifies the types of illicit drugs used before alcohol and tobacco among those who violated the gateway sequence. Cannabis was the most common drug initiated before that time (69.2% of the group). Cocaine was more commonly initiated prior to alcohol and tobacco for the 18–29 years age group (18.7%) compared to older groups.
130.9*
955
0.6
14.5
21
0.5
1.6
223
1.2
13.3
437
1.6
21.0
Standard error.
A statistically reliable estimate could not be made.
* Signiﬁcant at 0.01 level, two-tailed test.
S.E.,
a

1.5
19.6

274

163
471
94
31
161
57
252
341
0.2
0.4
0.3
0.1
0.3
0.1
0.2
0.3
2.5
7.0
1.6
0.4
2.2
0.8
3.7
5.2
–
–
–
0.3
–
–
0.5
0.5
1.0
1.1
0.7
0.1
0.4
0.3
0.6
0.9
4.7
9.5
2.0
0.2
2.0
1.2
3.9
5.9

01. Cannabis before alcohol, not tobacco
02. Cannabis before tobacco, not alcohol
03. Cannabis before alcohol and tobacco
04. Other illicit drugs before alcohol, not tobacco
05. Other illicit drugs before tobacco, not alcohol
06. Other illicit drugs before alcohol and tobacco
07. Other illicit drugs before cannabis
Any violation of the gateway order of
initiation (03, 06, 07)
Any of 01 to 07

51
144
23
5
35
18
64
87

3.6
10.2
3.0
0.7
3.7
1.1
4.6
7.4

0.5
1.0
0.8
0.2
0.5
0.3
0.6
1.0

87
222
50
16
86
25
91
137

1.1
6.8
1.1
0.3
2.6
0.9
4.4
5.4

0.3
0.9
0.2
0.1
0.7
0.3
0.6
0.7

24
102
20
7
40
14
81
100

–a
–a
–a
0.5
–a
–a
1.3
1.3

1
3
1
3
0
0
16
17

n
S.E.

%
n
S.E.

%
n
S.E.

n
%
Order of onset of use

S.E.

%

S.E.

n

%

Total (n=5692)
o60 yr (n=974)
45–59 yr (n=1521)
30–44 yr (n=1826)
18–29 yr (n=1371)

Table 1. Distribution of each violation of the gateway pattern of drug use initiation by age cohort. Data from the National Comorbidity Survey Replication (NCS-R), 2001–2003

88.2*
138.2*
45.7*
5.6
75.9*
50.9*
22.9*
35.3*

L. Degenhardt et al.
Signiﬁcance

160

Table 3 presents the results of regressions examining predictors of gateway violations. Sex was not related to the initiation of illicit drug use prior to both
alcohol and tobacco, but was related to initiation of
other illicit drugs prior to cannabis, with females less
likely than males to have done so. Age was strongly
related to violations of all three kinds, with younger
age groups signiﬁcantly more likely than the oldest
age group to have initiated substance use out of the
gateway sequence.
Mental disorders by age 15 years were unrelated to
the precocious initiation of cannabis use (i.e. before
alcohol and tobacco use). Internalizing disorders were
related to precocious initiation of other illicits (deﬁned
as cocaine, sedatives/stimulants/analgesics or other
drugs including heroin). With each additional internalizing disorder, the likelihood of initiating such
drug use before alcohol and tobacco increased by 40 %
on average [OR 1.4, 95 % conﬁdence interval (CI)
1.1–1.8], and of initiating such drug use before cannabis use by 50 % on average (OR 1.5, 95 % CI 1.2–1.8).
Externalizing disorders by 15 years were unrelated to
initiation order.
Table 4 shows the results of multivariable survival
analyses examining the risk of incident dependence
among users of each drug. When other factors were
controlled, gateway violations were unrelated to the
risk of developing nicotine dependence, or drug
dependence among cannabis and cocaine users.
Initiation of any other illicit drugs (cocaine, sedatives/
stimulants/analgesics or other drugs) before cannabis
use was signiﬁcantly related to the risk of incident
alcohol dependence among alcohol users (OR 1.5, 95 %
CI 1.0–2.2), and drug dependence among sedative/
stimulant/analgesic/other drug users (OR 2.3, 95 % CI
1.4–3.9).
Consistently signiﬁcant predictors of transitioning
to dependent use in a given year were : earlier age of
onset of use, recency since onset of use, and the extent
of illicit drug use to date. Further analyses were conducted to evaluate the possibility that precocious initiation into illicit drug use might also reﬂect greater
polydrug use, such that gateway violations were related to the number of drug types used. Additional
analyses were conducted without controlling for
the number of illicit drugs used by that age (see
Appendix). In almost all cases, there was no diﬀerence
in the signiﬁcance of the observed associations. Two
notable exceptions were the risk of incident nicotine
dependence among tobacco users, where initiation of
cannabis use prior to tobacco/alcohol use predicted
incident nicotine dependence, and dependence among
cannabis users, where initiation of other illicit drugs
prior to cannabis predicted incident dependence. In
both cases, inclusion of the number of illicit drugs

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used made this association non-significant, suggesting that violation of the gateway order of onset in these cases was related to a higher likelihood of using a greater number of illicit drugs, and also related to incident dependence.

Finally, a greater degree of psychiatric co-morbidity by 15 years was associated with risk of incident dependence. The odds of users transitioning to dependent use increased by 20% (nicotine) to 50% (alcohol, other drugs) with each additional internalizing disorder by 15 years; and similarly with each additional externalizing disorder (20% for nicotine to 60% for alcohol). As noted in Table 3, pre-existing internalizing disorders were also significant predictors of gateway violations, meaning that failure to control for these disorders would allow a spuriously positive

### Table 2. Drugs used among those who had used any illicit drugs prior to alcohol and tobacco, by age. Data from the National Comorbidity Survey Replication (NCS-R), 2001–2003

| Age group (years) | n   | Cannabis | | S.E. | | Cocaine | | S.E. | | Other illicit drugs | | S.E. |
|-------------------|-----|----------|---|------|---|----------|---|------|-----------------|---|------|
| 18–29             | 39  | 64.9     | 10.0 | | | 18.5 | 7.7 | | 24.7 | 7.9 |
| 30–44             | 68  | 77.0     | 7.9  | | | 3.9 | 2.0 | | 26.9 | 8.0 |
| 45–59             | 33  | 57.1     | 7.8  | | | 0.0 | 0.0 | | 45.9 | 8.5 |
| ≥60               | 1   | _b_      | _  | | | _b_ | _  | | _b_ | _  |
| Total             | 141 | 69.2     | 5.0  | | | 7.5 | 2.7 | | 30.2 | 5.4 |

S.E., Standard error.

_a_ Includes sedatives/stimulants/analgesics and any other drugs.

_b_ A statistically reliable estimate could not be made.

### Table 3. Multivariable predictors of violation of the gateway sequence of drug use initiation. Data from the National Comorbidity Survey Replication (NCS-R), 2001–2003

<table>
<thead>
<tr>
<th></th>
<th>Cannabis before both alcohol and tobacco</th>
<th>Other illicit drugs before both alcohol and tobacco</th>
<th>Other illicit drugs before cannabis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>1.1 (0.6–2.1)</td>
<td>1.1 (0.5–2.1)</td>
<td>0.7* (0.5–0.9)</td>
</tr>
<tr>
<td>Age at interview (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18–29</td>
<td>53.8* (6.3–459.7)</td>
<td>5457.0* (3255.8–9146.5)</td>
<td>2.7* (1.1–6.3)</td>
</tr>
<tr>
<td>30–44</td>
<td>82.4* (10.2–667.1)</td>
<td>5115.8* (2726.3–9599.8)</td>
<td>3.2* (1.3–7.4)</td>
</tr>
<tr>
<td>45–59</td>
<td>29.4* (3.7–232.5)</td>
<td>4130.1* (2064.8–8261.5)</td>
<td>3.2* (1.4–7.4)</td>
</tr>
<tr>
<td>≥60</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>No. internalizing disorders by 15 years</td>
<td>1.2 (0.8–1.7)</td>
<td>1.4* (1.1–1.8)</td>
<td>1.5* (1.2–1.8)</td>
</tr>
<tr>
<td>No. externalizing disorders by 15 years</td>
<td>1.0 (0.6–1.6)</td>
<td>1.1 (0.7–1.6)</td>
<td>1.1 (0.8–1.4)</td>
</tr>
</tbody>
</table>

aOR, Adjusted odds ratio; CI, confidence interval.

Results based upon multivariable logistic regression models.

‘Other illicit drugs’ include cocaine, opioids, analgesics, sedatives, and ‘other drugs’.

* DSM-IV internalizing disorders included: panic disorder, agoraphobia without panic disorder, social phobia, specific phobia, generalized anxiety disorder with hierarchy, post-traumatic stress disorder, and major depressive disorder with hierarchy/dysthymia with hierarchy.

* DSM-IV externalizing disorders included: bipolar disorder, oppositional-defiant disorder with hierarchy, conduct disorder, attention deficit hyperactivity disorder and intermittent explosive disorder with hierarchy.

* OR significant at 0.05 level, two-tailed test. x² statistics are available upon request.
Table 4. Multivariable predictors of onset of dependence by drug type. Data from the National Comorbidity Survey Replication (NCS-R), 2001–2003

<table>
<thead>
<tr>
<th>Drug Dependence</th>
<th>Alcohol Dependence among Alcohol Users</th>
<th>Tobacco Dependence among Tobacco Users</th>
<th>Drug Dependence among Cannabis Users</th>
<th>Drug Dependence among Cocaine Users</th>
<th>Drug Dependence among Other Drug Users</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>aOR 95% CI</td>
<td>aOR 95% CI</td>
<td>aOR 95% CI</td>
<td>aOR 95% CI</td>
<td>aOR 95% CI</td>
</tr>
<tr>
<td>Female</td>
<td>0.5* 0.4–0.7</td>
<td>1.1 0.9–1.2</td>
<td>0.9 0.6–1.2</td>
<td>1.1 0.7–1.9</td>
<td>1.0 0.7–1.5</td>
</tr>
<tr>
<td>Age at interview (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18–29</td>
<td>1.0 0.5–1.8</td>
<td>1.8* 1.4–2.4</td>
<td>0.5 0.1–2.5</td>
<td>0.4 0.1–2.4</td>
<td>0.7 0.1–4.2</td>
</tr>
<tr>
<td>30–44</td>
<td>0.6 0.3–1.0</td>
<td>0.8 0.7–1.0</td>
<td>0.4 0.1–2.0</td>
<td>0.3 0.1–1.9</td>
<td>0.6 0.1–3.5</td>
</tr>
<tr>
<td>45–59</td>
<td>0.9 0.5–1.6</td>
<td>1.0 0.8–1.2</td>
<td>0.5 0.1–2.3</td>
<td>0.3 0.0–1.8</td>
<td>0.6 0.1–3.4</td>
</tr>
<tr>
<td>≥60</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>No. internalizing disorders by 15 yearsa</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.5* 1.4–1.6</td>
<td>1.2* 1.2–1.3</td>
<td>1.4* 1.3–1.6</td>
<td>1.4* 1.2–1.7</td>
<td>1.4* 1.1–1.7</td>
<td>1.3* 1.1–1.6</td>
</tr>
<tr>
<td>No. externalizing disorders by 15 yearsb</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.6* 1.4–1.8</td>
<td>1.2* 1.1–1.4</td>
<td>1.4* 1.2–1.7</td>
<td>1.4* 1.1–1.7</td>
<td>1.3* 1.1–1.6</td>
<td>1.1–1.6</td>
</tr>
<tr>
<td>Age of onset of usec</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.9* 0.9–0.9</td>
<td>0.7* 0.6–0.9</td>
<td>0.4* 0.2–0.7</td>
<td>0.5* 0.3–1.0</td>
<td>0.5* 0.3–1.0</td>
<td>0.3–0.9</td>
</tr>
<tr>
<td>Years since first onset of usec</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.4* 0.3–0.6</td>
<td>1.0* 1.0–1.0</td>
<td>0.8* 0.8–0.9</td>
<td>0.8* 0.7–0.9</td>
<td>0.8* 0.5–0.8</td>
<td>0.8–0.8</td>
</tr>
<tr>
<td>Tobacco use</td>
<td>2.5* 1.8–3.4</td>
<td>2.0* 1.1–3.9</td>
<td>1.3 0.6–2.7</td>
<td>1.8 0.9–3.6</td>
<td>0.9–3.6</td>
</tr>
<tr>
<td>Alcohol use</td>
<td>2.5* 1.9–3.4</td>
<td>1.6 0.5–5.4</td>
<td>3.0 0.3–35.1</td>
<td>5.4 0.9–32.0</td>
<td></td>
</tr>
<tr>
<td>Number of illegal drugs usedd</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>3.1* 2.1–4.5</td>
<td>1.9* 1.6–2.2</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>6.5* 3.6–11.9</td>
<td>2.6* 2.3–3.1</td>
<td>6.9* 4.2–11.3</td>
<td>0.7 0.1–4.2</td>
<td>3.3* 1.1–9.9</td>
</tr>
<tr>
<td>3</td>
<td>5.8* 3.2–10.6</td>
<td>3.5* 2.8–4.5</td>
<td>13.3* 8.3–21.4</td>
<td>1.0 0.2–4.5</td>
<td>7.0* 2.2–22.1</td>
</tr>
<tr>
<td>4</td>
<td>10.4* 5.5–19.8</td>
<td>3.8* 2.8–5.3</td>
<td>33.7* 18.8–60.5</td>
<td>2.4 0.6–10.6</td>
<td>18.2* 5.8–57.6</td>
</tr>
<tr>
<td>‘Gateway violation’</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cannabis use before tobacco and alcohol</td>
<td>0.7 0.3–1.5</td>
<td>1.3 0.8–2.0</td>
<td>1.2 0.5–2.8</td>
<td>0.8 0.3–2.3</td>
<td>1.1 0.4–2.8</td>
</tr>
<tr>
<td>Other illicit drugs before tobacco and alcohol</td>
<td>0.4* 0.1–1.0</td>
<td>0.9 0.4–1.7</td>
<td>0.7 0.2–1.9</td>
<td>0.6 0.2–2.4</td>
<td>1.5 0.4–5.6</td>
</tr>
<tr>
<td>Other illicit drugs before cannabis</td>
<td>1.5* 1.0–2.2</td>
<td>0.9 0.6–1.2</td>
<td>1.4 0.8–2.3</td>
<td>1.7 0.7–3.9</td>
<td>2.3* 1.4–3.9</td>
</tr>
</tbody>
</table>

aOR, Adjusted odds ratio; CI, confidence interval.

Results based upon multivariable discrete time survival models.

‘Onset of dependence’ refers to onset of the full dependence syndrome.

aDSM-IV internalizing disorders included: panic disorder, agoraphobia without panic disorder, social phobia, specific phobia, generalized anxiety disorder with hierarchy, post-traumatic stress disorder, and major depressive disorder with hierarchy/dysthymia with hierarchy.

bDSM-IV externalizing disorders included: bipolar disorder, oppositional-defiant disorder with hierarchy, conduct disorder, attention deficit hyperactivity disorder and intermittent explosive disorder with hierarchy.

cAge of onset, or years since onset, of the drug use concerned.

dThis is a time-varying covariate and refers to the number of illicit drugs (grouped as cannabis, cocaine, sedatives/stimulants/analgesics, or ‘other’) the person had used by a given year.

‘Other illicit drugs’ includes sedatives/stimulants/analgesics and ‘other’.

‘Other drugs’ includes sedatives/stimulants/analgesics and ‘other’.

* OR significant at 0.05 level, two-tailed test. $\chi^2$ statistics are available upon request.
association between gateway violations and subsequent dependence.

Discussion

This study examined the order of onset of drug use, and considered the possible association between deviations from the normative (gateway) pattern of drug progression with subsequent onset of substance dependence in a representative sample of US adults. Three violations were examined: (a) cannabis use before alcohol and tobacco; (b) other illicit drug use before alcohol and tobacco, and (c) other illicit drug use before cannabis. Importantly, using a person-years approach, this study was able to consider the risk of first developing dependent use across each year of life for the participants in this study. In doing so, we could also control at each year for the age of onset of that drug use; time since initiation of such use; the participant’s lifetime-to-date use of other drugs; and comorbid mental health problems developed by early adolescence. This approach to the analysis of gateway patterns and their predictive associations with subsequent dependent use represents a significant advance, as previous studies of this issue have concentrated on unrepresentative samples of problematic drug users, with insufficient capacity to conduct detailed investigations of risk for problems while controlling for the important confounding variables considered here.

Deviations from the gateway order of onset were found to occur only for a minority of persons (5.2%). The most common violation was other illicit drug use before cannabis (3.7%), and the least common was other illicit drugs before both alcohol and tobacco use (0.8%). There were some strong cohort differences in the likelihood of these violations: they were less common among the oldest age group than the younger ones. These findings are consistent with historical trends in drug use; cannabis use is much more common in more recent birth cohorts (Degenhardt et al. 2000; Johnston et al. 2003), so it is not surprising that cannabis is also more likely to occur earlier in the sequence of drug use for some younger people.

Previous studies have found that, among disadvantaged samples of drug users, many of whom had co-morbid mental health problems, violations of the gateway order of initiation involving precocious initiation into illicit drug use (such as cocaine use very early on in their drug use career) were common (Golub & Johnson, 1994a, b, 2002; Mackesy-Amiti et al. 1997). The current study demonstrated that one significant predictor of such deviations was the early development of internalizing mental disorders such as depression, post-traumatic stress disorder, social phobia or generalized anxiety disorder. This suggests that pre-morbid mental health problems are related to precocious initiation of illicit drug use.

This same deviation, the use of other illicit drugs (cocaine, sedatives, stimulants, opioids or other drugs) before cannabis use, was the only one significantly associated with the risk of subsequently developing dependent use. Among cocaine and other illicit drug users, risk for dependent use was elevated among those who had initiated use of these drugs before cannabis use and was significant after controlling for important potential mediators of dependence risk and common causes of the violation and dependence. This finding is consistent with the finding in studies of persons who have developed serious illicit drug use problems that high rates of atypical patterns of progression through stages of drug use exist in such samples, usually involving initiation of illicit drugs before cannabis or other drug use (Golub & Johnson, 1994a, b, 2002; Mackesy-Amiti et al. 1997).

Why do violations of normative patterns of illicit drug use onset play some part in the development of drug dependence, but others do not? This is the first study that has investigated this issue using a survival analytic framework, so few comparable data exist. One rather obvious possibility is that deviations from normative patterns matter much more for drugs that are infrequently used than for drugs that are themselves much more normative to use. Thus, alcohol, tobacco and cannabis are by far the most frequently used drugs in the USA; by comparison, cocaine and other illicit drugs are used by far fewer people (Anthony et al. 1994; Johnston et al. 2003; Degenhardt et al. 2007c). This supports the view that the significance of a gateway sequence is not related to a particular order of the initiation of particular drugs, but rather to a reflection of relative social or psychiatric deviance, and perhaps a pattern of escalating deviance.

A second possibility is that the violation documented here, the onset of cocaine or other illicit drug use before cannabis use, reflects a greater and earlier prominence of these drugs earlier in the user’s drug history, irrespective of the age of onset of use. The multitude of studies examining the risks of early-onset cannabis use have never been able to tease apart the possible contributions of the primacy of this drug in many people’s illicit drug use careers. The fact that cannabis typically begins first makes it difficult to know whether associations of early-onset cannabis use with later drug use problems reflect the order of onset or a specific drug effect (Degenhardt et al. 2007d). The findings of the current study suggest that both the type and order of onset of drug use may be influential in conferring risk upon the development of dependent use.
Finally, it is very plausible that gateway violations reflect important individual characteristics. Young people who choose to use drugs are more likely to be impulsive and take risks; the gateway violation that was a significant marker of dependence risk here was that which involved premature entry into illicit drug use. The finding that violations reflecting precocious entry into drug use were associated with elevated risks for later dependence would be consistent with the possibility that violation of gateway patterns reflects a broader underlying vulnerability to drug problems. It also suggests that the nature of this gateway sequence does not matter; it is a description of a normative sequence of entry into drug use that differs across countries and time (Patton et al. 2005; Grau et al. 2007; Reid et al. 2007), violations of which (or adherence to) reflect other factors, including individual characteristics (Shedler & Block, 1990; Morral et al. 2002), that may ultimately matter more for the development of dependence.

Mental health appeared to be important for both the order of initiation of illicit drug use and particularly for the development of dependent use once use had begun. In this study, those who had early-onset (by age 15 years) internalizing disorders were more likely to deviate from the normative order of onset of illicit drug use. Early-onset mental disorders, early-onset drug use and more extensive polydrug use were all important moderators of risk for developing dependent use, and were more important risk factors than violations of the ‘normative’ order of onset of drug use.

The finding that adolescents with both externalizing and internalizing disorders were at elevated risk of developing drug use problems later in life if they began using such drugs is consistent with prospective cohort studies, which have found that early-onset drug use and mental health problems are risk factors for later dependent drug use (Toumbourou et al. 2007), and that mental health problems escalate risk of developing dependent use. Detailed investigation of the specific mental disorders related to drug dependence was beyond the scope of the current paper, but further work is under way to investigate in more detail the nature of these co-morbidities, particularly to tease apart possible differences across different internalizing and externalizing disorders in their importance for predicting incident substance dependence.

There are clear public health and clinical implications, nonetheless, of the broad findings documented here. Adolescents with mental health problems are a particular risk group for the development of dependent use should they begin using legal or illegal drugs. Preventive interventions that address multiple areas of risk for both drug use and mental health among young people, including family social disadvantage, early school engagement and social inclusion, are effective (Patel et al. 2007; Toumbourou et al. 2007).

Limitations

Any cross-sectional retrospective survey research has limitations (Wu et al. 2003). Some of the observed cohort differences might be traced to higher mortality among individuals in the older cohorts who began drug use at an early age. Nonetheless, we believe that differential mortality is unlikely to explain the fairly large differences in cumulative incidence for illegal drug use across adjacent age groups given that mortality associated with cannabis use is highly unlikely to be substantial (Hall et al. 2001). Conversely, the evidence of tobacco-related premature mortality is substantial, but tobacco use showed the least prominent age-associated variation.

Retrospective reporting of age of first drug use may be subject to error, given that respondents are being asked about events that, for older persons, may have occurred decades ago. Although it is likely that some proportion of participant reports contained an element of recall bias, longitudinal studies of adolescents have found that estimates of the age of first use do tend to increase upon repeat assessment (i.e. as people age), but the rank ordering for different drugs does not change (Henry et al. 1994; Engels et al. 1997; Labouvie et al. 1997).

One possible limitation of the study relates to potential underestimation of dependence because the NCS-R used a ‘gated’ assessment of dependence, whereby dependence was only assessed among those who met criteria for abuse. We examined the impact of a ‘gated’ assessment approach upon alcohol, cannabis and illicit drug dependence prevalence estimates in the USA (Degenhardt et al. 2007a, b, 2008). We found a very modest attenuation of the prevalence of past year cannabis dependence (0.26% v. 0.32%), but not for cannabis use disorders (Degenhardt et al. 2007b); the reduction was greater for alcohol dependence (2.5% v. 3.8%) (Degenhardt et al. 2007a). There was no appreciable reduction of cocaine dependence prevalence estimates, and for other drugs estimates were so low that there was insufficient power to detect any difference at a general population level, even with a sample of over 40,000 persons (Degenhardt et al. 2008). Relationships with demographic variables of interest remained remarkably consistent across the gated and ungated assessment approaches, suggesting that any attenuation of estimated prevalence was not strongly concentrated within certain subpopulations (Degenhardt et al. 2007a, b, 2008).
Conclusions

Deviations from normative patterns of drug use initiation that involve the initiation of illicit drug use earlier than usual in the gateway pattern of initiation may carry small risks for dependence, but other factors seem to be more important in the development of drug dependence. Drug use and initiation are clearly nested within a social normative context, yet neither adherence nor deviation from this order signals highly elevated risks of drug problems in and of themselves, although some violations are predicted by pre-existing mental disorders that seem to be more powerful risk factors for subsequent substance dependence. Although a gateway violation might be a marker of such risk factors, their associations with gateway violations are relatively modest. In targeting intervention efforts, it would probably be more productive to screen directly for these factors (i.e. internalizing disorders, early-onset substance use) than to screen for gateway violations.

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Declaration of Interest

Professor Kessler has been a consultant for Astra Zeneca, Bristol–Myers Squibb, Eli Lilly and Co., GlaxoSmithKline, Pfizer, Sanofi-Aventis, and Wyeth and has had research support for his epidemiological studies from Bristol–Myers Squibb, Eli Lilly and Company, Ortho-McNeil, Pfizer, and the Pfizer Foundation. Professor Degenhardt has received an untied educational grant from Reckitt Benckiser to examine the diversion and injection of opioid substitution treatment in Australia.

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## Table A1. Comparison of the association between gateway violations and incident drug dependence, with and without control for the number of drug types used. Data from the National Comorbidity Survey Replication (NCS-R), 2001–2003

<table>
<thead>
<tr>
<th>Drug dependence among</th>
<th>Alcohol users</th>
<th>Tobacco users</th>
<th>Cannabis users</th>
<th>Cocaine users</th>
<th>Other drug usersa</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Cannabis use before tobacco and alcohol</td>
<td>0.7 0.3–1.5</td>
<td>1.3 0.8–2.0</td>
<td>1.2 0.5–2.8</td>
<td>0.8 0.3–2.3</td>
<td>1.1 0.4–2.8</td>
</tr>
<tr>
<td>B. Cannabis use before tobacco and alcohol without controlling for the number of illicit drugs usedb</td>
<td>1.2 0.5–2.5</td>
<td>1.9* 1.2–2.9</td>
<td>1.0 0.4–2.1</td>
<td>0.7 0.2–2.0</td>
<td>1.2 0.5–2.5</td>
</tr>
<tr>
<td>A. Other illicit drugs before tobacco and alcoholc</td>
<td>0.4* 0.1–1.0</td>
<td>0.9 0.4–1.7</td>
<td>0.7 0.2–1.9</td>
<td>0.6 0.2–2.4</td>
<td>1.5 0.4–5.6</td>
</tr>
<tr>
<td>B. Other illicit drugs before tobacco and alcohol without controlling for the number of illicit drugs usedb</td>
<td>0.4 0.2–1.2</td>
<td>0.9 0.5–1.8</td>
<td>0.6 0.2–1.9</td>
<td>0.6 0.2–2.3</td>
<td>1.2 0.4–3.7</td>
</tr>
<tr>
<td>A. Other illicit drugs before cannabisc</td>
<td>1.5* 1.0–2.2</td>
<td>0.9 0.6–1.2</td>
<td>1.4 0.8–2.3</td>
<td>1.7 0.7–3.9</td>
<td>2.3* 1.4–3.9</td>
</tr>
<tr>
<td>B. Other illicit drugs before cannabis without controlling for the number of illicit drugs usedb</td>
<td>2.5* 1.6–3.9</td>
<td>1.2 0.9–1.7</td>
<td>3.7* 2.2–6.3</td>
<td>1.9 1.0–3.6</td>
<td>1.0 0.7–1.5</td>
</tr>
</tbody>
</table>

OR, Odds ratio; CI, confidence interval.

Results based upon multivariable discrete time survival models.

Model A presents the coefficients from the model as shown in Table 4. Model B was the same analysis as model A with the exception that the number of illicit drug types used was removed from the model.

‘Onset of dependence’ refers to onset of the full dependence syndrome.

a ‘Other drugs’ includes sedatives/stimulants/analgesics and ‘other’.

b This is a time-varying covariate and refers to the number of illicit drugs (grouped as cannabis, cocaine, sedatives/stimulants/analgesics, or ‘other’) the person had used by a given year.

c Other illicit drugs: includes any of cocaine, sedatives/stimulants/analgesics, or ‘other’.

* OR significant at 0.05 level, two-tailed test. χ² statistics are available upon request.
Tests of causal linkages between cannabis use and psychotic symptoms

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ABSTRACT

Aim To examine possible causal linkages between cannabis use and psychosis using data gathered over the course of a 25-year longitudinal study.

Design A 25-year longitudinal study of the health, development and adjustment of a birth cohort of 1265 New Zealand children (635 males, 630 females).

Setting The Christchurch Health and Development Study, a general community sample.

Participants A total of 1055 participants from the Christchurch Health and Development Study (CHDS) cohort for whom data on cannabis use and psychotic symptoms were available on at least one occasion from 18, 21 and 25 years.

Measurements As part of this study, data were gathered on frequency of cannabis use and psychotic symptoms at ages 18, 21 and 25 years.

Findings Regression models adjusting for observed and non-observed confounding suggested that daily users of cannabis had rates of psychotic symptoms that were between 1.6 and 1.8 times higher ($P < 0.001$) than non-users of cannabis. Structural equation modelling suggested that these associations reflected the effects of cannabis use on symptom levels rather than the effects of symptom levels on cannabis use.

Conclusions The results of the present study add to a growing body of evidence suggesting that regular cannabis use may increase risks of psychosis. The present study suggests that: (a) the association between cannabis use and psychotic symptoms is unlikely to be due to confounding factors; and (b) the direction of causality is from cannabis use to psychotic symptoms.

KEYWORDS Cannabis, longitudinal study, psychosis, psychotic symptoms, structural equation modelling.

INTRODUCTION

Over the last decade there has been growing research into the linkages between the use of cannabis and the development of psychosis and psychotic symptoms (for reviews see [1–3]). This research has resulted in a growing body of evidence that suggests that the use (and particularly heavy use) of cannabis may be associated with increased risks of psychosis or psychotic symptoms. This conclusion has been supported by evidence from a series of longitudinal studies, all of which have found increased risks of psychosis or psychotic symptoms among cannabis users after control for confounding factors [4–7]. Epidemiological research linking cannabis use and psychosis has also been underwritten by laboratory-based research examining the psychogenic effects of cannabis (e.g. [8–11]) and by increasing evidence on the effects of cannabis on brain chemistry and functioning (e.g. [12–14]). Collectively, this evidence has provided growing support for the hypothesis that heavy cannabis use may precipitate or exacerbate psychosis or psychotic symptoms in vulnerable individuals. None the less, considerable uncertainty still remains about this topic and there is a clear need for further evidence to confirm the causal
Key issues in determining the causal role of cannabis in psychosis

It has now been well established that the use of cannabis is statistically linked to increased risks of psychosis. In a review of five studies, Arseneault et al. [1] found that all the studies were in agreement that the use of cannabis increases the risk of subsequent schizophrenia and psychotic symptoms. Similarly, in a parallel review of this topic Smit et al. [1] concluded that cannabis use is associated with the onset of psychosis, especially in those prone to developing schizophrenia, and also makes a unique contribution to the risk of developing schizophrenia. However, the extent to which these statistical associations reflect a cause and effect association in which the consumption of cannabis leads to an increased susceptibility to psychosis/psychotic symptoms remains open to debate. There are two potential major threats to validity that need to be addressed.

Residual confounding

The largest threat to the validity of causal conclusions in this area comes from the possibility of uncontrolled residual confounding. In reviewing this issue, Macleod et al. [15] concluded that while a number of studies had shown linkages between cannabis use and mental health that persisted following control for confounders the possibility remained that these linkages reflected uncontrolled residual confounding rather than the causal effects of cannabis use on psychotic symptoms. There is thus a need for more searching methods for controlling confounding factors.

Reverse causality

However, even if it were possible to establish that an association existed between cannabis use and psychosis net of confounders, this evidence would not establish the direction of causation. In particular, there are potentially two causal pathways that may link cannabis use and psychosis. First, cannabis use may lead (via changes in brain chemistry) to an increased susceptibility to psychotic symptoms. Alternatively, those developing psychosis may have an increased susceptibility to using cannabis as a consequence of their psychological state.

The above suggests that to clarify further the role of cannabis in the development of psychotic symptoms and psychosis there is a need for further research to address issues relating to the control of residual confounding and reverse causality in the association between cannabis use and psychosis. Below we describe methods using longitudinal data to address each of these problems.

Controlling residual confounding with the fixed effects regression model

Although it is often believed that epidemiological research can control only for the effects of observed confounders, in fact this is not strictly correct and there are a number of analytical approaches that permit the control of non-observed confounders in non-experimental research. Perhaps the best-known of these is the so-called discordant twin design, in which monozygotic twins who are discordant for some exposure variable (e.g. cannabis use) are compared on an outcome measure (e.g. psychosis). Because the twin pairs share both common genes and common environment, this comparison controls for these factors even though the common genes and common environment are not observed [16,17].

The principles underlying the discordant twin design can also be applied to longitudinal data on singletons via the fixed effects regression model. In particular, subject to the availability of longitudinal data, it proves possible to estimate the associations between a time-varying exposure variable (such as cannabis use) and a time-varying outcome measure (such as psychosis) net of any non-observed factors that are associated with the outcome and that may be correlated with the exposure variable [18]. The underlying logic of the fixed effects regression model is described later in Statistical methods. In effect, this model makes it possible to eliminate one major source of confounding from fixed factors. However, the model does not address the issue of confounders that may vary over time and to control for such confounding, the fixed effects model needs to be augmented by observed time-dynamic confounding factors.

Ascertaining causal direction using structural equation modelling

Establishing that cannabis use and psychosis are related, even following control for confounding, is an important step in ascertaining a causal relationship between cannabis use and psychosis. However, such analysis does not resolve the issue of the direction of causality between cannabis use and psychosis: does cannabis use cause psychosis or does psychosis lead to an increased use of cannabis?
Answering such questions proves to be difficult and even with well collected longitudinal data, establishing which factor is antecedent and which factor is consequent proves difficult [1,19]. Furthermore, there is a possibility that cannabis use and psychosis are related to each other reciprocally by a feedback loop in which the use of cannabis increases risks of psychosis while at the same time the onset of psychosis leads to an increased consumption of cannabis. Structural equation models provide one means of addressing such a complex issue by devising statistical models that permit reciprocal relationships between cannabis use and psychosis and using these models to provide a guide to probable patterns of causation. An account of the ways in which structural equation modelling may be employed to examine reciprocal pathways is given in the Statistical methods section of this paper.

**Aims of the present study**

The present study seeks to examine these issues using extensive data collected on the development of cannabis use and psychotic symptoms in a birth cohort of New Zealand young people studied throughout adolescence and young adulthood. The aims of this study were twofold:

1. To control the association between cannabis use and psychotic symptoms using a range of statistical methods including fixed effects regression to control for non-observed confounding factors.
2. To employ structural equation modelling methods to explore the direction of any causal influence between the use of cannabis and psychotic symptoms.

More generally, the aims of the paper are to apply complex multivariate methods to an extensive body of data on cannabis use and psychotic symptoms to address issues relating to both residual confounding and causal direction.

**METHOD**

**Participants**

The data described in this report were gathered during the course of the Christchurch Health and Development Study (CHDS). The CHDS is a longitudinal study of an unselected birth cohort of 1265 children (635 males, 630 females) born in the Christchurch (New Zealand) urban region in mid-1977. This cohort has now been studied at birth, 4 months, 1 year and at annual intervals to age 16 years, and again at ages 18, 21 and 25 years. As part of the study, information has been gathered from a range of sources including; parental interview, teacher reports, psychometric testing, self-reports, and medical and police records. The present analysis is based on a sample of 1055 participants for whom information on cannabis use and psychotic symptoms was available for at least one assessment from age 18, 21 or 25 years. All phases of data collection were subject to written, informed consent from study participants. The following measures were used in the analysis.

**Psychotic symptomatology**

At ages 18, 21 and 25 years, sample members were administered a comprehensive mental health interview designed to assess a number of aspects of the individual’s mental health and psychosocial adjustment. As part of this interview, participants were questioned on current (over the past month) psychotic symptomatology using items from the Symptom Checklist 90 (SCL-90) [20]. A series of 10 items were selected as representative of psychotic symptoms [5]. These items spanned the following symptoms: hearing voices that other people do not hear; the idea that someone else can control your thoughts; other people being aware of your private thoughts; having thoughts that are not your own; having ideas and beliefs that others do not share; the idea that something is seriously wrong with your body; never feeling close to another person; the idea that something is wrong with your mind; feeling other people cannot be trusted; feeling that you are watched or talked about by others. Confirmatory factor analysis of the item set has shown previously that the items formed a unidimensional scale reflecting the extent of psychotic symptomatology [5]. Scale scores were estimated by summing the number of symptoms reported by each participant at each age. Reliability was assessed using coefficient alpha, \( \alpha = 0.74 \) (18 years), \( \alpha = 0.73 \) (21 years) and \( \alpha = 0.75 \) (25 years).

**Frequency of cannabis use**

At each assessment from 18 to 25 years, sample members were questioned about their use of cannabis use since the previous interview. As part of this questioning, information was obtained on the frequency of cannabis use over the previous 12-month period. This information was used to classify sample members on a five-point scale reflecting the average level of cannabis use throughout the year. This scale was: 1 = non-user; 2 = used cannabis on less than a monthly basis; 3 = used cannabis on at least a monthly basis; 4 = used cannabis on at least a weekly basis; 5 = used cannabis on a daily basis. To examine the accuracy of reports of cannabis use, data on the participant’s cannabis use were also obtained from a nominated informant. There was good agreement between respondent and informant reports (\( r = 0.68; P < 0.001 \)).
Time-dynamic covariate factors
To control the associations between cannabis dependence and psychotic symptoms for time-varying sources of confounding factors, measures of the frequency of cannabis use and psychotic symptoms at the time of the preceding assessment were included as confounding factors. Thus, for 18 years, psychotic symptoms and cannabis use at age 16 years were controlled, for 21 years psychotic symptoms and cannabis use at age 18 years were controlled and for 25 years psychotic symptoms and cannabis use at age 21 were controlled.

Prior history of cannabis use/psychotic symptoms
To control for the individual’s prior history of cannabis use and psychotic symptoms, measures of the frequency of cannabis use and psychotic symptoms at the time of the preceding assessment were included as confounding factors. Thus, for 18 years, psychotic symptoms and cannabis use at age 16 years were controlled, for 21 years psychotic symptoms and cannabis use at age 18 years were controlled and for 25 years psychotic symptoms and cannabis use at age 21 were controlled.

Concurrent/prior mental disorders
As part of the mental health interviews administered at ages 16, 18, 21 and 25 years, questioning was conducted to assess standardized diagnostic criteria for a range of mental disorders. At age 16, questioning was conducted using an interview that combined components of the Diagnostic Interview Schedule for Children [21], the Self-Report Delinquency Inventory [22], the Rutgers Alcohol Problems Index [23] and custom-written survey items to assess Diagnostic and Statistical Manual version III–revised (DSM-III-R) symptom criteria. From age 18 onwards the interview combined components of the Composite International Diagnostic Interview [24], the Self-Report Early Delinquency Scale [25] and custom-written survey items to assess relevant DSM-IV diagnostic criteria. Using these data, sample members were classified on the following DSM disorders at each age: major depression in the past 12 months; anxiety disorders (including generalized anxiety disorder, panic disorder/agoraphobia, social phobia and specific phobia); alcohol and illicit drug dependence in the past 12 months; current nicotine dependence; conduct and/or antisocial personality disorder. For the purposes of the present analysis, measures of both concurrently assessed disorders and disorders at the time of the previous assessment were included as covariates.

Other factors
Parallel to questioning on mental health, information was also obtained on other time-dynamic aspects of the individual’s life-style, including the extent of affiliations with deviant peers and exposure to adverse life events. At each age sample members were questioned on a series of items concerning the extent to which their friends used or had problems associated with alcohol, tobacco or illicit drugs, had problems with aggression or were involved in criminal offending. These items were combined to derive a scale score measure of the extent of deviant peer affiliations at each age [26]. The reliability of all three measures, assessed using coefficient alpha, was 0.85. In addition, at each assessment sample members were questioned about exposure to adverse life events over the past 12 months using a scale based on the life events scale described by Henderson, Byrne & Duncan-Jones [27]. At each age, the number of life events reported was summed to provide a measure of the extent of adversity experienced in the previous 12 months.

Fixed covariate factors
A wide range of measures of social, family and individual functioning that were assessed prior to age 18 and were correlated with either cannabis use or psychotic symptoms were considered in the analysis. These factors included the following.

Measures of family socio-economic circumstances
(a) Maternal education at the time of the survey child’s birth was classified in three levels according to the mother’s highest level of educational attainment (no formal qualifications; high school qualifications; and tertiary qualifications). (b) Maternal age was coded in whole years at the time of the survey child’s birth. (c) Family socio-economic status was assessed at the point of birth using the Elley-Irving [28] scale of socio-economic status for New Zealand. This index classifies families into six levels on the basis of paternal occupation, (d) Family living standards (0–10 years): The quality of family living standards was assessed at annual intervals from age 1–10 years on the basis of interviewer ratings made on a five-point scale from very good to very poor. These ratings were averaged over the 10-year period to provide a global measure of the family’s averaged standard of living over this period.

Measures of family functioning
(a) Changes of parents (0–15 years): as part of the study detailed information was obtained at annual intervals from birth to age 15 years on any changes in family composition. An index of family instability during childhood was constructed on the basis of a count of the total number of changes of parents experienced by the child up to age 15 years. (b) Parental attachment (15 years): the quality of parental attachments during adolescence was assessed at age 15 years using the Armsden & Greenberg [29] Parental Attachment Scale. The reliability of this
scale, assessed using coefficient alpha, was 0.87. (c) Parental history of depression/anxiety (15 years): when sample members were aged 15, parents were questioned about their history of depression or anxiety problems: 29.9% of the sample had at least one parent who reported problems of depression or anxiety. (d) Parental criminality (15 years): when sample members were aged 15, parents were questioned about their history of involvement in criminal offending: 13.3% of the sample had at least one parent who reported a history of criminality. (e) Parental alcohol problems (15 years): when sample members were aged 15, parents were questioned about their history of alcoholism or problems with alcohol: 12.1% of the sample had at least one parent who reported alcohol problems. (f) Parental illicit drug use (11 years): when sample members were aged 11 years, parents were questioned about their use of cannabis or other illicit drugs: 24.9% of the sample had at least one parent with a history of illicit drug use.

Measures of child abuse
(a) Childhood sexual abuse (0–16 years): at ages 18 and 21 years sample members were questioned concerning their experience of childhood sexual abuse prior to age 16 years, and the nature/context of any episodes of abuse. Using these data, a four-level classification of the severity of abuse experience was constructed based on the worst episode of abuse reported at either age [30]. This classification was: no sexual abuse (86.0% of the sample); non-contact sexual abuse only (2.7%); contact sexual abuse not involving attempted or completed intercourse (5.1%); attempted or completed intercourse (6.2%). (b) Childhood physical abuse (0–16 years): the extent of childhood physical abuse was assessed on the basis of the young person’s reports of the extent of parental use of physical punishment during their childhood (prior to age 16 years), also obtained when sample members were aged 18 years and 21 years. The extent of physical punishment was coded on a four-point scale based on the highest level of physical punishment reported at either age [30]: parents never used physical punishment (4.5% of the sample); parents rarely used physical punishment (78.2%); at least one parent regularly used physical punishment (11.3%); at least one parent used physical punishment too often or too severely (6.0%).

Measures of individual characteristics
(a) Gender. (b) Child neuroticism (14 years): this was assessed using a short-form version of the neuroticism scale of the Eysenck Personality Inventory [31] administered when sample members were aged 14 years. The reliability of this scale, assessed using coefficient alpha, was 0.80. (c) Novelty seeking (16 years): the extent of novelty seeking behaviours was assessed using the novelty seeking subscale of the Tridimensional Personality Inventory [32] administered when sample members were aged 16 years. The reliability of this scale, assessed using coefficient alpha, was 0.76. (d) Self-esteem (15 years): a measure of self-esteem was obtained at age 15 years using the Coopersmith Self-Esteem Inventory [33]. The full scale score was used in the present analysis and this measure had reliability (alpha) of 0.76. (e) Child IQ (8 years): when sample members were aged 8 years, children were assessed on the Revised Wechsler Intelligence Scale for Children [34]. The full scale score was used in the present analysis. The reliability of this scale, assessed using split half methods, was 0.93.

Statistical analysis

Associations between frequency of cannabis use and psychotic symptoms
The first stage of the analysis reports the bivariate associations between the extent of cannabis use over the age intervals 17–18, 20–21 and 24–25 years and rates of psychotic symptoms reported at ages 18, 21 and 25. The association between the level of cannabis use and the rate of psychotic symptoms in each year was assessed using a negative binomial regression model in which the rate of psychotic symptoms was modelled as a log-linear function of the level of cannabis use. The negative binomial model provides a useful alternative to Poisson regression for count data in the presence of overdispersion, that is where the variance of the outcome variable is greater than would be expected of a true Poisson [35]. In each case the significance of the association was assessed using the log likelihood ratio $\chi^2$ statistic for the effect of cannabis use from the fitted model. Tests were conducted using both linear models and design variates to assess the impact of cannabis use. These tests showed that, in all cases, the linear model provided the best fit to the observed data.

Covariate adjustment models
To adjust the associations between cannabis use and psychotic symptoms for confounding factors, a series of covariate adjustment models were fitted to the joint data over the three measurement periods. These models were as follows.

Model 1: the population averaged model. In this model the rate of psychotic symptoms at each time was modelled as a log-linear function of (a) the level of cannabis use in the
past year. (b) the set of observed fixed covariates described above and (c) the set of observed time-dynamic covariates described above. The kernel of this model was a Poisson regression model of the form:

\[
\text{Log} (Y_{it}) = B0 + B1 X_{it} + \Sigma B_j Z_j + \Sigma B_k Z_{kt}
\]

where \(Y_{it}\) was the rate of psychotic symptoms for the \(i\)th participant at time \(t\), \(X_{it}\) was the corresponding measure of cannabis use at time \(t\), \(Z_j\) were the set of observed fixed covariates and \(Z_{kt}\) the set of observed time-dynamic covariates. In this model, the coefficient \(B1\) represents the effect of cannabis use on the rate of psychotic symptoms after adjustment for covariates. This coefficient gives an estimate of the averaged effect of cannabis use on psychotic symptoms after adjustment for covariates obtained by pooling observations over the three measurement periods. To take account of the correlations between repeated measures for the same participant over time the model also assumed an unstructured covariance matrix of the model disturbances over time.

**Model 2: the random effects model.** This model also adjusted the pooled association between frequency of cannabis use and psychotic symptoms for observed fixed and time-dynamic covariates. However, the model differed from Model 1 in that it also permitted an individual specific intercept term. The general form of this model was:

\[
\text{Log} (Y_{it}) = a_i + B1 X_{it} + \Sigma B_j Z_j + \Sigma B_k Z_{kt}
\]

where \(a_i\) was the individual specific intercept and all other variables were as defined above. The random effects model assumes that the individual intercept terms are independent of each other and are uncorrelated with the other predictors in the equation [36].

**Model 3: the conditional fixed effects model.** The general form of this model was:

\[
\text{Log} (Y_{it}) = a_i + B1 X_{it} + \Sigma B_k Z_{kt}
\]

In this model the \(a_i\) are individual specific terms that are assumed to reflect the effects of all fixed sources of variation in the outcome \(Y_{it}\). These effects are assumed to be constant over time and may be correlated with other predictors in the model. The major advantage of the fixed effects model is that it can adjust for all sources of fixed covariate effects, including non-observed fixed confounders [37]. Thus, for example, the fixed effects model can adjust for such non-observed factors as fixed genetic factors that influence the risks of both cannabis use and psychotic symptoms.

More detailed accounts of the differences between these three models can be found in [35–37]. In the first instance, all three models were fitted to the data using Poisson regression methods. The analyses were then repeated using equivalent negative binomial regression models to account for overdispersion in the distribution of psychotic symptoms. Both sets of analyses produced the same conclusions, and the negative binomial results are reported in the paper. All models were fitted using Stata 6.0 [38].

From the fitted models, estimates of the adjusted incidence rate ratios (IRRs) of psychotic symptoms for varying levels of cannabis use were calculated relative to non-users of cannabis. For a given model, the adjusted IRR for a one-level increase in the frequency of cannabis use was given by \(e^{B1}\), where \(B1\) was the regression coefficient associated with cannabis use in the fitted model and \(e\) is the base of natural logarithms.

**Structural equation modelling**

Although the covariate adjustment models above address sources of confounding, these models do not provide tests of the direction of causality (if any) between cannabis use and psychotic symptoms. To explore this issue, a series of structural equation models were fitted to the data. These models are depicted in Figs 1 and 2.

The model in Fig. 1 assumes that: (a) the observed measures of cannabis use (\(C_t, t = 1,2,3\)) over the three time periods are linked by an autoregressive structure in which past cannabis use predicts future cannabis use; (b) the observed measures of psychotic symptoms (\(P_t, t = 1,2,3\)) are also linked by a similar autoregressive structure in which past symptoms predict future symptoms; (c) within time periods cannabis use and psychotic symptoms are potentially reciprocally related so that (i) current cannabis use may influence current psychotic symptoms and (ii) current psychotic symptoms may influence current cannabis use. These reciprocal effects are assumed to be constant over time. The model specification is:

**Model equations**

\[
C1 = B1 P1 + B3 C2 + B5 C1 + v1 \quad P3 = B2 C3 + B6 P2 + B8 P1 + t3
\]

\[
C2 = B1 P2 + B4 C1 + v2 \quad P2 = B2 C2 + B7 P1 + t2
\]

\[
C1 = B1 P1 + v1 \quad P1 = B2 C1 + t1
\]

**Model assumptions**

\[
\text{Cov} (\text{tr}, ts) = \text{Cov} (\text{tr}, vs) = \text{Cov} (\text{tr}, ts) = 0 \text{ for } r \neq s
\]

\[
\text{Cov} (C_r, vs) = \text{Cov} (P_r, vs) = 0 \text{ for } r < s
\]

\[
\text{Cov} (C_r, ts) = \text{Cov} (P_r, ts) = 0 \text{ for } r < s
\]

In terms of assessing the direction of causality between cannabis use and psychotic symptoms, the values of the parameters \(B1, B2\) may provide important information about both the size and direction of this influence.

A limitation of the autoregressive model in Fig. 1 is that this model does not take into account common con-
founding factors that may influence both cannabis use and psychotic symptoms. This issue is addressed in the model in Fig. 2 which includes fixed effects factors to take into account: (i) fixed factors that influence cannabis use and (ii) fixed factors that influence psychotic symptoms. Specifically, the model assumes that: (a) the observed measures of cannabis use (Ct) are influenced by fixed sources of variance (C) that are constant over time and time-dynamic sources of variation (Ut); (b) the observed measures of psychotic symptoms (Pt) are also influenced by fixed sources of variation (P) that are constant over time and time-dynamic sources of variation (Wt); (c) the fixed factors C and P are permitted to be correlated; (d) the time-dynamic components of cannabis use (Ut) and psychotic symptoms (Wt) are linked by autoregressive processes in which past cannabis use predicts future cannabis use and past psychotic symptoms predict future psychotic symptoms, respectively; (e) the time dynamic components of cannabis use and psychotic symptoms are reciprocally related so that current Ut influences current Wt and vice versa. These reciprocal effects are assumed to be constant over time. The specification for this model as follows:

Model equations
\[ C_t = C + U_t \quad (t = 1, 2, 3) \]
\[ P_t = P + W_t \quad (t = 1, 2, 3) \]
\[ U_3 = B_1 W_3 + B_3 U_2 + v_3 \]
\[ W_3 = B_4 U_3 + B_5 W_2 + \tau_3 \]
\[ U_2 = B_1 W_2 + B_4 U_1 + v_2 \]
\[ W_2 = B_2 U_2 + B_6 W_1 + \tau_2 \]
\[ U_1 = B_1 W_1 + v_1 \]
\[ W_1 = B_2 U_1 + \tau_1 \]

Model assumptions
\[ \text{Cov} (C, U_t) = \text{Cov} (C, W_t) = \text{Cov} (C, v_t) = \text{Cov} (C, \tau_t) = 0 \]
\[ (t = 1, 2, 3) \]
\[ \text{Cov} (P, U_t) = \text{Cov} (P, W_t) = \text{Cov} (P, v_t) = \text{Cov} (P, \tau_t) = 0 \]
\[ (t = 1, 2, 3) \]
\[ \text{Cov} (P, v_t) = \text{Cov} (P, \tau_t) = 0 \text{ for } r < s \]
\[ \text{Cov} (U_t, v_t) = \text{Cov} (U_t, \tau_t) = \text{Cov} (W_t, v_t) = \text{Cov} (W_t, \tau_t) = 0 \text{ for } r < s \]

The advantage of the model specification in Fig. 2 is that it estimates the pathways between cannabis use and psychotic symptoms, taking into account non-observed fixed factors associated with these measures.

The models depicted in Figs 1 and 2 were fitted to the observed measures of cannabis use and psychotic symptoms at age 18, 21 and 25 years. As the observed measures were markedly non-normally distributed the models were fitted to the covariance matrix of the observed data using the method of weighted least squares. All models were fitted using LISREL 8 [39]. Model goodness of fit was assessed on the basis of a number of indices including: (a) the log-likelihood ratio \( \chi^2 \) statistic; (b) the root mean squared error of approximation (RMSEA). Values of RMSEA less than 0.05 are assumed to be indicative of a well-fitting model; (c) the standardized root mean squared residual correlation (RMSR) between the observed measures. Values of RMSR close to zero indicate a well-fitting model. (d) The Comparative Fit Index (CFI). This index varies between 0 and 1 with values close to 1 indicating a well-fitting model [39].

Missing data and sample bias
As noted above, the analysis is based on the sample of 1055 participants for whom data on cannabis use and psychotic symptoms at age 18, 21 and 25 years.
psychotic symptoms were available on at least one occasion from 18, 21 and 25 years. However, as not all participants were assessed at all ages the observed sample numbers vary between age 18 \((n=1025)\), age 21 \((n=1011)\) and age 25 \((n=1003)\). These samples represented between 79% and 81% of the initial cohort of 1265 participants. In addition, as a result of missing data on some covariates the sample number included in the covariate adjustment analyses was reduced to approximately 900.

To examine the implications of sample attrition and missing data for study conclusions a series of additional analyses were undertaken. First, regression imputation methods were used to impute estimates for the missing data on covariate factors, and the covariate adjustment analyses were repeated with the missing data replaced by their imputed values. The regression imputation was conducted using the impute procedure of Stata 6.0 [38]. Secondly, to adjust for possible sample selection bias resulting from sample attrition, the methods described by Carlin et al. [40] were used. These methods involved a two-stage analysis process. In the first stage of the analysis, a sample selection model was constructed by using data gathered at birth to predict participation at each age. This analysis showed that there were statistically significant \((P<0.05)\) tendencies for the obtained sample at each age to under-represent children from more socially disadvantaged backgrounds (low parental education, low socio-economic status, single-parent family).

On the basis of the fitted selection models, the sample was then poststratified into a series of groups and the probability of study participation estimated for each group at each age.

In the second stage of the analysis the data were re-analysed by fitting a negative binomial regression model to the full data with the observations for each individual weighted by the inverse of the probability of study participation estimated for each group at each age.

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RESULTS

Associations between cannabis use and rates of psychotic symptoms at 18, 21 and 25 years

Table 1 shows the relationship between reported rates of cannabis use in the past 12 months at ages 18, 21 and 25 years, and self-reported psychotic symptoms at these ages. Each comparison is tested for statistical significance using the log likelihood ratio \(\chi^2\) statistic derived from a negative binomial regression model. The analysis shows that at all ages there were clear and highly statistically
significant \((P < 0.0001)\) trends for increasing use of cannabis to be associated with increasing rates of psychotic symptoms: young people who were daily users of cannabis had rates of psychotic symptoms that were between 2.3 and 3.3 times higher than the rates for those who did not use cannabis.

**Adjustments for covariate factors**

As explained in the Methods, the associations between cannabis use and psychotic symptoms were adjusted for observed covariates using three approaches to covariate adjustment: (a) a population averaged model using observed fixed and time dynamic covariates; (b) a random effects model using observed fixed and time-dynamic covariates; and (c) a fixed effects model that took into account both non-observed fixed factors and observed time dynamic covariates. The results of these analyses are given in Table 2, which shows the incidence rate ratios (IRRs) of psychotic symptoms and corresponding 95\% confidence intervals associated with each model after adjustment for covariates. In each case the IRRs show the rate of psychotic symptoms for a given level of cannabis use relative to non-users. All models yield highly consistent estimates that suggest that those who used cannabis daily had rates of psychotic symptoms that were in the region of 1.6–1.8 times higher than those who did not use cannabis. Furthermore, the findings suggest that the adjustments for observed covariates in Models 1 and 2 produce conclusions that are consistent with the adjustments for non-observed covariates using the fixed effects model.

**Results from reciprocal causes models**

The findings in Table 2 are consistent with the view that cannabis use and psychotic symptoms may be linked by a cause-and-effect model. However, the analysis does not establish that this association is one in which increasing frequency of cannabis use leads to increased psychotic symptoms. To address this issue, the data were analysed using the reciprocal cause structural equation models described in the Methods. These models include the autoregressive model shown in Fig. 1 and the autoregressive model including fixed effects factors shown in Fig. 2. The key findings of this analysis are summarized in Table 3 which shows: (a) estimates of the fitted model

![Table 1](image1.png)

![Table 2](image2.png)

\(^1\)Observed fixed covariates included: gender; parental education; family socio-economic status; family living standards; changes of parents; parental alcohol problems; parental illicit drug use; parental depression/anxiety; parental criminality; childhood sexual abuse; childhood physical abuse; neuroticism; novelty seeking; self-esteem; parental attachment; child IQ. \(^2\)Observed time dynamic covariates included: prior psychotic symptoms; prior frequency of cannabis use; concurrent and prior mental disorders (major depression, anxiety disorders, alcohol dependence, nicotine dependence, illicit drug dependence, conduct disorder/asd); adverse life events; deviant peer affiliations.
parameters and standard errors for the effects of cannabis use on psychotic symptoms and the effects of psychotic symptoms on the frequency of cannabis use: (b) measures of model fit including the log likelihood ratio $\chi^2$ test statistic, the (RMSEA), the standardized root mean squared residual correlation (SRMR) and the comparative fit index (CFI). The results of the structural equation models suggest the following conclusions:

1. For both models, cannabis use had a positive and significant effect ($P < 0.001$) on psychotic symptoms, implying that increasing cannabis use was associated with increased symptom levels.

2. For both models, the effect of psychotic symptoms on cannabis use was negative and, for Model 2, statistically non-significant. These results imply that it was unlikely that the development of psychotic symptoms led to increased use of cannabis and that, if anything, the development of these symptoms may have inhibited rather than encouraged cannabis use.

3. Both models proved to be well fitting on the basis of a range of goodness of fit measures.

Collectively, the results in Tables 2 and 3 are consistent with two major conclusions. First, the use of cannabis and rates of psychotic symptoms were related to each other, independently of observed/non-observed fixed covariates and observed time dynamic factors (Table 2). Secondly, the results of structural equation modelling suggest that the direction of causation is that the use of cannabis leads to increases in levels of psychotic symptoms rather than psychotic symptoms increasing the use of cannabis. Indeed, there is a suggestion from the model results that increases in psychotic symptoms may inhibit the use of cannabis.

DISCUSSION

This analysis has used data gathered over the course of a 25-year longitudinal study to address two issues regarding the linkages between the use of cannabis and psychotic symptoms. The first issue concerned the extent to which the association between cannabis use and psychotic symptoms reflected uncontrolled confounding factors. The second issue addressed the direction of causality (if any) between cannabis use and psychotic symptoms. The findings of these analyses are reviewed below.

The effects of confounding factors

One of the more controversial issues regarding linkages between cannabis use and psychosis/psychotic symptoms has concerned the extent to which these linkages reflect uncontrolled residual confounding [15]. In this paper we have attempted to address this problem by adjusting these associations using two approaches to covariate control. In the first approach we controlled for observed confounders using extensive prospectively collected covariate data. In the second approach we used fixed effects regression to control for non-observed fixed sources of confounding. Both methods of adjustment gave similar results and suggested the presence of a dose–response relationship between the frequency of cannabis use and rates of psychotic symptoms. It was estimated that daily users of cannabis had rates of these symptoms that were 1.6–1.8 times higher than non-users of cannabis even after both observed and non-observed sources of confounding were taken into account.

These results add to a growing body of evidence that now suggests that the linkages between cannabis use and psychotic symptoms are likely to be causal and are unlikely to be due to sources of uncontrolled residual confounding. None the less, the possibility of residual confounding cannot be dismissed entirely because although the regression models used in this analysis controlled for both observed and non-observed fixed factors, the possibility of confounding by (non-fixed) time-dynamic factors remains. A further issue concerns the assessment of psychotic symptoms. In this study we have used a scale measure based on a count of symptoms. However, it could be suggested that this measure differs

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Estimated reciprocal effects of frequency of cannabis use and psychotic symptoms for alternative structural equation models.</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Effect of cannabis use on psychotic symptoms</td>
</tr>
<tr>
<td>Model</td>
<td>$B$ (SE)</td>
</tr>
<tr>
<td>Model 1: autoregressive model on observed variables</td>
<td>0.154 (.044)</td>
</tr>
<tr>
<td>Model 2: autoregressive model incorporating non-observed fixed effects</td>
<td>0.352 (.087)</td>
</tr>
</tbody>
</table>

Goodness of fit indices: (a) for model 1, LR $\chi^2(4) = 7.6$, $P > 0.10$; RMSEA = 0.03, $P > 0.80$; SRMR = 0.029; CFI = 0.998. (b) For model 2, LR $\chi^2(5) = 4.00$, $P > 0.50$; RMSEA = 0.00, $P > 0.98$; SRMR = 0.017; CFI = 1.00.

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from diagnostic classification and also may not disclose all aspects of psychosis. While measurement issues are a potential threat to validity in studies of cannabis and psychosis, this threat does not appear to be large. As recent reviews [1–3] have shown, authors using range of measures including diagnostic classifications and scale dimensions have been able to show linkages between the use of cannabis and rates of psychosis/psychotic symptoms. Despite these caveats we believe that the weight of the evidence is now firmly in favour of the view that cannabis use and psychosis/psychotic symptoms are likely to be causally related.

**Direction of causality**

The demonstration that cannabis use and psychotic symptoms remain associated even following control for confounding suggests a causal linkage, but does not establish the direction of causality. There are potentially two causal pathways by which cannabis use and psychosis may be linked. First cannabis use may lead (via biochemical changes in the brain) to increased rates of psychotic symptoms amongst susceptible users. Alternatively, those prone to psychosis or psychotic symptoms may be more prone to use cannabis as a consequence of their condition and perhaps as an attempt at self-medication [41,42]. Resolving this issue is clearly critical to understanding the causal role that cannabis use may play in psychosis. To address this issue we have employed methods of structural equation modelling that permit estimation of reciprocal causal pathways. Two models were fitted, with the first using a relatively simple autoregressive structure to identify model parameters and the second incorporating fixed effects models for cannabis use and psychotic symptoms. Both models led to similar conclusions about the possible causal linkages between cannabis use and psychotic symptoms. First, there was clear evidence to suggest that increasing use of cannabis was associated with statistically significant increases in the risks of psychotic symptoms. Secondly, increasing psychotic symptoms were not positively associated with increased rates of cannabis use and indeed the fitted autoregressive model suggested that the association between psychosis and cannabis use may be negative, so that increasing psychotic symptoms were associated with a decline in the use of cannabis. The weight of the evidence from the SEM approach clearly suggests the presence of a causal process in which increasing use of cannabis is associated with increasing rates of psychotic symptoms.

Of course, these conclusions rest upon some of the relatively strong assumptions (see Methods) required to identify these models, but it is important to note that these assumptions did not favour finding a particular causal pathway between cannabis use and psychotic symptoms.

**Does cannabis use cause psychosis?**

Finally, the present study needs to be seen in the context of a wider literature that has explored the issue of cannabis use and psychosis. This literature is beginning to provide the foundations of a coherent picture that supports the view that cannabis use may contribute to psychosis or psychotic symptoms in individuals vulnerable to these conditions. This evidence includes:

1. The growing epidemiological evidence (including the present study) that suggests evidence of dose–response relationships between the extent of cannabis use and subsequent psychosis/psychotic symptoms even following control for sources of confounding and possible reverse causality [4–7].
2. Evidence from clinical studies suggesting that cannabis use is associated with an increased relapse rate in individuals with schizophrenia [43,44].
3. Growing neuropsychological evidence on the multiple effects of cannabis on the brain and brain biochemistry [12,13].
4. Evidence from laboratory-based studies suggesting that the acute effects of cannabis intoxication may create psychotic-like symptoms and may be used as a ‘model’ psychosis [8,11].

Although each of these lines of evidence is subject to uncertainty and debate, the weight of the evidence clearly suggests that the use of cannabis (and particularly the heavy use of cannabis) may alter underlying brain chemistry and precipitate the onset of psychosis/psychotic symptoms in vulnerable individuals. The present study adds to this evidence by showing: (a) it is unlikely (although not impossible) that the association between cannabis use and psychotic symptoms in a population sample was due to confounding factors, and (b) the predominant direction of causality is likely to involve a path from cannabis use to psychotic symptoms rather than a path from psychotic symptoms to cannabis use.

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**References**

Testing hypotheses about the relationship between cannabis use and psychosis

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Abstract

Aim: To model the impact of rising rates of cannabis use on the incidence and prevalence of psychosis under four hypotheses about the relationship between cannabis use and psychosis. Methods: The study modelled the effects on the prevalence of schizophrenia over the lifespan of cannabis in eight birth cohorts: 1940–1944, 1945–1949, 1950–1954, 1955–1959, 1960–1964, 1965–1969, 1970–1974, 1975–1979. It derived predictions as to the number of cases of schizophrenia that would be observed in these birth cohorts, given the following four hypotheses: (1) that there is a causal relationship between cannabis use and schizophrenia; (2) that cannabis use precipitates schizophrenia in vulnerable persons; (3) that cannabis use exacerbates schizophrenia; and (4) that persons with schizophrenia are more liable to become regular cannabis users. Results: There was a steep rise in the prevalence of cannabis use in Australia over the past 30 years and a corresponding decrease in the age of initiation of cannabis use. There was no evidence of a significant increase in the incidence of schizophrenia over the past 30 years. Data on trends the age of onset of schizophrenia did not show a clear pattern. Cannabis use among persons with schizophrenia has consistently been found to be more common than in the general population. Conclusions: Cannabis use does not appear to be causally related to the incidence of schizophrenia, but its use may precipitate disorders in persons who are vulnerable to developing psychosis and worsen the course of the disorder among those who have already developed it.

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Keywords: Cannabis use; Psychosis; Schizophrenia

1. Introduction

Clinical research has shown that high proportions of persons with schizophrenia report regular cannabis use and meet criteria for cannabis use disorders (Fowler et al., 1998; Mueser et al., 1990; Ziedonis and Trudeau, 1997). Epidemiological studies have also found an association between cannabis use and psychosis in the general population (Anthony and Helzer, 1991; Cuffel et al., 1993; Degenhardt and Hall, 2001; Tien and Anthony, 1990). There has been considerable debate about the reasons for this association (Batel, 2000; Blanchard et al., 2000; Gruber and Pope, 1994; Hall, 1998; Hall and Degenhardt, 2000; McKay and Tennant, 2000; Mueser et al., 1998; Rosenthal, 1998; Thornicroft, 1990). Depending upon the nature of the relationship between cannabis use and psychosis, changes in the prevalence of cannabis use may potentially lead to changes in the incidence, prevalence or age of onset of psychosis.

In Australia, there has been a dramatic increase in the prevalence of cannabis use since the early 1970s (Degenhardt et al., 2000; Donnelly and Hall, 1994; Makkai and McAllister, 1998; McCoy, 1980). The present report assesses the evidence for four hypothesised relationships between cannabis use and psychosis, which would each predict different effects of increased cannabis use on the incidence, prevalence and age of onset of schizophrenia and the prevalence of chronic cannabis use among persons with the disorder.

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E-mail address: l.degenhardt@unsw.edu.au (L. Degenhardt).
1.1. **Hypothesis 1: Cannabis use causes psychosis**

According to this hypothesis there is a causal link between cannabis use and schizophrenia in the sense that cannabis use causes cases of the disorder that would not otherwise have occurred. This hypothesis has arisen from reports of ‘cannabis psychoses’ (Basu et al., 1999; Bernardson and Gunne, 1972; Carney et al., 1984; Chopra and Smith, 1974; Eva, 1992; Solomons et al., 1990; Tennant and Groesbeck, 1972; Wylie et al., 1995) and there is some evidence that cannabis users are more likely to report psychotic symptoms (e.g. Andreasen et al., 1987; Degenhardt and Hall, 2001; Tien and Anthony, 1990).

If this hypothesis is correct, then an increase in prevalence of cannabis use among young adults should increase the incidence and ultimately the prevalence of schizophrenia. Since there has been a dramatic rise in the prevalence of cannabis use in Australia, this hypothesis predicts an increase in the greater number of cases of schizophrenia among recent birth cohorts. Since the age of cannabis initiation has also declined, this hypothesis also predicts that the age of onset of schizophrenia would decline in recent birth cohorts. This hypothesis also predicts a rising prevalence of cannabis use among persons with schizophrenia.

1.2. **Hypothesis 2: Cannabis use precipitates psychosis among vulnerable individuals**

A second hypothesis is that regular cannabis use precipitates schizophrenia among vulnerable individuals, that is, among persons who would have developed the disorder regardless of whether they used cannabis or not (Hall, 1998). This is supported by evidence that: (a) persons with first-episode schizophrenia who use cannabis are younger than those who do not (Linszen et al., 1994; Mathers et al., 1991; Rolfe et al., 1993); (b) cannabis use usually precedes the development of psychotic symptoms (Allebeck et al., 1993; Hambrecht and Haefner, 2000; Linszen et al., 1994); and (c) among first-episode cases of psychosis, those who used cannabis were more likely to have a family history of psychosis (McGuire et al., 1995).

According to this hypothesis, an increase in regular cannabis use in the general population would not affect the incidence of schizophrenia but it would reduce the age of onset of psychotic illness among those who used cannabis. That is, the incidence rates of persons using cannabis would be ‘brought forward’. If this led to more chronic psychotic disorders (e.g. because earlier onset cases are more likely to relapse) the prevalence of chronic cases of psychosis would increase. This would increase the prevalence of regular cannabis use among persons with schizophrenia.

1.3. **Hypothesis 3: Cannabis use worsens the prognosis of persons with schizophrenia**

According to this hypothesis, cannabis use would worsen the prognosis of schizophrenic persons by increasing relapse to schizophrenia. It is supported by evidence that persons with schizophrenia who use cannabis are more likely to suffer a relapse (Jablensky et al., 1991; Linszen et al., 1994). This hypothesis does not predict an increased incidence of schizophrenia among regular cannabis users. Instead, it predicts that persons with schizophrenia who are regular cannabis users will be more likely to have a relapse after their initial episode. This could increase the number of persons in the population with chronic schizophrenia. It would not affect the age of onset of psychosis. The prevalence of cannabis use among persons with schizophrenia would increase because there would be more cannabis users among chronic cases.

1.4. **Hypothesis 4: Regular cannabis use is more likely among persons with psychosis**

According to this hypothesis, persons with schizophrenia are more likely to become regular cannabis users, if they use the drug (Mueser et al., 1998). There is no causal relationship between cannabis use and psychosis, so increasing rates of cannabis use will have no effect upon the incidence or prevalence of schizophrenia and there would not be a change in age of onset. There would be an increased prevalence of cannabis use among persons with psychosis.

The predictions generated from each of these four hypotheses are summarised in Table 1; notably, each hypothesis has a unique set of predictions. We used mathematical modelling to assess the plausibility of these four hypotheses. We combined empirically derived information about the epidemiology of cannabis use and psychosis to predict trends in incidence, prevalence and age of onset of schizophrenia according to each of these hypotheses. These predicted trends were compared with evidence on observed trends in schizophrenia and cannabis use.

2. **Method**

2.1. **Parameters for schizophrenia**

2.1.1. **Incidence**

It was assumed that schizophrenia does not develop before the age of 15 years (Goldstein et al., 1984), and that new cases do not occur after the age of 54 years (Goldstein et al., 1984). Separate specific incidence rates were used for males and females because males have an earlier onset of schizophrenia on average than females.
Table 1
Predicted trends in schizophrenia, and in cannabis use among persons with schizophrenia, given an increase in the prevalence of regular cannabis use in the general population

<table>
<thead>
<tr>
<th>Trends in schizophrenia</th>
<th>Trends in cannabis use</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Incidence</td>
</tr>
<tr>
<td>(1) Causal</td>
<td>↑</td>
</tr>
<tr>
<td>(2) Precipitation</td>
<td>→</td>
</tr>
<tr>
<td>(3) Worse prognosis</td>
<td>→</td>
</tr>
<tr>
<td>(4) Increased risk of dependence</td>
<td>→</td>
</tr>
</tbody>
</table>

Note: → = no change; ↑ = increase; ↓ = decrease.

(Jablensky et al., 1991; Jones and Cannon, 1998). Estimates of the average incidence rate of schizophrenia per 100 000 population per year by age and gender were obtained from a case register in New South Wales, Australia (Goldstein et al., 1984) that covered a period when cannabis was not widely used in Australia (Donnelly and Hall, 1994).

2.1.2. Chronicity of schizophrenia
An earlier expert consensus view on the long-term outcomes of schizophrenia in Australia (Hall et al., 1985) was that: 25% of persons with schizophrenia would have a ‘good’ outcome (a single episode with 60 days in hospital); 40% would have a ‘median’ outcome (an average of 0.08 admissions to hospital per year for life); and 35% would have a ‘poor’ outcome (0.16 admission per year for life).

More recent evidence has supported the estimate that 25% of patients will not relapse after long follow-up periods (Eaton et al., 1992a,b; Mason et al., 1996). A number of other studies have found that relapse tends to be in the first few years after the initial episode, with rates levelling off afterwards (Carone et al., 1991; Eaton et al., 1992a,b; Mason et al., 1996). For the purposes of the present study, we assumed that over a period of 4 years, 75% of incident cases of schizophrenia will relapse and that 25% of cases will have a ‘good’ outcome (Eaton et al., 1992a,b; Hall et al., 1985; Mason et al., 1996).

Relapse rates are higher for cases with an earlier age of onset (Eaton et al., 1992a,b). Studies using a case register in Victoria, Australia, found that persons with the earliest age of onset (15–19 age group) were most likely to relapse, with the following relative risks (compared to the 15–19 age group) for older age groups: 0.84 (20–29), 0.73 (30–39), 0.68 (40–49), 0.59 (50–59) (Eaton et al., 1992a,b). These data were used to predict the probability of relapse (assuming an overall relapse rate of 75%; Fig. 1).

2.1.3. Mortality in schizophrenia
A meta-analysis by Brown (1997) estimated that the aggregate crude mortality rate of schizophrenia was 189 deaths per 10 000 population per year. The population mortality rate was obtained from Australian Bureau of Statistics and the rate in the general population was assumed equal to the rate among non-schizophrenic persons. For males the average rate of death was nine per 10 000 males per year and for females it was five per 10 000 females per year.

2.2. Parameters for cannabis use
We examined the natural history of cannabis use because it changes during a person’s lifetime. We therefore needed estimates of prevalence of cannabis use at each age over the life span of each of the birth cohorts. By combining the estimates of the cumulative lifetime prevalence of cannabis use with the pattern of persistence of cannabis use from the cohort study, we could estimate the number of people at each age in the birth cohort who were still using cannabis.

Data on lifetime patterns of cannabis use were obtained from two sources: a longitudinal study of the natural history of cannabis use (Chen and Kandel, 1995); and an analysis of birth cohorts trends in drug use (Degenhardt et al., 2000) derived from the Australian National Drug Strategy Household Survey (NDSHS).

2.2.1. Natural history of cannabis use
Data on patterns of cannabis use in a longitudinal study of cannabis use in the USA (Chen and Kandel, 1995) were used to estimate of the prevalence of monthly cannabis use in Australian birth cohorts using data on the lifetime prevalence of cannabis use in the 1998 NDSHS of the Australian population. The proportion using cannabis at least monthly for each birth cohort was estimated by multiplying the above rates by the ratio of the proportion of persons in the birth cohort who had used cannabis to the proportion in Chen and Kandel’s cohort.

The modelling also took account of the substantial decline in the age of first cannabis use among successive birth cohorts in Australia (Degenhardt et al., 2000). The mean age of first reported use of cannabis has decreased.
by approximately 2 years with each successive birth cohort. The following assumptions were made:

- that the curve for each birth cohort was that observed by Chen and Kandel (1995);
- that each of these curves moved to the left by 2 years for each successive birth cohort;
- that the absolute position of these curves could be estimated by anchoring the birth cohort that was the same as the cohort in Chen and Kandel’s study (i.e. the 1955–1959 birth cohort). The peak periods of cannabis use for the 1965–1969, 1970–1974, 1975–1979 birth cohorts between were estimated to be between the ages of 15 and 20, compared to 17–22 years for the 1960–1964 birth cohort, 19–24 years for the 1955–1959 birth cohort and so on;
- that there were no differences between birth cohorts in the duration of monthly cannabis use. There were no good data on birth cohort trends in the peak period of use of cannabis, so this simpler assumption was made. It is likely to reduce differences between birth cohorts;
- it was assumed that the prevalence of weekly or more frequent cannabis use was half of the proportion reporting monthly or more frequent use.

2.2.2. Mortality of cannabis users

Our analyses assume that there was no increase in mortality among cannabis users. Research has failed to find increased mortality among cannabis using males aged 34–36 years, after adjusting for alcohol and other drug use (Andreasson and Allebeck, 1990) or among cannabis using males and females aged 15–49 years (Sidney et al., 1997) over 8 years of follow up.

Details of formulae used to generate the models and their predictions are provided in Appendix A.

2.3. Application to Australian population numbers

The size of each birth cohort (by gender) was estimated from data published by the Australian Bureau of Statistics on June 30th of each year. The cohort sizes were estimated from the number in each year of birth who were still alive at 15 years.

3. Results

3.1. Modelling the natural history of cannabis use

Fig. 2 shows the estimated natural history of cannabis use in each of the birth cohorts. The peak prevalence of regular cannabis use occurs earlier in recent birth cohorts while peak prevalence of weekly use was higher for earlier birth cohorts.

3.2. Modelling the prevalence of schizophrenia

Fig. 3 shows the estimated prevalence of schizophrenia among Australian males and females according to age. The prevalence of schizophrenia by age 54 was 1.17% for males, and 1.08% for females. This is at the higher end of the estimated prevalence of schizophrenia (Jablensky et al., 1991; Robins and Regier, 1991) but it corresponds to a point prevalence of schizophrenia in 1998 of 0.7% for the population born between 1940 and 1979. This is very similar to previous estimates of the population prevalence of schizophrenia (Jablensky et al., 2000, 1991; Robins and Regier, 1991).

3.3. Modelling the hypothesised relationships

3.3.1. Hypothesis 1: Causal relationship

On this hypothesis, the prevalence of schizophrenia by age 25 years is estimated to be 0.38% among those in the 1940–1944 birth cohort, compared to 0.43% in the 1975–1979 birth cohort. The difference of 0.05% is a 14% increase in prevalence. At age 20 years, the difference between the oldest and youngest birth cohorts in the number of cases of schizophrenia—caused by cannabis use—is 125 cases. The total would increase from 736 males aged 20 years in the 1940–1944 birth cohort, to 861 in the 1975–1979 birth cohort. This is an increase of 17% (between the calendar years 1960–1964 and 1995–2000) in the number of cases aged 20 years with schizophrenia coming to the attention of treatment services.

Table 2 shows these results in terms of the number of additional incident cases that would have occurred by age 35 years on this hypothesis. Among the more recent birth cohorts—those born from the 1960s and later—by
the time they were 35 years old, there would be an additional 1225–1438 cases of schizophrenia per birth cohort. This would be an increase in the number of incident cases of schizophrenia of around 10% for each birth cohort. The number of new cases in the later cohorts (1225 cases) is almost 10 times larger than those in the oldest birth cohort (180 additional cases).

3.3.2. Hypothesis 2: Cannabis precipitates schizophrenia among vulnerable individuals

Table 3 shows the number of cases in each birth cohort whose onset would occur a year earlier if cannabis use precipitated schizophrenia. The age at which this would have the most marked effect would be age 14, when the only incident cases would be among...
cannabis users, and at age 19, when persons using cannabis regularly have higher incidence rates. In the 1940–1944 cohort, less than one case would have been precipitated at age 14 years whereas this would rise to 50 cases by age 14 among the younger male cohorts.

3.3.3. Hypothesis 3: Cannabis worsens prognosis

According to the hypothesis that cannabis use worsens prognosis, there would be an additional 106–130 chronic cases of schizophrenia caused by cannabis use by age of 35 years in the more recent birth cohorts (Table 4). However, these would comprise only 1% of all chronic cases by this age. This is because relapse rates among young adults were already very high so most cases would relapse regardless of whether they used cannabis use or not.

3.3.4. Hypothesis 4: Regular cannabis use is more likely among persons with psychosis

Fig. 4 shows the predicted prevalence of weekly cannabis use among persons with schizophrenia if such persons are twice as likely as those in the general population to become weekly users if they use cannabis in the past year. The prevalence of weekly cannabis use increases markedly among successive birth cohorts: among males 5% of those aged 20 years, among the 1940–1944 birth cohort would report weekly cannabis use, compared to over 40% of those born after 1965. A similar pattern is observed among females with schizophrenia.

3.4. Evaluation of the four hypotheses

The sections below discuss the available data on trends in the incidence and prevalence of psychosis, in the age of onset of psychosis, and in the prevalence of cannabis use among persons with psychosis; and compare these data with the predictions of the four hypotheses. Table 5 summarises the results of these comparisons.

3.4.1. Trends in the incidence of psychosis

Numerous studies conducted in many countries, including Australia (Parker et al., 1985), have reported declines in the incidence of schizophrenia over the past 30 years (Eagles and Whalley, 1985; Geddes et al., 1993; Joyce, 1987; Kendell et al., 1993; Munk-Jorgensen, 1995; Munk-Jorgensen and Mortensen, 1992; Suvisaari

---

### Table 2
Hypothesis 1 — Modelled number of incident cases of psychosis by 35 years caused by cannabis use by the age of 35 years, by gender and birth cohort

<table>
<thead>
<tr>
<th>Birth Cohort</th>
<th>Total incident cases by 35 years assuming no link</th>
<th>Total incident cases by 35 years if cannabis use caused psychosis</th>
<th>Number of incident cases by 35 years caused by cannabis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males</td>
<td>Females</td>
<td>Males</td>
</tr>
<tr>
<td>1940–44</td>
<td>3891</td>
<td>2898</td>
<td>3900</td>
</tr>
<tr>
<td>1945–49</td>
<td>5444</td>
<td>3903</td>
<td>5759</td>
</tr>
<tr>
<td>1950–54</td>
<td>3870</td>
<td>4380</td>
<td>6482</td>
</tr>
<tr>
<td>1955–59</td>
<td>6572</td>
<td>4896</td>
<td>7373</td>
</tr>
<tr>
<td>1960–64</td>
<td>7181</td>
<td>5301</td>
<td>7984</td>
</tr>
<tr>
<td>1965–69</td>
<td>6995</td>
<td>5197</td>
<td>7768</td>
</tr>
<tr>
<td>1970–74</td>
<td>7625</td>
<td>5664</td>
<td>8480</td>
</tr>
<tr>
<td>1975–79</td>
<td>6948</td>
<td>5128</td>
<td>7689</td>
</tr>
</tbody>
</table>

---

### Table 3
Hypothesis 2 — Modelled number of additional cases that would be precipitated 1 year earlier by cannabis use by gender and birth cohort

<table>
<thead>
<tr>
<th>Birth Cohort</th>
<th>Cases precipitated at 14 years</th>
<th>Cases precipitated at 19 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males</td>
<td>Females</td>
</tr>
<tr>
<td>1940–44</td>
<td>0.2</td>
<td>0.01</td>
</tr>
<tr>
<td>1945–49</td>
<td>0.4</td>
<td>0.05</td>
</tr>
<tr>
<td>1950–54</td>
<td>0.07</td>
<td>0.07</td>
</tr>
<tr>
<td>1955–59</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>1960–64</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>1965–69</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>1970–74</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>1975–79</td>
<td>17</td>
<td>17</td>
</tr>
</tbody>
</table>

---

### Table 4
Hypothesis 3 — Modelled number of additional chronic cases of psychosis due to cannabis use observed by the age of 35 years, by gender and birth cohort

<table>
<thead>
<tr>
<th>Birth Cohort</th>
<th>Additional chronic cases by age 35 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males</td>
</tr>
<tr>
<td>1940–44</td>
<td>12</td>
</tr>
<tr>
<td>1945–49</td>
<td>38</td>
</tr>
<tr>
<td>1950–54</td>
<td>68</td>
</tr>
<tr>
<td>1955–59</td>
<td>82</td>
</tr>
<tr>
<td>1960–64</td>
<td>77</td>
</tr>
<tr>
<td>1965–69</td>
<td>70</td>
</tr>
<tr>
<td>1970–74</td>
<td>76</td>
</tr>
<tr>
<td>1975–79</td>
<td>63</td>
</tr>
</tbody>
</table>
et al., 1999). This has not been universal, however, with some reporting stable or increased rates (Bamrah et al., 1992; Castle et al., 1991; Haefner and an der Heiden, 1986; Harrison et al., 1991). One study concluded that incidence rates of psychosis in Australia had not changed in the period 1848–1978 (Haefner, 1987). It appears unlikely that there has been an increase in the incidence of schizophrenia in Australia. Given uncertainty about whether there has been a decrease in incidence, the most conservative conclusion is that the incidence rates of schizophrenia have remained stable and possibly decreased over the past several decades. It is unlikely that they have increased.

As hypothesis 1 predicted an increase in the incidence of psychosis, the available evidence does not support hypothesis 1. The other three hypotheses were consistent with this evidence: all predicted that increases in the prevalence of cannabis use would have little or no effect upon the incidence of psychosis.

The evidence that the incidence of psychosis has remained stable is consistent with hypothesis 2. So too is: recent evidence that more cases of schizophrenia are diagnosed as ‘drug-induced’ (although this could reflect clinicians’ assumptions that substance use is precipitating the disorder, Brewin et al., 1997); and the fact that cases in more recent birth cohorts have a younger average age of onset (DiMaggio et al., 2001).

3.4.2. Trends in the prevalence of psychosis

The data presented above also suggested that the prevalence of psychosis has not increased. This was not consistent with the increased prevalence of hypothesis 1,

Table 5
Consistency of predicted and actual trends in schizophrenia, and in cannabis use among persons with schizophrenia

<table>
<thead>
<tr>
<th>Trends in schizophrenia</th>
<th>Trends in cannabis use</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Incidence</td>
</tr>
<tr>
<td>(1) Causal</td>
<td>X</td>
</tr>
<tr>
<td>(2) Precipitation</td>
<td>✓</td>
</tr>
<tr>
<td>(3) Worse prognosis</td>
<td>✓</td>
</tr>
<tr>
<td>(4) Increased risk of dependence</td>
<td>✓</td>
</tr>
</tbody>
</table>

Note: ✓ = evidence appeared to support the prediction of this hypothesis; X = evidence did not appear to support the prediction of this hypothesis; ? = there was insufficient evidence to determine the nature of the trends.
something that would certainly have been noted by case registers.

It is more difficult to assess the validity of hypothesis 3, which predicted a very small (at most 1%) increase in the number of chronic cases of schizophrenia by age 35 years. An increase of this size would be difficult, if not impossible, to detect using existing epidemiological and clinical data. This means that even if cannabis use increases the rate of relapse, it will make a very small difference to the number of persons with chronic schizophrenia.

Hypotheses 3 and 4 did not predict any change in the prevalence of psychosis. These predictions are also consistent with the limited data on the prevalence of schizophrenia.

3.4.3. Trends in the age of onset of schizophrenia

A recent study of first episode psychosis found a lower age of onset in more recent birth cohorts (DiMaggio et al., 2001). The evidence on the age of onset among first-episode cases of schizophrenia who use cannabis use is less certain. Some studies have found that such cases had a significantly younger age of onset than non-users of cannabis (Rolfe et al., 1993) but a number of studies have not done so (Gut-Fayand et al., 2001; McGuire et al., 1995).

The limited evidence on the average age of onset of schizophrenia makes it difficult to draw any conclusions about this indicator. Some evidence that the age of onset of schizophrenia has decreased in more recent birth cohorts is consistent with hypotheses 1 and 2 but clinical samples of first-episode psychosis have not consistently found that cannabis use is associated with an earlier onset of psychosis. Better controlled studies may clarify this issue.

3.5. Trends in the prevalence of cannabis use among persons with schizophrenia

It is difficult to interpret evidence on changes in the prevalence of regular cannabis use among schizophrenic persons over the past three decades. First, many studies report rates of cannabis use disorders in the lifetime rather than the past year. Second, selection biases in clinical samples (Berkson, 1946; Caron and Rutter, 1991; Galbaud Du Fort et al., 1993) make it difficult to know whether variations in prevalence across different samples reflect changes in referral processes or changes in prevalence of use. Third, there are few data on the prevalence of cannabis use among persons with schizophrenia in the Australian population. These have shown higher rates of lifetime (Fowler et al., 1998) and past year prevalence of dependence (Fowler et al., 1998) than in the Australian population (Hall et al., 1999). Because these studies are all recent, there is not much that can be concluded about trends in the prevalence of cannabis use among persons with psychosis in Australia. A conservative assumption is that the prevalence of cannabis use has increased among persons with schizophrenia at a similar rate to that in the general population of Australia over this period (Degenhardt et al., 2000).

The data on trends in the prevalence of cannabis use among persons with psychosis in Australia or anywhere else are so limited that it is impossible to draw any conclusions. The high rates predicted by hypothesis 4 are consistent with the findings in recent studies (Degenhardt et al., 2000; Fowler et al., 1998; Jablensky et al., 2000) but we do not know what rates of cannabis use were in previous years. If we make the reasonable assumption that rates of lifetime cannabis use have gone up among persons with schizophrenia at the same rate as in the Australian community (Donnelly and Hall, 1994), then these recent data are consistent with the hypothesis that persons with schizophrenia are more likely to become regular cannabis users than peers without the disorder.

4. Discussion

4.1. Does cannabis use cause psychosis?

The hypothesis that cannabis causes schizophrenia was not supported by the data on trends in the incidence of this psychosis in Australia. There was no evidence that there has been an increase in incidence over the past 30 years of the magnitude predicted by the hypothesis. This suggests that cannabis use has not caused cases of psychosis that would not otherwise have occurred. Even if regular cannabis use did double the risk of users developing schizophrenia (the ‘doubling’ of risk being the best estimate), the prevalence of schizophrenia in the population would increase from 1 to 2%. An increase of 1000 cases per birth cohort—as was predicted by our modelling—would have been noticed in clinical settings. The widespread discussion of apparent declines in the incidence of schizophrenia suggests that this hasn’t occurred. Even if some of the environmental risk factors for schizophrenia have been reduced, such as poor maternal nutrition, infectious disease, and poor antenatal and perinatal care (Eagles, 1991; Takei et al., 1996), it seems unlikely that the decline in incidence from these causes would have exactly offset an increase of 1000 incident cases per birth cohort predicted by the hypothesis that cannabis causes schizophrenia.

4.2. Does cannabis use precipitate psychosis?

This hypothesis is consistent with the evidence of a reduction in the age of onset of psychosis among persons born in more recent cohorts (DiMaggio et al.,
and with some findings that first episode psychosis cases who used cannabis were younger than non-users. It would also explain the recent increase in the diagnosis of ‘drug-induced’ psychoses (Brewin et al., 1997).

4.3. Does cannabis use worsen prognosis?

The third hypothesis made surprisingly little difference to the number of chronic cases that would be seen by age 35 years. It is consistent with the elevated rates of cannabis use among persons with psychotic illnesses, and with the results of prospective studies that have been carried out evaluating this issue.

4.4. Is regular cannabis use more likely among persons with psychosis?

This hypothesis is consistent with the high prevalence of cannabis use in Australian samples of persons with psychosis. If we assume that rates of cannabis use among persons with schizophrenia have gone up in parallel with those in the Australian community (Donnelly and Hall, 1994), then these recent data are consistent with this hypothesis.

4.5. Study limitations

Modelling of any trends such as those examined here has limitations, since it is based upon assumptions that may not be completely accurate. In the case of the present paper, two issues in particular must be noted.

The first is potential changes in the potency of cannabis use over time. This is an issue that has been a matter of some debate in recent years in Australia, as in other countries, with some claims that the THC content of cannabis has increased 30-fold over the past three decades. The data on this issue have been examined by Hall and Swift, who concluded that the limited evidence available suggested that the THC content of cannabis may have increased by 3–4% over this period (Hall and Swift, 2000). In any rate, if cannabis use were a cause of psychosis de novo, an increase in the potency of cannabis would be expected to result in an increase in the prevalence of psychosis, given the rise in cannabis use over the same period.

The second concerns changes in the classification of schizophrenia over the period examined here. Over time, the criteria used to define schizophrenia have become increasingly based upon empirically validated and rigorous definitions of the disorder. In particular, there has been increasing precision with which subtypes of psychotic illness have been defined. Unfortunately, given the limitations of the data available, it is not possible to examine trends in the clinical subtypes of psychosis with any degree of confidence.

5. Conclusions

This study has used modelling (incorporating data-based parameters) to predict what changes we would expect to see in the incidence and prevalence of schizophrenia if each of four hypotheses about the relationships between cannabis use and psychosis were true. The claim about cannabis and psychosis is widely understood in the popular media and public debate in Australia to imply that cannabis use has increased the number of cases of psychosis in the population (in the sense of causing cases of psychosis that would not otherwise have occurred). It is therefore interesting that using plausible assumptions, the present modelling exercise suggests that (a) cannabis use as a cause of cases of psychosis does not fit the data; and (b) it would be difficult to detect any increases even if cannabis use was a cause of incidence among those vulnerable to the disorder.

Notably, if there were a common causal mechanism for the association between cannabis use and psychosis, whereby common factors increased the likelihood of both cannabis use and psychosis, we would expect to see increases in psychosis along with increases in cannabis use. Since this was not the case, there does not appear to be strong support for common causes completely explaining the association that has been observed.

The other three hypotheses provided a better fit to the available data but because of data limitations it was difficult to decide between them. If cannabis use acts as a precipitant of psychosis, we would have seen small increases in the number of early onset cases. If cannabis use made relapse to psychotic symptoms, we would have seen small increases in the number of chronic cases. Finally, if persons with psychosis were more likely to become regular cannabis users, we would expect to see only a higher prevalence of regular cannabis use in this population. Future research needs to test these hypotheses in prospective studies. The results of this study suggest that persons at risk of psychosis may be advised of this possible relationship and counselled against using cannabis.

A similar approach to modelling may be useful in empirically assessing the plausibility of hypotheses about relationships between risk factors and the incidence and prevalence of other mental disorders in the population.

Appendix A: Equations

| C | prevalence of regular cannabis use |
| I | age-specific incidence rate of schizophrenia |
| R | age-specific relapse rate of schizophrenia |
Hypothesis 1: causal relationship

It was hypothesised that weekly cannabis use doubled the risk of developing schizophrenia—in other words, that regular cannabis users had an incidence rate of schizophrenia that was double that among persons who did not use cannabis. This risk ratio is based on previous work by Tien and Anthony (1990), Andreasson et al. (1987), and the NSMHWB (Degenhardt and Hall, 2001).

\[
N(\text{incident cases at year } n) \quad = (I_C C_n) + I_C (1 - C_n) \cdot N(\text{without schizophrenia at year } n)
\]

\[
N(\text{chronic cases at year } 2) \quad = N(\text{incident cases year } 1) \cdot R \cdot 0.25
\]

\[
N(\text{chronic cases at year } 3) \quad = N(\text{incident cases year } 2) \cdot R \cdot 0.25 + N(\text{incident cases year } 1) \cdot R \cdot 0.5
\]

\[
N(\text{chronic cases at year } 4) \quad = N(\text{incident cases year } 3) \cdot R \cdot 0.25 + N(\text{incident cases year } 2) \cdot R \cdot 0.5 + N(\text{incident cases year } 1) \cdot R \cdot 0.75
\]

\[
N(\text{chronic cases at year } 5) \quad = N(\text{incident cases year } 4) \cdot R \cdot 0.25 + N(\text{incident cases year } 3) \cdot R \cdot 0.5 + N(\text{incident cases year } 2) \cdot R \cdot 0.75 + N(\text{incident cases year } 1) \cdot R
\]

Hypothesis 2: Cannabis use precipitates psychosis among vulnerable individuals

This hypothesis assumes that there is no effect of regular cannabis use upon overall incidence or chronicity of psychosis, but that among persons who use cannabis there is a reduced age of onset of psychosis. It was assumed that persons using cannabis develop the illness 1 year earlier than those who do not use cannabis regularly. This estimate was taken from the study of Linszen and others in which those using cannabis were on average 1 year younger than those who did not use cannabis (Linszen et al., 1994).

\[
N(\text{incident cases at year } n) \quad = I_C^n \cdot N(\text{without schizophrenia at year } n)
\]

\[
N(\text{chronic cases at year } 2) \quad = N(\text{incident cases year } 1) \cdot (2 \cdot R \cdot C + R \cdot (1 - C))/4
\]

\[
N(\text{chronic cases at year } 3) \quad = N(\text{incident cases year } 2) \cdot (2 \cdot R \cdot C + R \cdot (1 - C))/4 + N(\text{incident cases year } 1) \cdot (2 \cdot R \cdot C + R \cdot (1 - C))/2
\]

\[
N(\text{chronic cases at year } 4) \quad = N(\text{incident cases year } 3) \cdot (2 \cdot R \cdot C + R \cdot (1 - C))/4 + N(\text{incident cases year } 2) \cdot (2 \cdot R \cdot C + R \cdot (1 - C))/2 + N(\text{incident cases year } 1) \cdot (2 \cdot R \cdot C + R \cdot (1 - C))/0.75
\]

Hypothesis 3: Cannabis use worsens prognosis

It was assumed that the chance of relapse (i.e. the occurrence of further psychotic episodes) was increased by 2.5 times among weekly cannabis users. This was based upon the findings of the Linszen and colleagues study, which found that those using cannabis at least weekly were 2.5 times more likely to relapse to psychotic symptoms (Linszen et al., 1994).

The model also assumed that (a) there is no association between cannabis use and precipitation of psychosis; and (b) that the percentage of persons using cannabis is initially the same among schizophrenic and non-schizophrenic persons.

\[
N(\text{incident cases at year } n) \quad = I_C^n \cdot N(\text{without schizophrenia})
\]

\[
N(\text{chronic cases at year } 2) \quad = N(\text{incident cases year } 1) \cdot (2 \cdot R \cdot C + R \cdot (1 - C))/4
\]

\[
N(\text{chronic cases at year } 3) \quad = N(\text{incident cases year } 2) \cdot (2 \cdot R \cdot C + R \cdot (1 - C))/4 + N(\text{incident cases year } 1) \cdot (2 \cdot R \cdot C + R \cdot (1 - C))/2
\]

\[
N(\text{chronic cases at year } 4) \quad = N(\text{incident cases year } 3) \cdot (2 \cdot R \cdot C + R \cdot (1 - C))/4 + N(\text{incident cases year } 2) \cdot (2 \cdot R \cdot C + R \cdot (1 - C))/2 + N(\text{incident cases year } 1) \cdot (2 \cdot R \cdot C + R \cdot (1 - C))/0.75
\]
N(chronic cases at year 5)  
= N(incident cases year 2)*(2*R*C + R*(1 - C))/4  
+ N(incident cases year 2)*(2*R*C  
+ R*(1 - C))/2 + 1²(2*R*C + R*(1 - C))*0.75  
+ N(incident cases year 2)*(2*R*C + R*(1 - C))

Hypothesis 4: Regular cannabis use is more likely among persons with psychosis

This hypothesis assumes that there is no effect of cannabis use upon either incidence or outcome (chronicity) of psychosis. The prevalence of regular (weekly) cannabis use among persons with psychosis was assumed to be double that in the general population. This is taken from research suggesting that regular or dependent cannabis use is twice as likely among persons who meet criteria for psychosis (Andreasson et al., 1987; Tien and Anthony, 1990). This hypothesis assumes that there is no effect of cannabis use upon either incidence or outcome (chronicity) of psychosis. The prevalence of regular (weekly) cannabis use among persons with psychosis will be assumed to be double that in the general population. This is taken from research suggesting that regular or dependent cannabis use is twice as likely among persons who are likely to meet criteria for psychosis (Andreasson et al., 1987; Tien and Anthony, 1990).

References


Types of Marijuana Users by Longitudinal Course*

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ABSTRACT. Objective: Taxonomies of alcoholism and antisocial behaviors based on developmental course converge on two-group classifications that emphasize early and late onset. Typologies for users of illicit drugs remain to be developed. This article proposes a developmental taxonomy of marijuana users. Method: Cluster analysis was applied to a representative community sample of 708 (364 male, 344 female) marijuana users followed from adolescence to age 34-35. The Ward method, followed by relocation, was used to classify marijuana users into different types based on age of onset, chronicity of heavy use and persistence of use. ANOVA and logit analyses were utilized to describe the cluster solution and examine the correlates of cluster membership. Results: Four marijuana use clusters were identified: early onset-heavy use, early onset-light use, mid onset-heavy use and late onset-light use. The groups differed from each other in degree of involvement in marijuana and other drugs, sociodemographic and lifestyle characteristics. The majority of those with early onset did not become heavily involved in marijuana. Unique factors were associated with membership in each group. Factors differentiating early from mid-onset heavy use included association with marijuana-using peers and having had a mental disorder. Peer delinquency was an additional factor differentiating early initiators who became heavy users from those who did not. Conclusions: A simple two-type classification fails to take into account the heterogeneity of early and late onset groups. By itself, early onset into marijuana will not lead to problematic use or rapid progression into the use of other drugs. Motivation underlying use and dysfunctional behaviors are associated with the development of problematic drug use and dependence. (J. Stud. Alcohol 61: 367-378, 2000)

THE STUDY OF developmental trajectories of involvement in the use of drugs can be approached using three strategies. One strategy identifies pathways of progression from one drug class to another, including legal, illegal and medically prescribed psychotropic drugs (Ensminger et al., 1982; Fleming et al., 1989; Huba, 1983; Kandel and Yamaguchi, 1993; Kandel et al., 1992; Mills and Noyes, 1984; Windle et al., 1989). A second strategy investigates increasing involvement within one drug class, from experimentation to casual use, abuse, dependence, desistence and relapse (Chen and Kandel, 1995; Raveis and Kandel, 1987). A third strategy investigates taxonomies based on developmental course.

Much research has been carried out to define taxonomies for alcoholism (Babor, 1996; Babor et al., 1992, 1994; Cloninger et al., 1981, 1986; Weber et al., 1989; Zucker et al., 1994, 1996) and antisocial behavior (Achenbach, 1993; Zucker, 1993). In alcoholics, the main forms are early-onset heavy users and late-onset light users, and the groups differ in each other in degree of involvement in marijuana and other drugs, sociodemographic and lifestyle characteristics. The majority of those with early onset did not become heavily involved in marijuana. Unique factors were associated with membership in each group. Factors differentiating early from mid-onset heavy use included association with marijuana-using peers and having had a mental disorder. Peer delinquency was an additional factor differentiating early initiators who became heavy users from those who did not. Conclusions: A simple two-type classification fails to take into account the heterogeneity of early and late onset groups. By itself, early onset into marijuana will not lead to problematic use or rapid progression into the use of other drugs. Motivation underlying use and dysfunctional behaviors are associated with the development of problematic drug use and dependence. (J. Stud. Alcohol 61: 367-378, 2000)

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included as a basis for classification. The differences are rooted in the dissimilar goals of clinicians and epidemiologists: treatment matching in one case, elucidation of causal processes in the other. Clinicians include, among the distinguishing characteristics of the types, variables that are causes or consequences of the behaviors of interest, thereby precluding gaining a clear understanding of their etiologies. One difference between the two types of alcoholism defined by Cloninger et al. (1981, 1986) and others, for example, is the presence or absence of delinquency. The variables selected for the present cluster analysis were restricted to those describing the individual's history of marijuana involvement.

The goals of our study are: (1) to identify developmental taxonomies of marijuana use in a general population sample and (2) to examine factors associated with each identified subtype. We relied on etiological research on adolescent drug use (Brook et al., 1990; Clayton, 1992; Costa et al., 1999; DeWit et al., 1995; Felix-Ortiz and Newcomb, 1992; Hawkins et al., 1992; Jessor et al., 1995; Kandel, 1984; Kandel et al., 1978; Stacy et al., 1992) to select variables that would be associated with membership in a specific developmental cluster. Factors predictive of substance use belong to four domains of variables: individual, family, peer group and more distal contextual factors. It is assumed that strong attachment and commitment to the major social institutions in the youth's life (i.e., family and school) foster the adoption of conventional norms and beliefs and protect against risk factors for drug use, including involvement with deviant drug-using peers and participation in delinquency activities. Familial influences include overall family climate, the quality of parent-child interaction, parental drug use and psychopathology. The role of deviant peers in the etiology and maintenance of drug use is one of the best replicated findings in drug research. Characteristics of the child, in particular difficult temperament, early childhood aggression and adolescent depressive symptoms, are associated with the development of drug use. Overall, four risk factors have been found to be most salient (directly or indirectly) in the development of adolescent substance use: poor parenting, particularly lack of monitoring and low closeness; parental drug use; association with a drug-using peer group; and the child’s prior behavioral difficulties and delinquency. We considered these risk and protective factors in relation to marijuana cluster membership, although not all relevant variables were available in our study.

Method

Sample

Data are derived from adults (N = 708; 364 male, 344 female) who ever used marijuana at least 10 times from the New York State Follow-Up Cohort. The cohort constitutes a representative sample of former adolescents, enrolled in grades 10 and 11 in 18 New York State public high schools in 1971-72, who were followed over 19 years, to age 34-35 (Kandel et al., 1976). Students who had not participated in the initial survey and, presumably, were chronic absentes, were also selected to permit unbiased estimates of the former student population at the follow-ups. Respondents were first contacted in 1971 (age 15-16) and reinterviewed in 1980 (age 24-25), 1984 (age 28-29) and 1990 (age 34-35). Of the initial target sample of adolescents still alive, 1,160 (71.7%) were reinterviewed in 1990. Informed consent was given for participation in the study.

Data were obtained through structured personal household interviews that included two charts designed to reconstruct the respondent’s life and drug histories on a monthly basis. The drug histories were obtained from respondents who had ever used each drug at least 10 times. At each interview respondents were asked about their frequency and quantity of use of each drug during the past 12 months, the months when they used each drug since the last interview, the periods of highest use, and frequencies and quantities used in those periods. Two analytical samples were used. Descriptive analyses were based on subjects (N = 708) who used marijuana at least 10 times and reported an age of first marijuana use; this number represents 81.4% of all those who reported ever using marijuana by ages 34-35. By the time of the initial survey, 40% had started using marijuana. Multivariate analyses were based on those who participated in the initial school survey and provided answers at each of the three interviews (n = 589).

Analytical strategies

Clustering procedure. The cluster analysis was based on three variables that described marijuana use from adolescence to middle adulthood: age of onset, months of near-daily marijuana use and use in the last year preceding the last interview.

The choice of a clustering method is a critical issue. Milligan and Cooper (1985) reviewed the 30 most popular cluster methods in a Monte Carlo simulation and concluded that no existing procedure provided sufficient information to identify the number of clusters in the data. Three statistics performed best for recovering the true cluster structure in the artificial data: a pseudo F statistic (Calinski and Harabasz, 1974); the Jc(2)/Jc(1) statistic (Duda and Hart, 1973), transformed by SAS into a pseudo r² statistic; and Sarle’s (1983) cubic clustering criterion (CCC). The statistics indicate the statistical significance of the change due to each specific combination but not which solution is the best in absolute terms. A good-fitting solution should explain at least two thirds of the variance in the clustering variables (Bergman, 1998).

Ward’s (1963) minimum-variance hierarchical method was implemented and estimated by SAS. The procedure
combines the two closest cases or clusters in terms of their standardized scores on the criteria variables, step-by-step until all cases are grouped into a single cluster. The estimated similarity coefficient is the squared Euclidean distance to the cluster means. These distances are summed for all the cases. At each step, the two cases or clusters that merge are those that result in the smallest increase in the overall sum of the squared within-cluster distances. At each step, the three statistics described above are also provided. A change of direction or a large change in values of the three statistics signal a significant difference between two solutions (Aldenderfer and Blashfield, 1984; SAS Institute, 1990). To further minimize the distance within each cluster and increase the proportion of variance explained by the solution selected, we applied the k-mean cluster technique to relocate some of the cases, while retaining the cluster center generated by the Ward method (Bergman, 1998). To validate the solution, we examined the differentiation of the clusters by individuals’ sociodemographic characteristics, and patterns and consequences of marijuana use (ANOVA).

**Multivariate models**

We estimated multivariate logistic regressions to identify the unique predictors of membership in each cluster. Since many predictors were measured at age 15-16, the multivariate models were estimated on the 589 marijuana users who ever used marijuana at least 10 times and participated in the initial school survey. As compared with these participants, users who had been absent from school at the initial survey were more likely to be male (61% vs 49%, $p < .05$), black (18% vs 6%, $p < .01$) and of lower education (mean years education = 13.2 vs 14.5, $p < .01$). They tended to report more extensive lifetime experience with marijuana than participants (used 1,000+ times: 39.5% vs 27.7%, $p < .05$), to be more likely to have been near-daily users (53.8% vs 42.9%, $p < .05$), and to have experienced a greater number of drug-related problems by 1990 ($p < .05$); they had lower school grades and were more delinquent in high school ($p < .05$). There were no significant differences between the two groups on ages of onset of marijuana, alcohol or cigarette use, proportion of last year marijuana users, and number of months used marijuana near-daily.

**Measures**

Selected sociodemographic and drug history variables were used to describe and validate the clusters in ANOVA. Variables, mostly measured in adolescence, were included as predictors of cluster membership in multivariate logistic regressions. There were 19 variables measuring: sociodemographic characteristics; drug use history; family history of drug use and psychiatric disorders; quality of parent-adoles-cent relationships in adolescence; drug use in the person’s immediate social network at ages 15-16 and 24-25; conventionality/deviance in adolescence; personality characteristics and psychiatric problem (see Tables 1-3). All cumulative drug consumption measures from 1971 to 1990 were calculated on the retrospective monthly drug use histories obtained at each follow-up interview in 1980, 1984 and 1990. Marijuana near-daily was defined as use 4 or more days a week. Highest frequency of marijuana use was coded from 1 = 1-2 times a year to 8 = daily. Ever used illicit drugs other than marijuana (OID) included ever used at least 10 times cocaine/crack, heroin, psychedelics or, nonmedically, minor tranquilizers, sedatives and stimulants. Number of drug-related problems counted drug-specific problems checked from a list of 11 problems (e.g., with health, hurt performance in school and/or on the job, less energy, made depressed, got into trouble with the police). Last-year dependence on alcohol was based on approximate measure of DSM-IV alcohol dependence (Kandel et al., 1997). Most important reasons for using marijuana in the past 12 months classified 11 reasons into three types. Each respondent was scored positively for that type if checked any component reason: (1) for social reason, 2 items (e.g., “to go along with what my friends are doing”); (2) to reduce negative feelings, 3 items (e.g., “to overcome depression”); (3) to enhance positive feeling, 4 items (e.g., “to get pleasure, feel good, get high”). Frequency of church attendance coded 1 = never to 7 = almost daily. Last-year delinquency index counted positive responses to a list of 15 delinquent behaviors (e.g., gotten into a serious fight in school or at work, taken something from a store without paying for it, forged or passed bad checks). Depressive symptoms (Kandel and Davies, 1982) was a six-item scale (e.g., feeling too tired to do things, feeling unhappy, feeling nervous). With the exception of lifetime experience of psychiatric problems for self and family members, reasons for using marijuana and drug use by peers and delinquency at ages 24-25, the predictive variables were measured at age 15-16. The reasons underlying use were not available in 1971 for all users, since only 38.4% had started using marijuana by that time. Variables measured in adulthood could be predictors or consequences of belonging to a particular cluster.

**Results**

**A four-type cluster solution**

Three marijuana use variables were used to identify the clusters: age of onset into marijuana, extent of chronic use and persistence of use by age 34-35 (see above). Of total users ($N = 708$), 45% ever used marijuana near-daily; 23% were still using marijuana by age 34-35. The two-cluster and three-cluster solutions differed significantly from each other.
Drug histories. The four groups differed significantly from each other on 6 of the 17 drug history characteristics that were not used in the clustering (Table 1). Heavy users differed according to early- or mid-onset on 8 of the remaining 11 variables; light users differed according to age of onset on 4 of these 11 variables. To place these marijuana users in a broader context, we also display the characteristics of those who only ever used marijuana at most 9 times, and those who never used marijuana.

The early onset-heavy use group (Group 1) started experimenting with marijuana the earliest and its members experienced the highest frequency of marijuana use. All became near-daily users and did so by age 17.5, earlier than any other group. Except for the late starters (Group 4), the interval between the ages of first and near-daily use increased by about a year for each successive group of users. Among late-onset marijuana users (Group 4), a minority progressed to near-daily use rapidly. The two heavy-using groups (Groups 1 and 3) had higher numbers of near-daily marijuana use spells than the two light-using groups. The chronicity of the spells of near-daily use in the early onset-heavy use group is striking: 93.1 months on average versus 18.5 to 26.1 months in the other three groups.

The four groups also differed significantly from each other regarding their involvement in alcohol, cigarettes and other illicit drugs (OIDs). The early-heavy group became the most involved in almost every class of drugs, including cigarettes and dependence on alcohol. Heavy marijuana users (Groups 1 and 3) were most likely to be long-term heavy smokers and drinkers, irrespective of age of onset into marijuana. The groups are consistently arrayed from heaviest to lightest involvement in OID use. While more than 90% of the early-heavy group ever experimented with OIDs and had done so by age 16.9 years on average, fewer than a quarter of the late-light group ever did so, and they did so 5 years later (21.8 years). Progression from the use of a legal drug to the use of marijuana took longer for each successive group, from early-heavy (3 years), to early-light (2.9 years), mid-heavy (4 years) and late-light group (6 years). The groups also differed significantly from each other in age of onset and number of years they used OIDs. Furthermore, the early-heavy group reported a higher number of drug-related problems, and marijuana problems specifically, than the mid-heavy users who started a year later. They were also more likely than any other group to report ever having felt addicted to any drug, to meet criteria for alcohol dependence, to report the longest period of heavy smoking, treatment for a drug-related problem, and having had a psychiatric problem.

The two light-using groups (Groups 2 and 4) were significantly different from each other in the proportions smoking cigarettes heavily and having been treated for drug-related problems.

With rare exceptions, those who used marijuana fewer than 10 times and were not included in the clustering were
Table 1. Drug use history and drug-related problems in the four clusters of marijuana (mja) users (N = 708)

<table>
<thead>
<tr>
<th>Drug use history</th>
<th>Group 1 Early-heavy</th>
<th>Group 2 Early-light</th>
<th>Group 3 Mid-heavy</th>
<th>Group 4 Late-light</th>
<th>Overall F test</th>
<th>Used less than 10 times</th>
<th>Nonusers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clustering variables</td>
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<td></td>
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<tr>
<td>Any mja use by age 34-35 (%)</td>
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<td>Months used mja near-daily</td>
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<td>(SD)</td>
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<tr>
<td>Age of first mja use (yrs)</td>
<td>(mean)</td>
<td>(SD)</td>
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<tr>
<td>Mja use history</td>
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<tr>
<td>Ever used mja near-daily (%)</td>
<td>(mean yrs)</td>
<td>(SD)</td>
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<tr>
<td>Interval from onset to near-daily</td>
<td>(mean yrs)</td>
<td>(SD)</td>
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<tr>
<td>Number of near-daily use spells</td>
<td>(mean)</td>
<td>(SD)</td>
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<td>Mean length near-daily spells</td>
<td>(mean mths)</td>
<td>(SD)</td>
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<td>Highest frequency ever used</td>
<td>(mean)</td>
<td>(SD)</td>
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<td>Use of other substances</td>
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<tr>
<td>% ever used OID 1+ times</td>
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<tr>
<td>Age of first OID use</td>
<td>(mean yrs)</td>
<td>(SD)</td>
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<td>Years any OID used monthly</td>
<td>(mean)</td>
<td>(SD)</td>
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<tr>
<td>Years smoked 1+ pack a day</td>
<td>(mean)</td>
<td>(SD)</td>
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<td>% ever drank alcohol near daily</td>
<td>(mean)</td>
<td>(SD)</td>
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<td>Problems</td>
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<tr>
<td>No. mja-related problems</td>
<td>(mean)</td>
<td>(SD)</td>
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<tr>
<td>No. any drug-related problems (except cigarettes)</td>
<td>(mean)</td>
<td>(SD)</td>
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<tr>
<td>% dependent on alcohol (1990)</td>
<td>(mean)</td>
<td>(SD)</td>
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<tr>
<td>% felt addicted to drugs (by 1990)</td>
<td>(mean)</td>
<td>(SD)</td>
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<td>% treated for drug problem (by 1990)</td>
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<td>% had psychiatric problem (by 1990)</td>
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<td>Total N</td>
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</tbody>
</table>

\(^1\)F test of between-group effects: \(^p < .01\); \(^2p < .001\). Student-Newman-Kuels (SNK) test was applied to test group differences. Identical superscript letters indicate significant differences in means between groups \((p < .05)\). Those who used less than 10 times and nonusers are not included in the F test.

\(^2\)Restricted to near-daily users.

\(^3\)OID = illicit drugs other than marijuana.
Demographic and lifestyle characteristics

The four marijuana user types also differed significantly from each other with respect to sociodemographic and lifestyle characteristics (Table 2). Male users started using marijuana earlier and were more likely than women to become heavily involved. Whereas the two light-using groups were almost evenly divided between men and women, men constituted the majority of the heavy-using groups, especially of the early-heavy group (75.4% early and 62.7% mid). Indeed, three times as many men as women were classified in the early-heavy group (12.6% vs 4.4%) and almost twice as many in the mid-heavy group (23.1% vs 14.5%). The two groups of light users were evenly divided between the genders.

The sharpest differences were observed between the early-heavy and late-light groups. On the sociodemographic characteristics the two heavy- and the two light-using groups were generally similar to each other, irrespective of age of onset into marijuana. As compared with light users, heavy users had lower education, lower overall high school GPA and lower church attendance; they were also more delinquent in adolescence and adulthood, more likely to take risks in adulthood, more likely to be in networks of marijuana-using friends in adolescence and early adulthood, and changed jobs more frequently. Among heavy users, those who started using marijuana later (mid-heavy) had higher overall GPA in high school, lower delinquent participation in adolescence and adulthood, and fewer marijuana-using friends than the early-heavy group. The significant differences in patterns of the use of legal drugs and OIDs, drug-related problems, lifestyle and sociodemographic factors among the four types of marijuana users support the typology derived on the basis of the cluster analysis.

Again, the marijuana users who had ever used marijuana fewer than 10 times were very similar to the late onset-light use group. There were three differences: Compared with the late-light group, those who used marijuana fewer than 10 times attended church more frequently as young adults; they were much less likely to be embedded in social networks of marijuana-using friends or spouses; and they were less likely to have parents who were problem drinkers. These same factors, with even lower values plus lower delinquent participation in adolescence and early adulthood, differentiated those who had never used marijuana from the marijuana users.

Unique predictors of specific types of marijuana users

To identify unique predictors of cluster membership, we estimated four sets of multivariate logistic regressions in which we compared two clusters at a time (Table 3). We compared the heavy users who started using early with those who started later (Groups 1 and 3, early vs mid). We compared the two early onset groups with each other (Groups 1 and 2, heavy vs light). To identify the distinguishing characteristics of heavy versus light users irrespective of age of onset, we compared combined Groups 1 and 3 versus combined Groups 2 and 4. Finally, to examine typologies parallel to those described for alcoholism and criminal behavior, we compared the two combined early-onset groups (Groups 1 and 2) with the two late-onset groups (Groups 3 and 4). The analyses were restricted to users who had participated in the initial school survey (n = 589). The covariates (see Table 3) included a subset of variables in Tables 1 and 2.

We were most successful in identifying the unique correlates of early versus late onset and of heavy versus light involvement. Few unique variables differentiated heavy users who started using early from those who started later. Two factors did so (first column): perceiving many friends to be using marijuana in young adulthood, and ever having had a psychiatric disorder. Early onset-heavy users were over three times more likely to ever have had a psychiatric disorder than heavy users who started a year later.

The strongest factors differentiating early onset-heavy users from early onset-light users (second column) were: having friends using marijuana in young adulthood, ever having had a psychiatric disorder, and minor delinquency in adolescence. Additional predictors, all marginally significant (p < .10), were being male, using marijuana to enhance positive feelings and growing up in a nonintact family.

The factors that differentiated the two aggregated heavy-using groups from the two aggregated light-using groups (third column) were, with one important exception, similar to those that differentiated heavy versus light use among those with early onset: being male, using marijuana to enhance positive feelings, having marijuana-using friends in young adulthood, and being delinquent in adolescence. Having ever had a psychiatric disorder, however, was not significant.

The most significant differences between early versus late onset (fourth column), irrespective of degree of involvement, were: age of onset into alcohol and cigarettes, number of friends using marijuana in adolescence, and GPA in high school. Using marijuana to overcome negative feelings was associated with reduced odds of early initiation.
### Table 2. Sociodemographic and lifestyle characteristics of four clusters of marijuana (mja) users (N = 708)

<table>
<thead>
<tr>
<th>Sociodemographic and lifestyle characteristics</th>
<th>Group 1 Early-heavy</th>
<th>Group 2 Early-light</th>
<th>Group 3 Mid-heavy</th>
<th>Group 4 Late-light</th>
<th>Overall F test</th>
<th>Used less than 10 times</th>
<th>Nonusers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sociodemographic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males (%)</td>
<td>75.4&lt;sup&gt;b,d&lt;/sup&gt;</td>
<td>46.4&lt;sup&gt;c,d&lt;/sup&gt;</td>
<td>62.7&lt;sup&gt;c&lt;/sup&gt;</td>
<td>44.9&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>9.63&lt;sup&gt;*&lt;/sup&gt;</td>
<td>40.1</td>
<td>38.4</td>
</tr>
<tr>
<td>Highest year of schooling (mean)</td>
<td>13.6&lt;sup&gt;a&lt;/sup&gt;</td>
<td>14.3</td>
<td>14.1</td>
<td>14.5&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3.12&lt;sup&gt;*&lt;/sup&gt;</td>
<td>14.3</td>
<td>14.0</td>
</tr>
<tr>
<td></td>
<td>(2.3)</td>
<td>(2.4)</td>
<td>(2.3)</td>
<td>(2.5)</td>
<td></td>
<td>(2.5)</td>
<td>(2.3)</td>
</tr>
<tr>
<td>Social role participation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall high school GPA (mean)</td>
<td>74.8&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>77.5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>77.9&lt;sup&gt;a&lt;/sup&gt;</td>
<td>79.5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>6.76&lt;sup&gt;*&lt;/sup&gt;</td>
<td>79.5</td>
<td>79.3</td>
</tr>
<tr>
<td></td>
<td>(8.6)</td>
<td>(8.2)</td>
<td>(8.4)</td>
<td>(7.4)</td>
<td></td>
<td>(7.7)</td>
<td>(8.3)</td>
</tr>
<tr>
<td>Currently married (1990) (%)</td>
<td>59.0</td>
<td>65.2</td>
<td>53.7&lt;sup&gt;a&lt;/sup&gt;</td>
<td>69.6&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3.54&lt;sup&gt;*&lt;/sup&gt;</td>
<td>73.5</td>
<td>68.2</td>
</tr>
<tr>
<td>Total no. of employer spells by 1990 (mean)</td>
<td>6.9&lt;sup&gt;b&lt;/sup&gt;</td>
<td>5.8&lt;sup&gt;c&lt;/sup&gt;</td>
<td>6.8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5.0&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>10.71&lt;sup&gt;i&lt;/sup&gt;</td>
<td>4.9</td>
<td>4.3</td>
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<td>(3.8)</td>
<td>(3.5)</td>
<td>(3.7)</td>
<td>(2.9)</td>
<td></td>
<td>(3.0)</td>
<td>(2.6)</td>
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<tr>
<td>Commitment/deviance</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attended church 2-3/month or more (1980) (%)</td>
<td>1.6&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>15.2&lt;sup&gt;c&lt;/sup&gt;</td>
<td>11.2</td>
<td>14.1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.94&lt;sup&gt;*&lt;/sup&gt;</td>
<td>27.7</td>
<td>37.7</td>
</tr>
<tr>
<td>Minor delinquency (1971)&lt;sup&gt;2&lt;/sup&gt; (mean)</td>
<td>2.5&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.61&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2.0&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>11.59&lt;sup&gt;i&lt;/sup&gt;</td>
<td>1.7</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td>(1.6)</td>
<td>(1.4)</td>
<td>(1.7)</td>
<td>(1.3)</td>
<td></td>
<td>(1.5)</td>
<td>(1.2)</td>
</tr>
<tr>
<td>Last year delinquency (1980) (mean)</td>
<td>1.5&lt;sup&gt;a,b,c&lt;/sup&gt;</td>
<td>0.7&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.0&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.6&lt;sup&gt;a&lt;/sup&gt;</td>
<td>6.72&lt;sup&gt;i&lt;/sup&gt;</td>
<td>0.4</td>
<td>0.2</td>
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<td></td>
<td>(2.1)</td>
<td>(1.4)</td>
<td>(1.5)</td>
<td>(1.3)</td>
<td></td>
<td>(0.8)</td>
<td>(0.6)</td>
</tr>
<tr>
<td>Last year delinquency (1990) (mean)</td>
<td>0.8&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>0.2&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.5&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>0.2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>10.08&lt;sup&gt;i&lt;/sup&gt;</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td>(1.6)</td>
<td>(0.7)</td>
<td>(0.9)</td>
<td>(0.7)</td>
<td></td>
<td>(0.5)</td>
<td>(0.4)</td>
</tr>
<tr>
<td>Personality/psychological symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk-taking (1980) (mean)</td>
<td>2.8&lt;sup&gt;a,b,d&lt;/sup&gt;</td>
<td>2.5&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2.7&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2.4&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>5.93&lt;sup&gt;i&lt;/sup&gt;</td>
<td>2.2</td>
<td>2.1</td>
</tr>
<tr>
<td></td>
<td>(0.8)</td>
<td>(0.7)</td>
<td>(0.8)</td>
<td>(0.8)</td>
<td></td>
<td>(0.8)</td>
<td>(0.8)</td>
</tr>
<tr>
<td>Depression index at age 15-16&lt;sup&gt;2&lt;/sup&gt; (mean)</td>
<td>17.8</td>
<td>18.3</td>
<td>17.4</td>
<td>18.1</td>
<td>0.86</td>
<td>18.4</td>
<td>16.9</td>
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<td></td>
<td>(4.9)</td>
<td>(5.0)</td>
<td>(4.4)</td>
<td>(4.7)</td>
<td></td>
<td>(5.4)</td>
<td>(4.8)</td>
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<tr>
<td>Family history</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother/father smoked when R&lt;sup&gt;i&lt;/sup&gt; was in high school Heavy smoking (%)</td>
<td>54.1</td>
<td>51.2</td>
<td>49.3</td>
<td>48.3</td>
<td>0.30</td>
<td>42.6</td>
<td>43.9</td>
</tr>
<tr>
<td>Mother/father drank when R&lt;sup&gt;i&lt;/sup&gt; was in high school Heavy drinking (%)</td>
<td>11.5</td>
<td>10.0</td>
<td>12.7</td>
<td>11.8</td>
<td>0.25</td>
<td>8.6</td>
<td>8.3</td>
</tr>
<tr>
<td>Problem drinking/alcoholic (%)</td>
<td>11.5</td>
<td>7.2</td>
<td>5.2</td>
<td>5.9</td>
<td>1.08</td>
<td>3.1</td>
<td>2.8</td>
</tr>
<tr>
<td>Parent/sib. ever treated for emotional disorder (%)</td>
<td>41.0</td>
<td>32.4</td>
<td>33.6</td>
<td>30.8</td>
<td>0.51</td>
<td>30.9</td>
<td>22.1</td>
</tr>
<tr>
<td>Drug involvement in social context</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Most friends used mja&lt;sup&gt;2&lt;/sup&gt; (1971) (%)</td>
<td>40.9&lt;sup&gt;b&lt;/sup&gt;</td>
<td>39.9&lt;sup&gt;a&lt;/sup&gt;</td>
<td>29.3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>12.2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>16.56&lt;sup&gt;i&lt;/sup&gt;</td>
<td>9.7</td>
<td>3.4</td>
</tr>
<tr>
<td>Most friends use mja (1980) (%)</td>
<td>90.2&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>40.8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>60.9&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>33.6&lt;sup&gt;a&lt;/sup&gt;</td>
<td>29.36&lt;sup&gt;i&lt;/sup&gt;</td>
<td>11.2</td>
<td>5.9</td>
</tr>
<tr>
<td>Spouse/partner used mja&lt;sup&gt;4&lt;/sup&gt; (1980) (%)</td>
<td>51.2</td>
<td>41.8</td>
<td>48.2</td>
<td>36.8</td>
<td>1.46</td>
<td>16.1</td>
<td>7.7</td>
</tr>
<tr>
<td>(Total N)</td>
<td>61</td>
<td>250</td>
<td>134</td>
<td>263</td>
<td></td>
<td>162</td>
<td>289</td>
</tr>
</tbody>
</table>

<sup>1</sup>F test of between-group effects: *p < .05; *p < .001. Student-Newman-Kuels (SNK) test was applied to test group differences: Identical superscript letters indicate significant differences between groups at p < .05.

<sup>2</sup>Based on 589 cases surveyed in 1971.

<sup>3</sup>R = respondent.

<sup>4</sup>Based on 441 cases who ever married or lived with a partner by 1980.
Discussion

Four clusters of marijuana users were identified by longitudinal course in a cohort followed from adolescence to age 34-35. These types were identified by including three aspects of marijuana-use history in a cluster analysis: age of first marijuana use, duration of nearly daily use and persistence of use into adulthood. Adolescents with early onset at age 15-16 could be distinguished by their subsequent extensiveness of involvement into early onset-heavy use and early onset-light use groups. The two other groups were one that started a year later and became heavily involved, the mid onset-heavy use group, and one that started 4 years later than the early-onset groups and never became heavily involved, the

<table>
<thead>
<tr>
<th>Covariates</th>
<th>(1 vs 3) Early-heavy (vs mid-heavy) AOR</th>
<th>(1 vs 2) Early-heavy (vs early-light) AOR</th>
<th>(1&amp;3 vs 2&amp;4) Heavy use (vs light use) AOR</th>
<th>(1&amp;2 vs 3&amp;4) Early onset (vs late onset) AOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (1 = male)</td>
<td>1.58</td>
<td>2.53</td>
<td>2.36†</td>
<td>0.97</td>
</tr>
<tr>
<td>Race (1 = black)</td>
<td>0.19</td>
<td>0.42</td>
<td>1.38</td>
<td>0.71</td>
</tr>
<tr>
<td>Highest years of schooling by either parent</td>
<td>1.03</td>
<td>0.96</td>
<td>1.02</td>
<td>1.04</td>
</tr>
<tr>
<td>Age of onset into alcohol/cigarettes</td>
<td>0.98</td>
<td>1.02</td>
<td>0.96</td>
<td>0.94*</td>
</tr>
<tr>
<td>Used mjA to overcome negative feelings</td>
<td>1.73</td>
<td>1.98</td>
<td>1.32</td>
<td>0.62*</td>
</tr>
<tr>
<td>Used mjA to enhance positive feelings</td>
<td>3.09</td>
<td>7.78‡</td>
<td>2.57‡</td>
<td>1.38</td>
</tr>
<tr>
<td>Used mjA for social reasons</td>
<td>0.66</td>
<td>0.68</td>
<td>0.77</td>
<td>0.91</td>
</tr>
<tr>
<td>Parental smoking status at age 15-16‡</td>
<td>1.02</td>
<td>1.13</td>
<td>1.03</td>
<td>0.93</td>
</tr>
<tr>
<td>Parental drinking status at age 15-16</td>
<td>1.70</td>
<td>1.37</td>
<td>1.19</td>
<td>1.06</td>
</tr>
<tr>
<td>Parent/sib, ever treated for mental disorder</td>
<td>0.67</td>
<td>1.04</td>
<td>1.10</td>
<td>0.86</td>
</tr>
<tr>
<td>Family intactness in adolescence (1 = intact)</td>
<td>1.03</td>
<td>0.44</td>
<td>0.91</td>
<td>1.21</td>
</tr>
<tr>
<td>Closeness to parent</td>
<td>0.99</td>
<td>1.01</td>
<td>0.99</td>
<td>0.99</td>
</tr>
<tr>
<td>No. of friends using mjA at age 15-16</td>
<td>1.08</td>
<td>0.84</td>
<td>1.04</td>
<td>1.56*</td>
</tr>
<tr>
<td>No. of friends using mjA at age 24-25</td>
<td>2.39‡</td>
<td>2.77‡</td>
<td>1.68‡</td>
<td>1.15</td>
</tr>
<tr>
<td>Church attendance</td>
<td>0.90</td>
<td>0.97</td>
<td>0.88</td>
<td>0.93</td>
</tr>
<tr>
<td>Minor delinquency index at age 15-16†</td>
<td>0.99</td>
<td>1.37‡</td>
<td>1.23‡</td>
<td>0.99</td>
</tr>
<tr>
<td>Last year GPA in high school</td>
<td>0.97</td>
<td>0.99</td>
<td>1.00</td>
<td>0.97*</td>
</tr>
<tr>
<td>Depression index at age 15-16</td>
<td>1.03</td>
<td>0.98</td>
<td>0.98</td>
<td>0.996</td>
</tr>
<tr>
<td>Ever had psychiatric problem (by age 34-35)</td>
<td>3.21*</td>
<td>2.96*</td>
<td>1.43‡</td>
<td>1.22</td>
</tr>
<tr>
<td>Model $\chi^2$ (20 df)</td>
<td>33.7*</td>
<td>75.8‡</td>
<td>108.4‡</td>
<td>80.7†</td>
</tr>
<tr>
<td>Total N</td>
<td>152</td>
<td>256</td>
<td>589</td>
<td>589</td>
</tr>
</tbody>
</table>

*p < .10; †p < .05; ‡p < .01; †p < .001.

$N$ for early-heavy = 45; early-light = 211; mid-heavy = 107; late-light = 226.

AOR = adjusted odds ratios.

*Missing category coded as a separate dummy variable but not shown.

*Difference between goodness-of-fit chi squares for the current and baseline models.
late onset-light use group. The early-heavy group repre-
sented a minority of individuals and contained more than
three times as many men as women. The majority of users re-
maind light users irrespective of their age of initiation into
marijuana use. Persistent and heavy users did not necessarily
initiate marijuana use at the earliest ages.

The four groups differed from each other in their degree of
involvement in marijuana and other drugs. The early-heavy
group consisted of the most involved and most problematic
marijuana users. Surprisingly, this group was less likely to
persist in using marijuana into adulthood than the mid onset-
heavy use group who started using marijuana use a year later.
The fact that the first group was much more likely than any
other to have been in treatment may partially explain this re-
sult. The late onset-light use type was one of the two largest
clusters in the cohort, accounting for over a third of the sam-
ple, and was characterized by light marijuana involvement
and nonpersistent use. In comparison with the other types
these users were also the least involved in drugs other than
marijuana, they reported the fewest drug-related problems
and were more likely to have conventional participation in
the social roles of adulthood (e.g., marriage and labor force
participation).

A most striking difference between marijuana users who
never used marijuana more than 10 times and other users is
their greater religiosity in early adulthood and lesser in-
volvement in marijuana-using networks. Those who never
used marijuana were even more religious, less involved in
marijuana using groups and much less likely to report any
psychiatric problems than those who ever used marijuana
fewer than 10 times.

Several findings deserve comments. Different factors
were important for different clusters. Risk factors important
for differentiating at least one cluster from all others included
being male, early age of onset into alcohol or cigarettes, us-
ing marijuana to enhance positive feelings, membership in a
marijuana using group, delinquent participation in adoles-
cence, and ever having had a mental disorder. Factors pre-
dicting delayed use included superior academic performance
in high school and using marijuana to overcome negative
feelings. Youths who onset late may be especially likely to
do so to self-medicate. Quality of parenting in adolescence
failed to have long-term protective effects on the child’s pat-
tern of marijuana involvement. The protectiveness of reli-
giosity observed at the univariate level disappeared with
control for other factors.

In conclusion, membership in social contexts of drug-us-
ing peers, using drugs to achieve euphoria, the presence of
psychiatric problems, and personal deviance foster the de-
velopment of early and heavy marijuana involvement. Hav-
ing experienced a psychiatric disorder is an important
distinguishing characteristic of heavy users who started the
earliest. By correlation, the absence of psychopathology
seems to be a particularly distinguishing characteristic of the
group of marijuana users that did not become heavily in-
volved in using marijuana. Whether mental disorders are
consequences of or risk factors for early and heavy involve-
ment in marijuana cannot be determined from our data. The
majority of studies have found that psychopathology (e.g.,
major depression, anxiety and, especially, conduct disorders)
precedes substance use disorders (Burke et al., 1994; Christie
et al., 1988; Deykin et al., 1987; Giaconia et al., 1994; Nel-
son et al., 1996), although mood disorders have also been re-
ported to follow the onset of alcohol or drug abuse and
dependence (Rohde et al., 1991). Psychiatric symptoms and
disorders other than depression probably constitute a risk
factor for heavy involvement in marijuana.

Age of onset into alcohol and cigarettes differentiated
early from late onset marijuana use, but not extent of use
within each type. This suggests that, while use of a legal drug
facilitates early progression to the use of an illicit drug, other
factors come into play to account for degree of involvement
in these drugs. The differential importance of peers’ mari-
juana use, which differentiates early from late marijuana use
onset in adolescence and heavy from light use in adulthood,
suggests that different etiological processes come into play
different phases of the lifecycle. Drug-using peer networks
in adolescence may predict the timing of marijuana use on-
set, while in adulthood the networks may be associated with
sustaining extensiveness of use. We have argued elsewhere
that extent of peer influence confounds selection and social-
ization effects (Kandel, 1996). The selection of drug-using
peers might be stronger in adulthood than in adolescence.

Existing taxonomies developed for alcoholism and crim-
inality emphasize the distinction between early and late on-
set. The ages associated with early onset vary for different
behaviors: starting to drink in adolescence for alcoholism,
manifesting conduct problems in childhood for criminality.
Midadolescence represents early onset for marijuana, as sug-
gested by the present results. As for alcoholism, delinquent
participation in adolescence is associated with early onset
and heavy subsequent involvement in marijuana. While ado-
lescent delinquency did not differentiate heavy marijuana
users according to age of marijuana onset, it discriminated
between all heavy and all light users and between early on-
set users who became heavy users and those who did not.
Thus, two contrasting groups of marijuana users, the com-
bined heavy users (early onset and mid onset groups) and the
late onset-light use group, correspond to the dual taxonomies
developed for early and late onset alcoholics and antisocial
individuals. The characteristics of the early and late onset
groups for marijuana use are very similar to those for alco-
holism and antisocial behavior. However, the present study,
conducted in a general population sample, highlights the im-
portance of recognizing that there can be heterogeneity
within the early and late onset groups themselves (for a sim-
ilar point regarding alcoholism see Mezzich et al., 1993). We
have identified an early onset group that does not become heavily involved in using marijuana. Early onset by itself will not lead to problematic use or rapid progress into the use of other drugs. The desire to enhance one's mood by using marijuana and dysfunctional behaviors (e.g., delinquency or psychopathology) are associated with the development of problematic drug use and dependence.

Motivations underlying marijuana use play a complex role and require distinguishing among different types of reasons for use. While the enhancement of positive mood is a strong motivating factor underlying heavy involvement but not early onset, the reverse appears to hold for the reduction of negative mood. The use of marijuana to reduce negative mood and deal with problems reduces the risk of heavy involvement but does not appear to be a risk factor for early onset. The importance of marijuana use to enhance positive feelings as a risk factor for heavy involvement parallels the motivations distinguishing the two types of alcoholics identified by Cloninger et al. (1986). The more severe alcoholics (Type II), characterized by early onset, were more likely to drink to induce euphoria than Type I, characterized by later onset. Type I alcoholics were more likely than Type II to drink to relieve anxiety.

Several limitations of the study must be noted. One limitation pertains to the identification of the clusters and reflects the state of methodology in the field. The methods available to identify clusters do not by themselves provide unique and unequivocal solutions. Furthermore, the resulting typologies are functions of the variables selected for clustering. The developmental taxonomy of marijuana use proposed here is suggestive rather than definitive. The analyses need to be replicated on other data sets to provide confirmatory evidence for the typology. Another limitation derives from the nature of the data. The measures of several constructs were psychometrically weak; in particular, measures of psychosocial development and develop more effective early prevention and intervention programs targeted toward specific types of substance users or abusers. It is clear that simple two-type classifications of deviant behavior fail to take into account the heterogeneity of early and late onset groups. We consider the documentation of this heterogeneity to be a major contribution of this study.

As noted earlier, three different strategies can be pursued to understand progression into various forms of drug use. These include investigations of pathways of progression from one class of drug to another, degree of involvement into a particular class of drug, and taxonomies based on developmental course. The three strategies are complementary and not mutually exclusive. For instance, individuals at a particular stage of drug use are heavier users of preceding drugs than those remaining at the preceding stage(s) (Kandel and Yamaguchi, 1999; Kandel et al., 1992). A complete developmental accounting of drug behavior over the life course requires an integration of all three strategies and a specification of the interrelationships and points of intersection among them. Such a perspective would bring us closer to the person-centered approach advocated by Magnusson (Bergman et al., 1998; Magnusson, 1998) for understanding behavioral development, including substance use and abuse.

Acknowledgment

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Effects of smoking cannabis on lung function

Marcus HS Lee & Robert J Hancox

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Although cannabis (or marijuana) is the world’s most widely-used illicit drug, there has been surprisingly little research into its effects on respiratory health. Part of the problem is the inherent difficulty of studying the long-term effects of an illegal habit. It has often been assumed that smoking cannabis will have similar long-term effects to smoking tobacco. Several recent observational studies suggest that this is not the case and that cannabis has quite different effects on the lung function. There are consistent findings that smoking cannabis is associated with large airway inflammation, symptoms of bronchitis, increased airway resistance and lung hyperinflation. The evidence that smoking cannabis leads to features of chronic obstructive pulmonary disease, such as airflow obstruction and emphysema is not convincing. However, there are numerous case reports of bullous emphysema among cannabis smokers. These findings have not been confirmed in systematic analytical studies and probably represent uncommon adverse effects in very heavy cannabis smokers. There is now additional controversial evidence that cannabis is at least an occasional cause of respiratory malignancies, but again the evidence is inconclusive.

**Keywords:** bronchitis • bullae • cannabis • cigarettes • emphysema • lung cancer • lung function • marijuana • respiratory • tobacco
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Cannabis is the most widely used illicit drug worldwide [1]. It has been hailed for its analgesic properties [2] and pilloried for both its psychoactive and addictive nature [3]. It is illegal in most countries but decriminalized in some. In our country, New Zealand, cannabis is the third most commonly used drug after tobacco and alcohol, and the most commonly used illegal drug. Approximately three-quarters of New Zealanders have tried cannabis by age 25 and 13.7% of New Zealanders have used cannabis in recent years [4]. It is most often smoked although it can also be taken orally [5].

The widespread use of cannabis has raised many concerns over its long-term effects. Often these have been about the effects of chronic cannabis use on mental health [6]. However, the frequent practice of smoking cannabis also raises concerns over its potential for adverse effects on the respiratory system. Unfortunately, the illegal status of cannabis makes it difficult to obtain reliable data on cannabis use and its effects. Self-reports of cannabis consumption are likely to be inaccurate owing to social desirability bias and the fear of legal consequences. Furthermore, as most cannabis users also smoke tobacco, the effects of cannabis on the respiratory system may be obscured by the effects of tobacco.

Even if cannabis use is honestly reported by users, quantifying cannabis consumption is inherently difficult because, as an illegal substance, there is no standardization of supply and significant variations in strengths and amounts of cannabis occur. In addition, cannabis can be smoked via various methods including bongs and bubble pipes, as well as directly from a cannabis cigarette. These different methods of smoking cannabis may have influenced the quantity and composition of smoke inhaled. Most studies quantify exposure to cannabis smoke as ‘joint-years’ whereby one joint-year is equivalent to one joint smoked daily for a year. This approach is pragmatic but focuses on the frequency of cannabis use and ignores differences in the quantity of cannabis leaf in each joint and in the methods of smoking it. An internet survey of cannabis users found that two measures of the quantity of cannabis consumed – the amount of cannabis purchased each month and the usual level of intoxication after using it – predicted respiratory symptoms after using it and in addition to the reported frequency of use [7]. Unfortunately, few studies have gathered such detailed information.

Taken together, the difficulties in obtaining accurate information about cannabis use, the problem of quantifying consumption and the difficulty of separating the effects of cannabis from those of tobacco have meant that the respiratory side effects of cannabis have not been well studied. The likelihood that smoking cannabis harms the respiratory systems has usually been extrapolated from the well-documented effects of smoking tobacco. At face value, it seems reasonable to assume that cannabis and tobacco would have similar effects, since, apart from the main psychoactive ingredients of tetrahydrocannabinol and nicotine, the substances contain a broadly similar mix of chemicals [8]. However, recent reports suggest that the effects of cannabis and tobacco on lung function may be quite different. The paucity of direct evidence on the respiratory effects of chronic cannabis use therefore leaves a major gap in our understanding of one of the world’s most commonly inhaled substances. This article appraises recent evidence that cannabis is harmful to lungs.

Cannabis & bronchitis

Numerous studies confirm that smoking cannabis can lead to respiratory symptoms. These studies show that cough, increased sputum production and wheeze are present in approximately a fifth to a third of cannabis smokers [9–11]. Cannabis smoking is also associated with dyspnea, pharyngitis, hoarsening of voice and exacerbations of asthma [10]. These symptoms appear to result from the toxic effects of cannabis smoke on the bronchial mucosa. Bronchoscopic mucosal biopsies from 40 cannabis-only smokers and 31 tobacco-only smokers have demonstrated that both cannabis and tobacco smoking cause significant bronchial damage, with an increase in basal cell hyperplasia, goblet cell hyperplasia, cell disorganization, nuclear variation, and an increase in nuclear/cytoplasm ratio [12]. This study also
demonstrated an increase in squamous cell metaplasia in cannabis smokers, raising the possibility that smoking cannabis may be a risk factor for developing lung cancer.

Another report found that even asymptomatic cannabis smokers with normal physical examinations and spirometric function have central airway inflammation under direct bronchoscopic visualization, bronchial mucosal biopsies and bronchial lavage fluid [13]. Those who smoked both cannabis and tobacco also had distal airway inflammation. There was a high incidence of erythema, edema and airway secretions in both exclusive cannabis smokers and exclusive tobacco smokers. These findings demonstrate that routine physical examination and spirometry may be insensitive measures of lung injury caused by cannabis. While the finding that cannabis smoke causes mucosal damage is not surprising, the most striking result of this study was the fact that cannabis smokers of an average of a few joints a day had the same degree of airway damage as tobacco smokers of 20–30 cigarettes a day. Moreover, this damage was present in young and asymptomatic cannabis smokers.

Effect of cannabis on airflow obstruction

Acute effects
Cannabis has long been recognized as a bronchodilator. Indeed, newspapers in New Zealand (and presumably many other countries) carried advertisements for imported cannabis cigarettes as a treatment for asthma in the late 1800s [10]. Hence, inhaling cannabis appears to predate inhaled adrenergic broncho dilator therapy by at least half a century [14]. There appears to be no doubt that smoking cannabis does have acute bronchodilator effects: in a recent systematic review, 11 out of 12 studies demonstrated a bronchodilator effect of cannabis [10]. However, this acute bronchodilator effect is modest and does not appear to be sustained with continued use over 6–8 weeks [15]. It has been shown to be of slower onset than salbutamol, which has greater bronchodilator effects at 5 min compared to tetrahydrocannabinol [16]. The potential short-term therapeutic effects also need to be weighed against the adverse effects of increased bronchitis and exacerbations of asthma that have been associated with regular cannabis use. Consequently, cannabis is not currently considered to have a therapeutic role in acute bronchospasm (although this is occasionally claimed by cannabis users to justify their habit) and the acute effects will not be considered further in this article.

Long-term effects
Although it has often been assumed that chronic cannabis use will have similar effects on the airways to tobacco, objective evidence for this is lacking. Since the early 1970s, studies have looked for evidence of airflow obstruction in cannabis smokers. Most of these have failed to show an association between chronic cannabis use and forced expiratory volume (FEV₁) values (Table 1). A systematic review by Tetrault et al. in 2007 found that the evidence that cannabis was associated with airflow obstruction was inconclusive [10]. Since then, at least three further studies have explored the association between cannabis smoking and airflow obstruction and/or chronic obstructive pulmonary disease (COPD).

Aldington et al. studied lung function in a convenience sample of 339 people in Wellington, New Zealand, who were either nonsmokers, smokers of either tobacco or cannabis only, or smokers of both substances [11]. This study found that unlike tobacco, cannabis smoking had no effect on FEV₁ values, although there was a borderline statistically significant trend to lower FEV₁/forced vital capacity (FVC) ratios in cannabis smokers which appeared to show a dose-dependant relationship. There were also statistically significant dose-dependent associations between a lifetime cumulative use of cannabis and specific airway conductance (sGaw) as well as an association between cannabis smoking and hyperinflation measured as total lung capacity by body plethysmography. Among those who smoked both substances, cannabis appeared to attenuate the effect of tobacco smoking on measures of airflow obstruction including FEV₁, FEV₁/FVC ratios and mid-expiratory flow values, although these effects were also of borderline statistical significance [8].

A Canadian population-based study of 878 individuals aged 40 years and over found no association between exclusive cannabis smoking and COPD. Only four COPD patients were exclusive current cannabis smokers, and this small number limits definite conclusions [17]. However, there was a statistically significant interaction with tobacco smoking: smokers of both cannabis and tobacco had an increased risk of developing airflow obstruction compared to nonsmokers, suggesting a synergistic effect of tobacco smoking and cannabis in the development of COPD. Smoking tobacco alone was also associated with an increased risk of COPD [17].

The lack of association between cannabis use and airflow obstruction was confirmed in a recent report from the Dunedin Multidisciplinary Health and Development Study, which tracked a population-based birth cohort of 1037 individuals with information on cannabis and tobacco use and lung function at 18, 21, 26 and 32 years of age [18]. Unlike tobacco, cannabis was not associated with lower FEV₁ values or with the FEV₁/FVC ratios once tobacco use had been adjusted for. Nor was there evidence of airflow obstruction among cannabis smokers who did not smoke tobacco. However, there was evidence of increased resistance to flow in the central airways with significant associations between cannabis use, lower sGaw and increased airway resistance. These effects were much stronger for cannabis than for tobacco. There was also a significant association between cannabis use and hyperinflation as measured by the FVC on spirometry (12 ml per joint-year [95% CI: 3.0–21.0]), total lung capacity (TLC; 25 ml per joint-year [95% CI: 13.9–36.0]), functional residual capacity (15.1 ml per joint-year [95% CI: 4.8–25.4]) and residual volume (12.6 ml per joint-year [95% CI: 7.0–18.3]) by plethysmography, and alveolar volume (17.8 ml per joint-year [95% CI: 6.8–28.9]) by gas dilution. This association with hyperinflation was stronger for cannabis than for tobacco.

Like the Aldington study, earlier reports from the Dunedin study had documented a borderline-significant association between cannabis use and lower FEV₁/FVC ratios [8,19]. It is now apparent that this trend to lower FEV₁/FVC ratios was owing to
increases in the FVC rather than cannabis-induced decreases in the absolute value of the FEV1 [18]. Taken together, the pattern of findings from the studies by Aldington et al. and the Dunedin study suggests that cannabis causes central airways resistance to airflow (lower sGaw), associated with prominent symptoms of bronchitis [8,10,18,19] and hyperinflation, but that there is little or no effect on the FEV1 and airflow obstruction. Of note, the practice of mixing cannabis and tobacco in the same joint is uncommon in New Zealand, enabling the researchers to study the effects of tobacco and cannabis separately.

In summary, there is currently no convincing evidence that smoking cannabis causes airflow obstruction. This may be surprising and appears to conflict with the consistent evidence for increased resistance to airflow in the large airways. In addition to the studies reported previously, four other studies have found that cannabis smokers have increased levels of airway Raw and/or lower levels of SGaw than nonusers or tobacco smokers [11,18,20,21]. These findings suggest that cannabis has significant effects on large airway function associated with bronchitis and mucous production, which are greater than those found for tobacco, but has little or no effect on airflow obstruction and the risk of COPD.

### Emphysema & bullous disease

There are now at least 36 case reports of bullous lung disease attributable to heavy cannabis smoking in English literature. These cases consistently report upper lobe predominance with relatively preserved lower lung parenchyma (Table 2). Despite the presence of bullae on high resolution CT scans, lung function tests and chest x-ray appearances have largely been unremarkable in these patients. Most of these cases have been reported in young adults under the age of 45 years. This age distribution may reflect the fact that older generations may not have smoked much cannabis or may be owing to a reporting bias. How cannabis might cause such severe lung damage is not clear. It has been postulated that the methods of inhalation of cannabis smoke may cause significant barotrauma. Cannabis smokers tend to hold their breath for up to four-times longer than cigarette smokers, with a nearly 70% increase in inspiratory volume [22]. This high lung volume and breath holding results in the prolonged exposure to inhaled particulates at very high temperatures, which in turn may be responsible for epithelial injury and inflammation.

Currently, the evidence that smoking cannabis causes emphysema and bullae is limited to these case reports and therefore

### Table 1. Epidemiological associations between cannabis use and lung function.

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Study design</th>
<th>Subjects (n)</th>
<th>Results</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hancox et al. (2010)</td>
<td>Observational cohort</td>
<td>919</td>
<td>Increased lung capacity and airway resistance in marijuana smokers. No evidence of airway obstruction, gas trapping or impaired gas transfer</td>
<td>[18]</td>
</tr>
<tr>
<td>Tan et al. (2009)</td>
<td>Observational cohort</td>
<td>878</td>
<td>Marijuana smoking not associated with increased bronchitic symptoms and COPD</td>
<td>[17]</td>
</tr>
<tr>
<td>Sherrill et al. (1991)</td>
<td>Observational cohort</td>
<td>856</td>
<td>Pulmonary function was reduced in subjects reporting marijuana smoking</td>
<td>[50]</td>
</tr>
<tr>
<td>Tashkin et al. (1997)</td>
<td>Observational cohort</td>
<td>394</td>
<td>No effect of marijuana smoking on FEV1 decline</td>
<td>[51]</td>
</tr>
<tr>
<td>Bloom et al. (1987)</td>
<td>Cross-sectional</td>
<td>990</td>
<td>No effect of marijuana on FEV1 or FVC</td>
<td>[45]</td>
</tr>
<tr>
<td>Cruickshank (1976)</td>
<td>Cross-sectional</td>
<td>60</td>
<td>No difference between marijuana smokers and controls</td>
<td>[46]</td>
</tr>
<tr>
<td>Moore et al. (2005)</td>
<td>Cross-sectional</td>
<td>6728</td>
<td>Marijuana use not associated with decreased FEV1/FVC ratio</td>
<td>[48]</td>
</tr>
<tr>
<td>Sherman et al. (1991)</td>
<td>Cross-sectional</td>
<td>63</td>
<td>No significant difference in FEV1/FVC and DLco in marijuana smokers and nonsmokers</td>
<td>[49]</td>
</tr>
<tr>
<td>Tashkin et al. (1980)</td>
<td>Cross-sectional</td>
<td>189</td>
<td>Marijuana smokers had lower sGaw compared with controls (p &lt; 0.001)</td>
<td>[21]</td>
</tr>
<tr>
<td>Tashkin et al. (1993)</td>
<td>Cross-sectional</td>
<td>542</td>
<td>Marijuana smoking associated with airway hyper-responsiveness with low-dose methacholine</td>
<td>[52]</td>
</tr>
<tr>
<td>Tilles et al. (1986)</td>
<td>Cross-sectional</td>
<td>68</td>
<td>Marijuana smoking regardless of tobacco smoking, resulted in reduction of single breath DLco compared with nonsmokers</td>
<td>[53]</td>
</tr>
<tr>
<td>Tashkin et al. (1987)</td>
<td>Cross-sectional</td>
<td>446</td>
<td>Male marijuana smokers had reduced sGaw compared with male tobacco smokers. No difference in DLco</td>
<td>[20]</td>
</tr>
</tbody>
</table>

Total: 12,613

Taylor et al. performed two studies (2000 [8] and 2002 [19]) on the same cohort that have been superseded by Hancox et al. [18].

COPD: Chronic obstructive pulmonary disease; DLco: Diffusing capacity for carbon monoxide; FEV1: Forced expiratory volume after 1 s; FVC: Forced vital capacity; sGaw: Specific airway conductance.
remains anecdotal. Although Tashkin et al. demonstrated modest short-term decreases in gas transfer (DLco) among 30 men allowed to smoke cannabis ad libitum for 94 days [15], none of the population-based studies have been able to confirm that cannabis consumption is associated with persistent impairment of DLco [11,15,16]. This is in stark contrast to tobacco smoking, for which a reduction in DLco is probably the most sensitive indicator of parenchymal lung damage.

In Aldington’s cross-sectional study, exclusive smokers of cannabis were much less likely to show evidence of emphysema on high-resolution CT scans than tobacco smokers, suggesting that macroscopic emphysema is not a common consequence of cannabis use [11].

Even though cannabis smoking is infrequently associated with emphysema in population-based studies, two studies have found a trend towards increased static lung volumes among cannabis users. Both the cohort study by Hancox et al. [18] and the cross-sectional study by Aldington et al. [11] found greater total lung capacities among cannabis users, while Aldington also found evidence that cannabis was associated with hyperinflation on high-resolution CT scans. This is consistent with other studies demonstrating that cannabis is associated with statistically significant increases in FVC on spirometry [17]. It is difficult to interpret the significance of these increases in static and dynamic lung volumes: whereas hyperinflation is usually a feature of emphysema, this seems to be unlikely without evidence that cannabis causes either airflow obstruction (measured by FEV1/FVC ratios), impaired gas transfer (DLco), or parenchymal destruction on high-resolution CT scans.

There are at least two reasons why these observational studies conflict with numerous case reports of severe emphysematous bullae among cannabis smokers. Perhaps the most likely explanation relates to the dose of cannabis smoked. Most of the reported cases of bullous emphysema have been in very heavy cannabis smokers. For example, in the largest series of patients (n = 17) the mean lifetime consumption of cannabis was 54 joint-years [23]. Although cannabis use is very common, such prolonged heavy use is not. Even in large population-based studies there may only be a small number of heavy cannabis users. Indeed, in the cohort study by Hancox et al., none of the participants had accumulated more than a 30 joint-year history by the age of 32 [Hancox RJ, unpublished data]. Purposeful samples, such as that used by Aldington, may be more likely to identify such heavy users, but it is important to note that Aldington et al. applied very strict exclusion criteria to their sample to exclude the possibility of respiratory effects owing to other illicit drugs. This may have also excluded the heaviest users of cannabis. The only exclusive cannabis smoker with macroscopic emphysema on high-resolution CT scanning in their study had a 437 joint-year history [11].

The other reason why systematic studies have failed to identify the lung function changes reported in individual case reports may be that bullous lung disease is a rare complication. The number of cases reported in the literature is small in relation to the widespread use of cannabis. It is possible that, when compared to tobacco, only a relatively small proportion of people are susceptible to developing parenchymal lung damage from cannabis smoke and even then, only if they smoke a very large amount. Hence, impairment of gas transfer and macroscopic evidence of emphysema are unlikely to be detected among general population samples. This explanation would require parenchymal lung damage to be caused by a process distinct from the central inflammation that is observed in most regular cannabis users.

In summary, the existing data are unable to confirm a definite link between cannabis and bullous emphysema. However, the case reports support the likelihood that at least occasional heavy cannabis smokers are susceptible to this disease. Further evidence from systematic observational studies is required to confirm this.

**Different to tobacco?**

The findings previously summarized suggest that smoking cannabis does have adverse effects on respiratory function, but contrary to what is often assumed, the pattern of damage in cannabis smokers is different from that associated with tobacco. There is now clear evidence that smoking cannabis causes inflammatory changes in the central bronchi and a consistent trend to increased airway resistance (or reduced conductance). Surprisingly, this does not appear to have a great impact on the FEV1. Trends to lower FEV1/FVC ratios have also been observed in several studies, but this seems to be due to an increase in the FVC, rather than a reduction in FEV1. The higher FVC observed among cannabis users is consistent with evidence of hyperinflation seen on plethysmography and on CT scans. The patterns of effects associated with tobacco and cannabis smoking in a cohort of 32 year olds are compared in Table 3.

### Table 2. Reports of bullous lung disease in cannabis users.

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Patients (n)</th>
<th>Mean age (years)</th>
<th>Mean joint-years</th>
<th>Results</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beshay et al. (2007)</td>
<td>17</td>
<td>27</td>
<td>53</td>
<td>Upper lobe predominance with bullae ranging from 0.3 to 12 cm</td>
<td>[23]</td>
</tr>
<tr>
<td>Johnson et al. (2000)</td>
<td>4</td>
<td>38</td>
<td>NS</td>
<td>All had upper lobe bullae and normal lower lobes</td>
<td>[40]</td>
</tr>
<tr>
<td>Gao et al. (2010)</td>
<td>1</td>
<td>23</td>
<td>NS</td>
<td>Bilateral upper lobe bullae, more prominent on the right</td>
<td>[41]</td>
</tr>
<tr>
<td>Hii et al. (2008)</td>
<td>10</td>
<td>41</td>
<td>74</td>
<td>Upper and mid-zone emphysematous bullae</td>
<td>[42]</td>
</tr>
<tr>
<td>Phan et al. (2005)</td>
<td>1</td>
<td>26</td>
<td>&gt;10</td>
<td>Extensive cystic and bullous lung changes primarily affecting lower lobes</td>
<td>[43]</td>
</tr>
<tr>
<td>Thompson et al. (2002)</td>
<td>3</td>
<td>39</td>
<td>NS</td>
<td>Large apical lung bullae</td>
<td>[44]</td>
</tr>
</tbody>
</table>

NS: Not stated.
Why cannabis and tobacco should have different effects on the lungs is not clear. As noted, other than nicotine and cannabinoids, smoke from the two substances contains a similar mix of chemicals. It is possible that tetrahydrocannabinol, a known short-term bronchodilator [10], has long-lasting effects on lung function (although the short-term bronchodilator effect seen in single-dose studies does not persist during continued use [15]). It is also possible that differences in the concentration of some unidentified substance in the smoke results in these differences. However, it seems more likely that the different methods of smoking cannabis compared to smoking tobacco are responsible for the different effects on lung function. Cannabis is usually smoked unfiltered and the smoke from cannabis is hotter compared to filtered tobacco smoking [22]. Cannabis smokers also tend to take much deeper breaths and employ breath-holding techniques to increase the absorption of tetrahydrocannabinol as bioavailability ranges from 18 to 50%, depending on the volume of air inhaled, the depth of inhalation and the duration of retention of smoke in the alveoli [24,25]. It is possible that by using Valsalva manoeuvres to increase the uptake of tetrahydrocannabinol, smokers also subject themselves to hyperexpansion of the chest and the potential for barotrauma. Interestingly, although prolonged breath-holding and Valsalva manoeuvres appear to be widely used by cannabis smokers, studies indicate that is not necessary to perform these manoeuvres because the psychoactive effects of cannabis are similar if it is smoked normally [26,27].

Cannabis can also be taken in a variety of ways: either rolled and smoked like cigarettes, inhaled through specialized devices that use water filtration, bongs or such as vaporizers, and can also be consumed in cakes, beverages and oils. To date, we are not aware of any research looking specifically at the methods of cannabis delivery to the lungs and their long-term impact on lung function.

Importantly, whether cannabis and tobacco have synergistic effects on lung function is a question that remains unanswered. Most cannabis smokers also smoke tobacco and it seems likely that they would be predisposed to a combination of effects. Tan et al. found that although cannabis smoking alone was not associated with an increased risk of COPD in their sample of older adults, it appeared to increase the risk among those who also smoked tobacco [17]. However, other studies have found little evidence that cannabis modifies the effects of tobacco on lung function. Rather, the pattern of abnormalities found in those who smoke both substances suggests an additive effect or a combination of the different tobacco and cannabis effects, rather than synergistic action [11,12,18,19].

The fact that there appears to be a difference in the pattern of lung function abnormalities associated with tobacco and cannabis does not necessarily mean that cannabis will not have a similar effect to tobacco for lung cancer and other health problems. However, conflicting reports published in recent years have also been unable to resolve the issue of whether cannabis smoking causes lung malignancies.

While it has been found that cannabis condensates are more cytotoxic, mutagenic and have a greater tendency to induce chromosomal damage and in a more erratic fashion compared with tobacco [28], a systematic review of the evidence by Mehra et al. in 2006 failed to demonstrate a clear increased risk of lung cancer among cannabis smokers after accounting for tobacco use. They cite methodological deficiencies in the observational studies that they reviewed and a lack of adjustment for tobacco smoking as the main reason they were unable to reach the conclusion that cannabis is a cause of lung cancer [29]. The evidence that cannabis smoking causes lung cancer remains elusive [30]. For example, a large American cohort study found no evidence of an increase in overall cancer risk, and no increased risk of lung cancer in particular among cannabis smokers [31].

Recently, a New Zealand case–control study of 79 cases of lung cancer showed a trend towards an increased risk of lung cancer of about 8% for each joint-year smoked (compared with a 7% increase in risk for each pack-year of cigarette smoking). This increase in risk was only evident for the heaviest tertile (>10.5 joint-years) of cannabis smokers who had a relative risk of 5.7 (95% CI: 1.5–21.6) after adjusting for cigarette smoking and other potential confounding variables [32]. By contrast, a larger case–control study of 2252 subjects in Los Angeles (CA, USA) did not find an increased risk of lung cancer nor for oropharyngeal cancers in cannabis smokers despite some subjects smoking very large amounts of cannabis (in excess of 60 joint-years) [33]. Possible reasons for the differences between these findings include differences in study design and the selection of controls, selection bias of the cases, difficulty in quantifying cannabis use, and the difficulty in separating the effects of tobacco from those of cannabis in people who smoke both [29,30,32]. Further data are urgently required to resolve this issue.

The continuing uncertainty about the risk of lung cancer associated with cannabis highlights the problems associated with studying the effects of an illegal and unstandardized substance such as cannabis. On the other hand, these conflicting epidemiological findings are matched by contradictory biological data from in vitro studies which have found that that cannabinoids have both antineoplastic effects [34] and can also stimulate growth of

<table>
<thead>
<tr>
<th>Measure</th>
<th>Cannabis</th>
<th>Tobacco</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;</td>
<td>↔</td>
<td>↔/↓</td>
</tr>
<tr>
<td>FVC</td>
<td>↑</td>
<td>↔</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;/FVC&lt;/sub&gt; ratio</td>
<td>↔</td>
<td>↓</td>
</tr>
<tr>
<td>TLC</td>
<td>↑</td>
<td>↔/↑</td>
</tr>
<tr>
<td>RV</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>DL&lt;sub&gt;CO&lt;/sub&gt;</td>
<td>↔</td>
<td>↓</td>
</tr>
<tr>
<td>sGaw</td>
<td>↓</td>
<td>↔/↓</td>
</tr>
</tbody>
</table>

↔ No association; ↑ Increase; ↓ Decrease.
DL<sub>CO</sub>: Diffusing capacity for carbon monoxide; FEV<sub>1</sub>: Forced expiratory volume; FVC: Forced vital capacity; RV: Residual volume; sGaw: Specific airway conductance; TLC: Total lung capacity.

Data taken from [18].
Effects of smoking cannabis on lung function

Review

CME

Expert commentary

For a substance that is so widely used, the paucity of evidence on the respiratory effects of smoking cannabis is surprising. The evidence that we have suggests that cannabis definitely does have respiratory effects, but that these are different to tobacco. The relationship between cannabis smoking and the common smoking-related problems associated with tobacco such as airway obstruction, emphysema and lung cancer is not clear. Notwithstanding the difficulties in conducting research on illegal substances and the problems of quantifying cannabis consumption, further studies with large population samples and long-term follow-up are needed.

Case reports of bullous emphysema among cannabis smokers are difficult to reconcile with systematic observational data. These cases are probably rare, although they may also be under-recognized because of under-reporting of cannabis use. They are likely to represent the extreme end of the spectrum of cannabis-related lung disease, occurring only in very heavy smokers. However, the evidence remains anecdotal and the development of bullae and emphysema as a consequence of smoking cannabis is not supported by the available systematic observational studies. Clearly, more needs to be done to confirm whether there is a genuine cause-and-effect relationship between smoking cannabis and lung bullae and, if such a relationship exists, a threshold at which irreversible damage occurs.

We also need research into the methods of inhaling cannabis and the influence that this may have on its respiratory effects. Whether breath-holding and Valsalva manoeuvres can explain the association between cannabis use and lung hyperinflation is intriguing: nothing in our understanding of lung physiology appears to indicate that such simple manoeuvres could make such a marked difference to lung function.

A relatively unexplored area is whether cannabis has therapeutic potential as an acute bronchodilator, either as an adjunct or an alternative to current drugs. As noted, cannabis has a long history as treatment for asthma [101]. It is unlikely that anyone would advocate smoking cannabis to treat obstructive airways disease, but there may be less harmful ways to deliver the drug. Early research investigated the effects of cannabis aerosols [15,37]. More recently, vaporizers have been proposed as a method of inhaling ‘medical cannabis’ in a smoke-free form. An internet survey suggested that users of vaporizers had fewer respiratory symptoms but we are not aware of any published long-term studies of their effects [38].

Despite the continuing uncertainty regarding the effects of cannabis on the lungs, we suggest that health practitioners routinely ask about cannabis use when taking a medical history. Although medical students are taught to ask about illicit drugs (particularly intravenous drugs), until recently, little attention has been given to quantifying cannabis use [39]. Given the widespread use of this substance in many countries, this should be carried out far more often. It is particularly important for patients with unexplained respiratory symptoms, apparently ‘idiopathic’ lung bullae or pneumothorax, lung, and head and neck cancers. While the relationship between cannabis and these diseases may still be unproven, by raising awareness of cannabis use, we are more likely to establish whether there is a causal relationship or not.

The research findings may also have implications for drug policy. We have strong evidence that cannabis causes bronchial inflammation, respiratory symptoms and affects lung function. While we do not yet understand the full significance of the pattern of lung function changes documented by the research, it is clear that smoking cannabis is not harmless to the lungs. Cannabis is also a controversial cause of lung cancer and emphysema in a small but uncertain number of users. It is beyond the scope of this article to consider whether these harms are best reduced by maintaining the illegal status of cannabis, decriminalization, or by legalising and regulating its use. What we can say is that cannabis is harmful to lungs and that drug policies should take this into consideration. We also recommend that future policies should encourage further research into the health effects of smoking cannabis.

In conclusion, cannabis has been shown to have a range of effects on lung function that are different to those found with tobacco. Acute inhalation of cannabis produces bronchodilation, but chronic use is associated with bronchitic symptoms, central airway inflammation, and increased large airway resistance to airflow. There is also evidence for lung hyperinflation, but no convincing evidence that cannabis smoking leads to airflow obstruction and COPD. Despite the case reports of emphysema in heavy cannabis users, it has not yet been proven that cannabis causes emphysema. Cannabis also contains many carcinogenic substances but it remains controversial whether it is a cause of lung malignancies.

Five-year view

We have a great deal to learn about the effects of cannabis on the lungs. Over the next 5 years we anticipate more studies examining the effect of smoking cannabis on lung function:

- Large population-based cohort studies with longer periods of follow-up. Hopefully these will include heavier cannabis smokers to clarify the effects of cannabis smoking on the risk of developing COPD;
- Case–control studies of lung cancer to assess the link between cannabis smoking and lung malignancies. The current evidence is conflicting and further studies are urgently needed;
- Case–control studies of cannabis use in patients with bullous emphysema and correlation to quantity of cannabis smoked. To date, we only have anecdotal evidence from case reports and case series linking cannabis to lung bullae. This contrasts with the failure to demonstrate a link between cannabis exposure and emphysema in population-based cohort studies. More case reports will not resolve this issue; we need analytical studies of cannabis exposure among people with bullous lung disease and control subjects;
In addition, we hope to see research into the different ways of inhaling cannabis, for example, comparing ‘bongs’ or water filtration devices with unfiltered ‘joints’ (direct cigarette smoking) and with other devices such as vaporizers. These methods of inhalation may have markedly different effects on the lung, but we are not aware of any systematic studies of this; A better understanding of the long-term pulmonary effects of repeated Valsalva manoeuvres and deep breath holding commonly used by cannabis smokers is also needed. This is a difficult issue to study, but we hope that more imaginative researchers than ourselves will find a way; We hope that there will be research into cannabis users perspectives of the health risks of cannabis smoking. How do they decide which method to use for smoking it? What limits cannabis consumption – do users titrate the dose according to their level of intoxication? This would identify educational needs and the potential for harm reduction. This information may also inform future drug policies; We expect medical marijuana to become more widely used in the coming years and that more countries will legalise its use. We need to know more about the potential adverse effects of this and also of the potential effects of synthetic cannabinoids on the lung. An intriguing possibility is that cannabinoids have an unexploited potential as a bronchodilator. While the bronchodilator action of cannabis has been known for more than a century, we still do not know if this could be useful in practice; Finally, we anticipate that taking and quantifying an individuals cannabis smoking history will become as routine in clinical practice as recording tobacco exposure. Doctors should inform their patients about the known effects of cannabis smoke in causing bronchitis. It may be difficult to persuade users to stop smoking cannabis but they need to be advised of the possible risk of lung cancer.

Key issues

- Cannabis is widely used throughout the world and is currently the most common illegal drug.
- The pattern of lung function abnormalities among cannabis smokers is clearly different from those associated with tobacco smoking.
- Cannabis smoke has potent effects on the bronchial mucosa and is associated with large airway inflammation and symptoms of bronchitis.
- Systematic research into the long-term effects of smoking cannabis on lung function show increased large airways resistance and hyperinflation.
- By contrast there is no convincing evidence that smoking cannabis causes obstructive airways disease or emphysema.
- The numerous case reports of bullous emphysema in the literature have not been replicated in systematic studies. It is likely that these represent occasional complications among extremely heavy cannabis smokers.
- More data are needed on the controversial issue of whether smoking cannabis causes lung cancer.
- The advantages and disadvantages of the different methods of inhaling cannabis (joint, bong, pipe or vaporizer) are unknown.
- Cannabis has acute bronchodilator effects but there is no evidence that this is clinically useful.

References

Papers of special note have been highlighted as:
• of interest
** of considerable interest
13 Roth MD, Arora A, Barsky SH, Kleerup EC, Simmons M, Tashkin DP. Airway inflammation in young


• Canadian study in an older population of over 40 years of age, which identifies the risk of chronic obstructive pulmonary disease among cannabis and tobacco smokers and those who smoke both.


• Population-based birth-cohort study of 1037 participants suggesting that cannabis and tobacco use have different patterns of effects on respiratory function.


• Compares different methods of smoking cannabis and tobacco and highlights the risk of injury from the differential methods of inhalation.


• Review up until 2005 of studies of cannabis and its association with lung cancer.


• Case–control study suggesting that there is an increased risk of developing lung cancer in heavy cannabis smokers.


• Large case–control study (n = 2252) that demonstrated no increased risk of developing lung cancer with cannabis use.


• Article that suggests that cannabis is not as carcinogenic as tobacco because of fundamental differences in the pharmacologic properties of cannabinoids and nicotine.


Website

101 PAPERSPAST – Star, Issue 6298, 1 October 1898, page 7
http://paperspast.natlib.govt.nz/cgi-bin/paperspast
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### Activity Evaluation

Where 1 is strongly disagree and 5 is strongly agree

1. The activity supported the learning objectives.
2. The material was organized clearly for learning to occur.
3. The content learned from this activity will impact my practice.
4. The activity was presented objectively and free of commercial bias.

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1. **42-year-old man presents with coughing. He quit smoking cigarettes 20 years ago but has smoked cannabis several times per week over the last 15 years. He says that he is worried “that the pot is hurting my lungs.”**
   - **What should you consider in regard to the effects of cannabis on respiratory health?**
   - **A** Cannabis is a potent bronchoconstrictor
   - **B** The acute airway effects of cannabis do not appear to be sustained after 8 weeks of regular use
   - **C** Many respiratory abnormalities related to cannabis use may be detected on physical examination
   - **D** Many respiratory abnormalities related to cannabis use may be detected on spirometry

2. **Which of the following lung function values is most likely to be abnormal in this patient?**
   - **A** Forced expiratory volume in 1 second (FEV1)
   - **B** Forced vital capacity (FVC)
   - **C** Airway resistance (Raw)
   - **D** FEV1/FVC

3. **What can you tell this patient about the association between cannabis use and emphysema/bullous disease?**
   - **A** Most adults with chronic cannabis use have evidence of pulmonary bullae
   - **B** Bullae associated with cannabis are invariably located in the lower lobes
   - **C** Chronic cannabis use reduces diffusion lung capacity for carbon monoxide (DLCO)
   - **D** Cannabis does not appear to promote emphysema

4. **The patient is also concerned about the effects of cannabis on his risk for cancer. What can you tell him?**
   - **A** There is conflicting evidence as to whether cannabis can promote lung cancer
   - **B** Cannabis condensates are less mutagenic than tobacco condensates
   - **C** Cannabis appears to increase the risk for oropharyngeal cancer but not lung cancer
   - **D** Bong smoking appears to confer a lower risk for lung cancer compared with smoking joints
Continued cannabis use and risk of incidence and persistence of psychotic symptoms: 10 year follow-up cohort study

Rebecca Kuepper, research psychologist,1 Jim van Os, professor,1 visiting professor,2 Roselind Lieb, professor,3,4 Hans-Ulrich Wittchen, professor,4,5 Michael Höfler, research statistician,6 Cécile Henquet, lecturer1

ABSTRACT

Objective To determine whether use of cannabis in adolescence increases the risk for psychotic outcomes by affecting the incidence and persistence of subclinical expression of psychosis in the general population (that is, expression of psychosis below the level required for a clinical diagnosis).

Design Analysis of data from a prospective population based cohort study in Germany (early developmental stages of psychopathology study).

Setting Population based cohort study in Germany.

Participants 1923 individuals from the general population, aged 14-24 at baseline.

Main outcome measure Incidence and persistence of subthreshold psychotic symptoms after use of cannabis in adolescence. Cannabis use and psychotic symptoms were assessed at three time points (baseline, T2 (3.5 years), T3 (8.4 years)) over a 10 year follow-up period with the Munich version of the composite international diagnostic interview (M-CIDI).

Results In individuals who had no reported lifetime psychotic symptoms and no reported lifetime cannabis use at baseline, incident cannabis use over the period from baseline to T2 increased the risk of later incident psychotic symptoms over the period from T2 to T3 (adjusted odds ratio 1.9, 95% confidence interval 1.1 to 3.1; P=0.021). Furthermore, continued use of cannabis increased the risk of persistent psychotic symptoms over the period from T2 to T3 (2.2, 1.2 to 4.2; P=0.016). The incidence rate of psychotic symptoms over the period from baseline to T2 was 31% (152) in exposed individuals versus 20% (284) in non-exposed individuals; over the period from T2 to T3 these rates were 14% (108) and 8% (49), respectively.

Conclusion Cannabis use is a risk factor for the development of incident psychotic symptoms. Continued cannabis use might increase the risk for psychotic disorder by impacting on the persistence of symptoms.

INTRODUCTION

Cannabis is the most commonly used illicit drug in the world, particularly among adolescents.1,2 The use of cannabis is consistently associated with mental illness,3 in particular psychotic disorder.4-9 It remains a matter of debate, however, whether the association between cannabis and psychosis is causal, or whether early psychotic experiences might in fact prompt cannabis use as a means of self medication.10,11 This issue can be resolved only if incident cannabis use is investigated in relation to later incident psychotic symptoms or disorder. Rarely have studies been able to examine the longitudinal relation between cannabis use and psychosis in this fashion.

The issue of self medication was addressed by Henquet and colleagues,4,6 using data from the German prospective early developmental stages of psychopathology study.10,11 The authors investigated the association between cannabis use at baseline and subsequent development of psychotic symptoms at four year follow-up and reported that after adjustment for pre-existing psychotic symptoms, cannabis use at baseline still remained significantly associated with psychotic symptoms at follow-up. There was no evidence of an effect of self medication as pre-existing psychotic symptoms did not significantly predict later cannabis use.6 Ferdinand and co-workers investigated the role of pre-existing self reported psychotic symptoms and showed a bi-directional association between cannabis and psychotic symptoms over a 14 year follow-up study in the general population.12 They showed that cannabis use predicted later psychotic symptoms in individuals with no evidence of psychotic symptoms before starting to use cannabis and that the reverse was also true, in that psychotic symptoms predicted cannabis use in those who had not used cannabis before the onset of those symptoms.11 A prospective population based cohort study also found evidence for a self medication effect.14 Individuals with self reported hallucinations at the age of 14 had a higher risk of using cannabis on a daily basis at the age of 21. In a sibling pair analysis, however, this study also suggested an independent effect of cannabis use on self reported delusional ideation later in life.14 Thus, although the cannabis-psychosis link has been investigated in
many studies, results on the temporal association between cannabis use and psychotic symptoms remain conflicting. Longitudinal cohort studies with multiple repeated interview based measures of cannabis use and psychotic symptoms are needed to clarify this issue. The EDSP study, which completed its recent 10 year follow-up representing the fourth assessment (assessments at baseline, T1, T2, and T3, see also fig 1), is uniquely suitable for the investigation of the temporal association between cannabis and psychosis.

Another issue is the mechanism by which cannabis might increase the risk of psychotic symptoms, particularly whether it might increase the risk by causing persistence of normally transitory developmental expression of psychotic experiences. For most individuals, subclinical expression of psychotic phenomena (that is, expression of psychosis below the level required for a clinical diagnosis) is transitory and never progresses to psychotic illness. Subthreshold psychotic experiences could, however, become abnormally persistent, depending on the degree of additional exposure to environmental risk factors, and progressively greater levels of persistence might be associated with a greater risk for transition to clinical psychotic disorder. Spauwen and colleagues showed that the persistence rate of psychotic experiences was much higher for individuals growing up in an urban rather than a rural environment. Similarly, Cougnard and co-workers provided evidence that childhood trauma, urban environment, and cannabis act additively in increasing the risk of persistence of psychotic experiences. The fact that cannabis use increases risk of psychosis in a dose-response fashion and that patients with psychosis who continue to use cannabis show more severe and persistent symptoms suggests that cannabis use might increase the risk for psychotic illness by impacting on the persistence rate of psychotic experiences that under normal circumstances would have remained transitory phenomena for most people. In a population based 10 year follow-up cohort study of adolescents and young adults, we investigated the association between incident cannabis use and true incidence of psychotic experiences (that is, after exclusion of individuals with lifetime pre-existing psychotic experiences) and risk of persistence of psychotic experiences.

**METHOD**

**Sample and study design**

The observation frame was part of the early developmental stages of psychopathology (EDSP) study, which collected data on the prevalence, incidence, risk factors, comorbidity, and course of mental disorders in a random representative population sample of adolescents and young adults in the general population. After ethical approval, the baseline sample was randomly drawn in 1994 from the respective population registry offices of Munich and its 29 counties to mirror the distribution of individuals aged 14-24 at the time of the baseline interview in 1995. The base population comprised people born from 1 June 1970 to 31 May 1981 registered as residents in these localities and having German citizenship. These registers are highly accurate because each German is registered by his or her town, registers are regularly updated, for scientific studies any number of randomly drawn addresses with a given sex and age group can be

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**Table 1** (Characteristics of participants by use of cannabis at T2 (3.5 years after baseline) (n=1923). Figures are numbers (percentages))

<table>
<thead>
<tr>
<th></th>
<th>Used cannabis (n=393)</th>
<th>Did not use cannabis (n=1530)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>119 (30)</td>
<td>807 (53)</td>
</tr>
<tr>
<td>Women</td>
<td>274 (70)</td>
<td>723 (47)</td>
</tr>
<tr>
<td><strong>Socioeconomic status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower</td>
<td>30 (7)</td>
<td>85 (6)</td>
</tr>
<tr>
<td>Middle</td>
<td>220 (54)</td>
<td>894 (59)</td>
</tr>
<tr>
<td>Upper</td>
<td>137 (34)</td>
<td>524 (35)</td>
</tr>
<tr>
<td>Other</td>
<td>22 (5)</td>
<td>6 (0.4)</td>
</tr>
<tr>
<td><strong>Urban/rural environment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>295 (75)</td>
<td>1050 (69)</td>
</tr>
<tr>
<td>Rural</td>
<td>98 (25)</td>
<td>480 (31)</td>
</tr>
<tr>
<td><strong>Childhood trauma</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>97 (25)</td>
<td>266 (17)</td>
</tr>
<tr>
<td>No</td>
<td>296 (75)</td>
<td>1264 (83)</td>
</tr>
<tr>
<td><strong>Use of other drugs at baseline</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>25 (6)</td>
<td>11 (1)</td>
</tr>
<tr>
<td>No</td>
<td>368 (94)</td>
<td>1519 (99)</td>
</tr>
<tr>
<td><strong>Use of other drugs at T2</strong></td>
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<td></td>
</tr>
<tr>
<td>Yes</td>
<td>40 (10)</td>
<td>3 (0.2)</td>
</tr>
<tr>
<td>No</td>
<td>353 (90)</td>
<td>1527 (99)</td>
</tr>
<tr>
<td><strong>Any psychiatric disorder at baseline</strong></td>
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<td></td>
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<tr>
<td>Yes</td>
<td>76 (19)</td>
<td>180 (12)</td>
</tr>
<tr>
<td>No</td>
<td>317 (81)</td>
<td>1350 (88)</td>
</tr>
</tbody>
</table>

*Socioeconomic status: lower (lower class, lower middle class), middle (middle middle class), upper (higher middle class, upper class), other (none of the above or missing). Data missing for five participants. 
†Urban (city of Munich, 10 559/km²), rural (surroundings of Munich, 1432/km²). 
‡Childhood trauma: any traumatic experience during childhood. 
§On more than five occasions. 
¶Other than psychosis, according to M-CIDI diagnoses. 

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**Fig 1** Study design. Top: testing association between incident cannabis use with onset in period from baseline to T2 and incident psychotic symptoms with onset in period from T2 to T3 in individuals who had not used cannabis at baseline and who had not reported any psychotic experience at T2 (that is, no lifetime psychotic experiences by T2). Bottom: testing association between different cannabis exposure states (combinations of cannabis use at baseline (lifetime), or T2 or both (interval) and persistence of psychotic experiences (that is, presence of psychotic experiences at both T2 (lifetime) and T3 (interval))
obtained, and registration is strictly enforced by law and the police. More details on the sampling, representativeness, instruments, procedures, and statistical methods of the study sample can be found elsewhere.12,13

The overall design of study is longitudinal and prospective, consisting of a baseline and three follow-up surveys. The first (baseline to T1) covered a mean of 1.6 years (SD 0.2), the second (baseline to T2) covered a mean of 3.5 years (SD 0.3), and the third (baseline to T3) covered a mean of 8.4 years (range 7.3-10.5, SD 0.7). Because our primary goal was to examine the incidence and developmental risk factors for psychopathology, we sampled the younger group (age 14-15), presumed to have the highest incidence density, at twice the rate of people aged 16-21 and sampled the oldest group (age 22-24) at half this rate. For the same reason we examined people aged 14-17 at baseline at the four time points and those aged 18-24 only three times (baseline, T2, T3). The present study is based on the whole cohort assessed at baseline, T2, and T3. Figure 1 shows a schematic illustration of the overall design and the current analyses. Response rates were 84% (2548) at T2 and 73% (2210) at T3 (fig 2).

**Instruments**

We used the computerised version of the Munich composite international diagnostic interview (DIA-X/M-CIDI), an updated version of the World Health Organization’s CIDI version 1.2. The DIA-X/M-CIDI is a comprehensive fully standardised diagnostic interview that assesses symptoms, syndromes, and diagnoses of various mental disorders in accordance with the definitions and criteria of ICD-10 (international classification of diseases, 10th revision) and DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, fourth edition), along with information about onset, duration, severity of symptoms, and psychosocial impairment. The CIDI has been primarily designed for use in epidemiological studies of mental disorders and can also be used for clinical purposes. It is divided into 16 sections; one sociodemographic section, 12 sections assessing 288 symptoms of groups of mental disorders (including somatoform and dissociative, phobic and other anxiety, depressive and dysthymic, manic and bipolar affective, schizophrenia and other psychotic, eating, dementia and other cognitive, post-traumatic stress, as well as tobacco, alcohol, and substance related disorders), and three final sections containing concluding questions, interviewers’ observations, and interviewers’ ratings. The instrument, designed for use by trained interviewers who are not clinicians, has shown high inter-rater24 25 and test-retest reliability.22 26 The assessment of psychosis with CIDI by lay interviewers is not considered reliable so trained clinical interviewers at the level of clinical psychologist, who were allowed to probe with follow-up clinical questions, conducted the interviews in the respondents’ homes. At baseline, the DIA-X/M-CIDI lifetime version was used. At each of the follow-up assessments, the interval version was used to assess the period from the last interview until the next. Data on the G section concerning psychosis and its clinical relevance were collected only at T2 (lifetime version) and T3 (interval version). As the assessment of substance use was part of the diagnostic interview with the DIA-X/M-CIDI, psychologists who did the interviews were not blinded for cannabis use.

**Assessment of psychotic symptoms**

Data on psychotic experiences were collected at time T2 (lifetime version) and T3 (interval version) with the G section of the DIA-X/M-CIDI. As the primary objective of the EDSP study was to investigate the early stages of substance misuse in adolescents and young adults, data on the occurrence of psychotic symptoms as assessed with the G section were added at T2 (measuring lifetime experience of psychotic symptoms) and T3 (measuring interval experience of psychotic symptoms).13 As in previous work61 9 presence of psychotic experiences was broadly defined as any rating of present on any of the 20 DIAX/M-CIDI core psychosis items (G1, G2a, G3-G5, G7-G13, G13b, G14, G17, G18, G20, G20C, G21, and G22a), including 14 delusion items, five hallucination items, and one item on passivity phenomena. Items relate to classic psychotic symptoms involving, for example, persecution, thought interference, auditory hallucinations, and passivity phenomena. The

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**Table 2** Patterns of cannabis use in relation to presence of psychotic symptoms* at T2 (3.5 years after baseline) and T3 (8.4 years after baseline) in risk set (n=1923). Figures are numbers (percentage) of participants

<table>
<thead>
<tr>
<th>Cannabis use†‡‡</th>
<th>Psychotic symptoms at T2</th>
<th>Psychotic symptoms at T3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>81  (4)</td>
<td>166 (9)</td>
</tr>
<tr>
<td>No</td>
<td>355 (18)</td>
<td>1321 (69)</td>
</tr>
<tr>
<td><strong>T2</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>126 (7)</td>
<td>267 (14)</td>
</tr>
<tr>
<td>No</td>
<td>310 (16)</td>
<td>1220 (64)</td>
</tr>
</tbody>
</table>

*Any psychotic symptom lifetime (T2) and interval (T3) as assessed with M-CIDI (G) section.
†Some percentages do not total 100 because of rounding.
‡On more than five occasions as assessed with M-CIDI (L) section.
psychotic experiences at T3. Figures are odds ratios (95% confidence intervals) and P values

<table>
<thead>
<tr>
<th>Cannabis use at T2</th>
<th>Risk of psychotic experiences at T3</th>
<th>Unadjusted</th>
<th>Adjusted*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole sample</td>
<td>1.8 (1.3 to 2.4), 0.001</td>
<td>1.5 (1.1 to 2.1), 0.018</td>
<td></td>
</tr>
<tr>
<td>After exclusion†</td>
<td>2.1 (1.3 to 3.4), 0.004</td>
<td>1.9 (1.1 to 3.1), 0.021</td>
<td></td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, socioeconomic status, use of other drugs, childhood trauma, and urban/rural environment.
†Excludes individuals with baseline cannabis use and pre-existing psychotic symptoms.

We calculated a dichotomous persistence variable (no persistence versus persistence), with no persistence referring to experience of psychotic symptoms after cannabis use, rather than persistence of pre-existing psychotic experiences, we excluded from the analysis individuals who had admitted to lifetime presence of any psychotic symptom at T2 (n=574, 23%). We also excluded all individuals with cannabis use at baseline, thus including only individuals with new cannabis exposure between baseline and T2.

We investigated reverse causality (that is, self mediation) by testing the association between cannabis consumption and pre-existing psychotic experiences, we excluded the analysis individuals who had admitted to lifetime presence of any psychotic symptom at T2 (n=574, 23%). We also excluded all individuals with cannabis use at baseline, thus including only individuals with new cannabis exposure between baseline and T2.

We carried out sensitivity analyses to investigate whether attrition occurred at random and to assess potential bias introduced by missing data. This was done by multiple imputation of missing values with the ICE routine in Stata 11.1. This method imputes several alternative versions of the complete dataset from the available data.

Incident use of cannabis and incidence of psychotic symptoms

We used logistic regression analyses to investigate the association between incident cannabis use from baseline to T2 and incident psychosis outcome from T2 to T3 (see fig 1, top). To investigate the true incidence of psychotic symptoms after cannabis use, rather than persistence of pre-existing psychotic experiences, we excluded from the analysis individuals who had admitted to lifetime presence of any psychotic symptom at T2 (n=574, 23%). We also excluded all individuals with cannabis use at baseline, thus including only individuals with new cannabis exposure between baseline and T2.

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We investigated reverse causality (that is, self mediation) by testing the association between cannabis use and pre-existing psychotic experiences, we excluded from the analysis individuals who had admitted to lifetime presence of any psychotic symptom at T2 (n=574, 23%). We also excluded all individuals with cannabis use at baseline, thus including only individuals with new cannabis exposure between baseline and T2.
referring to experience of psychotic symptoms at both T2 and T3. To investigate whether different levels of exposure to cannabis affected persistence of psychotic symptoms differentially, we calculated a categorical cannabis continuation variable (0 = never used cannabis; 1 = cannabis use at baseline but not at T2; 2 = cannabis use at T2 but not at baseline, 3 = cannabis use at both baseline and T2). We used logistic regression analyses to investigate the association between cannabis continuation and psychosis persistence (fig 1 bottom).

RESULTS
Sample
A total of 2210 individuals completed the T3 assessment; information on substance use and psychotic symptoms was missing for 287 participants, resulting in a final risk set for analysis of 1923 individuals, of whom 926 (48%) were men (fig 2). Mean age was 18.3 (SD 3.3) at baseline, 21.8 (SD 3.4) at T2, and 26.6 (SD 3.5) at T3. Table 1 gives further characteristics of participants.

At baseline, 247 participants reported using cannabis (13% lifetime use). Of those, 56 participants (23%) used cannabis almost every day, 69 (28%) reported weekly use, 57 (23%) used cannabis monthly, and 65 (26%) reported using cannabis less than once a month. At T2, 392 participants reported using cannabis (20% interval use). The mean frequency of those who reported cannabis use at T2 was 130 times within the period from baseline to T2 (range 5-997). Psychotic symptoms were reported by 436 participants (23%) at T2 (lifetime) and by 231 participants (12%) at T3 (interval). Table 2 summarises patterns of cannabis use in relation to psychotic symptoms.

Incident cannabis use and incidence of psychotic symptoms
The incidence rate of psychotic symptoms over the period from baseline to T2 was 31% (152) in exposed individuals and 20% (284) in non-exposed individuals; over the period from T2 to T3 these rates were 14% (108) and 8% (49), respectively.

Lifetime cannabis use as assessed at T2 significantly increased the risk of psychotic experiences at T3 (adjusted odds ratio 1.5, 95% confidence interval 1.1 to 2.1; P = 0.018; tables 3 and 4). After we excluded all individuals who had used cannabis at baseline and had reported psychotic experiences at T2, incident cannabis use over the period from baseline to T2 similarly increased the risk for incident psychotic experiences between T2 and T3 (1.9, 1.1 to 3.1; P = 0.021). Results were unchanged after additional adjustment for any psychiatric diagnosis other than psychosis at baseline (1.9, 1.1 to 3.1; P = 0.020).

There was no evidence for self medication effects, as psychotic experiences at T2 did not predict incident cannabis use between T2 and T3 (0.8, 0.6 to 1.2; P = 0.3).

Cannabis use and persistence of psychotic experiences
Analyses showed a significant association between continuation of cannabis use and risk of persistence of psychotic experiences (adjusted χ² 16.22, P = 0.001; tables 4 and 5). After adjustment for age, sex, socioeconomic status, use of other drugs at baseline and T2, urban/rural environment, childhood trauma, and occasional cannabis use (cannabis use at either baseline or T2, exposure states 1 and 2), effect sizes were attenuated, with significance only for the combination of cannabis use at both baseline and T2 (exposure state 3; adjusted odds ratio 2.2, 1.2 to 4.2; P = 0.016). Additional adjustment for any psychiatric diagnosis other than psychosis at baseline occasioned a slight reduction in the association between cannabis use at both baseline and T2 and the risk for persistence of psychotic symptoms (2.0, 1.0 to 3.8; P = 0.037).

Missing data
Imputation of 20 datasets with the ICE routine in Stata 11.1, which imputes multiple alternatives based on available data, showed that the association between continued cannabis use and the risk of persistence of psychotic symptoms remained significant (adjusted χ² 16.65; P = 0.001). Again, the strongest association was found for exposure state 3 (that is, cannabis use at both baseline and T2), with an adjusted odds ratio of 2.0 (1.1 to 3.7; P = 0.028).

DISCUSSION
This 10 year follow-up study showed that incident cannabis use significantly increased the risk of incident psychotic experiences. The association was independent of age, sex, socioeconomic status, use of other drugs, urban/rural environment, and childhood trauma; additional adjustment for other psychiatric diagnoses similarly did not change the results. There was no evidence for self medication effects as psychotic experiences did not predict later cannabis use. The results thus help to clarify the temporal association between cannabis use and psychotic experiences by systematically addressing the issue of reverse causality, given that the long follow-up period allowed exclusion of all individuals with pre-existing psychotic experiences or pre-existing cannabis use. In addition, cannabis use was confirmed as an environmental risk factor impacting on the risk of persistence of psychotic experiences (fig 3).

Table 4
| Course of psychotic experiences in relation to level of continued cannabis use at T2 (3.5 years after baseline) and T3 (8.4 years after baseline). Figures are numbers (percentages) of participants |
|---|---|---|---|
| Cannabis continuation | Psychotic experiences at follow-up | None | At T2 or T3 | At T2 and T3 |
| No use | 1071 (75) | 303 (21) | 64 (4) |
| At baseline but not at T2 | 59 (64) | 25 (27) | 8 (9) |
| At T2 but not at baseline | 144 (60) | 75 (32) | 19 (8) |
| At baseline and T2 | 90 (58) | 48 (31) | 17 (11) |
The mechanism behind the association

We investigated the association between cannabis use and risk of psychosis by analysing the expression of psychotic experiences. Psychotic experiences share many characteristics with clinically relevant psychoses, such as demographic, environmental, and genetic risks, and are thought to represent a behavioural marker for psychosis liability.\textsuperscript{18,31,32} Psychotic experiences are a common and generally transitory phenomenon in the general population, that, nevertheless, might become abnormally persistent and progress to clinical psychotic disorder if combined with exposure to environmental risks.\textsuperscript{19,33,34} Our study confirmed cannabis as an environmental risk factor, impacting on risk of psychosis by increasing the risk of incident psychotic experiences, and, if use continues over time, increasing the risk of persistent psychotic experiences.

The finding that longer exposure to cannabis was associated with greater risk for persistence of psychotic experiences is in line with an earlier study showing that continued cannabis use over time increases the risk for psychosis in a dose-response fashion.\textsuperscript{2} This is also in agreement with the hypothesis that a process of sensitisation might underlie emergence and persistence of psychotic experiences\textsuperscript{33,35} as an indicator of liability to psychosis.\textsuperscript{18,31} Sensitisation refers to the phenomenon that repeated exposure to an (environmental) stressor leads to progressively greater responses over time.\textsuperscript{35-38} In rats, repeated exposure to THC (delta-9-tetrahydrocannabinol, the main psychoactive component of cannabis) induces behavioural sensitisation: rats pre-treated with increasing doses of THC show greater behavioural (locomotor) responses to a THC challenge after a 14 day washout period than THC naive rats.\textsuperscript{39,40} In humans, however, direct evidence for cannabis sensitisation is lacking. As our study showed that the risk of persistent psychotic experiences increases with longer periods of cannabis exposure, we suggest that a process of sensitisation underlies the association between cannabis and psychosis.\textsuperscript{32}

Methodological issues

The results should be interpreted in the light of several limitations. Firstly, information on substance use and psychosis outcome was acquired with the DIA-X/M-CIDI, which essentially provides self reported information. The interview was conducted face to face by clinical psychologists, however, who were allowed to follow up with clinical questioning to ensure systematic and valid assessment of outcomes and can therefore be assumed to yield better and more valid results than a self report questionnaire. Secondly, the analyses were not directly adjusted for the possible confounding effects of a family history of psychosis as this information was not available in the EDSP data. Previous research has shown that associations between cannabis use and psychotic symptoms are not reducible to family history of psychosis\textsuperscript{41,42} and that genetic liability for psychotic disorder does not predict cannabis use.\textsuperscript{43} In addition, individuals with a family history of psychosis report more positive symptoms than individuals without such predisposition.\textsuperscript{44,45} As we excluded all individuals with at least one T2 lifetime psychotic symptom from the analysis, the possible confounding effect of family history for psychosis was indirectly adjusted for to a degree. Furthermore, we used a rather broad outcome measure, defined as a minimum of one positive rating on a G section item, representing psychotic experiences rather than clinically relevant psychotic disorder. It has been shown, however, that psychotic experiences show continuity with psychotic disorders such as schizophrenia.\textsuperscript{18,46} In addition, given that fact transient psychotic experiences might, under certain circumstances, become abnormally persistent, giving rise to clinical psychotic disorder,\textsuperscript{15,17,19} psychotic experiences represent an important phenotype for the investigation of mechanisms and pathways by which environmental risk factors such as cannabis impact on psychosis risk. A further limitation concerns the use of the G section of the DIA-X/M-CIDI. This section was administered at T2 to assess lifetime occurrence of symptoms, which represents a long period for retrospective assessment of psychotic phenomena, possibly resulting in false negative results. As we excluded participants with T2 lifetime experience of psychotic symptoms from the analyses, under-reporting would have resulted in false negative results being incorrectly retained in the analyses. It is unlikely that

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**Table 5 | Association between continued use of cannabis (over period from baseline to T2) and persistence* of psychotic experiences over period from T2 to T3. Figures are odds ratios (95% confidence intervals) and P values**

<table>
<thead>
<tr>
<th>Cannabis continuation</th>
<th>Risk of persistence of psychotic experiences</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted</td>
</tr>
<tr>
<td>No use</td>
<td>1</td>
</tr>
<tr>
<td>At baseline but not at T2</td>
<td>2.0 (0.95 to 4.6), 0.068</td>
</tr>
<tr>
<td>At T2 but not at baseline</td>
<td>1.9 (1.1 to 3.2), 0.022</td>
</tr>
<tr>
<td>At baseline and T2</td>
<td>2.6 (1.5 to 4.6), 0.001</td>
</tr>
</tbody>
</table>

*Persistence of psychotic experiences; present at T2 and T3.
†Adjusted for age, sex, socioeconomic status, use of other drugs baseline and T2, childhood trauma, and urban/rural environment.

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**Fig 3 | Cannabis-psychosis persistence model. Person A has normal developmental expression of subthreshold psychotic experiences that are mild and transient. Person B has similar expression but longer persistence because of additional environmental exposure (here cannabis). Person C has prolonged persistence and subsequent transition to clinical psychotic disorder because of repeated environmental exposure—that is, repeated cannabis use**
under-reporting would have occurred as a function of cannabis use, which could have resulted in biased estimates. In addition, 23% of participants reported lifetime subclinical psychotic symptoms at T2, which is in keeping with the estimated 15-28% rate of subclinical psychotic symptoms in the general population. Therefore, the influence of under-reporting is probably limited. Finally, as the time between follow-up visits was four years on average, selective recall could have influenced the results. Spurious findings could have arisen if those with psychotic symptoms had better recall of earlier cannabis use. Given the well-known link between psychosis liability and cognitive alterations, including impaired memory, any influence of selective recall would probably have been conservative rather than anti-conservative.

Contributors: H-UW and RL were the principal investigators of the study. RK analysed the data in collaboration with CH, JvO, and MH. RK drafted the paper. All authors contributed to subsequent drafts of the paper and the final version. JvO is guarantor.

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Ethical approval: The EDSP project was approved by the ethics committee of the Medical Faculty of the Technische Universität Dresden (No EK-13811).

Data sharing: (No EK-13811).

The EDSP study is funded by grants of the German Ministry of Research, Education and Technology (O1EB9405/6 and O1EB990/16) and the Deutsche Forschungsgemeinschaft (DFG), and this paper is part of NIH grant RO1DA016977-01, PL. Competing interests: All authors have completed the Unified Competing Interest form at www.cmjm.org/coi-disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisation that might have an interest in the submitted work in the previous three years; and no other relationships or activities that could appear to have influenced the submitted work.

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Data sharing: (No EK-13811).
35 Collip D, Myin-Germeys I, Van Os J. Does the concept of sensitization provide a plausible mechanism for the putative link between the environment and schizophrenia? Schizophr Bull 2008;34:220-5.
43 Genetic Risk and Outcome in Psychosis (GROUP) Investigators. Evidence that familial liability for psychosis is expressed as differential sensitivity to cannabis: an analysis of patient-sibling and sibling-control pairs. Arch Gen Psychiatry 2010 Oct 4 [epub ahead of print].

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REVIEW

An overview of systematic reviews on cannabis and psychosis: Discussing apparently conflicting results

SILVIA MINOZZI, MARINA DAVOLI, ANNA M. BARGAGLI, LAURA AMATO, SIMONA VECCHI & CARLO A. PERUCCI

Department of Epidemiology, Local Health Unit Roma E, Roma, Italy

Abstract

Issues. Cross-sectional surveys have revealed that cannabis is the most widely used illicit substance in Western countries. Cannabis intoxication can lead to acute, transient psychotic symptoms and the short-term exacerbation of pre-existing psychotic symptoms. However, controversy exists about whether cannabis can actually cause long-term psychosis. Approach. We summarised the findings of systematic reviews on the association between cannabis use and psychosis, searching MEDLINE, EMBASE and CINAHL up to August 2007. We assessed the methodological quality, selected the better quality reviews and analysed reasons for discordant results. Key Findings. We included five systematic reviews. Four of the reviews performed a meta-analysis and showed a consistent association between cannabis use and psychosis; the fifth review considered psychological problems more broadly, did not perform a meta-analysis and reported an inconsistent association. The reasons for discordance were: different outcomes (psychosis vs. psychological problems), different inclusion criteria for primary studies and different methods for summarising the results. Implications. This overview shows a consistent association between cannabis use and psychotic symptoms, though it is not possible to draw firm conclusions about a causal relationship. Reverse causality and residual confounding cannot be excluded. An interaction with other environmental and genetic factors is difficult to ascertain. Conclusion. We conclude that there is insufficient knowledge to determine the level of risk associated with cannabis use in relation to psychotic symptoms and that more information is needed on both the risks of cannabis use and the benefits of preventive interventions to support evidence-based approaches in this area. [Minozzi S, Davoli M, Bargagli AM, Amato L, Vecchi S, Perucci CA. An overview of systematic reviews on cannabis and psychosis: Discussing apparently conflicting results. Drug Alcohol Rev 2010;29;304–317]

Key words: cannabis, marijuana abuse, psychotic disorders, systematic review.

Introduction

Cross-sectional studies of the general population and students have consistently revealed that cannabis is the most widely used illicit substance in many regions of the world, including Europe [1], North America and Australia [2,3]. Cannabis is also the second most frequently cited drug in reports on individuals entering substance abuse treatment for the first time [1–5]. Clients seeking treatment for cannabis use can present with social impairment, such as complaints from family members, loss of friendship, financial difficulties, impaired work or school performance, loss of self-confidence, memory loss, legal problems and psychiatric distress, such as somatisation, depression, anxiety, irritability, phobic anxiety, paranoid ideation and psychosis [6–8]. Cannabis intoxication can lead to acute, transient psychotic symptoms in some individuals [9] and produce a short-term exacerbation or recurrence of pre-existing psychotic symptoms [10–12]. However, controversy remains about whether cannabis use can actually cause long-term psychosis [1].

There is evidence of an association between cannabis use and the development of psychotic symptoms, but...
the nature of this association is widely debated. Four main hypotheses have been formulated to explain the observed association [13]:

1. Confounding: the association is spurious; cannabis use is often associated with the use of other drugs or with other factors responsible for the later onset of psychosis.
2. Interaction: cannabis is a component cause; psychosis is caused only in vulnerable people and in interaction with other environmental and genetic factors.
3. Reverse causality: people with psychosis use cannabis more often in an attempt to cope with negative symptoms that stem from psychosis (depression, anxiety or dysphoria) or to alleviate the side-effects of antipsychotic medication.
4. Etiological: cannabis is the direct cause of psychosis; it alone is a necessary and sufficient cause.

Systematic reviews critically appraise and summarise the published evidence concerning a particular problem and have gained prominence as useful tools for evidence-based decision making. The number of systematic reviews has increased at least 500-fold during the past 10 years, and they have been applied extensively in the field of drug addiction. This increase has lead to an increased number of reviews addressing very similar questions, with a concomitant increase in conflicting results. Such a discrepancy causes difficulties for decision makers, clinicians and patients.

The aim of this overview was to summarise the major findings of published systematic reviews on the association between cannabis use and psychosis, and to analyse the possible reasons for the discordant results among them.

Methods

Search strategy

We performed a systematic search of MEDLINE, EMBASE and CINAHL from 2000 to August 2007. For each database, separate detailed search strategies were developed based on controlled vocabulary and free text terms, combining the following search terms and the boolean operators or/and: [Substance-related disorders or cannabis or marihuana or marijuana] and [psychosis or psychotic disorders or schizophrenia or psychotic*]. A methodological search filter for review articles was added. We also checked the references of existing reviews for potentially relevant papers. There was no language restriction.

Inclusion criteria

We included systematic reviews that clearly state the objective, define the inclusion criteria for primary studies, report the raw data of the primary studies included, and include observational studies that assess the relationship between cannabis use and psychosis.

Data extraction and quality assessment

Two authors independently extracted data and assessed the quality of the included reviews using the Overview Quality Assessment Questionnaire (OQAQ) scale [14]; any disagreement was resolved by discussion among the authors.

The OQAQ scale is composed of nine items designed to assess specific aspects of the methodological quality of systematic reviews and one overall assessment item that requires assessors to assign a quality score on a 7-point scale, where 1 represents the presence of extensive flaws and 7 represents minimal flaws.

Analysis of discordant reviews

In order to analyse the reasons for discordant results among the reviews, we used the following criteria proposed by Jadad [15]:

- Differences in methodological quality.
- Differences in clinical question: population, exposure, outcomes.
- Differences in study selection: search strategy, inclusion criteria.
- Differences in data extraction: methods to measure exposure and outcomes.
- Differences in the assessment of study quality: methods and interpretation of quality assessments.
- Differences in methods to incorporate quality assessments into the review.
- Differences in the ability to combine studies: statistical methods, criteria to judge the ability to combine studies.

We also retrieved the full text of primary studies included in the reviews in order to understand better the reasons for inclusion or exclusion and to determine the appropriateness of any statistical synthesis of the results.

Results

We identified 41 reports. Twenty-one reports were excluded on the basis of the title and abstract because they were not pertinent to the objective of our review, and the full text of 20 articles was retrieved for more detailed evaluation. Fifteen of the 20 articles were excluded because they did not fulfil the inclusion criteria. Thus, five systematic reviews were included in the present review [16–20].
Characteristics of included reviews

Four of the five included reviews [16,17,19,20] assessed the association between cannabis exposure and the occurrence of schizophrenia (any type), schizophrenia-like disorders, psychosis not otherwise specified, or psychotic symptoms; the fifth review assessed the association between any illicit drug use and the occurrence of any psychological or social harm, but it also included studies assessing the association between cannabis use and psychosis considered as ‘psychological or social harm’ [18]. One of the reviews [20] also assessed the relationship between cannabis use and affective disorders (depression, suicidal ideation or attempt, anxiety). Three of the reviews [16,18,20] included only longitudinal cohort studies, whereas the other two [17,19] included both cross-sectional and longitudinal cohort studies. Table 1 shows the study design of each study included and excluded in each of the five reviews.

Overall, eight longitudinal cohort studies [21–32] assessing the association between cannabis exposure and psychosis development were identified and included in the reviews. Macleod [18] included 16 longitudinal studies, only four of which were on the association between cannabis use and psychosis and included in the other reviews. The other studies in that review assessed the effect of cannabis use on affective disorders, adult role, job success and quality of social relationships.

Methodological quality

The methodological quality of three of the reviews was poor (overall quality score 2/7 [16,17] and 3/7 [19]), whereas the other two were of good quality (overall quality score 5/7 [18] and 6/7 [20]) (Table 2). The main weaknesses concerned the comprehensiveness of the bibliographic search (cannot tell for 2/5 reviews), the avoidance of selection bias (cannot tell for 4/5 reviews), the assessment of the methodological quality of primary studies (not done in 3/5 reviews). In one review [18], conclusions were not supported by the data because the results of the primary studies were not clearly described. Only one review [20] reported the number of excluded studies and the reasons for exclusion. The information provided about the studies included in the reviews was not detailed enough to ascertain important information on the primary studies for all but one of the reviews [20], which provided a detailed table of the study characteristics. In particular, the reviews had no clear information regarding:

- Study design: some studies were described as case–control studies but appear in the description as cross-sectional studies, which invalidated any result on possible causal association;
- Exposure assessment: how cannabis use was assessed and if frequency, length and amount of use were considered;
- The assessment of confounding: how the use of other drugs was assessed and if frequency, length and amount of other drug use were considered;
- The outcome definition: whether primary studies considered ‘schizophrenia’ using the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) or International Classification of Disease (ICD-10) criteria, or ‘schizophreniform disorders’ or ‘psychotic symptoms’. One review [18] used the term ‘psychological problems’ as the outcome, and it is not clear which outcomes used in the primary studies were considered under this broader term;
- Effect measure estimate: why and how odds ratios (OR) were calculated in cohort studies, how they took losses to follow up into consideration; if the overall estimates reported in the reviews were computed using consistent measures of exposure (‘heavy users’ or ‘any users’) and outcome; and how confounding was incorporated into the pooled estimate.

Findings

Four of the reviews [16,17,19,20] performed a meta-analysis and were concordant in finding an association between cannabis use and the occurrence of psychotic disorders (Table 3). Nevertheless, the way of combining results varied among the individual reviews: Arsenault et al. [16] included a duplication of Swedish conscript data in the meta-analysis and combined results for ‘ever use’ and dependence; Henquet et al. [17] and Semple et al. [19] combined cross-sectional and longitudinal data in the meta-analysis and did not distinguish between ‘ever use’ and dependence; Semple et al. [19] combined the crude odd ratios; and Moore et al. [20] combined only longitudinal studies, presented separate results for ‘ever use’ and ‘most frequent use’ and combined the adjusted OR. None of the reviews found significant statistical heterogeneity. The review without a meta-analysis [18] found an inconsistent association between cannabis use and psychological problems. The authors reported that the adjustment for confounding factors lead to substantial attenuation of the association but did not report the original data.

To analyse possible reasons for the discordant results, we restricted our analysis to the two higher quality reviews [18,20]. The comparability of the two reviews using Jadad’s criteria is reported in Table 4. The main difference between the two reviews was outcome defi-
Table 1. Primary studies included and excluded in systematic reviews

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</tr>
</thead>
<tbody>
<tr>
<td>Date of bibliographic search</td>
<td></td>
<td>Not reported</td>
<td>Not reported</td>
<td>June 2003</td>
<td>January 2004</td>
<td>September 2006</td>
</tr>
<tr>
<td>Andréasson et al. 1987 [21], Zammit et al. 2002 [22], Zammit 2004 [23] (Swedish Conscripts study)</td>
<td>Longitudinal population based (conscripts) schizophrenia</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Arsenault et al. 2002 [24], Caspi et al. 2005 [25] (Dunedin study)</td>
<td>Birth cohort Psychotic symptoms Schizophreniform disorders</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>van Os et al. 2002 [26] (NEMESIS study)</td>
<td>Longitudinal population based Psychotic symptoms</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Fergusson et al. 2003 [27], 2005 [28] (CHDS study)</td>
<td>Birth cohort Psychotic symptoms</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>(not included in meta-analysis)</td>
<td>Yes</td>
</tr>
<tr>
<td>Henquet et al. 2005 [29] (EDSP study)</td>
<td>Longitudinal population based Psychotic symptoms</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Weiser et al. 2002 [30]</td>
<td>Adolescent longitudinal population based. Schizophrenia spectrum personality disorders</td>
<td>No</td>
<td>Yes</td>
<td>Included as low quality study. Not considered for summary results</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Tien &amp; Anthony 1990 [31] (ECA study)</td>
<td>Longitudinal Population based Psychotic symptoms</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes (not included in meta-analysis)</td>
<td>Yes</td>
</tr>
<tr>
<td>Wiles et al. 2006 [32] (NPMS)</td>
<td>Longitudinal Population based Psychotic symptoms</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No. Excluded because cross sectional</td>
</tr>
<tr>
<td>Stefanis et al. 2004 [33]</td>
<td>Cross-sectional Psychotic symptoms</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No. Excluded because cross sectional</td>
</tr>
<tr>
<td>Rolfe et al. 1993 [34]</td>
<td>Cross sectional Schizophrenia</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
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<tr>
<td>Agosti et al. 2002 [35]</td>
<td>Cross sectional Non affective psychosis</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes. Excluded because cross sectional</td>
</tr>
<tr>
<td>Degenhardt &amp; Hall 2001a [36]</td>
<td>Cross sectional Psychotic symptoms</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes. Excluded because cross sectional</td>
</tr>
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</table>

(continued)
### Table 1. (Continued)

<table>
<thead>
<tr>
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<tbody>
<tr>
<td><strong>Date of bibliographic search</strong></td>
<td></td>
<td>Not reported</td>
<td>Not reported</td>
<td>June 2003</td>
<td>January 2004</td>
<td>September 2006</td>
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<tr>
<td>Degenhardt et al. 2001b [37]</td>
<td>Cross sectional. Psychotic symptoms</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No. Excluded because cross sectional</td>
</tr>
<tr>
<td>Farrel et al. 2002 [38]</td>
<td>Cross sectional. Psychosis</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No. Excluded because population are prison sample</td>
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<tr>
<td>Grech et al. 1998 [39]</td>
<td>Cross sectional. Psychosis</td>
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<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No. Excluded because participants had already psychotic symptoms</td>
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<tr>
<td>Miller et al. 2002 [40]</td>
<td>Cross sectional. Psychotic symptoms</td>
<td>No</td>
<td>No</td>
<td>No</td>
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<td>No. Excluded because cross sectional</td>
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<tr>
<td>Phillips &amp; Johnson 2002 [41]</td>
<td>Longitudinal study; very high-risk population Psychotic symptoms</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No. Excluded because cross sectional</td>
</tr>
<tr>
<td>Resnick et al. 1997 [42], Dornbusch et al. 1999 [43] (National Longitudinal Study on adolescent health)</td>
<td>Longitudinal Population based Violent behavior</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No. Excluded because no data specifically on cannabis use</td>
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<tr>
<td>Guy et al. 1993 [44], Stein et al. 1993 [45] (Boston Schools project)</td>
<td>Longitudinal Population based Job involvement</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No. Excluded because not examined psychotic or affective outcomes</td>
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<tr>
<td>Brook et al. 1998 [46] (Children in the community project)</td>
<td>Longitudinal Population based Affective outcomes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No. Excluded because not examined psychotic or affective outcomes</td>
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<tr>
<td>Brook et al. 1996 [47], 1999 [48] (Children in the community project)</td>
<td>Longitudinal Population based Violent behaviour, adult role</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No. Excluded because not examined psychotic or affective outcomes</td>
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<tr>
<td>Brook et al. 1999 [49] (East Harlem study)</td>
<td>Longitudinal Population based. Behavioural outcomes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No. Excluded because not examined psychotic or affective outcomes</td>
</tr>
<tr>
<td>Brunswick &amp; Messeri 1986 [50], 1999 [51] (Central Harlem Study)</td>
<td>Longitudinal Population based. Physical health, behaviour outcomes, social attainment</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No. Excluded because not examined psychotic or affective outcomes</td>
</tr>
<tr>
<td>Study ID</td>
<td>Year</td>
<td>Study Details</td>
<td>Inclusion Criteria</td>
<td>Exclusion Criteria</td>
<td></td>
<td></td>
</tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>Newcomb et al. 1993 [52], 1999 [53] (LA schools study)</td>
<td>Longitudinal Population based. Affective outcomes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No. Included for affective outcomes</td>
<td></td>
</tr>
<tr>
<td>Kandel et al. 1995 [54] (New York schools study)</td>
<td>Longitudinal Population based. Income outcome</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No. Excluded because not examined psychotic or affective outcomes</td>
<td></td>
</tr>
<tr>
<td>Friedman et al. 1996 [55] (National Collaborative Perinatal Project, NCPP)</td>
<td>Longitudinal Population based. Delinquency, antisocial behaviour</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Kaestner 1994 [56], Windle 1997 [57] (National Longitudinal survey of youth)</td>
<td>Longitudinal Population based. Income outcome</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>White et al. 1999 [58] (Pittsburgh Youth Study)</td>
<td>Longitudinal Population based. Violent behaviour</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Ellickson et al. 1998 [59], 2000 [60] (Project Alert)</td>
<td>Longitudinal Population based. Violent behaviour</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
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<tr>
<td>Bray et al. 2000 [61] (South eastern public schools study)</td>
<td>Longitudinal Population based. Educational attainment</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Bates &amp; Labouvie 1997 [62] (Woodlawn study)</td>
<td>Longitudinal Population based. Alcohol use</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No. Excluded because not examined psychotic or affective outcomes</td>
<td></td>
</tr>
<tr>
<td>Juon &amp; Ensminger 1997 [63] (Woodlawn study)</td>
<td>Longitudinal Population based. Suicidal ideation or attempts</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No. included for affective outcome</td>
<td></td>
</tr>
</tbody>
</table>
nition, which could also explain differences in the included studies. Macleod et al. [18] considered any psychological problem without any further explanation or definition, whereas Moore et al. [20] considered only psychotic disorders and affective disorders defined by the DSM-IV. Furthermore, six studies included by Macleod as studies considering psychosocial problems as the outcome measure were also included by Moore, but three were defined as studies assessing affective disorders and three as studies assessing psychosis as the outcome measures. Again, in the list of studies excluded by Moore, there were six that were included by Macleod as high-quality studies; the reason for excluding these studies was a lack of considering psychotic or affective outcomes (four studies) or no specific data on cannabis use (two studies). The other major difference was in reporting the outcomes of primary studies: Moore reported an adjusted OR with a 95% confidence interval for each study, whereas Macleod gave a generic qualitative description that was more prone to interpretation. Macleod stated that the association was often substantially reduced, adjusting for confounding factors, but did not report the data, whereas Moore clearly reported how much the association was reduced for each study.

Table 2. Quality of conduct (OQAQ checklist)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Search methods described</td>
<td>Partially</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Search comprehensive</td>
<td>Can’t tell</td>
<td>Can’t tell</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Inclusion criteria reported</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Selection bias avoided</td>
<td>Can’t tell</td>
<td>Can’t tell</td>
<td>Can’t tell</td>
<td>Can’t tell</td>
<td>Yes</td>
</tr>
<tr>
<td>Criteria for quality assessment reported</td>
<td>Partially</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Partially</td>
</tr>
<tr>
<td>Criteria used appropriate</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Methods to combine findings reported</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Findings appropriately combined</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Conclusions supported by the data</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Overall score of scientific quality (*)</td>
<td>2</td>
<td>2</td>
<td>5</td>
<td>3</td>
<td>6</td>
</tr>
</tbody>
</table>

*Score from 1 (extensive flaws) to 7 (minimal flaws); OQAQ: Overview Quality Assessment Questionnaire.

Table 3. Results of meta-analysis

<table>
<thead>
<tr>
<th>Author</th>
<th>Meta-analysis of included studies</th>
<th>n studies included</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arseneault et al. 2004</td>
<td>Adjusted OR: 2.34 (95% CI: 1.69, 2.95)</td>
<td>Five studies, n of participants 101 497</td>
</tr>
<tr>
<td>Henquet et al. 2005</td>
<td>Adjusted OR: 2.1 (95% CI: 1.7, 2.5)</td>
<td>Seven studies, n of participants 112 218</td>
</tr>
<tr>
<td>Macleod et al. 2004</td>
<td>Meta-analysis not performed</td>
<td>Sixteen studies, n of participants not reported</td>
</tr>
<tr>
<td>Semple et al. 2005</td>
<td>Crude OR: 2.93 (95% CI: 2.36, 3.64)</td>
<td>Seven studies, n of participants 51 688</td>
</tr>
<tr>
<td>Moore et al. 2007</td>
<td>Adjusted OR: ever use OR 1.41 (95% CI: 1.20, 1.65)</td>
<td>Seven studies, n of participants not reported</td>
</tr>
</tbody>
</table>

CI, confidence interval; OR, odds ratio.
Characteristics of longitudinal primary studies

We analysed the primary studies included in the meta-analysis by Moore et al. [20] to assess if they were homogeneous enough to allow the pooling of their results (Table 5).

The main difference among the studies was in the length of follow up: 1–1.5 years in two studies [33,35], 4–5 years in two studies [28,32] and more than 9 years in three studies [24,26,30] (range 1–27 years).

The other parameters that were considered did not differ among the studies:

- The presence of psychotic symptoms at baseline were assessed using structured and validated instruments;
<table>
<thead>
<tr>
<th>Study</th>
<th>Participants and baseline screening</th>
<th>Exposure</th>
<th>Outcome</th>
<th>Follow-up attrition</th>
<th>Confounding factor considered</th>
<th>Dose-response effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andréasson et al. 1987 [21], Zammit et al. 2002 [22], Zammit 2004 [23] (Swedish Conscripts study)</td>
<td>n: 50,053 Adult population based conscripts Sweden Baseline: psychiatric interview for ICD-8 diagnosis</td>
<td>Ever use Frequency: 1 time, 2–4 times, 5–10 times, 11–50 times, &gt;50 times</td>
<td>Admission for ICD-10 diagnosis of schizophrenia or schizoaffective disorders</td>
<td>27 years Attrition: data not reported</td>
<td>Psychiatric diagnosis at baseline, IQ, interpersonal relationship, disturbed behaviour in childhood, family history of psychiatric illness, alcohol misuse, other drug use</td>
<td>Evidence of a dose-response effect</td>
</tr>
<tr>
<td>Tien &amp; Anthony 1990 [31] (ECA study)</td>
<td>n: 2,295 adult population based cohort USA Baseline: DIS interview for psychotic symptoms</td>
<td>DIS interview for lifetime ever use and daily use</td>
<td>DIS interview for any self-reported psychotic experience</td>
<td>1 year Attrition: 20%</td>
<td>Age, gender, school attendance, educational level, employment and marital status, baseline mental health problem, other drug and alcohol use sex, socioeconomic status, other drug use</td>
<td>Not studied. Stronger effect for daily use than ever use</td>
</tr>
<tr>
<td>Arséault et al. 2002 [24], Caspi et al. 2005 [25] (DUNEDIN study)</td>
<td>n: 759 Birth cohort New Zealand Baseline: 11 years DIS-C for psychotic symptoms</td>
<td>Ever use in the past year Frequency of use in the past year Use before age 15</td>
<td>DIS for schizotypal or schizoid personality disorders (DSM-IV criteria) and psychotic symptoms</td>
<td>11 years</td>
<td></td>
<td>Not studied</td>
</tr>
<tr>
<td>van Os et al. 2002 [26] (NEMESIS study)</td>
<td>n: 4,045 adult population based cohort Netherlands Baseline: G section of M-CIDI for psychotic symptoms</td>
<td>L section of M-CIDI Any use Frequency: &lt;1 month, 3–4 months, 1–2 weeks, 3–4 weeks, daily</td>
<td>BPRS for any psychotic symptoms</td>
<td>3 years Attrition: 30%</td>
<td>Age, sex, ethnic group, level of education, previous risk factor for psychosis, other drug use Subjects with psychotic symptoms at baseline excluded</td>
<td>Evidence of a dose-response effect</td>
</tr>
<tr>
<td>Weiser et al. 2002 [30]</td>
<td>n: 50,413 Adolescent population based cohort (male) Israeli Baseline: 16–17 years Draft board compulsory assessment (intelligence, personality, behavioural traits)</td>
<td>Use of drug, frequency, addiction Type of drug not specified, but cross sectional surveys made in the same time period indicated that the majority of adolescents used cannabis</td>
<td>Israeli National Psychiatric Hospitalization Registry ; Diagnosis of schizophrenia-spectrum personality disorders (ICD-9)</td>
<td>4–15 years Attrition: data not reported</td>
<td>Intellectual functioning, social functioning, non psychotic psychiatric disorders at baseline</td>
<td>Not studied</td>
</tr>
<tr>
<td>Study</td>
<td>Sample Size</td>
<td>Country</td>
<td>Baseline Age</td>
<td>Measures</td>
<td>Follow-Up</td>
<td>Attrition</td>
</tr>
<tr>
<td>----------------------------</td>
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</tr>
<tr>
<td>Fergusson et al. 2003</td>
<td>n=1055</td>
<td>New Zealand</td>
<td>16 years</td>
<td>SCL-90 for psychotic symptoms</td>
<td>9 years</td>
<td>17%</td>
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<tr>
<td>Henquet et al. 2005</td>
<td>n=2437</td>
<td>Germany</td>
<td></td>
<td>L section of M-CIDI</td>
<td>Ever use (&gt;5 times)</td>
<td>G section of M-CIDI for psychotic symptoms (at least two psychotic symptoms)</td>
</tr>
<tr>
<td>Wiles et al. 2006</td>
<td>n=3045</td>
<td>UK</td>
<td></td>
<td>Any use in the past year but not dependent Dependency</td>
<td>PSQ for psychotic symptoms</td>
<td>18 months</td>
</tr>
</tbody>
</table>

BPRS, Brief Psychiatric Rating Scale; DIS, diagnostic interview schedule; DIS-C, Diagnostic Interview Schedule for children; ICD, International Classification of Diseases; M-CIDI, Munich-Composite International Diagnostic Interview; PSQ, Psychosis Screening Questionnaire; SCL-90, Symptoms checklist 90.
• Exposure was assessed considering both ‘ever use’ and frequency, and the way to assess exposure was quite similar; all studies distinguished between sporadic and frequent use, also if in a different way;
• The outcome assessed was similar: psychotic symptoms for six studies [26,28,30,31,33,35] and schizophrenia or schizophreniform disorders for two studies [24,26];
• The potential confounders considered were substantially similar: age, sex, psychotic symptoms at baseline, use of alcohol and/or other drugs and socio-economical variables.

Discussion

Four reviews [16,17,19,20] found a consistent association between cannabis use and the onset of psychotic symptoms. Three reviews, which considered adjusted OR, reported that the association remains, although it is reduced, after adjusting for confounding factors. On the other hand, the review that did not perform a meta-analysis [18] found an inconsistent association between cannabis use and psychological problems.

Three reviews had many methodological limitations [16,17,19]. Only two reviews [18,20] met almost all relevant quality standards but provided inconsistent conclusions. One review [20] reported and quantified a clear association between cannabis use and the onset of psychotic symptoms, whereas the other review [18] reported an inconsistent association between cannabis use and psychological problems. These two reviews are only partially overlapping because they considered different outcomes and different inclusion criteria for primary studies. The reviews included different studies and used a different definition of outcomes to reach discordant conclusions and judgements about the safety of cannabis use and the implication for public health.

Pooling longitudinal study results seems to be a reasonable approach because they were quite homogeneous for all of the relevant characteristics: population, exposure and outcome assessment, and confounding factors. The only big difference was in the length of follow up, which could cause non-comparability of the results if a long latency is expected or if a cumulative dangerous effect of cannabis is supposed, but it is unknown if these two situations happen. However, the availability of an overall cumulative estimate of the association between cannabis use and the occurrence of psychotic symptoms does not alone prove causality of the association and can be easily misinterpreted [64].

All of the reviews draw the conclusion that cannabis is neither a necessary nor a sufficient cause of psychosis but that it could be a component cause that interacts with genetic and environmental factors in vulnerable individuals. Arseneault et al. [16] pointed out that most studies were unable to determine whether prodromal manifestations of psychosis precede the onset of cannabis use. Henquet et al. [17] concluded that the confounding hypothesis can be ruled out because all of the studies adjusted for confounding (preceding psychotic symptoms, socio-demographic characteristics, other drug use) and the association persisted, although reduced, and that the reverse causality hypothesis can be ruled out because the association remained significant in studies that excluded subjects with preceding psychotic illness. Semple et al. [19] concluded that the question of whether cannabis is a precipitating factor in vulnerable individuals or a causative agent is still unanswered.

Macleod et al. [18] concluded that the causal nature of this association is far from clear because of flaws in the primary studies: a dose–response relationship was difficult to assess because only binary exposure categories were examined in many of the studies, and the reverse causation hypothesis cannot be excluded because unreported or sub-clinical problems might have preceded cannabis use, even in studies that adjusted for psychological symptoms at baseline. Moreover, cannabis use and psychological problems seem to share common antecedents, and the relationship between cannabis use and psychosocial problems could simply reflect this association. Adjusting for confounding factors is useful, but its power to abolish the confounding component depends on the completeness and precision of the measures used. Moore et al.’s review [20], the best from a methodological point of view, concluded that the association between cannabis use and psychosis seems consistent and remains, even if attenuated by roughly 45%, after adjusting for comprehensive lists of confounding factors. The authors reported that associations are unlikely to reflect reverse causality because all studies excluded people with psychosis at baseline or were adjusted for. Nevertheless, the possibility that the observed association between cannabis exposure and psychosis was a result of unaccounted for confounding factors cannot be ruled out, and these uncertainties are unlikely to be resolved in the near future. The authors concluded that there is enough evidence to inform people that using cannabis could increase their risk of developing a psychotic illness in the near future.

Other authors [65] have discussed the issue of a lack of specificity as poor criteria for causality, given that one of the included studies [30] shows an association only among cannabis addicted individuals and not among non-addicted individuals; the study also found an association between tobacco smoking and the occurrence of psychosis independent of the use of cannabis. Therefore, the considered studies are not able to dis-
tinguish between the effect of use from the effect of dependence, and the effect of tobacco use from the effect of cannabis use.

Many narrative reviews published on this topic considered the same original studies, and all of them agree with the conclusion that the use of cannabis is a component cause that can lead to adult psychosis. Genes are likely to moderate the association between cannabis use and later psychosis by increasing susceptibility to psychotic outcomes, but no study has verified an interaction effect between candidate genes and cannabis use. The question of whether cannabis is the precipitating or causative factor in the development of psychosis is unanswered.

In conclusion, the findings provided by these reviews show a potential risk of psychotic symptoms associated with the use of cannabis, but these results are by no means definitive as far as the causality of the association is concerned.

The issue of whether further longitudinal studies could provide more evidence is still open to debate; some have argued that Mendelian randomisation could be of help [17], but others have suggested that such an approach would require the presence of genetic variants that are strongly associated with cannabis use, which is not yet the case [66].

We can conclude that there is insufficient knowledge to determine the level of risk associated with cannabis use in relation to psychotic symptoms and that more information is needed on both the risks of cannabis use and the benefits of preventive interventions to support evidence-based approaches in this area.

References

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