SB

74

TESTIMONY AGAINST (FILE 2)

Testimony to Senate Health and Social Services Committee
April 1, 2005

My name is Bill Parker. I am a former member of the Alaska House of Representatives, and I retired from state service as Deputy Commissioner of Corrections. Today I speak for Alaskans for Marijuana Regulation and Control.

S.B.74 attempts to recriminalize marijuana for adults in Alaska, in violation of the Alaska Constitution.

In 1975, in a landmark case known as Ravin, the Alaska Supreme Court ruled the privacy clause of the Alaska Constitution protects possession of a small amount of marijuana by adult Alaskans in their own homes for their own use. In 1975, the Alaska Legislature changed the statutes to decriminalize marijuana in Alaska.

Various attempts have been made in the 30 years since to attack this de-criminalization, both legally and politically.

An initiative in 1990 attempted to re-criminalize marijuana in Alaska, but initiatives change statutes, not the Constitution, and the initiative had no effect.

Many legal attempts have been made to test the constitutionality in the courts, all unsuccessful. The latest was last fall when the Alaska Supreme Court declined to take up the Appellate Court's latest ruling upholding Ravin.

S.B.74 is another attempt to attack the constitutional issue in a legal and political manner.

If S.B.74 passes with these findings, they will be admissible in court, and the administration will have new arguments that marijuana is much more potent and dangerous than in 1975, so much so that it is almost a different substance.

That is why the findings section of this bill is important. The findings are flawed. Expert witnesses from Alaska and Outside are going to explain those flaws today.

They will discuss the complex medical and sociological issues that other government panels have studied at length.

- The Shafer Commission's report to President Nixon in 1972, "Marijuana: Signal of Misunderstanding."
- The National Research Council's 1982 report, "An Analysis of Marijuana Policy."
- The Institute of Medicine's 1999 report, "Marijuana and Medicine: Assessing the Scientific Base."
- The 2002 report of the British Advisory Council on the misuse of drugs, "The Classification of Cannabis."
- The House of Commons Home Affairs Committee 2002 study, "The Government's Drug Policy: Is It Working?"
- Jamaica's 2001 National Commission on Ganja came to the same conclusion;

  Marijuana is not so harmful that the penalties for possession need to be increased.

S.B.74 would take Alaska in the opposite and wrong direction.

The State's witnesses could not be called objective observers. Those directly involved in implementing an administration's policies cannot evaluate those policies impartially. Evaluators should be independent academics.

The testimony today will show that the time schedule alone for S.B.74 is inadequate to evaluate marijuana in Alaska. We have submitted, in writing, the findings of experts in their fields who determine marijuana to be relatively harmless compared to alcohol. Each finding must be examined individually as the other commissions and committees have done with scientific integrity.

Here is a quick review of the evidence you will hear today:

Experts will point out the differences between scientific research and pseudo-science, the confusion between correlation and causation.

The administration's assertions about increased potency of marijuana are inaccurate and misleading in several respects:

- There are serious questions about the actual potency of marijuana today and yesterday. There is no reliable way to measure potency.
- There is no proof that marijuana is more addictive or dangerous than previously.
- In fact, more potent marijuana would result in people using less, because of the effect of autotitration.

The administration's treatment of statistics is misleading because most of their conclusions are court-ordered, not a clinical diagnosis of marijuana addiction or even a self-referral. Most had to choose between treatment or incarceration. Most chose treatment.

The rate of marijuana use among minors in Alaska is no higher today than it was in 1975. In fact, according to the government's own statistics, overall use in grades 6 through 12 in Alaska schools is lower now after 30 years of decriminalization.

Marijuana use by minors has not been shown to cause psychosis later in life.

Marijuana use does not induce violent behavior, rape, or child abuse.

The emergency room data used to show that marijuana is more dangerous today is not conclusive. The relation to marijuana in patients is so widely construed as to be meaningless. And the administration has overstated and misinterpreted the evidence of marijuana's link to lung cancer, juvenile crime, and the possibility of addiction and dependence.

The weight of scientific evidence available today discredits the old 'gateway drug' theory.

There are laws already in place to prohibit driving while impaired by alcohol or marijuana. These laws will remain in effect.

S.B.74 would have a bad effect on medical marijuana patients by jeopardizing their ability to possess marijuana if adult use of marijuana in the home is criminalized.

If the administration's aim is to promote the public health and welfare, re-criminalizing personal, adult use of marijuana in the home won't do it. Re-criminalization will only feed the black market and increase the social costs that flow from it.

Science shows marijuana causes far less harm to the public health and welfare than alcohol or tobacco. And that's as true today as it was in 1975.

Shafer Commission, 1972

(National Commission on Marihuana and Drug Abuse), Commissioned by President Richard M. Nixon

- Commission members included 4 MD's, 2 PhD's, 1 theologian, and 5 elected officials
- 26 staff professionals, including additional MD's and PhD's, assisted the commission
- 49 support staff, analysts, and researchers were involved
- More than 1 year was spent in its investigations and preparation of its report

National Research Council of the National Academy of Science, 1982

"An Analysis of Marijuana Policy"

- 4 years of effort
- Included a review of the 1972 National Commission on Marijuana and Drug Abuse report
- Conclusion: "On balance, we believe that a policy of partial prohibition is clearly preferable to a policy of complete prohibition."

Institute of Medicine, 1999

"Marijuana and Medicine: Assessing the Science Base"

- Division of Neuroscience and Behavioral Health, IOM
- Took testimony from hundreds of doctors, scientists, treatment professionals, and many others
- Worked from 1997 to 1999
- Conclusions included:

"Compared to most other drugs...dependence among marijuana users is relatively rare."

"There is no conclusive evidence that marijuana causes cancer in humans, including cancers usually related to tobacco use"

"It does not appear to be a gateway drug"

"Earlier studies purporting to show structural changes in the brains of heavy marijuana users have not been replicated with more sophisticated techniques."

Report of the National Commission on Ganja, Jamaica, 2001

- "nine months of consultation and reflection,
- "visits to every parish and hearings amounting to 3776 pages of transcriptions"
- "The Commission is persuaded that the criminalisation of thousands of people for simple possession for consumption does more harm to the society than could be done by the use of ganja itself."

Advisory Council on the Misuse of Drugs, Great Britain, 2002

"The Classification of Cannabis under the Misuse of Drugs Act 1971"

- "…based on a detailed scrutiny of the relevant scientific literature, including four reviews commissioned by the Department of Health in 1998, as well as an update commissioned by the Home Office and completed in November 2001"
- "The Council … recommends the reclassification of all cannabis preparations to Class C [least harmful]."

House of Commons Home Affairs Committee, 2002

"The government's drugs policy: Is it working?"

- "We have taken oral evidence from 45 witnesses over a total of 11 evidence sessions."
- "…more than 200 people and organisations…provided written submissions…"
- "We support, therefore, the Home Secretary's proposal to reclassify cannabis from Class B to Class C."

Report of the Canadian Senate Special Committee on Illegal Drugs, 2002

"Cannabis: Position for Canadian Public Policy"

- "product of a team effort over a period of 2 years"
- The Parliamentary Research Branch synthesized and analyzed literature on legal studies and socio-criminological studies. In all, the Committee received 23 reports.
- Heard testimony from expert sociologists and lawyers, psychologists and physicians, police officers and criminologists
- The Committee held more than 40 days of public hearings…more than 100 persons from all backgrounds.

Even the most recent commission reports echo the findings of many earlier commissions, including the LaGuardia Commission in 1944, and going back to the British Indian Hemp Drugs Commission in 1894.

The independent reports have been astonishingly consistent for well over a century:

"...continued criminalization of cannabis remains unjustified based on scientific data on the danger it poses."

--Final Report of the Canadian Senate Special Committee, 2002

Alaska Civil Liberties Union

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Testimony of Michael W. Macleod-Ball, Executive Director, Alaska Civil Liberties Union
Senate Health, Education and Social Services Committee
Friday, April 1, 2005

RE: SB 74 – *An Act making findings relating to marijuana use and possession...*

Chairman Dyson, members of the committee:

Thank you for providing us this opportunity to present evidence countering the administration's misleading characterization of marijuana as a substance that has grown dangerous over the last 30 years.

As the administration has acknowledged, both before this committee and in public statements, the purpose of this bill is to provide a framework for overturning the Alaska Supreme Court's decision that our constitutional right to privacy includes the right to possess and use small amounts of marijuana in the home for purely personal purposes. The bill also significantly steps up the penalties in a manner to bring the bill directly into conflict with existing case law. The administration hopes that a legislative finding concerning marijuana's risks will be sufficient for the court to reverse itself if and when this bill is enacted and then challenged in court. Because this legislation directly impacts a fundamental right – the right to privacy – the ACLU believes that any legislative finding not reflective of the weight of evidence available for review will be set aside by the courts. Alternatively, if this committee takes on the heavy burden of weighing the available science fully and completely, and produces findings that are reflective of the weight of the evidence, we believe the court would consider such balanced findings an insufficient basis for justifying a restriction on the constitutional right to privacy. The ACLU believes that drug policy based on imposing criminal sentences on mere users is counterproductive – and this bill tries to do that. But our disagreement with this bill on a policy level won't defeat the legislation – that will be accomplished by the very nature of this proposal – enactment of a restriction on a fundamental constitutional right based on incomplete hearings and biased or inadequate findings.

It cannot seriously be argued that in order for this committee to properly evaluate the risks of marijuana use and possession in the privacy of the home, it must consider far more evidence than it has been able to take in over the course of three one or two hour sessions. We believe the weight of the evidence clearly shows that marijuana is not significantly more dangerous than it was in the 1970s, when Alaska law legalized use and possession in the home. However, we acknowledge the availability of dozens, perhaps hundreds, of studies and papers on the subject and that all of those papers present detailed, scientific analysis and conclusions. This five person committee, with all of your various backgrounds and experiences, and even supported as you are by an insightful and dedicated staff, cannot possibly come to a well-rounded decision based on a fair evaluation of the available evidence on such an abbreviated schedule. National and international panels have tackled this subject over the years – and they typically take months, if

not years, to do a thorough evaluation of all the evidence and opinions. Uniformly, those panels conclude that marijuana is significantly less dangerous than alcohol and uniformly, the findings of those panels cannot be read to show any substantial increase in the risks associated with marijuana over the last 30 years. The administration's proposed bill offers you a pre-set list of findings – obviously and not unexpectedly slanted far in favor of the proposition that marijuana is dangerous. We understand that the administration would want you to believe those proposed findings – but if you examine all the information to be presented to you today, together with all the evidence presented to you by the administration, you should be unable in good conscience to vote in support of a bill including those findings. The findings associated with this bill are clearly one-sided, ignore the weight of evidence on the subject, and in some cases are simply wrong.

We believe the administration is offering misleading information to you. Others with more scientific expertise may speak to this, but I will offer one small example. I might offer more, but the committee declined to provide us with a copy of the studies submitted by the government. I was limited to a review of no more than five or ten minutes of one copy of the package. In that short amount of time, I happened across one of the administration's assertions – that 15% of rape suspects were under the influence of marijuana. This assertion presumably supports finding #5 – that a high percentage of domestic violence arrestees are under the influence of marijuana – and finding #12 – that a large percentage of violent offenders have marijuana in their systems upon arrest . If you examine the report in question, you will see that 70 % - 70% - of the suspects were under the influence of alcohol. You will also see that there is no information about whether the marijuana users had also used alcohol. You would also see that the authors of the report were so concerned about the correlation between alcohol and violence that they parsed out the alcohol subject for further detail. You would also see that the authors deemed the marijuana correlation too slight to warrant further evaluation. But the administration didn't tell you that in their bullet pointed highlights – they simply said that 15% of rape suspect had marijuana in their systems – hoping that no one would take attention to the narrative of the report. And the findings proposed in this bill are – each and every one of them – as the experts to follow will tell you – misleading assertions based on similar kinds of half truths and omissions. We believe strongly that findings such as these, if left to stand, will be the downfall of this bill in court.

In most cases, legislative findings really wouldn't matter all that much, because the courts generally defer to the Legislature's findings on a subject. However, when a bill restricts a suspect class or, as in this case, a fundamental right, a different standard applies. In such cases, the court will examine the Legislature's consideration of the facts – or will conduct its own fact-finding. The courts will not blindly accept legislative findings when a law has distinctions based on religion or ethnicity, when a law restricts free speech – especially political speech, restricts freedom of worship, or – as here – restricts an individual's right of privacy.

Privacy is a fundamental right in Alaska – stronger than the privacy right inferred to exist under the US Constitution. Legislators, acting on a 2/3 vote in the 1970's and backed by referendum of the voters, amended the Alaska Constitution to write in an express right of privacy. Because the right is express, not merely inferred as the federal right is, it is generally considered to be stronger than the federal right. But the Constitution doesn't say how far the right of privacy

extends – and so the courts have been asked to do the job of defining the meaning of our right of privacy.

Shortly after the amendment adding the privacy right, the Ravin case came along. At its core, Ravin has less to do with marijuana possession than with attempting to define the scope of the privacy right. Ravin stands for the proposition that activities in the home are entitled to a higher degree of privacy protection than other kinds of activities. Also, activities that are purely personal and don't pose a significant risk to others are entitled to some degree of privacy protection. The court was rather eloquent in describing its reasoning:

> "...the authority of the state to exert control over the individual extends only to activities of the individual which affect others or the public at large as it relates to matters of public health or safety, or to provide for the general welfare. We believe this to be a tenet of a free society. The state cannot impose its own notions of morality, propriety, or fashion on individuals when the public has no legitimate interest in the affairs of those individuals."

Having come to these conclusions about the scope of the privacy right, the court had to determine whether marijuana use and possession fell within its protective ambit.

In order to do so, the court considered voluminous materials and heard from numerous experts. The Supreme Court concurred with lower court rulings that marijuana was not without risk. However, it said the health effects were not so severe as to warrant a government intrusion on a basic human right. So, the administration's argument in support of this bill will now stand or fall on whether it can demonstrate that marijuana is so much more dangerous now than in the 1970's, when Ravin was decided, that justification now exists to restrict individual privacy rights where none existed before. Be clear on this point: it's not enough to find that marijuana has risks – the court already decided in the 1970's that there was some risk in the use of marijuana – albeit far less than in the use of alcohol. The court heard evidence from some that marijuana was dangerous, offset by others who said that it had some risks, but not many. The court decided that balance of evidence was insufficient to justify a restriction on privacy rights. In order to make this legislation fly, you need to determine that marijuana is far more dangerous than it was in 1975. Unfortunately, the evidence won't tell you that marijuana spurs violence. It won't tell you there has been a significant increase in young users. It won't tell you there is any significant increase in potency that isn't offset by decreased doses and reduced health impacts. We don't think the case can be made that there is any increased danger in marijuana use today and, if you consider all evidence available to you, we are certain you'll have to agree.

Why should you be concerned about the available evidence, making sure you've fully evaluated everything, and made accurate findings? Because the legislation will stand or fall on whether you do the job fully and fairly. As noted before, courts will generally defer to fact-finding done by the legislature – but not if a fundamental right is restricted. In that case, the court will look for a substantial relationship between the proposed restriction and a compelling state interest. And it will be far less likely to defer to the legislature's findings....for lack of a better term, the court will take a "hard look" at what the legislature did in adopting the legislation.

There isn't a lot of Alaska precedent on this issue, but there is plenty on the federal level – and it's likely the reasoning would be the same among the Alaska judiciary. Even when fundamental rights are not implicated, the courts will not just blindly accept legislative reasoning. As Justice Clarence Thomas said, when he was an appellate justice, with respect to federal legislation, if Congress "could make a statute constitutional simply by 'finding' that black is white or freedom, slavery, judicial review would be an elaborate farce." Lambrecht v. FCC, 958 F.2d 382, 392 n. 2 (D.C. Cir. 1992). When a fundamental right is restricted, though, the court will not merely look at the legislative record, it can go beyond that to find facts relevant to the nature of the law. So, for example, in a 1994 case, Turner Broadcasting v. FCC, the US Supreme Court said that when First Amendment rights are implicated, deference afforded to legislative findings does not foreclose a court's independent judgment of the facts bearing on an issue of constitutional law. It should be noted that in several cases, the courts have looked disparagingly on findings that were the result of pre-ordained decisions, insufficient hearings, or hasty deliberations. Even in Alaska, the few precedents suggest that the ordinary deference to legislative action disappears when constitutionally protected rights are at issue.

Examining all precedents on this issue, if the court is at all likely inclined to defer to the legislature in this context, it will only be if the legislature has comprehensively reviewed the available evidence and arrives at conclusions – "findings", if you will – that accurately reflect that evidence. The courts will not tolerate proceedings that are merely a show to make it seem as if the legislature has taken a comprehensive look at the available evidence. They will not stand for a paper record of several hundred pages if the result is directly contrary to the evidence submitted. Based on our experience before this committee, it is our view that the attention given to the issues falls far short of what the court would expect.

I do not mean to belittle the effort this committee has made. Far from it. We have been treated cordially and have been helped at every turn by committee members and staff. We have provided documentary evidence, which has been accepted willingly. But to understand the complexity of the issue involved here requires commitment of far more time and expertise. By rights, this panel should convene something akin to a Blue Ribbon Commission – as has been done elsewhere – to advise and inform the committee on this issue. But there seems to be no interest in conducting such a thorough review of the issues. It's understandable – this committee and this body has many important issues to address and there is a natural urge to push things along – get things done. But when a restriction on a fundamental right is involved, you need to do more.

Even in the absence of such an obligation, other panels have done more – much, much more. Starting with the commission that examined the marijuana issue in the 1970's and continuing through recent panels in Canada and elsewhere, experts have testified for days and deliberations have continued for months. This is very complicated information and no one can be expected to fully comprehend all of the findings in a short review lasting a few hours. And we believe strongly that the court will not let stand the restrictions you are contemplating adopting based merely on the record that will be before you as of the day's end.

I will let others speak to the findings relating to scientific issues, but I would like to address two findings in particular.

Finding #19 purports to "reconfirm that it is illegal to possess any amount of marijuana anywhere in this state...." In fact, by adopting such a finding, the Legislature wholly discounts the judiciary's role in our three-branch system of government. Pursuant to judicial decision, it in fact has NOT been illegal to possess small amounts of marijuana in the home for personal use. To adopt a finding that Reconfirms illegality, this body asserts, in effect, that the judiciary has no role in determining the constitutionality of legislative enactments.

Finding #18 asserts that the holding in Crocker v. State imposes "unnecessary and unreasonable requirements for search warrants to investigate marijuana growing...that inhibit law enforcement efforts to reduce the amount of marijuana illegally grown indoors and illegally sold or exported." This is simply inaccurate. Crocker merely held that "a judicial officer should not issue a warrant to search a person's home for evidence of marijuana possession unless the State's warrant application establishes probable cause to believe that the person's possession of marijuana exceeds the scope of the possession that is constitutionally protected under Ravin.... Before a search warrant can lawfully issue, the government must establish probably cause to believe that the evidence being sought is connected to a crime. This same rule governs search warrants for all controlled substances, not just marijuana." This is neither unnecessary nor unreasonable – it's the law. Probable cause means probable cause to suspect a violation of the law, not probable cause to suspect the occurrence of constitutionally protected activity. Could you get a warrant to enter a home if you suspected someone was exercising his or her right to freedom of speech? It's a silly point – but you understand my point. The finding in question is blatantly slanted and there is no need for it.

I'd also like to point out that much of the administration's claims and assertions are irrelevant to the consideration of this bill. For example, you heard about marijuana being a huge cash crop in Alaska – about huge discoveries of marijuana in the state. You have heard about crime and driving issues. Your ability to legislate with respect to those issues is now and has always been unhindered. Those things are illegal now and this bill does nothing to change those laws – therefore, those comments are simply irrelevant – again, designed to appeal to your gut instincts to legislate against this substance. The court has simply said that the right to privacy is fundamental – and therefore there must be a direct connection between some compelling state interest and the invasion of privacy that goes with restricting use and possession of small amounts in the home.

We would strongly urge this committee to remove or drastically alter the findings in this bill. As they stand, they do not reflect the state of the science on the subject. They will serve as the basis for a challenge to this bill. We strongly urge this committee undertake a far more comprehensive look at the science – or work for the creation of a truly independent panel to examine the science. The Alaska Civil Liberties Union would be please to help establish and/or inform such a panel. We believe that is the only way this Legislature can successfully adopt a restriction to the basic right of privacy without subjecting itself to challenge. We also believe the adoption of findings more fairly reflective of the science will lead to a judicial conclusion that the risks associated with marijuana use and possession do not justify a restriction on the right of privacy.

We understand the basic reflex to criminalize marijuana possession is based on a fear that our kids are being harmed. But there are better ways to deal with this than to make marijuana users criminals. There have been success stories – with tobacco and with other drugs at other times and places. Prison is not the best place to put someone who needs to stop using marijuana....and invading someone's privacy is not the best means to find the people who need to stop using marijuana. And another judicial challenge to another legislative enactment will do nothing to advance either the cause of personal privacy or the goal of reducing drug use. We urge you please not to pass Senate Bill 74.

Thank you Mr. Chairman:

My name is Dr. Lester Grinspoon. I believe that you have copies of my curriculum vitae and two of my books: Marihuana Reconsidered (Harvard University press, 1971, 1977 and Marihuana, the Forbidden Medicine (Yale University press1993, 1997).

To be very brief, I am an associate professor of psychiatry, emeritus at the Harvard Medical School. Shortly after graduating from the Harvard Medical School in 1955, I joined the faculty and over the ensuing 45 years combined research and teaching with some clinical practice. In 1967, I had finished writing my part of a book on our seven-year study of schizophrenia. As the senior author I had to wait to finally put it together for what two junior co-authors estimated would be two to three months before they completed their parts. Because I was at that time very m[illegible] concerned about the great danger young people were exposing themselves to as they recklessly ignored government warnings about its dangers, I decided to devote this unanticipated free time to studying marihuana in the Countway library with the object of producing a scientifically sound paper on the subject, one which I hoped to publish in a journal or periodical accessible to college-age people. Perhaps some would pay more attention to such a review than they apparently were to the material produced by the US Public Health Service. (A shortened version of the paper was published in Scientific American). As I delved into the medical, scientific and other literature I soon discovered, to my great surprise and consternation, that, despite my training in medicine and science, I had been brainwashed like most other American citizens about the dangers of this drug. After I finished the book on schizophrenia, I began work on Marihuana Reconsidered which was published by Harvard University press in 1971, a second edition in 1977 and republished as a classic in 1997. Briefly, after documenting that most of what we believe about the dangers of cannabis were mythical, I concluded that marihuana was far less harmful than either alcohol or tobacco and that its greatest harmfulness arose from the way we as a society were dealing with it. (At that time we were arresting about 300,000 mostly young people on marihuana charges; today the figure is about 750,000.).

Let me say at the outset that marihuana is no more harmful today than it was in 1975 when I testified in the Ravin case. Street marihuana is arguably more potent than it was at that time but this does not mean increased risk because both medicinal and recreational users very quickly learn how to titrate the dose to achieve the desired effect. A user who smokes (or vaporizes) marihuana has to inhale less of a more potent sample and, conversely, more of one that is less potent. It follows that to the extent that inhaling the smoke is considered a risk factor for pulmonary disease, the more potent sample provides a healthier choice. However, I should hasten to add that the pulmonary risk from smoking marihuana has been greatly exaggerated. There is not a single case of lung cancer or emphysema attributable to smoking marihuana to be found in the

medical literature. I believe that the lungs of marihuana smokers are at greater risk from the air of cities like Los Angeles or Houston (or any other city with poor air quality). However, for those, particularly in today's anti-smoking atmosphere, who wish to avoid smoke for any reason, there is now available a device called a vaporizer which holds the temperature of the marihuana to be consumed in a temperature window which vaporizes the cannabinoids at a temperature which is below the ignition point; thus no smoke.

I wish I had time to address the other 18 "Findings" because so many are erroneous and none is supported by documentation. Let me briefly consider another "Finding", the one that states... "marihuana use by children is associated with an increased risk of attempting suicide." I believe that the intention here is to suggest that because there is an association cannabis must be causal in this increment of risk. Psychiatry is becoming increasingly aware that children suffer from depression and some of them commit suicide. Like other children, some of the depressed children will use marihuana. In fact, because marihuana is an effective antidepressant, some of them may have discovered it as a self-medication. However, there is no credible evidence that I know of that establishes marihuana as a causal.

I am struck by the fact that so many of these "Findings" are the same claims of marihuana toxicity that have been made and discredited more than once in the history of this substance. For example, schizophrenics and patients suffering from other psychoses were thought to comprise a significant number of the patients admitted to Indian Insane Asylums in the second half of the 19th-century and the use of ganja was thought to be causative. It was for this reason that the British organized the Indian Hemp Drug Commission Study which was published in 1894. The commission examined 800 doctors, superintendents of insane asylums, and so forth. In a 3000 page, seven volume report the commission concluded that "There is no evidence of any weight regarding mental and moral injuries from the moderate use of these drugs." This report put to rest the belief that cannabis led to schizophrenia and other psychoses for a while, but it has recurred periodically most recently during the last year are so. For example, a report from New Zealand with a study group of only 759 subjects, claims to have established that those who smoked marijuana three or more times by the age of 15 had a 10% higher chance of developing schizophrenia. Similarly, other studies from Great Britain and the Netherlands would predict greater numbers of schizophrenic patients. If these predictions were correct, given the number of young people who are or who have used cannabis, we would expect an increment in the incidence of schizophrenia. However, no such increment exists.

In "Finding" number two the assertion is made that "... [marihuana] has addictive properties similar to heroin and other similar illegal controlled substances .." Most of those who are sophisticated about cannabis would question whether the word addiction is even appropriate to this drug, and all would agree that the withdrawal syndrome seen with "heroin and other illegal controlled substances" are not

observed upon cessation of marihuana use. The assertion made in "Finding" number four, that marihuana use "... makes it more likely that the person will go on to use more potent illegal controlled substances..." is simply a restatement of what was known as the "stepping stone hypothesis"; a belief which has long since been thoroughly discredited.

As I participate in these hearings, I am reminded of those which preceded the passage of the Federal Marihuana Tax Act of 1937 the first of the draconian legislation aimed at marihuana. A reading of the hearings before the House Ways and Means Committee that preceded the passage of the legislation demonstrates quite clearly how little empirical data was found to support the Act. Indeed, the enactment reflected far more the mass hysteria surrounding the subject than any concrete evidence of the drug's harmfulness. The hearings were characterized by brevity and lack of information. Little expert medical, sociological, or of the scientific evidence was produced or listened to. I would urge this committee to acquaint itself with some of the excellent comprehensive special reports and commission reports which have been developed over the past half-century. They would include:

The La Guardia Report (1944)
The Wooten Report (1968)
The Shafer Report (1972)
The Le Dain Commission (1973)
The Canadian Senate Special Committee on Illegal Drugs Report (2002)

I think that if this legislative body is as meticulous and comprehensive in collecting and assessing the data as these Commissions were, it will have a better chance of arriving at a sound judgment about whether the "harmfulness" of marihuana is sufficient to enact such a restrictive bill.

In conclusion, I must tell you that I have much more to say on this topic than I will be able to now, but given the extremely short time allotted for these hearings, there is no way I can thoroughly respond to the erroneous findings proposed in this bill. It would take days, if not weeks, to carefully review each of the studies and reports submitted by the government in order to fully explain to you the fallacies and inaccuracies. In short, this committee cannot possibly hope to seriously consider in the amount of time allocated the relevant evidence necessary to reach conclusions about the public health effects of marijuana. I would urge the committee to postpone action on this legislation until such time as a full and fair review of all the evidence has occurred. If the legislature does adopt "findings" I would urge you to fully annotate those findings with specific references to specific evidence in the legislative record.

LESTER GRINSPOON, M.D.

Date of birth: June 24, 1928, Newton, Massachusetts

Marital status: married, three children

EDUCATION:

1951 B.S., Tufts College, Medford, Massachusetts, magna cum laude.

1955 M.D., Harvard Medical School, Boston, cum laude.

POSTGRADUATE TRAINING AND EXPERIENCE:

1955-1956 Intern in Medicine, Beth Israel Hospital, Boston, Massachusetts.

1956-1958 Field Investigator for the National Cancer Institute, Los Angeles, California.

1958-1961 Resident in Psychiatry, Massachusetts Mental Health Center, (Chief of Drug Unit 1959-1960; Chief of Service 1960-1961).

RESEARCH AND TEACHING APPOINTMENTS:

1950-1951 Olmstead Fellow in Biology, Tufts College, Medford, Massachusetts

1956-1958 Assistant in Medicine, University of Southern California School of Medicine, Los Angeles, California

1958-1959 Teaching Fellow in Psychiatry, Harvard Medical School, Boston, Massachusetts

1961-1962 Assistant in Psychiatry, Harvard Medical School, Boston, Massachusetts

1961-1963 Lecturer on Social Relations, Harvard University, Cambridge, Massachusetts

1962-1964 Instructor in Psychiatry, Harvard Medical School,
1962-1965 Boston, Massachusetts

1961-1991 Senior Psychiatrist, Massachusetts Mental Health Center, Boston, Massachusetts

1964-1965 Clinical Associate in Psychiatry, Harvard Medical School, Boston, Massachusetts

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1965-1968	Assistant Clinical Professor of Psychiatry, Harvard Medical School, Boston, Massachusetts
1968-1973	Associate Clinical Professor of Psychiatry, Harvard Medical School, Boston, Massachusetts
1973-1998	Associate Professor of Psychiatry, Harvard Medical School, Boston, Massachusetts
1998-2000	Associate Clinical Professor of Psychiatry, Harvard Medical School, Boston, Massachusetts
2000-	Associate Professor of Psychiatry Emeritus, Harvard Medical School, Boston, Massachusetts

OTHER APPOINTMENTS:

1961-1968	Director, Clinical Research Center, Massachusetts Mental Health Center
1962	Director, Summer Institute on Alternative Ways of Handling Conflict: Behavioral Science Research Toward Peace, Sponsored by the American Academy of Arts and Sciences
1963-1970	Consultant in Psychiatry and Research, Boston State Hospital
1969-	Examiner, American Board of Psychiatry and Neurology
1972-1988	Advisory Board, National Organization for the Reform of Marijuana Laws
1973-1974	Budget Committee, American Psychiatric Association
1973-	Executive Director, Massachusetts Mental Health Research Corporation
1974-1979	Consultant, Task Force on Interface between Psychiatry and Industry, American Psychiatric Association
1974-1979	Council on Research, American Psychiatric Association
1975-1977	Vice-Chairperson, Council on Research, American Psychiatric Association
1976-1981	Advisory Board, The Center for the Study of Non-Medical Drug Use

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1977-1979	American Psychiatric Association Representative to the American Association for the Advancement of Science
1977-1979	Chairperson, Council on Research, American Psychiatric Association
1979-1980	Vice-Chairperson, Scientific Program Committee, American Psychiatric Association
1979-1980	Chairperson, Subcommittee on Awards for Scientific Exhibits, American Psychiatric Association
1979-	Council on Marihuana and Health, National Organization for the Reform of Marijuana Laws
1980-1984	Chairperson, Scientific Program Committee, American Psychiatric Association
1980-1984	Scientific Advisory Board, Beneficial Plant Research Association
1984-1985	Chairperson, Task Force on Soviet/American Relations, American Psychiatric Association
1986-1990	Founding Board of Directors, Physicians for Human Rights
1987-	Advisory Board, The Drug Policy Foundation
1987-	Board of Advisors, The Albert Hofmann Foundation
1989-	Vice President, International Antiprohibitionist League
1989-1991	Advisory Board, Civil Liberties Union of Massachusetts/ACLU
1989-1991	Board of Directors, Center for Psychological Studies in the Nuclear Age
1990-	Advisory Board, Physicians for Human Rights
1990-1992	Board of Directors, Drug Policy Foundation
1991-1993	Board of Directors, Civil Liberties Union of Massachusetts
1993-1996	Faculty Member, Zinberg Center for Addiction Studies, Cambridge, Massachusetts
1994-1995	Chairperson, Board of Directors, National Organization for the Reform of Marihuana Laws

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1995-	Advisory Board, The Drug Research Group
1997-	Board of Scientific and Policy Advisors of the American Council on Science and Health
1997-	Honorary Member, Arbeitsgemeinschaft Cannabis als Medizin (Alliance for Cannabis as Medicine), Germany
1997-	International Advisory Committee, Physicians for Human Rights
1999	Reviewer of the draft report on the usefulness of marijuana as a medicine by the Institute of Medicine, subsequently published (Marijuana and Medicine: Assessing the Science Base) by National Academy Press, Washington, D.C., 1999
2000-	National Advisory Council, Center for Cannabis Research, University of California

EDITORIAL BOARDS:

1982-1984	Editor, Psychiatry Update: The American Psychiatric Association Annual Review; Volumes I-III
1982-1993	Journal of Psychiatric Research
1984-2000	Editor, The Harvard Mental Health Letter
1985-	Journal of Social Pharmacology
1985-	The Harvard Health Letter
1991-	Addiction Research
1998-	Journal of Cognitive Liberty and Ethics
2001	Journal of Cannabis Therapeutics

OTHER PROFESSIONAL ACTIVITIES:

Testified before legislative committees in the states of Massachusetts, Colorado, New Jersey, Washington, Vermont, and New York. Also testified before the National Marijuana Commission (1972), the House Armed Services Committee (1962), the Monopoly Subcommittee of the Senate Small Business Committee (1976), the House Select Committee on Narcotics (1977, 1979, 1989), the Controlled Substances Advisory Committee, the Drug Abuse Research Advisory Committee (1978), and the Senate Judiciary Committee (1980), etc.

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HONORARY SOCIETIES:

Phi Beta Kappa
Alpha Omega Alpha
Boylston Society, Harvard Medical School
Columbia University Seminar Associate

PROFESSIONAL ORGANIZATIONS:

Massachusetts Medical Society
American Psychiatric Association (Fellow)
American Association for the Advancement of Science (Fellow)
Group for the Advancement of Psychiatry
Society of Biological Psychiatry
World Federation of Mental Health

MEDICAL LICENSING AND CERTIFICATION:

Diplomate, National Board of Medical Examiners
Licensed, State of Massachusetts
Diplomate, American Board of Psychiatry

PSYCHOANALYTIC TRAINING:

Graduate, Boston Psychoanalytic Institute, Boston, Massachusetts, April 1967

Member, Boston Psychoanalytic Society, Boston, Massachusetts, 1967-1985

AWARDS:

Mencken Award: Honorable Mention Winner for contribution to Dealing with Drugs, 1988

Alfred R. Lindesmith Award for Achievement in the Field of Scholarship, a $10,000 award of the Drug Policy Foundation, Washington, D.C., 1990*

Norman E. Zinberg Award for Marihuana Research, an award of The National Organization for the Reform of Marijuana Laws, Washington, D.C., 1990

National Organization for the Reform of Marijuana Laws, First Annual Lester Grinspoon Award For Outstanding Achievement in Marijuana Law Reform: In grateful recognition of a lifetime dedicated to reforming unjust marijuana laws, selfless devotion to healing the sick with medical marijuana, and willingness to champion an unpopular cause, regardless of professional consequences, November 14, 1998

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Alliance of Reform Organizations, The ARO Lifetime Achievement Award for Distinguished Service in Drug Policy Reform, 1998

*see citation, page 25

PUBLICATIONS:

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2. Alexander, B., Meyers, L., Kenny, J., Goldstein, R., Gurewich, V., and Grinspoon, L.: Blood coagulation in pregnancy: Proconvertin and prothrombin, and the hypercoagulable state. New England Journal of Medicine, 254:358-363, 1956.

3. Grinspoon, L. and Dunn, J.E.: A study of the frequency of achlorhydria among Japanese in Los Angeles. Journal of the National Cancer Institute, 22:617-631, 1959.

4. Ewalt, J.R., Alexander, G.L., and Grinspoon, L.: Changing practices: A plea and some predictions. Mental Hospitals, 11(6):9-13, June 1960.

5. Grinspoon, L., Courtney, P.H., and Bergen, H.M.: The usefulness of a structured parents' group in rehabilitation. In Mental Patients in Transition, Greenblatt, M., Levinson, D.J., and Klerman, G.L. (eds.). Springfield, Illinois: Charles C. Thomas, Publishers, 1961, pp. 229-260.

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8. Grinspoon, L. and Cohen, R.E.: The introduction of a part-time hospitalization program into an acute psychiatric treatment service. New England Journal of Medicine, 267:752-756, 1962.

9. Grinspoon, L.: The psychological problems of life in a fall-out shelter. In No Place to Hide, Melman, S. (ed.). New York: Grove Press, 1962.

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10. Cohen, R.E. and Grinspoon, L.: Limit setting as a corrective ego experience. Archives of General Psychiatry, 8:74-79, 1963.

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17. Grinspoon, L.: Interpersonal constraints and the decision-maker. In International Conflict and Behavioral Science: The Craigville Papers, Fisher, R. (ed.). New York: Basic Books, 1964, pp. 238-247.

18. Grinspoon, L.: The truth is not enough. In International Conflict and Behavioral Science: The Craigville Papers, Fisher, R. (ed.). New York: Basic Books, 1964, pp. 272-281.

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Conference, "Schizophrenia: An Appraisal," November 14-16, 1968, New York. Published in Schizophrenia: Current Concepts and Research, D.V. Siva Sankar (ed.). New York: PJD Publications, 1969, pp. 161-173.

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52. Grinspoon, L.: Review of Artificial Paradise, Charles Baudelaire, trans. by Ellen Fox. The New York Times Review, October 24, 1971, p.58.

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58. Grinspoon, L.: Half a loaf: A reaction to the marihuana report. Saturday Review: Science, Guest Editorial, April 15, 1972, pp. 21-22.

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Citation for
The Alfred R. Lindesmith Award for Achievement
in the Field of Scholarship

Presented to Dr. Lester Grinspoon
1990

Dr. Lester Grinspoon of Harvard Medical School is the complete medical scholar. His research and writing have covered a broad spectrum but perhaps his most important work has been his pursuit of truth about the nature of certain illegal drugs. In the course of that work, like Alfred R. Lindesmith, he upset many powerful people, including some in the medical establishment, who viewed impartial research on feared drugs as tantamount to heresy. Yet, in the face of that criticism, Dr. Grinspoon has persisted in his heretical pursuit of truth.

Although his earlier medical education had convinced him that the drug was dangerous, upon reviewing all of the available scientific and clinical evidence, he found marijuana to be relatively benign and to have several helpful applications for human beings.

Dr. Grinspoon was one of the most important witnesses in the suit which won a ruling from the chief administrative law judge of the DEA that marijuana was one of the safest therapeutically active drugs known to the human race.

Lester Grinspoon represents all those scholars who report the results of their research truthfully, despite the political consequences of this unwelcomed honesty.

STATEMENT REGARDING S.B. 74 AND H.B. 96

MITCH EARLEYWINE, PH.D., Associate Professor of Psychology, University of Southern California; author, *Understanding Marijuana* (Oxford University Press, 2002)

Like the language in S.B. 74 and H.B. 96, many media reports suggest that cannabis (marijuana) has increased in potency quite dramatically in recent years. These reports have generated considerable debate, and in fact the magnitude of the increase is difficult to document and is most likely greatly exaggerated. In addition, the assur ption -- clearly implied in the bills' findings -- that increased marijuana potency translates into greater danger from the drug is untrue.

Reports of a stronger drug actually began over 30 years ago. By the middle of the 1980s, some authors suggested that marijuana's potency had increased by a factor of 100 (MacDonald, 1984). These claims clearly suffered from exaggeration or misinformation. Other arguments about increased potency arose from the University of Mississippi's Potency Monitoring Project, a program that reports the average THC content of cannabis taken in drug arrests. Estimates were extremely low in the 1970s, sometimes below 1%. But these figures are inherently suspect, because cannabis with this little THC has no impact on subjective experience -- that is, it does not produce a "high." The idea that a drug with no effects would increase dramatically in popularity over the years, as marijuana clearly did during the 1960s and 1970s, makes little sense. Thus, these estimates from the 1970s were probably inaccurate reflections of the amount of THC in marijuana available at the time.

Investigators hypothesize that the data from the Potency Monitoring Project underestimate the true amount of THC in marijuana from the 1970s. First, the estimates were based on very few samples of seized cannabis. In some years there were no more than 50 samples to analyze (PMP, 1974-1996). In addition, police may have stored the marijuana in hot lockers that allowed the THC to degrade rapidly (Mikuriya & Aldrich, 1988). Despite the small samples and poor storage, the average THC content in 1976 was 2% (ElSohly, Holley, & Turner, 1984).

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

Potency data from the 1980s through the middle of the 1990s suggest that THC content continued to vary dramatically from strain to strain and sample to sample. With improved storage techniques and much larger samples, the Potency Monitoring Project found THC concentrations varied from 2% to almost 4%. Average concentrations approached 4% THC in 1984, 1988, 1990, and 1991 (PMP, 1974-1994). Trends in the rest of the 1990s showed comparable THC content, with a peak around 4.5% THC in 1997. Other cannabinoids like cannabinol and cannabidiol have not increased in

concentration over the years (ElSohly, et al., 2000). Thus, claims of 1000% (Cohen, 1986) or 10,000% (MacDonald, 1984) increases in marijuana potency are clearly inaccurate. A threefold elevation from approximately 1.5% in the early 1970s to 4.5% in the late 1990s may be closer to the truth. A simple doubling from an average of 2% to an average of 4% also seems the most plausible.

Although many media reports warn that increased potency translates into greater danger, scientific data suggest otherwise. Recent alarms about increased mentions of marijuana in emergency rooms have received a great deal of attention, with many authors positing that stronger cannabis has created more emergency room visits. In fact, the data that allegedly support these allegations are extremely questionable. Emergency rooms have no estimates of the strength of the cannabis used by those who appear for treatment. The purported increase in reports of cannabis use in emergency rooms likely stem from improved assessments by emergency room personnel or a gradual decrease in the stigma associated with use of the plant, not from ill-effects caused by marijuana use. Previous work suggests that emergency room assessments of drug use were wildly inaccurate (Roberts, 1996). Because marijuana appears incapable of causing fatal overdoses, it is implausible that the reported increase in ER "mentions" of marijuana is due to life- or health-threatening reactions caused by cannabis.

Marijuana with greater amounts of THC is probably less hazardous than weaker cannabis. First of all, acute administration of the drug is essentially non-toxic. No one has ever died from THC poisoning. Smoking enough cannabis to ingest a lethal amount of THC may be physically impossible. Estimates of a fatal dose of any drug arise from some rather gruesome animal research. Different groups of animals receive large amounts of a

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

Marijuana with larger percentages of THC actually has benefits. Stronger cannabis leads to smoking smaller amounts. Smoking smaller quantities could provide some protection against the health problems normally associated with inhaling smoke. Smokers may take smaller, shorter puffs when using more potent marijuana (Heishman, Stitzer, & Yingling, 1989). Smoking less may decrease the amount of tars and noxious gases inhaled, limiting the risk for mouth, throat, and lung damage (Matthias, et al., 1997). Obviously, avoiding smoke completely would eliminate these problems. Thus, eating or vaporizing cannabis products may have fewer negative consequences than smoking them.

For the reasons outlined above, I believe it is inappropriate to base penalties for marijuana-related offenses on purported dangers related to an increase in cannabis potency.

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STATE OF ALASKA, SENATE BILL No 74 "An Act making findings relating to marijuana use and possession;"

EXPERT WITNESS STATEMENT:

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Statement:

It is an honor and privilege to address the Alaskan State Senate about an issue that affects a large number of Alaskans and their families. Our purpose is to assess risks of marijuana use and ask if increased penalties are warranted based on these risks. First, I would like to introduce myself and testify to my expertise in the area of drug abuse and marijuana. I am a life-long Alaskan. I moved to Alaska with my family in 1976. I am an alumni of West Valley High School and UAF. I left Alaska in 1981 for graduate and post-doctoral training. I returned to Alaska in 1990 and have since been employed at UAF where I am currently an Associate Professor in the Department of Chemistry and Biochemistry. I have devoted my life to the study of the brain and how drugs and naturally occurring drug-like chemicals affect the brain. After receiving a bachelors of science degree in psychology at UAF, I did graduate work at Mount Sinai School of Medicine in New York, NY; and at Albany Medical College in Albany, New York. My Ph.D. training and research was in neuropharmacology. Pharmacology is the study of the theory and principles of drug action. Neuropharmacology is the study of the theory and principles of drug action on the brain. I was trained by Dr. Stanley Glick, an established neuropharmacologist who has studied drug addiction and abuse and pharmacotherapies for drug addiction for more than 4 decades. My Ph.D. thesis showed how learning is involved in drug addiction. Learned, drug seeking behavior, is now recognized as a primary target for treatment of addictions. I received 3 years of post-doctoral training at the Karolinska Institute in Stockholm, Sweden in the laboratory of Dr. Urban Ungerstedt, another preeminent neuropharmacologist who pioneered our understanding of dopamine, a neurotransmitter now known to lie at the heart of addiction, motivation and reward. I have published 33 peer reviewed papers and 5 book chapters regarding addiction and aspects of drugs and the brain. I was a leader in establishing a neuroscience program at UAF funded in 2000 by a $7.5 million grant from the National Institutes of Health. Most recently I am recognized as an expert on neuroprotection and neuroplasticity in hibernation, a phenomenon my laboratory studies as a model of tolerance to stroke and neurodegenerative disease such as Alzheimer's and Parkinson's disease. Here I comment on findings purported by the legislature to suggest that marijuana poses a threat to the

public health that justifies prohibiting its use and possession in the state of Alaska, even by adults in private.

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

Estimates of the number of Alaskans who use marijuana emphasizes the numbers of Alaskans who will be affected by this legislation. In addition to users of marijuana, their families are affected by legal and health related consequences of marijuana use and highlights the importance of rational and informed discussion of these risks. As a wife, mother, and long-time Alaskan, I have witnessed devastating consequences of federal marijuana use and trafficking laws on families in the Fairbanks area. In my professional opinion as a neuropharmacologist, the health and social risks of marijuana do not in any way, justify the severity of consequences imposed by federal law. Indeed, legal risks far outweigh health and social risks associated with marijuana use.

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

Addiction, (operationally defined as drug seeking behavior), is a combined effect of drug reward and drug withdrawal. Reward, as well as desire to reduce unpleasant symptoms of withdrawal, increases frequency of drug seeking behavior. Human epidemiological data (i.e., statistical analysis of patterns of use) as well as animal data rank addictive properties of marijuana below tobacco, alcohol, cocaine and heroin. Regarding human use, evidence suggests that as few as 10% of individuals who experiment with marijuana become daily users (cf. McRae et al., 2003), and others (Anthony et al., 1994) report that dependence among users is highest for tobacco, followed by heroin, alcohol, cocaine and finally cannabis.

Drug	*Dependence* among users (%)*	
	Male	Female
Tobacco	33	31
Heroin	22	25
Alcohol	21	9
Cocaine	18	15
Cannabis	12	5

* Dependence is defined by DSM-III criteria, evaluated via a modified Composite International Diagnostic Interview. Adapted from Anthony et al., (1994).

Laboratory animal data is consistent with low addictive potential of cannabis where positive-reinforcing and dependence-producing actions of THC, the active ingredient in marijuana, have been difficult to demonstrate (reviewed by Tanda and

Goldberg, 2003). Three standard techniques known as, conditioned place preference, intracranial self-stimulation and self-administration are used to assess addictive potential. All three of these techniques have failed to show consistent, positive reinforcing effects of THC. While Tanda and Goldberg (2003) argue that 3 decades of negative findings regarding abuse potential of marijuana are due to suboptimal conditions of drug preparation and rates of intravenous administration, other drugs of abuse have not been difficult to optimize for animal studies.

The low addictive potential of cannabis may be due, in part, to the fact that abstinence seldom produces pronounced signs of withdrawal (Anthony et al., 1994; Tanda and Goldberg, 2003). THC is stored in fat tissue, due to its high fat solubility and then slowly released. This slow release likely prevents development of a pronounced withdrawal syndrome when cannabis use is abruptly stopped (Grotenhermen, 2003). Overall, given the difficulty in training animals to self-administer THC and the absence of pronounced withdrawal symptoms, the suggestion that marijuana has addictive properties similar to heroin and other illegal substances is not warranted.

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(3) in addition to concerns about marijuana use generally, the legislature is particularly concerned with the rates of use of marijuana by young people and Alaska Natives, which exceed national averages; and,
(4) early exposure of children to marijuana increases the likelihood of lifelong health and social problems, and makes it much more likely that the person will go on to use more potent illegal controlled substances;

A model known as the "gateway theory" of adolescent drug use was first proposed in 1975 (Kandel, 1975). The gateway theory suggests that adolescents typically use tobacco or alcohol before progressing to illicit substances including marijuana. Later studies showed that cigarette or alcohol use predicts subsequent illicit drug use for females while alcohol use predicts progression to illicit drug use in males (reviewed in Helstrom et al., 2004). After cigarette and alcohol use, progression may continue to marijuana, however, the cause of this progression is unknown. The simplest explanation for the observed progression is that early access to and use of cannabis may reduce perceived barriers against the use of other illegal drugs and provide access through the illicit market to more addictive drugs of abuse such as heroin, cocaine and methamphetamine (Lynskey et al., 2003).

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Lynskey et al., 2003, JAMA. 2003;289:427-433
Helstrom et al., 2004, Prevention Science,Vol 5(4), 267-277

As a mother I want my 14 year old daughter to know the difference between risks associated with marijuana and "harder" more addictive and life-threatening drugs such as cocaine, heroin, methamphetamine and the broad, poorly defined class of inhalants.

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

Marijuana intoxication reduces incidence of violence (Hoaken and Stewart, 2003) so a causal relationship is unlikely. Marijuana persists in fatty tissues and consequently plasma where the half-life for elimination varies between 20 to 57 hours (Grotenhermen, 2003). To interpret the relationship between positive tests for marijuana and arrests for domestic violence one would need to know, first, what analytical tests were used to detect THC or its metabolites and second, if these individuals also tested positive for alcohol.

Grotenhermen, 2003, Drug Disposition, 42(4), 327-360.
Hoeken and Stewart, 2003, Addictive Behaviors, 28, 1533-1554.

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

Marijuana contains a large number of chemicals because it consists of the leaf and flowers of plants. Plants are complex mixtures of chemicals. Tobacco, for example is equally as complex, however, nicotine is the primary active ingredient in tobacco. Similarly, delta-9-tetrahydrocannabinol (THC) is the primary active ingredient in marijuana. THC is a chemical that affects the body by interacting with receptors. Receptors are specialized docking sites on cells and drugs bind to these receptors. Receptors that recognize THC are called cannabinoid receptors. There are two types of cannabinoid receptors, CB1 and CB2. Marijuana or THC will have effects where ever these receptors are located. Distribution of these receptors in the brain explains why marijuana intoxication is associated with effects on memory and motor function. Recently, it was found that activation of cannabinoid receptors on immune cells (microglia) in the brain prevents Alzheimer's disease pathology (Ramirez et al., 2005). Activation of CB1 receptors is also known to have therapeutic potential in Parkinson's disease and stroke.

Two other chemicals found in marijuana are cannabinol and cannabidiol. These compounds have some properties similar to THC, but cause less psychoactive effects. These chemicals do, however have beneficial effects because they, like THC, are antioxidants (Hampson et al., 2000). We consume complex mixtures of chemicals in the foods we eat everyday, and sometimes, worry that they may cause cancer or other adverse effects. Most evidence on marijuana, however, is pointing to positive effects. Like the complex mixture of chemicals in blueberries, red wine and chocolate, the mixture of chemicals in marijuana may have beneficial effects on health. Research is

focused on identifying the key beneficial components so that these may be isolated and developed as drugs. Most evidence suggests that THC, the ingredient that causes the high also causes positive effects elsewhere in the body through activation of CB1 receptors.

Ramirez et al., 2005, J. Neuroscience, 25(8), 1904-1913
Hampson et al., 2000, Ann N Y Acad Sci. 2000;899:274-82.

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

The real health risks associated with chronic marijuana use may include chronic bronchitis, impaired lung function and increased risks of some types of cancers of the respiratory tract (Moore et al., 2005) . Prohibition may be the greatest barrier in identifying these real health risks because prohibition interferes with accurate reporting of marijuana use.

Moore et al., 2005, J Gen Intern Med.,20(1), 33-7

(9) the potency of marijuana in the 1960s and 1970s was very low compared to the potency in 2005; the average amount of delta-9-tetrahydrocannabinol (THC), the main psychoactive ingredient, nationwide, was less than one percent in the 1960s and 1970s, but has increased steadily in the 1980s and especially the 1990s, and by 2003 was more than six times that level, at 6.4 percent; in addition, marijuana grown in this state is often more potent than national averages, and has been tested with THC levels of over 20 percent; marijuana of the potency generally available in 2005 is a strong hallucinogenic drug that can command hundreds of dollars per ounce on the illegal market; the increasing potency of marijuana corresponds to an increase in the number of persons seeking emergency medical care for marijuana-related incidents.

Increased potency does not mean that increased amounts are consumed. People (and animals) typically take less drug if the drug is more concentrated. This means that more potent marijuana will likely cause people to smoke less and this will decrease risk of respiratory complications. When research animals are enticed to self-administer THC (Justinova et al., 2003) the number of self-administered injections decreases as concentration is increased until animals stop taking the drug at all, presumably because the high concentrations produce unpleasant side-effects.

Justinova et al., 2003, Psychopharmacology, 169(2):135-40.

(11) Alaska consistently ranks in the top 10 states, and occasionally in the top five states, nationwide, in the amount of marijuana illegally grown indoors, and large amounts of marijuana grown in this state are sold throughout the state and exported to other parts of the

United States; the price of high-quality marijuana is hundreds of dollars per ounce and thousands of dollars per pound; testimony received by the legislature in 1999 and confirmed in 2005, shows that marijuana often sells for $500 or more per ounce;

The cost of marijuana seems irrelevant to the public health risks unless high costs are driving users to crime to pay for marijuana. In contrast to heroin, cocaine and methamphetamine abusers, no evidence exists to suggest that a significant proportion of marijuana users resort to crime to pay for the drug. This is consistent with a low addictive potential of marijuana.

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

Marijuana intoxication is known to decrease violent behaviors (Hoeken and Stewart, 2003) suggesting that other drugs, like alcohol, are involved (Parker, 2004)

Hoeken and Stewart, 2003, Addictive Behaviors, 28, 1533-1554.
Parker, 2004, J Psychoactive Drugs, Suppl 2,157-63.

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

Research shows that legal and financial hardship incurred on parents as a result of penalties for possessing marijuana may have as many detrimental consequences on families as increased risk of marijuana use by children (Robertson et al., 1996).

Roberson et al., 1996, Br J Gen Pract., 46(412), 671-4.

Summary and Conclusions:

In summary, evidence does not support the assertion that marijuana poses a threat to public health that justifies prohibiting its use and possession in this state, especially by adults in private. Issues regarding access to children warrant further investigation into the impact of access through illicit channels. As a mother, I want my daughter to know the difference between drugs such as methamphetamine and marijuana.

Final note: Given the growing presence of methamphetamine in Alaska, my personal and professional opinion is that it would be irresponsible to put time and money into persecuting marijuana users when resources are inadequate to respond to the growing threat of methamphetamine in our community. I hope you as legislatures can look beyond moral judgment of marijuana users and address real health risks associated with far more dangerous drugs.

CURRICULUM VITAE
Kelly L. Drew, Ph.D.

Personal:

Born:	September 19, 1959
Marital Status:	Married (1983), David N. Covey, Ph.D.
Children:	Amy J. Covey (1990)
Social Security No:	507-70-4178
Office Address:	Department of Chemistry and Biochemistry Institute of Arctic Biology Box 757000 Irving I, Rm 311 University of Alaska Fairbanks Fairbanks, AK 99775-7000
Fax:	907 474-6967
E-Mail:	ffkld@uaf.edu
Telephone:	907 474-7190
Home Address:	P.O. Box 84002 Fairbanks, AK 99708

Education:

1981	B.S. Psychology University of Alaska Fairbanks, Fairbanks, AK
1982-1984	Ph.D. Candidate, Pharmacology Mount Sinai School of Medicine New York, New York Advisor: Stanley D. Glick, M.D., Ph.D.
1984-1987	Ph.D. Pharmacology Albany Medical College Albany, New York Advisor: Stanley D. Glick, M.D., Ph.D.

Professional Training:

1987-1990	Post-doctoral Fellow Department of Pharmacology Karolinska Institute Stockholm, Sweden Advisor: Urban Ungerstedt, M.D., Ph.D.
1990 - 1993	Research Associate Institute of Arctic Biology University of Alaska Fairbanks, Fairbanks, AK

Professional Appointments:

1993 -1998	Research Assistant Professor

Institute of Arctic Biology
University of Alaska Fairbanks, Fairbanks, AK

1998 –July 2002 Assistant Professor
July 2002-present Associate Professor (Tenured)
Department of Chemistry and Biochemistry
Institute of Arctic Biology
University of Alaska Fairbanks, Fairbanks, AK

2001 – present Adjunct Assistant Professor
Department of Pathology
Case Western Reserve University

Teaching:

Honors/Awards/Fellowships:

2000-2001 Outstanding Advisor Award, UAF
2000 Laboratory Equipment for Chemistry 103 and 104: Basic Introductory Chemistry and Beginnings in Biochemistry ($8,400; funded by CSEM)
2000 Fellow, Educational Reform Institute, Oshkosh, Wisconsin
2001 Fellow, Summer Institute for the Teaching of Ethics, Snowmass, CO

Teaching Support:

Funded Research for Undergraduates

1998-1999 University of Alaska Fairbanks
Undergraduate Research (Bevin McNally – Neuroscience)
$5,000 (1998-1999)

1999 American Heart Association
Summer Intern (Margaret Krieg – Undergraduate – Chemistry)
$3,000 (Summer 1999)

2000 American Heart Association
Summer Intern (Allison Kelliher – Undergraduate - Indigenous Medicine)
$3,000 (Summer 2000

2001 American Heart Association
Summer Intern (Ryan Corrick – Undergraduate - Chemistry)
$3,000 (Summer 2001)

2003-2004 Alaska EPSCoR
Research for Undergraduates
Maegan Weltzin – (Undergraduate – Chemistry)
$10,000 (Spring and Summer 2003, Summer 2004)
Ben Warlick – (Undergraduate – Chemistry)
$5,000 (Spring 2003)

NIH Supplement for Underrepresented Minorities
(Ben Warlick – Undergraduate – Chemistry)
$60,000 (Fall 2003 – Fall 2005)
(Adrienne Orr – Postgraduate – Chemistry, BS)
$59,000 (Fall 2003 – Fall 2004)

2003-2004 Alaska BRIN

Research for Undergraduates
Maegan Weltzin – (Undergraduate – Chemistry)
$5000 (Summer 2004)
Johanna Fritsche –(Undergraduate – Anthropology)
$5000 (Summer 2004)

2004-2005 Alaska IBRE
Research for Undergraduates
Ben Warlick – (Undergraduate – Chemistry)
$2500 (Fall 2004)
Lonita Lohse –(Undergraduate – Chemistry)
$2500 (Fall 2004)

Teaching Experience and Certification:

Graduate:

1986-1987	Neuropharmacology/pharmacokinetics, Nurse Anesthetist Program, Albany Medical College
1991	Instructor, Pharmacology of Alcohol and Alcoholism, UAF, 3 credit hrs
2001	Basal Ganglia, WWAMI Medical School, Anchorage Alaska, guest lecturer
2001	Topics in Neurochemistry, UAF, 1 credit hr
2002	Stroke, WWAMI Medical School, Anchorage Alaska, guest lecturer

Undergraduate:

1998	Chemistry and Society (Chem F100X), UAF, 4 hrs
1997	Multiple Intelligences (ED F495), UAF, 3 credit hrs
1997-2003	Basic General Chemistry (Chem F103X), UAF, 4 credit hrs
1997-2005	Beginnings in Biochemistry, (Chem F104X) UAF, 4 credit hrs
2002	Biochemistry (Chem F451), UAF, 3 credit hrs
2003	Biochemistry Lab (Chem F456, 3 credit hrs)
2003	Neurochemistry (Chem 697, 3 credit hrs)
2005	General Chemistry (Chem F105X, UAF, 4 credit hrs

Certification:

1997	Alaska State Certification in Secondary Science Education (Chemistry)

Postdoctoral Fellows/Research Associate Mentored (Current Position):

1993-1998	Yong Hu, M.D. (Clinical Support Consultant, Solucient, LLC)
1998-1999	Peter Osborne, Ph.D. (Asahikawa Medical School, Hokkaido, Japan, Research Scientist)
1996-1998	Oivind Toein, Ph.D. (UAF, IAB, Research Associate)
2001-2004	YiLong Ma, Ph.D. (Received $670,000 R15 grant and promoted to Research Faculty Sept. 2004)
2001-2004	Brian Rasley, Ph.D. (Chemistry Instructor)
2004-present	Sherri Christian, Ph.D. (Research Associate, IAB)

Graduate Students Trained/Current Position:

1997-2001	Rafaella Stimmelmayr, Ph.D. Wildlife Biologist, Tanana Chiefs Conference, Alaska
1999-2001	Fang Zhou, MS, Technician, Johns Hopkins School of Medicine
2001-present	Austin Rosa, Masters Student, Research Assistant Alaska INBRE
2001-present	Huiwen Zhao, Ph.D. Student, Research Assistant Alaska EPSCoR
2001-present	Bongchu Chi, MS, Research Assistant NIH U54 NS4106

Graduate and Medical Student Rotations/Training:

1997	Kimberly Clapp, Ph.D. Student, Study of ultrastructure around microdialysis probe (Clapp-Lilly et al., 1999)

1997	Zachary Katz, M.S. student, Study of extracellular GABA in hibernating ground squirrels (Osborne et al., 1999)
1998-2000	Carol Stewart, D.V.M. Clotting times during hibernation

Graduate Student Committees:

1995-1997	Thesis Committee, Lars Ebbesson, Interdisciplinary Neuroscience, UAF (M.S.)
1996-1997	Thesis Committee, Philip Shelton, Psychology, UAF (M.S.)
1997-1999	Thesis Committee, Stephanie Dloniak, Biology, UAF (M.S.)
1996-1999	Thesis Committee, Kimberly Clapp, Biochemistry and Molecular Biology, UAF, (Ph.D.)
1997-1999	Thesis Committee, Nancy Matton, Biochemistry and Molecular Biology, UAA, (Ph.D.)
1995-2001	Thesis Committee, Michael Sullivan, M.D., Neuroscience, UAA, (Ph.D.)
1998-2001	Thesis Committee, Jo Simmonetti, Biochemistry and Molecular Biology, UAA, (Ph.D.)
1998-2001	Thesis Committee, Zhengyu Wei, Biochemistry and Molecular Biology, UAF, (Ph.D.)
1998-2001	Thesis Committee, Chance Riggins, Chemistry, UAF (M.S.)
1998-present	Thesis Committee, Chris Whittle, Chemistry, UAF, (Ph.D.)
1998-present	Thesis Committee, Carla Richardson, Biology and Wildlife, UAF, (M.S.)
2001-2001	Thesis Committee, Shawna Karpovich, Biology and Wildlife, (Ph.D.)
1997-2001	Thesis Committee (co-Chair), Rafaella Stimmelmayr, Biology and Wildlife UAF, (Ph.D.)
1999-2001	Thesis Committee (Chair) Fang Zhou, Biochemistry and Molecular Biology UAF, (M.S.)
2000-2002	Thesis Committee, Shelly Stewart, Biochemistry and Molecular Biology, UAF (M.S.)
2003	Thesis Committee, Shawna Karpovich, Biology and Wildlife, UAF (M.S.)
2001-present	Thesis Committee (Chair), Austin Ross, Biochemistry and Molecular Biol. UAF, (M.A.,Ph.D.)
2001-present	Thesis Committee (Chair), Huiwen Zhao, Biochem. and Molec. Biol. UAF, (Ph.D.)
2001-2003	Thesis Committee, Anna Godduhn, Interdisciplinary Environmental Science, UAF (M.S.)
2002-present	Thesis Committee, Sirisha Nerella, PhD in Engineering (PDE)
2002-present	Thesis Committee (Chair), Bongchu Chi, Chemistry, UAF (M.S.)
2002-present	Thesis Committee, Xioaming Zhao, Biochem. And Molec. Biol. UAF, (Ph.D.)
2003-present	Thesis Committee, Sarah Dirschel, Biochem. And Molec. Biol. UAA, (Ph.D.)
2003-present	Thesis Committee, Elvin Brown, Biochem. And Molec. Biol. UAA, (Ph.D.)
2003-present	Thesis Committee, Dana Green, Biology and Wildlife, UAF (Ph.D.)
2003-present	Thesis Committee, Kristian Swearingen, Biochem. And Molec. Biol. UAF, (M.S.)
2004-present	Thesis Committee, Asha Suryanarayanan, Biochem. And Molec. Biol. UAF, (Ph.D.)
2004-present	Thesis Committee, Prasad Joshi, Biochem. And Molec. Biol. UAF, (Ph.D.)

Undergraduate Students Trained (undergraduate research), current position:

1991-1995	Terri Fitka,* psychology
1995-1997	Zachary Katz, chemistry
1995-1996	Denise Newman*, psychology
1995-1996	Alex Dugaqua*, biology
1995-1997	Chena Bryan*, biology, Ph.D. Program in Neuroscience, Univ Hawaii
1995	Crystal Rublee, biology, BS, O.D. Program
1998	Maggie Kreig, chemistry, degree in progress
1995; 1998-1999	Nikoosh Carlo*, biology, Ph.D. Program in Neuroscience, UCSD
1998-1999	Bevin McNally, neuroscience (interdisciplinary), degree in progress
1998-present	Allison Kelliher*, indigenous medicine (interdisciplinary), MD program, WAMI
1999-2001	Ryan Corrick, chemistry, BS, MSTP University of Alabama
2000-2004	Lesa Hollen, BS biology
2001-present	Maegan Weltzin*, High School senior, BS chemistry degree in progress
2001-2002	Charles Peele*, chemistry, degree in progress
2002-2004	Adrienne Ore*, Ph.D. Program, Molecular Pharmacology, Stanford University
2002-2005	Lesa Hollen, MS, Interdisciplinary Program in Neuroscience Visualization, UAF
2002-present	Bongchu Chi, BS chemistry, MS program, Chemistry, UAF

2002-present	Ben Warlick*, BS chemistry, degree in progress
2004-present	Lonita Loshe*, BS chemistry, degree in progress
2004-present	Johanna Fritsche, BS anthropology, Technician, UAF CANHR

*under-represented minority students

Research:

Honors/Awards/Fellowships:

1982-1984	Predoctoral fellowship; PHS (#5T32-GM07163)
1984-1987	Trustee scholarship; Albany Medical College
1989-1990	Åke Wiberg Foundation Fellowship, Stockholm, Sweden
1987-1990	Visiting Scientist fellowship; Karolinska Institute

Research Support:

Postdoctoral ***($54,000)***:

1988 -1990	Individual National Research Service Award NS08240, Neurochemistry of postural Asymmetries Measured using *in vivo* Microdialysis

Principal Investigator:

1992-1993	National Science Foundation IBN 912-1-221, GABA and Dopamine Release in Coho Salmon Brain $40,000
1992 – 1995	National Institutes of Health A609483, GABA and Dopamine Release in Aged Rat Striatum, $100,000
1995 – 1998	American Heart Association, Natural Tolerance to Cerebral Ischemia and Hypothermia, $120,000
1998 – 2001	American Heart Association, Natural Tolerance to Cerebral Ischemia and Hypothermia, (Competitive Renewal) $145,000
2000- 2005	National Institutes of Health (NINDS, NIMH, NCRR), Alaskan Basic Neuroscience Program Project leader on "Mechanisms of Neuroprotection During Hibernation and Arousal", $1,500,000 for project ($7,500,000 for entire program)
2003-2004	National Institutes of Health (NINDS, NIMH, NCRR), Alaskan Basic Neuroscience Program, "Mechanisms of Neuroprotection During Hibernation and Arousal" Research Supplement for Underrepresented Minorities, $109,107
2003-2005	National Institutes of Health (NINDS, NIMH, NCRR), Alaskan Basic Neuroscience Program, "Mechanisms of Neuroprotection During Hibernation and Arousal" Research Supplement for Underrepresented Minorities, $60,198
2001-2004	Office of Naval Research, Central Nervous System Regulation of Metabolic Down Regulation During Hibernation: A Microdialysis Study using Capillary Electrophoresis with Laser Induced Fluorescence Detection, $300,000.
2002-2004	Office of Naval Research Supplement, Study of Metabolic and CNS Suppression during Hibernation Using Microdialysis and Capillary Electrophoresis with Laser-Induce Fluorescence Detection $27,416
2002-2004	Defense Advanced Research Projects Agency, Effects of Hibernation on Retention of Active Avoidance Tasks, $100,000

Co-Principle Investigator

2002-2004 CBD/Army Small Business Innovation Research (SBIR) program, Identification of Compounds to Induce Suspended Animation or Hypometabolism. PI: Karl Johe, Neuralstem Inc., Gaithersberg, MD, $119,419

2004-2006 National Institutes of health (NINDS) Brain 0_2 defense during hibernation and arousal. 1-R15-NS048873-01 (PI: Ma, UAF), $669,240

2005-2006 Research Supplement for Individuals with Disabilities to 1-R15-NS048873-01

Invited Seminars/Platform Presentations:

S1. Drew K.L., Origin of GABA sampled using microdialysis, Maryland Psychiatric Research Institute, May, 1992.
S2. Drew K.L., Hibernation: A model for studying the brain's tolerance to stroke. University of Alaska Anchorage, Biology Research and Graduate Seminar Series, Sept. 25, 1998
S3. Drew K.L., Rice M.E., Frerichs K.U. and Hallenbeck J.M., 1999, Stroke therapies from hibernating squirrels, Winter Conference on Brain Research, Snowmass, CO, Jan 23-30.
S4. Drew K.L., Osborne P.G., Hu Y., Stimmelmayr R., Barnes B.M., 1999, Hibernation: a natural model of tolerance to brain trauma. Hibernation and Adaptations to the Cold, Estes Park, CO, May 20-22.
S5. Drew K.L., Osborne P.G., Hu Y., Stimmelmayr R., Barnes B.M., Hibernation and Tolerance to Brain Trauma, 50th Arctic Science Conference, Science in the North: 50 Years of Change. Denali National Park and Preserve, Alaska, Sept. 19-22, 1999.
S6. Duffy L, Drew K, Kuhn T and Bult B, Neuroscience Research at the University of Alaska Fairbanks. May 5, 2000.
S7. Drew K.L., Neuroprotective correlates of hibernation. National Institute of Mental Health, August, 1999.
S8. Drew K.L., Hibernation, a natural model of neuroprotection, National Institute of Deafness and Other Communication Disorders, Sept. 23, 2000.
S9. Drew K.L. Hibernation: A model of neuroprotection, Institute of Pathology, Case Western Reserve University, April 16, 2001
S10. Drew K.L. Hibernation: Microdialysis in hibernating ground squirrels, Dept of Psychiatry, Case Western Reserve University, April 20,, 2001
S11. Drew K.L., Microdialysis, tissue trauma and glutamate in hibernating brains 9th Annual Meeting On In Vivo Methods For Monitoring Molecules In Neuroscience. Dublin, June 18, 2001.
S12. Drew K.L., Hibernation and Neuroprotection. Alaskan Summer Neuroscience Conference, Fairbanks, July 29, 2001
S13. Drew K.L. Antioxidant Protection in Hibernation. Workshop on comparative aspects of oxidative stress. La Paz, Mexico, October, 2001, Session Chair.
S14. Drew K.L. Neuroprotection in Hibernation. Life Science Seminar Series, Institute of Arctic Biology, University of Alaska Fairbanks, Dec. 9, 2001
S15. Drew K.L. Hypoxia Tolerance in Hibernation. The less you want the more you have. Winter Conference on Brain Research. Snowmass, CO, Jan 27, 2002
S16. Drew K.L. and Green T.K., Microdialysis: Theory, Application and Coupling to Capillary Electrophoresis with Laser-Induced Fluorescence Detection, Center for Nanosensor technology, University of Alaska Fairbanks, Feb 7, 2002.
S17. Drew K.L. Memory, Learning and Hibernation, PI meeting for Continuous Assisted Performance Program, Defense Advanced Research Projects Agency (DARPA). New Orleans, March 25, 2002.
S18. Drew K.L. Hibernation a Natural Model of Neuroprotection. Alaska Summer Neuroscience Conference. Fairbanks, Alaska, July 14-15, 2002.
S19. Drew K.L., Neuroprotection in Hibernating Arctic Ground Squirrels (Spermophilus parryii): Metabolic Suppression. Advanced Technology Applications for Combat Casualty Care (ATACCC). St. Pete Beach, Florida, Sept. 9-11, 2002
S20. Drew K.L., Learning and Memory in Hibernation. PI meeting for Continuous Assisted Performance Program, Defense Advanced Research Projects Agency (DARPA). Honolulu, Hawaii. Sept 22-26, 2002.

S21. Drew K.L. Neuroprotection in Hibernation. Pacific Biomedical Research Center, University of Hawaii, Sept 27, 2002.
S22. Drew K.L., Neuroprotection in Hibernation: Is it Clinically Relevant? University of Miami, Neurology Grand Rounds. October 31, 2002.
S23. Drew K.L., Neuroprotection in Hibernation: A comparative Perspective. University of Miami School of Marine Biology. October 31, 2002
S24. Drew K.L. JNK activation during arousal from hibernation: a pivotal pathway of regeneration. University of Nebraska Omaha Center for Neurovirology and Neurodegenerative Disorders. August 21, 2003
S25. Drew K.L. Novel therapeutics from hibernating brain? Neuralstem Inc. Gaithersburg, MD. August 23, 2003.
S26. Drew K.L. Hypoxia Tolerance in Mammalian Heterotherms. Journal of Experimental Biology Discussion Meeting, Defenses Against Brain Hypoxia: Molecule to Organism, Organised by R.G. Boutilier and P.L. Lutz, September 13th – September 17th 2003, Cicalino, Italy
S27. Drew K.L. Living without in Hibernation. Winter Conference on Brain Research. Copper Mountain, Colorado, Jan 29, 2004.
S28. Drew K.L. Neuroprotection in Hibernation. Life in the Cold. Vancouver, Canada to Seward, Alaska, July 31, 2004.
S29. Kelly Drew and Roger Edberg "Visualizing Chemistry: Tools for the ARSC Discovery Lab", Fairbanks, Alaska, Dec 7, 2004
S30. Drew K.L. Cellular stress and MAPK modulation in Hibernation. Workshop on comparative aspects of oxidative stress. La Paz, Mexico, February 15-19, 2005. Session Chair

Publications:

Full-Length Papers:

P1. K.L., Lyon, M., Tietler, M. and Glick, S.D., 1986. Asymmetry in D-2 binding in female rat striata. Brain Res. 363:192-195.
P2. Drew, K.L. and Glick, S.D. 1987. Classical conditioning of amphetamine-induced lateralized and nonlateralized activity in rats. Psychopharmacology. 92:52-57.
P3. Glick, S.D., Shapiro, R.M., Drew, K.L., Hinds, P.A. and Carlson, J.N. 1986. Differences in spontaneous and amphetamine-induced rotational behavior, and in sensitization to amphetamine, among Sprague-Dawley derived rats obtained from different sources. Physiol. Behav. 38:67-70
P4. Drew, K.L. and Glick, S.D. 1988. Characterization of the associative nature of sensitization to amphetamine-induced circling behavior and of the environment dependent placebo-like response. Psychopharmacology. 95:482-487.
P5. Drew, K.L. and Glick, S.D. 1988. Environment dependent sensitization to amphetamine-induced circling behavior. Pharmacology Biochemistry and Behavior 31:705-708.
P6. O'Connor, W.T., Drew, K.L. and Ungerstedt, U. 1989. Differences in dopamine release and metabolism in rat striatal subregions following acute clozapine using in vivo microdialysis. Neurosci. Lett. 98:211-216.
P7. Drew, K.L., O'Connor, W.T., Kehr, J. and Ungerstedt, U. 1989. Characterization of γ-aminobutyric acid and dopamine overflow following acute implantation of a microdialysis probe. Life Sci. 45(14):1307-1317.
P8. Drew, K.L. and Glick, S.D., 1990. Role of D-1 and D-2 receptor stimulation in sensitization to amphetamine-induced circling behavior and in expression and extinction of the Pavlovian conditioned response. Psychopharmacology. 101:465-471.
P9. Drew, K.L., O'Connor, W.T., Kehr, J. and Ungerstedt, U. 1990. Regional specific effects of clozapine and haloperidol on GABA and dopamine release in rat basal ganglia. Eur. J. Pharm 187(3):385-397.
P10. Osborne, P.G., O'Connor, W.T., Drew, K.L. and Ungerstedt, U. 1990. An in vivo microdialysis characterization of extracellular dopamine and GABA in dorsolateral striatum of awake freely moving and halothane anesthetized rats. J. Neurosci. Methods. 34:99-105.
P11. Drew, K.L. and Ungerstedt, U. 1991. Pergolide presynaptically inhibits calcium-stimulated release of γ-aminobutyric acid from rat dorsolateral striatum. J. Neurochem. 57:1927-1930.

P12. O'Connor, W.T., Drew, K.L. and Ungerstedt, U., 1995, Differential cholinergic regulation of dopamine release in the dorsal and ventral neostriatum of the rat. An in vivo microdialysis study. J. Neurosci., 15(12):8353-8361.
P13. Drew, K.L., Fitka T. and Hu, Y. and Ungerstedt, U. 1997, Non-exocytotic γ-aminobutyric acid efflux in rat striatum inhibits gnawing. Life Sciences, 61(16):1593-1601.
P14. Clapp-Lilly K.L., Roberts R.C., Duffy L.K., Irons K.P., Hu Y., Drew K.L., 1999, An Ultrastructural analysis of tissue surrounding a microdialysis probe. J. Neurosci. Methods, 90(2), 129-142.
P15. Drew, K.L., Osborne, P.G., Frerichs, K.U., Hu, Y., Koren, R.E. Hallenbeck J.M. and Rice, M.E., 1999, Ascorbate and glutathione regulation in hibernating ground squirrels. Brain Research, 851(1-2), 1-8.
P16. Osborne, P.G., Hu, Y., Covey D.N., Barnes, B.M., Katz, Z., and Drew, K.L., 1999, Determination of striatal extracellular γ-aminobutyric acid in non-hibernating and hibernating arctic ground squirrels using quantitative microdialysis. Brain Research, 839, 1-8.
P17. Tolen, O., Drew K.L. Chao, M.L., and Rice M.E., 2001, Ascorbate dynamics and oxygen consumption during arousal from hibernation in Arctic ground squirrels. American Journal of Physiology, 281, R572-R583
P18. Zhou, F., Zhu X., Castellani R.J., Stimmelmayr R., Perry G., Smith M.A. and Drew K.L., 2001, Hibernation, a Model of Neuroprotection. American Journal of Pathology, 158, 2145-2151.
P19. Smith MA, Drew KL, Nunomura A, Takeda A, Hirai K, Zhu X, Atwood CS, Raina AK, Rottkamp CA, Sayre LM, Friedland RP, Perry G. Amyloid-β, tau alterations and mitochondrial dysfunction in Alzheimer disease: the chickens or the eggs? Neurochem Int. 2002, 40(6), 527-531.
P20. Drew, K.L., Rice, M.E., Kuhn T.B. and Smith M.A., 2001, Neuroprotective adaptations in hibernation: therapeutic implications for ischemia-reperfusion, traumatic brain injury and neurodegenerative diseases. Free Radical Biology and Medicine. 31(5), 563-573
P21. Drew K. L, Tølen Ø., Rivera P., M. Smith M. A., Perry G. and Rice M. E., 2002, Role of the Antioxidant Ascorbate in Hibernation and Warming from Hibernation. Comparative Physiology and Biochemistry, 133(4):483-92.
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P28. Zhao H, Bucci D, Weltzin M, Drew KL., 2004, Effects of aversive stimuli on learning and memory in wild caught Arctic ground Squirrels. Behav. Brain Res., 151(1-2):219-224
P29. Ma YL, Rice ME, Chao ML, Rivera PM, Zhao HW, Ross AP, Zhu X, Smith MA, Drew KL, 2004, Ascorbate Distribution during Hibernation is Independent of Ascorbate Redox State. Free Radical Biology and Medicine, 37(4):511-20.
P30. Drew KL, Pehek EA, Rasley BT, Ma YL, Green TK (2004) Sampling Glutamate and GABA with Microdialysis: Suggestions on how to get the Dialysis Membrane Closer to the Synapse. J. Neuroscience Methods, 140 (1-2): 127-131.
P31. Drew KL, Harris MB, LaManna JC, Smith MA, Zhu XW, Ma YL, 2004, Hypoxia tolerance in mammalian heterotherms. J. Exp. Biol., 207:3155-62.

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P1. Ma YL, Zhu X, Rivera PM, Tolen O, Barnes BM, LaManna JC, Smith MA, Drew KL Cellular and physiological stress in hibernation and arousal, In preparation for Am. J. Physiol.,
P2. Weltzin MM, Zhao HW, Bucci D, Drew KL, Arousal from hibernation: a natural model of adult cognitive enhancement. in preparation for J. Neurosci.
P3. Drew KL, Warlick BP, Chi BC, Taylor BE, Harris MB, Green TK, Central Nervous System Control of Hibernation, invited review for J. Neurochem.
P4. Ross, AP, Christian, SL, and KL Drew, Intrinsic Tissue Tolerance in Arctic Ground Squirrel Hippocampal Slices, in preparation for submission for J Neurosci.
P5. Zhao H, Castillo MR, Christian SL, Bult-Ito A, Drew KL. Distribution of NMDA Receptors in the Arctic Ground Squirrel. In preparation for J. Comparative Neurobiology.
P6. Zhao H, Ross AP, Christian SL, Buchholz JN, Drew KL. NMDA Receptor Function in Hibernating Arctic Ground Squirrels. In preparation.

Book Chapters/Book Reviews/Letters to Editor:

C1. Shapiro, R.M., Drew, K.L. and Glick, S.D. 1988, Brain asymmetry, animal. In: Encyclopedia of Neuroscience. Birkhauser Boston, Inc., Cambridge, Mass.
C2. O'Connor, W.T., Drew, K.L., Carlsson, H. and Ungerstedt, U., 1992, Neostigmine enhances haloperidol-induced increases in acetylcholine release from rat striatal subregions: An in vivo microdialysis study. Current Separations. 10(3):115-116,
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C4. Drew KL, Zhou F, Zhu X, Castellani RJ, Smith MA (2004) Protection from traumatic brain injury during hibernation. Life in the cold. BM Barnes (Ed).
C5. Hermes-Lima M, Ramos-Vasconcelos GR, Cardoso LA, Orr AL, Rivera PM, Drew KL (2004), Animal adaptability to oxidative stress – gastropod estivation and mammalian hibernation. Life in the Cold, BM Barnes (Ed).

Book Chapters Submitted or in Preparation

C1. Ross A. and Drew, K.L., Clinical profiles of hibernating and euthermic arctic ground squirrels. In preparation

Abstracts

A1. Drew, K.L., Lyon, R.A., Tietler, M. and Glick, S.D. Right>left asymmetry in D-2 binding in female rat striatum. Neurosci. Abstr. 1985. 11:870.
A2. Drew, K.L. and Glick, S.D. Classical conditioning of amphetamine-induced rotation in unlesioned rats. Neurosci. Abstr. 1986. 12:1535.
A3. Drew, K.L. and Glick, S.D. Environment dependent sensitization to amphetamine-induced circling behavior in unlesioned female rats. Neurosci. Abstr. 1987.
A4. Baird, J.L., Glick, S.D., Carlson, J.N. and Drew, K.L. Epinephrine in rat corpus striatum: In vivo microdialysis and HPLC analysis. Neurosci. Abstr. 1987.
A5. Glick, S.D. Carlson, J.N., Baird, J.L. and Drew, K.L. Asymmetry in striatal dopamine release and metabolism: Bilateral in vivo dialysis in normal rats. Neurosci. Abstr. 1987.
A6. Drew, K.L., O'Connor W.T., Kehr, J. and Ungerstedt, U. GABA overflow in rat globus pallidus following neuroleptic and apomorphine administration measured by in vivo microdialysis. Neurosci. Abstr. 1988.

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A18. Osborne P.G. and Drew K.L., 1997, Arctic ground squirrels - from parkas to post stroke therapy; a medical resource comes to light. AAAS, 48th Arctic Division Science Conference, Valdez, AK.

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A20. Clapp K.L., Roberts R.C., Duffy L.K., Hu Y., Irons K. and Drew K.L., 1998, Ultrastructural analysis of microdialysis-induced trauma in rat brain. American Society for Neurochemistry, March 1998.

A21. Hu Y., Osborne P.G., Stimmelmayr R. and Drew K.L., 1998, Hibernation: A model of tolerance to brain trauma. Society for Neurosi. Abstr., 676.13.

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A23. Drew K.L., Rice M.E., Frerichs K.U. and Hallenbeck J.M., 1999. Stroke therapies from hibernating squirrels, Winter Conference on Brain Research, Snowmass, CO, Jan 23-30.

A24. Drew K.L., Clapp-Lilly K.L, Roberts R.C., Duffy L.K., Irons K.P., and Hu Y., 1999, An Ultrastructural Analysis of Tissue Surrounding a Microdialysis Probe. 8th International Conference on In Vivo Methods: "Monitoring Molecules in Neuroscience." Stony Brook, NY, June 19-23.

A25. Drew K.L., Osborne P.G., Hu Y., Stimmelmayr R., Barnes B.M., 1999. Hibernation: a natural model of tolerance to brain trauma. Hibernation and Adaptations to the Cold, Estes Park, CO, May 20-22.

A26. Drew K.L., Osborne P.G., Hu Y., Stimmelmayr R., Barnes B.M., 1999, Hibernation and Tolerance to Brain Trauma, 50th Arctic Science Conference, Science in the North: 50 Years of Change. Denali National Park and Preserve, Alaska, Sept. 19-22.

A27. Tøien, Ø. Rice, M.E. Barnes, B. M. and Drew, K.L. 1999, Plasma ascorbate and oxygen consumption during rewarming from hibernation in arctic ground squirrels. Society for Neurosi. Abstr., 736.21

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A33. Drew K.L., Rivera, P.M. Ross A.P. Corrick R. M., Toien Ø. Zhu X. Chao M.L. Smith M.A. Rice M.E., Antioxidant effects of ascorbate during rewarming from hibernation in arctic ground squirrels. Society for Neurosi. Abstr. San Diego, CA, Nov. 2001

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A35. Drew KL, Ma Y, Rivera P, Cozad K, Toien O, Arterial Blood Gases During Hibernation in the Arctic Ground Squirrel, Stroke - Molecular, Cellular, Pharmacological and Development of New Therapeutics, March 9 - March 14, 2002, Taos, New Mexico.

A36. Ross A and Drew KL, Neuroprotection during Hypoxia in the Arctic Ground Squirrel Molecular, Cellular, Pharmacological and Development of New Therapeutics, March 9 - March 14, 2002, Taos, New Mexico.

A37. Richardson C, Drew KL, Kuhn TB, Decreased Rise in Free Intracellular Ca^{2+} in Synaptosomes and Slices from Hibernating Arctic Ground Squirrels. 2nd Annual Conference of Specialized Programs in Neuroscience, May 15-17, 2002, San Antonio, Texas

A38. Cozad K, Ma Y, Rivera PM, Zhao H, Drew KL, Mechanisms of Hypoxia Tolerance Compared with Hibernation 2nd Annual Conference of Specialized Programs in Neuroscience, May 15-17, 2002, San Antonio, Texas

A39. Drew KL, Ma Y, Rivera PM, Cozad K, Toien O, Zhu X, Smith MA. Exit from Torpor: A Natural Model of Tolerance to Reperfusion 2nd Annual Conference of Specialized Programs in Neuroscience, May 15-17, 2002, San Antonio, Texas

A40. Rivera PM, Zhu X, Smith MA, Rice ME, Drew KL. Study of Oxidative Stress in CA-1 Region of Hippocampus during Euthermia, Torpor and Arousal from Torpor in Arctic Ground Squirrels (*Spermophilus parryii*) 2nd Annual Conference of Specialized Programs in Neuroscience, May 15-17, 2002, San Antonio, Texas

A41. Ross A, Drew KL NMDA Tolerance in Organotypic Hippocampal Slices : A Hibernating Versus Non – Hibernating Species 2nd Annual Conference of Specialized Programs in Neuroscience, May 15-17, 2002, San Antonio, Texas

A42. Zhao H, Weltzin M, Drew KL, Effects of Hibernation on Retention of an Active Avoidance Task 2nd Annual Conference of Specialized Programs in Neuroscience, May 15-17, 2002, San Antonio, Texas

A43. Cozad K, Ma Y, Rivera PM, Zhao H, Drew KL, Mechanisms of Hypoxia Tolerance Compared with Hibernation. Alaskan Summer Neuroscience Conference, July 14-15, 2002, Fairbanks, AK

A44. Drew KL, Ma Y, Rivera PM, Cozad K, Toien O, Zhu X, Smith MA. Hibernation: A Natural Model of Tolerance to Reperfusion Alaskan Summer Neuroscience Conference, July 14-15, 2002, Fairbanks, AK

A45. Rivera PM, Zhu X, Smith MA, Rice ME, Drew KL Study of Oxidative Stress in CA1 Region of Hippocampus in Arctic Ground Squirrels (*Spermophilus parryii*). Alaskan Summer Neuroscience Conference, July 14-15, 2002, Fairbanks, AK

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A47. Zhao H, Weltzin M, Drew KL, Effects of Hibernation on Retention of an Active Avoidance Task. Alaskan Summer Neuroscience Conference, July 14-15, 2002, Fairbanks, AK

A48. Ma Y, Rivera P, Kelliher A, Smith MA, Zhu X, Rice ME, Drew KL. Fate of Ascorbate During Hibernation in Arctic Ground Squirrels. Society for Neuroscience, November 2-7, 2002, Orlando, Florida.

A49. Zhao H, Weltzin M, Bucci D, Drew KL. Effects of Hibernation on Retention of an Active Avoidance Task. Society for Neuroscience, November 2-7, 2002, Orlando, Florida.

A50. Drew KL, Ma Y, Rivera P, Cozad K, Tolen O, Zhu X, LaManna J, Smith MA. Arousal from Hibernation: A Natural model of Tolerance to Reperfusion. Society for Neuroscience, November 2-7, 2002, Orlando, Florida.

A51. Rivera P.M. Ma Y.L. Zhu X. Ross A, Castellani R, Smith MA, Rice ME and Drew KL (2003) Study of oxidative stress in CA1 neurons and liver during euthermia, torpor and arousal from torpor in arctic ground squirrels (spermophilus parryii) 3rd Annual Conference of Specialized Programs in Neuroscience, May 28-30, 2002, Honolulu, Hawaii

A52. Green TK, McGill CG, Swearingen KE, Rasley BT, Drew KL, Characterization of Side Products from NDA/NaCN on-column derivatization of amino acid neurotransmitters. Proceedings of the 10th International Conference on In Vivo Methods, J. Kehr, K. Fuxe, U. Ungerstedt, T. Svensscn, eds. Karolinska Institute, 2003, p 478.

A53. Rasley BT, Drew KL, Dick E, Swearingen KE, Green TK, In Vivo Monitoring of Glutamate in Hibernating Ground Squirrels: Construction of an On-line Microdialsysis/Capillary Electmphoresis/Laser-induced Fluorescence Instrument. Proceedings of the 10th International Conference on In Vivo Methods, J. Kehr, K. Fuxe, U. Ungerstedt, T. Svensson, eds. Karolinska Institute Stockholm 2003, p 481.

A54. Drew KL, Pehek EA, Rasley BT, Ma Y, Green TK, Sampling Glutamate and GABA with Microdialysis: How to get the Membrane Closer to the Synapse? Proceedings of the 10th International Conference on In Vivo Methods, J. Kehr, K. Fuxe, U. Ungerstedt, T. Svensson, eds. Karolinska Institute Stockholm 2003,

A55. Zhao, H, Castillo MR, Bult-Ito, A, Drew KL, Distribution of NMDA receptors in Arctic ground squirrels. Society for Neuroscience, November 7-13, 2003, New Orleans, LA

A56. Ma YL, Rivera P, Wu SF, Drew KL, Enhanced plasma ascorbate stability in hibernation. Society for Neuroscience, November 7-13, 2003, New Orleans, LA

A57. Weltzin MM, Bucci DJ, Zhao H, Drew KL (2003) Hibernation, Learning and Memory, Cell Biology of the Neuron, November 7, 2003, New Orleans, LA.

A58. Zhao HW, Ross AP, Buchholz JN, Drew KL, Intracellular [Ca2+] in Cultured Hippocampal Slices of Hibernating Arctic Ground Squirrel. American Society for Neurochemistry, New York, NY, August 2004

A59. Ross, AP, Christian, SL, Zhao, HW, and KL Drew, Excitotoxic Tolerance in Hippocampal Slices from a Hibernating Species, Society For Neuroscience 34th Annual Meeting, San Diego, CA, Oct.23-27, 2004

A60. Ma YL, Cozad KD, Rivera PM, Zhao, HW, Drew KL (2004) Differences in hypoxia tolerance between AGS and rats. Society for Neurosci

A61. Dave KR, Prado R, Raval AP, Drew KL, Perez-Pinzon MA (2004) Remarkable ischemic tolerance by the Arctic ground squirrel against cardiac arrest during euthermia. Society for Neurosci.

A62. Ross AP, Drew KL (2004) Neuroprotection from excitotoxic insult in hippocampal slices from a hibernating species, arctic ground squirrel. 10th International Symposium on Pharmacology of Cerebral Ischemia Marburg, Germany, July 25-28, 2004

A63. Zhao H, Ross AP, Buchholz JN, Drew KL. (2004) Intracellular [Ca2+] in Cultured Hippocampal Slices of Hibernating Arctic Ground Squirrel Society For Neuroscience 34th Annual Meeting, Oct. 22-26, 2004, San Diego, CA.

Patents:

Ma Y and Drew KL, Adapter between microdialysis guide cannula and microsensors. Provisional Patent, United States Patent Office, filed Aug. 16, 2002 – Not pursued

Service:

Committee Appointments and Service:

University:

1995-1996 Appointed member, Research Advisory Committee

2001-2002	Appointed member, Institutional Review Board
2001-2003	Appointed duty, Center for Nanosensor Technology, Seminar Coordinator
2001-2003	Volunteer, Alaska Basic Neuroscience Program Summer Seminar Series Coordinator
2002-present	Appointed, Research Advisory Committee, Institute of Arctic Biology
2003-present	Appointed, BICS-Central Animal Facility Project Committee
2004-present	Appointed, Institutional Animal Care and Use Committee
2005-present	Appointed, Emergency Services Program Review Committee
2005-present	Appointed, Interdisciplinary Studies Program (INDS) Steering Committee

Departmental:

1999-2000	Appointed member, Search Committee (Assist. Professor, Organic Chemist)
2000-2001	Appointed member, Search Committee (Laboratory Coordinator)
2000-2001	Appointed member, Search Committee (Veterinary Technician)
2001-2002	Appointed member, Search Committee (Director, Alaskan Basic Neuroscience Program)
2001-2002	Appointed member, Search Committees (Assistant Professor, Cell/Molecular Neuroscientist)
2001-2002	Appointed member, Search Committee (Assistant Professor, Analytical Chemists)
2003	Appointed Chair, Search Committee (Assistant Professor, Molecular Physiologist)

Regional/National/International:

(i) Conferences:

Organizer, Stroke therapies from hibernating squirrels, Winter Conference on Brain Research, Snowmass, CO, Jan., 1998.

International Organizing Committee, Monitoring Molecules in Neuroscience, Conway Institute of Biomolecular and Biomedical Research, June 16-19 2001, University College Dublin, Ireland.

Organizer, Alaskan Summer Neuroscience Conference, Fairbanks, Alaska, July 29, 2001, Fairbanks, Alaska

Organizer, Hypoxia tolerance; the less you want, the more you have, Winter Conference on Brain Research, Snowmass, CO, Jan., 2002

International Organizing Committee, Monitoring Molecules in Neuroscience, June 2003, Karolinska Institute, Stockholm, Sweden.

Organizer, Alaskan Summer Neuroscience Conference, Fairbanks, Alaska, July 14-15, 2002, Fairbanks, Alaska

Organizing Committee, Living in the Cold, July 2004, Vancouver, BC

Organizer, Living without in Hibernation. Winter Conference on Brain Research. Copper Mountain, Colorado, Jan 29, 2004.

(ii) Societies/Agencies:

American Heart Association, Alaska Affiliate, Research Committee, Anchorage, Alaska, 1995- 1998
American Heart Association, Northwest Affiliate, Research Committee, Seattle, Washington, 1998 – present
American Heart Association, Northwest Affiliate, Summer Science Fellowship Task Force, 1999 – present
American Heart Association, National, Peer Review Steering Committee, 2000-present
National Institute of Deafness and Communication Disorders, Partnership Program Committee, 1994 – present
National Science Foundation, Ad-hoc reviewer, June, 2002

National Institutes of Health, Neurological Sciences and Disorders B Study Section, *Ad Hoc* Member, June, 2002

(iii) Grant:
Paid-Consultant, NIH Grant (1P50 NS34116), Ascorbate and glutathione in CNS injury, (Chesler, M., PI; Rice M.E., leader project 3), 1997-1998.

(iv) Corporations:
Paid-Consultant, Santa Fe Science & Technology, Inc., Santa Fe, New Mexico, 2000- present.

Community Service:

1990-present	Expert Witness, neuropharmacology of drugs of abuse (Ritalin, alcohol, cocaine, amphetamine, benzodiazepines etc.)
1997-present	Science Potpouri, College of Science, Engineering and Mathematics, UAF
1999-present	Science Education, Wood River Elementary School, "Dr. Science"
2003	Chilled Brains, Lathrop High School
2004	Pharmacology of drugs of abuse, Fairbanks North Star School District 1 day in-service
2004	Pharmacology of drugs of abuse, North Pole Alternative High School
2004	Job Shadow for Ana Davis, high school student
2004	Channel 11 interview concerning questions on Ballot Measure 2
2005	Invited testimony for public hearing on Alaska SB 74 and HB 96
2005	Chilled Brains, UAF Museum Lecture Series

Society Memberships:

1985-present	Society for Neuroscience
2001-2002	President, local chapter Society for Neuroscience
1995-present	American Association for the Advancement of Science
1998-present	American Chemical Society
1998-present	American Society for Neurochemsitry
2000-present	International Society for Neurochemistry
2000-present	Oxygen Society
2000-present	American Heart Association Stroke Council
2000-present	International Society of Cerebral Blood Flow and Metabolism

Granting Agencies:

American Heart Association, External Reviewer, 1997
Baker Fund Awards Committee, External Reviewer, 2002
NIH, Neurological Sciences and Disorders-B, 2002
DOD (ARO), External Reviewer, 2004
Maryland Industrial Partnerships, University of Maryland, External Reviewer, 2004
NIH, Biological Rhythms and Sleep [BRS], 2005

Ad Hoc Journal Reviewer:
Journal of Neuroscience, Journal of Neurochemistry, Brain Research, Journal of Neuroscience Methods, Life Sciences, Psychopharmacology, Redox Report, Cellular and Molecular Biology, Journal of Experimental Biology, American Journal of Physiology, Hippocampus, Journal of Cerebral Blood Flow and Metabolism, Neurobiology of Aging, Journal of Physiology

Textbook Reviewer
Horton et al., Principles of Biochemistry, 4th edition, Chapters 11-14. Prentice Hall, Upper Saddle River, NJ

References:

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My name is Jim Welch and for all of you except Fred Dyson I am a faceless name. Fred Dyson knows me and I hope because of that, he at least will listen to me. For almost 20 years now I have had MS. MS is a disease which short-circuits nerve pathways. So it can affect anything that depends upon nerve messages getting through, whether it be the functioning of a limb or an organ, or sensation, be it numbness or pain. There is no cure for it, so as things deteriorate doctors try to treat symptoms. One of the problems with this however, is that many of the drugs have side effects as least as prominent as the effects.

Over the years I've tried many prescription drugs for many different reasons, usually with very limited success and often with unpleasant side effects. In 1998 I was active in the campaign to pass the initiative legalizing medical marijuana. I found that for two or three years marijuana was the only thing that allowed me to get through most nights without racking muscle spasms or headaches that would not allow me to sleep and still allow me to function the next day.

I applaud what the Legislature has tried to do with crystal meth. That's a drug which I think everyone can agree has no redeeming qualities. But further demonizing marijuana is engaging in the wrong battle. Comparing marijuana to heroin is like comparing aspirin to morphine. Saying that the marijuana today is stronger than it was in the 70s and therefore dangerous is like saying Alleve is stronger than Tylenol, that you only have to take one pill instead of two.

To me that seems a good thing because it means you have to put less smoke into your lungs. I've never smoked tobacco and if I never had to put any more smoke in my lungs or take another drug in my life it would be fine with me.

This is not the 40s era of "Reefer Madness" or even the Nancy Reagan 80s of "just say no." This is the 21st century and in the last election 44% of Alaskans voted to legalize marijuana. You may have the power of the majority to make criminal penalties more severe, but it is a slap in the face to a very large portion of the Alaskan populace who believe that marijuana is okay and who just a few years before voted by a substantial majority to legalize the use of medical marijuana.

I don't know why the Governor has chosen to make marijuana the bad boy of his drug campaign. It doesn't make any sense to me. I know it's not addictive. I smoked marijuana several times a week for three years. When it was no longer effective I stopped. I experienced no withdrawal, no craving, no side effects, no problem.

Unlike tobacco or alcohol no one has ever died from marijuana. I would argue that at worst it's innocuous and at best it has some significant medical benefits.

As for its connection to violent criminals, anyone who has ever used marijuana knows the effects last only a few hours, whereas it can be detected as having been used up to 30 days ago. That's like blaming a DWI on a beer someone drank a month before.

In the last World Cup soccer matches in Portugal, Security checked the persons and all bags being brought into the stadium. Any alcohol was immediately seized, but any marijuana that fans were bringing into the game was not even confiscated. That tells you what kind of behavior the people in charge of security thought resulted from people using marijuana. They worried about the notoriously rowdy soccer fans, but not the ones using marijuana.

I have no illusion or intention to make you proponents of legalizing marijuana. That's not even the issue before you. I do ask you however, to recognize the folly of harsher criminalization penalties. It means putting more nonviolent offenders in jail, devoting more time and money resources of our police to what amounts to a low-priority use of their time. I ask you to put your anti-drug energies against something like crystal meth. Fighting marijuana is the wrong battle in any war on drugs. You have bigger issues to deal with.

Written Testimony – Senate Bill 74

For the Alaska Senate Health, Education and Social Services Committee

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Summary of Written Testimony

1. Teasing Apart....

"The relationship between frequent marijuana use and violence (and vice versa) was spurious; it was no longer significant when common risk factors such as race/ethnicity and hard drug use were controlled for."

2. Effects of Varying Marijuana Potency....

"Tar delivery is reduced relative to THC content in a minority of subjects, and this reduction appears to be due to a reduced intake of smake and/or a reduced tar yield from the stronger marijuana preparation."

3. The Limited Relevance of Drug Policy....

"...no evidence to support claims that criminalization reduces use or that decriminalization increases use."

4. Long-Term Effects....

"There is little evidence . . . that long-term cannabis use causes permanent cognitive impairment...."

5. The Good and Bad Effects....

"[THC] does not constitute a substantial risk to public health and its abuse is rare if at all."

6. The Health and Psychological Effects....

"...on current patterns of use, alcohol and tobacco are much more damaging to public health in developed societies than cannabis, which makes no known contribution to deaths and a minor contribution to morbidity."

7. An Overview of Cannabis Potency....

"Statements in the popular media that the potency of cannabis has increased by ten times or more in recent decades are not supported by the limited data that are available from either the USA or Europe."

8. Psychological and Social Sequelae....

"Available evidence does not strongly support an important causal relation between cannabis use by young people and psychosocial harm...."

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1.

TEASING APART...

"Teasing Apart the Developmental Associations Between Alcohol and Marijuana Use and Violence"

Evelyn H. Wei, Rolf Loeber, and Helene Raskin White
National Institute of Drug Abuse
Grant #MH050778

Teasing Apart the Developmental Associations Between Alcohol and Marijuana Use and Violence

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This study explored the longitudinal associations of alcohol and marijuana use and violence over ages 11-20 in the youngest sample of males from the Pittsburgh Youth Study (N = 503). We examined trends in alcohol and marijuana use and violence, how they covaried both concurrently and over time, and whether frequent substance use predicted violence and vice versa in multivariate models controlling for common risk factors. The analyses focused on frequent alcohol or marijuana users, those who scored in the highest 25% of frequency. Throughout adolescence, substance use was more prevalent than violence. Most substance users did not engage in violence, and the proportion of substance users who engaged in violence was smaller than the proportion of violent offenders who were also substance users. Concurrently, frequent use of alcohol and marijuana were both significantly associated with violence. Longitudinal associations between frequent drinking and violence were weak, whereas longitudinal associations between frequent marijuana use and violence were more consistent. However, the relationship between frequent marijuana use and violence (and vice versa) was spurious; it was no longer significant when common risk factors such as race/ethnicity and hard drug use were controlled for. We conclude that the marijuana-violence relationship is due to selection effects whereby these behaviors tend to co-occur in certain individuals, not because one behavior causes the other; rather, both are influenced by shared risk factors and/or an underlying tendency toward deviance.

Keywords: *alcohol; marijuana; violence; developmental associations*

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A substantial body of literature has addressed the link between substance use and violence. The substance use–violence relationship has been addressed by two angles of research: Acute or pharmacological effects have been examined in survey and laboratory studies, and longer term, developmental effects have been addressed by longitudinal survey studies. These studies have shown differences in the effects of alcohol and marijuana on violent behavior. Several key issues remain, such as developmental trends between substance use and violence throughout the adolescent period, and concurrent and predictive associations, especially when appropriate statistical controls are introduced.

Numerous studies have shown an association between alcohol use and violence (see reviews by Boles & Miotto, 2003; Chermack & Giancola, 1997; Miczek et al., 1994; White, 1997a). However, the evidence concerning the association between marijuana use and violence is much more ambiguous and controversial. Federal documentation on the Internet (Center for Substance Abuse and Prevention, 2003) cites as one of "ten good reasons to focus on marijuana use" that "violence and other crime have been attributed directly to marijuana use." In the year 2000, marijuana was the most popular drug used by juvenile male detainees; across nine sites nationwide, 42% to 55% of detainees tested positive for marijuana (U.S. Department of Justice, 2003).

Acute and Concurrent Associations

There is a consensus that most users of alcohol do not commit violence but that heavy or frequent alcohol use lowers the threshold for the manifestation of violence, especially among aggressive individuals. This consensus is supported by experimental laboratory studies, longitudinal survey studies, and reviews of the literature (Chermack & Giancola, 1997; Ito, Miller, & Pollock, 1996; Parker & Auerhahn, 1998; White, 1997a).

On the other hand, most studies do not support an acute or direct association between marijuana use and violence (Boles & Miotto, 2003; Dembo et al., 1991; Friedman, 1998; Miczek et al., 1994; Reiss & Roth, 1993; White, 1997a). Laboratory research has demonstrated that alcohol and marijuana have opposite psychopharmacological associations vis-à-vis aggression (Miczek et al., 1994). Survey data also fail to find that marijuana use psychopharmacologically induces violence (Boles & Miotto, 2003; Goldstein, 1985). According to Reiss and Roth (1993), "In general, scientific reviews have concluded that violent behavior is either decreased or unaffected by marijuana use" (pp. 1165-1167).

Most studies have examined the acute effects of substance use on violence among adults. In one survey study of adolescent males from the Pittsburgh

Youth Study (PYS). White, Tice, Loeber, and Stouthamer-Loeber (2002) found that offenses against persons were committed more often than general theft while under the influence of alcohol. In addition, aggressive acts were more often related to self-reported acute alcohol use than to marijuana use. Offenses committed under the influence were more prevalent among heavier alcohol and drug users, more serious offenders, more impulsive youth, and youth with more deviant peers. White and Hansell (1998) also found that acute use of alcohol compared to marijuana was more strongly associated with fighting, especially in late adolescence and early adulthood.

Most research on substance use and violence among adolescents has focused on the developmental associations rather than acute associations. Whereas studies of acute effects clarify the association between doses of substance use and immediate aggressive behavior, developmental studies help to clarify the temporal associations and to delineate longer term effects (Huang, White, Kosterman, Catalano, & Hawkins, 2000, p. 80). Rather than assuming a pharmacological association, much of the developmental research is based on the assumption that substance use and aggression are problem behaviors that co-occur during adolescence and that both types of problem behaviors are dependent on a similar set of common risk factors (White & Labouvie, 1994).

There are several plausible ways by which alcohol, and possibly marijuana use, can be developmentally implicated in violence. For example, (a) substance use may lead to violence; (b) violence may lead to substance use; (c) causation may be reciprocal (i.e., one causes the other and vice versa); (d) violence and substance use may be seen as aspects of general dispositions to deviance (i.e., they may be alternative manifestations of the same concept); and (e) substance use and violence may be seen as independent forms of deviance that share common precursors, resulting in a spurious relationship (Kaplan & Damphousse, 1995, pp. 189-191; see also White, 1997a, 1997b).

Developmental Associations and Direction of Effects

Studies examining developmental relationships in adolescence have generally found that early aggressive behavior predicts later substance use and that increases in substance use are related to increases in violent offending (Elliott, Huizinga, & Menard, 1989; White, 1997a, 1997b). The linkage between frequent alcohol use and violence has also been confirmed in longitudinal studies (e.g., Elliott et al., 1989; White, Loeber, Stouthamer-Loeber, & Farrington, 1999). Frequent alcohol use has been shown to predict violence, even when controlling for marijuana use and for other shared risk factors (White et al., 1999).

Using a sample of predominantly White, middle- and working-class adolescent males, White, Brick, and Hansell (1993) found that while controlling for concurrent associations and stability of behaviors over time, aggression in early adolescence (age 12) predicted increases in later alcohol use (age 15), but alcohol use did not predict increases in aggression. White and Hansell (1998) repeated these analyses after following their sample into young adulthood (ages 25-31) and did not find an association between early aggression and later substance use nor between early alcohol use and later aggression. They did find that marijuana use in adolescence (ages 12-18) was negatively related to later aggressive behavior (ages 15-21) and that marijuana use in later adolescence (ages 18-24) was positively related to aggression in young adulthood (ages 25-31). Cross-sectional correlations were much stronger between alcohol and aggression than between marijuana and aggression. In this latter study, aggression was measured by a single indicator of minor aggressive behavior.

In a study of a high-risk Seattle sample, Huang and colleagues (2000) found that the concurrent associations between alcohol use and aggression decreased with age from midadolescence (age 14) into late adolescence (age 18). In terms of cross-lagged associations, aggressive behavior at age 15 predicted increases in alcohol use at age 16, and alcohol use at age 16 predicted increases in aggressive behavior at age 18. However, when common risk factors were controlled for, only the association between alcohol use and later aggressive behavior remained significant. This study focused on aggression as measured by throwing objects, picking fights, and hitting to hurt, as opposed to more serious criminal acts of violence.

Similarly, White et al. (1999) also examined the cross-lagged associations between substance use and violence using data from the oldest cohort in the PYS from ages 13 to 18. The authors found reciprocal associations between alcohol and violence. These associations held even after risk factors that have been associated with both sets of behaviors were controlled for, thus ruling out a purely spurious relationship. White and colleagues found that the concurrent associations were stronger for marijuana and violence than for alcohol and violence, but the longitudinal associations were opposite. Nevertheless, marijuana use in early adolescence (at age 13) was a strong predictor of later violent behavior. However, although changes in marijuana use predicted changes in violence, the association was no longer significant once the effects of prior alcohol use and violence were partialled out. This finding is important, because frequent marijuana users also consume alcohol, and the pure effect of each substance on violence can best be investigated by means of partial correlations in which the effect of one substance on violence is examined while holding constant the effect of the other substance.

In summary, the relationship between substance use and violence appears to be a complicated one. Findings have not been consistent across studies and tend to differ depending on the substance that is examined and the sample that is used. Use of different age ranges and outcome measures (minor aggression versus violence) also contributes to the inconsistency in findings. In addition, previous studies have pointed to the importance of investigating developmental associations between substance and violence while partialling out the effects of co-occurring substance use.

These issues are addressed in this study, which is a replication and extension of prior developmental research in the Pittsburgh Youth Study on substance use and violence in the oldest sample from ages 13 to 18 (White et al., 1999). In this article, we use the youngest sample of the PYS to examine the concurrent and longitudinal associations between alcohol and marijuana use and violence over a 10-year period from ages 11 to 20 years. This study addresses the following questions:

1. What are the developmental trends of substance use and violence throughout adolescence in terms of the prevalence and frequency of each behavior?
2. What are the concurrent and longitudinal associations between frequent substance use and violence?
3. What is the direction of effect between substance use and violence when controlling for shared risk factors?

It is important to replicate findings across different samples. This study extends the earlier study with the older sample (White et al., 1999) in several ways. First, the earlier study was based on a shorter window of time (from ages 13 to 18 compared with 11 to 20). Second, those findings were for a sample that reached adolescence during the peak of the violence epidemic in Pittsburgh (Fabio, Loeber, & Farrington, 2003), whereas this sample is less violent but more involved in illegal drug use (White, Stouthamer-Loeber, Loeber, & Farrington, 2001). Finally, in this study we control for two important demographic factors that are related to violence and substance use (i.e., neighborhood context and race/ethnicity), which were not included in the earlier study.

Nevertheless, we anticipate replicating earlier associations between alcohol and violence. Second, we hypothesize that frequent marijuana use will predict violence and that violence will predict frequent marijuana use. However, we also predict that once statistical controls for confounding factors are taken into account, the association between frequent marijuana use and violence will appear to be spurious, whereas the association between frequent alcohol use and violence will remain.

METHOD

Data were collected as part of the PYS, a longitudinal study of the development of delinquency, substance use, and mental health problems among inner-city adolescent males (Loeber, Farrington, Stouthamer-Loeber, & Van Kammen, 1998). In 1987, three samples of boys were randomly drawn from the first, fourth, and seventh grades of public schools. Of the 3,436 randomly selected, 85% of the boys and their caretakers (93% of whom were biological mothers) consented to participate in a screening assessment. From each sample, the top 30% (about 250 from each grade) of boys with the highest rates of antisocial behavior were selected, along with an equal number randomly selected from the remaining 70%. This resulted in three samples of about 500 boys each. The present analyses focus on the youngest cohort (N = 503), those who were in the first grade when the study began.

At the first assessment, participants in the youngest sample were an average of 7 years old. Slightly more than half (56.3%) of the sample was African American, and almost half (41.4%) was Caucasian, reflecting the racial composition of Pittsburgh public schools when the study began. The population of other ethnic/racial minority groups in Pittsburgh is very low. About 40% of the boys lived with a single parent, and about 40% of the caretakers received public assistance. Further details about the study design and participants can be found in Loeber et al. (1998).

The first 8 assessments were conducted semiannually, and the next 10 were conducted annually. Information was collected from the boys and their caretakers and teachers until age 17 and then from interviews with the boys only. These analyses use data from ages 11 to 20. Data from the semiannual assessments were combined to reflect behaviors occurring in the past year. Data from ages 7 through 10 were not used, because few boys were using substances at these ages, and measures at the younger ages (ages 7-10) used categorical rather than continuous scales. At the last data collection phase (age 20), the participation rate was 82%, and the overall average follow-up rate was 92%, reflecting very low attrition.

Violence Measures

Violence was measured annually by the Self-Reported Delinquency scale (Loeber et al., 1998) and included the past year frequency (number of times) of gang fighting, strong-arming, attacking someone with a weapon or intent to seriously hurt or kill, and rape or forced sex.

Substance Use Measures

Self-reported frequency (number of times in the past year) of alcohol, marijuana, and hard drug use was assessed annually by the Substance Use Scale (Loeber et al., 1998). Hard drugs included hallucinogens, cocaine, crack, heroin, PCP, and nonmedical use of tranquilizers, barbiturates, codeine, amphetamines, and other prescription medications. The lifetime prevalence of hard drug use from ages 11 to 20 was too low ($n = 73$) to include hard drug use as an outcome measure. Therefore, the analysis focuses on the relationship of alcohol and marijuana use with violence. Hard drug use is controlled for in some of the analyses.

The frequency of alcohol consumption was the sum of the number of times participants drank beer, wine, or hard liquor and did not count trying a few sips or drinking with the permission of adults during special occasions/religious services.

Common Risk Factors

Based on findings of previous studies examining substance use and violence (Huang et al., 2000; White et al., 1999), several risk factors common to both substance use and violence were selected as covariates. Because many distributions were skewed, and to ease interpretability, risk factors were dichotomized at the top 25%. These risk factors included the *lifetime frequency of hard drug use*, assessed annually by self-report, and the *frequency of self-reported property crime* (theft, fraud, and vandalism), assessed at age 11. Other child factors were *low academic achievement*, assessed by the primary caretaker and teacher when the boy was age 7, and *depressed mood* and *hyperactivity/impulsivity/inattention problems* (from the Child Behavior Checklist; Achenbach & Edelbrock, 1979, 1983; Edelbrock & Achenbach, 1984), assessed by caretaker and teacher when the boy was age 7. Family risk factors were based on reports by caretakers and participants and included *poor communication with caretaker*, measured at age 11, and *poor supervision*, measured at age 7. In addition, we controlled for *caretaker perception of bad neighborhood*, assessed by the primary caretaker at the first interview (when the boy was age 7). This variable measured caretakers' perceptions of factors such as crime, unemployment, racial conflict, vandalism, and so on in their neighborhood. We also controlled for African American ethnicity because the prevalence of violence is much higher among African Americans (Reiss & Roth, 1993). However, we do not assert that race or ethnicity per se is a risk factor. Rather, we treat African American race/ethnicity as a *marker*

of environmental, socioeconomic, or psychosocial risk, for which we wish to control in investigating the substance use–violence relationship.

Analyses

Prevalence and frequency of substance use and violence over time were used to examine trends in the behaviors. For all analyses, frequent substance use was a dichotomous variable defined as being in the highest 25% of frequency. Concurrent associations between substance use and violence were tested with 2×2 contingency tables, and odds ratios are reported.

In examining longitudinal associations of frequent alcohol use and later violence, prior violence and frequent marijuana use were controlled for. Similarly, analysis of the relationship between frequent marijuana use and later violence controlled for prior violence as well as prior frequent alcohol use. Reverse associations were also tested (i.e., the relationship between violence in one year and frequent alcohol or marijuana use in the next, controlling for prior frequent alcohol and marijuana use). Logistic regression analyses were conducted and adjusted odds ratios are reported.

Longitudinal associations were examined first by cross-lagged (year-to-year) associations from ages 11 to 20. Then, several waves of data were aggregated into two time periods covering ages 11 to 14 and 15 to 20. Based on a cutoff point of the top 25% of alcohol use frequency, frequent users during the first time period drank a total of four or more times between ages 11 and 14, and frequent users during the second time period drank a total of 181 or more times between ages 15 and 20. Any use of marijuana between ages 11 and 14 classified participants as frequent users in the first time period, and for the second time period, the cutoff point was using a total of 300 or more times over ages 15 to 20. In terms of violence, participants who ever engaged in *any* violence were considered, and this applied to both time periods. To reduce false negative classification, participants who were not classified in the top 25% in terms of frequency *and* who missed three or more of the 10 assessments were excluded. Logistic regression analyses were repeated as described above.

Finally, to determine whether longitudinal associations between substance use and violence are spurious, common risk factors were added to the logistic regression models. First, univariate associations between the selected risk factors with frequent alcohol use, frequent marijuana use, and violence were tested, and tests for multicollinearity were conducted. Risk factors that were associated at the $p < .10$ level with both frequent alcohol use and violence, or with both frequent marijuana use and violence (or all three outcomes), and

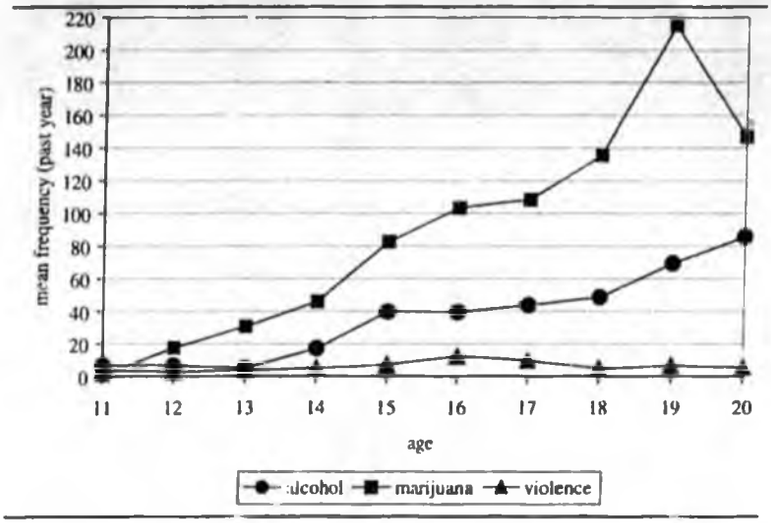

Figure 1 Mean Frequencies of Substance Use and Violence by Age Among Active Users/Offenders

were not highly collinear were selected as covariates. Predictors were entered simultaneously into logistic regression models.

RESULTS

In the youngest sample of the PYS, the lifetime prevalence of alcohol use by age 20 was 84%. The percentage of participants who had ever used marijuana by age 20 was 61.8%. Slightly more than a third (35.4%) had ever engaged in violence by age 20.

Figure 1 shows the mean frequency of alcohol consumption, marijuana use, and violence among active users/offenders by age. Among those who used alcohol, the frequency of consumption increased sharply between ages 13 and 15 and again after age 18. From age 12 on, marijuana use was more frequent among marijuana smokers than the frequency of alcohol use among drinkers, and the difference increased with age through age 19. Starting at age 15, marijuana users reported an average frequency reflecting use as often as once per week or more (i.e., frequencies > 52 times in past year), peaking at age 19. The frequency of violent behavior followed a typical age-crime curve, peaking at around age 16 (at about one time per month) and then declining (Farrington, 1986). Frequencies of substance use were substantially higher than frequencies of violence at all age levels.

TABLE 1
Associations Between Use and Frequent Use of Alcohol and Marijuana and Violence (ages 11-20)

	N	%
Ever used alcohol:	417	84.8
Also engaged in violence	162	38.8
Ever used alcohol frequently:	329	37.1
Also engaged in violence	154	46.8
Ever used marijuana:	417	61.8
Also engaged in violence	162	48.7
Ever used marijuana frequently:	329	51.4
Also engaged in violence	154	54.0
Ever engaged in violence:	174	35.4
Also ever used alcohol	162	93.1
Also ever used alcohol frequently	154	88.5
Also ever used marijuana	162	85.1
Also ever used marijuana frequently	154	78.2

Next, we examined the overall associations between the prevalence of substance use and violence. Table 1 shows the overall associations between *any* substance use and violence and between *frequent* substance use and violence. Of the 84.8% of participants who had ever used alcohol between ages 11 and 20, 38.8% had engaged in violence. Turning to frequent users, of the 67.1% of participants who had ever consumed alcohol frequently (had ever been in the top 25% frequency), 46.8% had engaged in violence.

Of the 61.8% of participants who had ever used marijuana, less than half (48.7%) had engaged in violence. Of the 51.4% of participants who had ever used marijuana frequently (had ever been in the top 25% frequency), slightly more than half (54.0%) had engaged in violence between ages 11 and 20. In contrast, of the 35.4% of participants who had ever engaged in violence, 93.1% had ever used alcohol, 88.5% had ever used alcohol frequently, 85.1% had ever smoked marijuana, and 78.2% had ever smoked marijuana frequently. Thus, throughout the adolescent period, the proportion of substance users who engaged in violence was lower than the proportion of violent individuals who used substances.

Table 2 shows the percentages and odds ratios of the concurrent associations of frequent alcohol and marijuana use with any violence for each age from 11 to 20. At every age, the percentage of violent individuals who used alcohol frequently was greater than the percentage of frequent drinkers who engaged in violence. This was also true for marijuana use starting at age 14; the percentage of violent individuals who used marijuana frequently exceeded the percentage of frequent marijuana smokers who engaged in violence. All associations were in the positive direction (i.e., all odds ratios were

TABLE 2
Concurrent Associations Between Frequent Alcohol and Marijuana Use and Violence by Age

		Frequent Alcohol Use & Violence				*Frequent Marijuana Use & Violence*			
Age	*Total* N	n	*% Violence With Alcohol*	*% Alcohol With Violence*	*Odds Ratio*	n	*% Violence With Marijuana*	*% Marijuana With Violence*	*Odds Ratio*
11	464	11	26.19	18.97	2.83**	0	.00	.00	—
12	475	22	45.83	29.33	5.97***	5	10.42	83.33	—
13	469	17	44.74	16.50	3.25***	10	26.32	34.48	7.74***
14	464	37	71.15	27.41	7.93***	26	50.00	39.39	9.30***
15	452	34	62.96	27.42	5.84***	31	57.41	31.00	6.43***
16	445	26	61.90	22.03	5.49***	26	61.90	22.61	5.73***
17	436	18	54.55	16.07	3.95***	21	63.64	19.27	6.26***
18	434	12	57.14	11.01	4.34**	16	76.19	14.68	11.01***
19	419	10	58.82	9.52	4.62**	11	64.71	10.48	6.01***
20	414	6	50.00	5.50	2.90	9	75.00	8.65	9.70***

NOTE: — = 1+ cell with $n < 5$.
** $p < .01$. *** $p < .001$.

greater than one). For example, at age 18, frequent marijuana users were 11 times more likely than nonfrequent users to also engage in violence (OR = 11.01), whereas frequent drinkers were 4 times as likely as nonfrequent drinkers to also engage in violence (OR = 4.34).

Table 3 summarizes the longitudinal associations between frequent alcohol and marijuana use and violence. Cross-lagged associations are presented first to address whether substance use in one year was associated with violence in the next year. For example, at age 11, frequent alcohol use was associated with violence at age 12, while controlling for violence and marijuana use at age 11 ($OR_{adj} = 2.68$). However, after age 11, there was no significant association between frequent alcohol use in one year and violence in the following year. Frequent use of marijuana was associated with violence in the following year (controlling for prior year violence and alcohol use) for five of the eight annual comparisons ($OR_{adj} = 2.67\text{-}3.83$).

We also addressed whether violence increased substance use in the following year. In terms of violence predicting frequent drinking in the following year, those who were violent at age 14 were more than twice as likely as those who were not violent to be frequent drinkers at age 15 ($OR_{adj} = 2.38$). However, violence during late adolescence, at age 19, was significantly associated with a *lower* likelihood of frequent drinking at age 20 ($OR_{adj} = .22$). Violence was significantly associated with frequent marijuana use in two of the nine comparisons ($OR_{adj} = 4.96$ from ages 13 to 14 and $OR_{adj} = 5.50$ from ages 17

TABLE 3
Longitudinal Associations Between Frequent Alcohol and Marijuana Use and Violence

	Adjusted Odds Ratios			
Prediction From Age to Age	*Alcohol → Violence*[a]	*Marijuana → Violence*[b]	*Violence → Alcohol*[c]	*Violence → Marijuana*[d]
11 → 12 (*N* = 461)	2.68*	n/a	1.36	2.23
12 → 13 (*N* = 465)	1.07	.00	1.69	2.22
13 → 14 (*N* = 456)	1.31	3.11*	1.83	4.96***
14 → 15 (*N* = 443)	1.79	3.07**	2.38*	1.71
15 → 16 (*N* = 432)	.79	3.36**	1.56	1.03
16 → 17 (*N* = 426)	.93	2.67*	1.67	1.31
17 → 18 (*N* = 413)	1.41	2.58	1.35	5.50***
18 → 19 (*N* = 407)	1.44	3.83*	.42	.65
19 → 20 (*N* = 394)	.61	1.31	.22*	.89
Ages 11-14 → 15-20 (*N* = 417)				
No risk factors	1.79	2.34*	1.36	1.90*
Risk factors included[e]	1.97*	1.91	1.70	1.67

a. Controlling for prior year violence and marijuana.
b. Controlling for prior year violence and alcohol.
c. Controlling for prior year alcohol and marijuana.
d. Controlling for prior year marijuana and alcohol.
e. Common risk factors = hard drug use, property crime (theft, fraud, and vandalism), low academic achievement, poor communication with caretaker, caretaker perception of bad neighborhood, and African American ethnicity.
* $p < .05$. ** $p < .01$. *** $p < .001$.

to 18). Thus, frequent marijuana use appears to predict violent behavior over time, especially during midadolescence, whereas frequent alcohol use only predicts later violence at the youngest age. In addition, violence does not appear to be a consistent predictor of frequent alcohol or marijuana use.

Next, data were aggregated into two time periods (ages 11-14 and 15-20) and the total frequency of each behavior was dichotomized to isolate the top 25%. The results are shown on the second to last line of Table 3. For these analyses, we only included boys for whom we also had complete data on risk factors so we could compare, for the same individuals, this model to the final model that includes the risk factors ($N = 417$). If we had not restricted the sample to participants for whom we had complete data on risk factors, the sample on the first model would have been 431. The results for this model ($N = 417$) were the same as for the sample of 431. Males who drank frequently were not significantly more likely to be violent later. However, those who used marijuana frequently between ages 11 and 14 were significantly more likely than nonusers and nonfrequent users to engage in violence later

($OR_{adj} = 2.34$, $p = .012$), and this was independent of prior violence or frequent use of alcohol. As frequent drinking did not increase the likelihood of violence, early violent behavior was not associated with later frequent drinking, when controlling for prior frequent alcohol or marijuana use. In terms of marijuana–violence relationships, a reciprocal association was found; early violence was significantly associated with later frequent use of marijuana, when controlling for prior frequent marijuana or alcohol use ($OR_{adj} = 1.90$, $p = .028$).

To determine whether the above relationships were spurious, common risk factors were added to the model. Following a univariate screening, the following risk factors were controlled for: lifetime hard drug use, frequency of self-reported property crime (theft, fraud, and vandalism), low academic achievement, poor communication with caretaker, caretaker perception of bad neighborhood, and African American race/ethnicity. The last line of Table 3 shows the results of the logistic regression analyses while controlling for common risk factors ($N = 417$). The prediction of alcohol to violence was not statistically significant until common risk factors were taken into account, indicating a suppressor effect ($OR_{adj} = 1.97$, $p = .033$; without the risk factors, it was $OR_{adj} = 1.79$, $p = .052$). Post-hoc analyses indicated that a disproportionate lower prevalence of frequent drinking and higher prevalence of violence among African Americans suppressed the effect of alcohol on violence. In converse, when common risk factors were considered, the prediction of marijuana use to violence was no longer statistically significant ($OR_{adj} = 1.91$, $p = .068$); this finding suggests that the association was spurious. Turning to the reverse associations, violence was still not associated with later frequent alcohol use. The prediction from early violence to later marijuana use was no longer statistically significant when common risk factors were included ($OR_{adj} = 1.67$, $p = .107$), again suggesting that the association was spurious. Common risk factors that predicted both violence and frequent marijuana use in the multivariate models were African American ethnicity ($OR_{adj} = 1.98$, $p = .043$ for violence; $OR_{adj} = 2.04$, $p = .029$ for marijuana) and lifetime hard drug use ($OR_{adj} = 2.28$, $p = .034$ for violence; $OR_{adj} = 5.25$, $p < .001$ for marijuana).

DISCUSSION

From ages 11 to 20, substance use was more prevalent and frequent than violence. Substance use continued to increase throughout late adolescence, whereas violence followed a typical age-crime curve, increasing to around age 16 and then decreasing. Frequent alcohol and marijuana use were both concurrently associated with violence. Overall, odds ratios showed that the longitudinal relationship with violence was stronger for marijuana use than

alcohol use, and the relationship between marijuana use and violence was bidirectional; earlier violence was also related to later marijuana use but not alcohol use. However, the association between marijuana use and later violence was spurious; it was mediated by common risk factors. Participants who were African American or hard drug users were more likely to engage in violence and also were more likely to become frequent marijuana users.

With regard to the associations between early frequent marijuana use and later violence, our conclusions are similar to those of White et al. (1999), in that what we are seeing is a selection effect. In other words, marijuana use is more atypical during early adolescence and becomes more normative with age, and the subset of males who begin marijuana use at younger ages are at elevated risk for several serious outcomes, including poly drug use, violence, and property offending. It is likely that this subgroup of males is inherently more deviant, engaging in multiple problem behaviors at earlier ages, choosing deviant peers, and being more likely to manifest their individual propensity for aggression and antisocial behavior later on. Our findings reinforce the benefits of primary prevention efforts that address multiple risk factors early on, as well as early intervention with high risk or aggressive males.

Because the proportion of violent individuals who used marijuana frequently was larger than the proportion of frequent marijuana users engaging in violence, and because the prediction of violence from earlier frequent marijuana use was mediated by common risk factors, our results do not indicate that early frequent marijuana use causes later violence. Rather, we conclude that frequent marijuana use and violence co-occur because they share common risk factors (e.g., race/ethnicity, hard drug use). It is important to keep in mind that marijuana has been used for centuries and is the most widely used illicit drug today and that the majority of marijuana users do not engage in violence (Boles & Miotto, 2003). Our findings indicate that intervention with young violent offenders to prevent or treat substance use problems may be more practical than targeting marijuana users for violence prevention.

Selection effects may also explain why we did not find a longitudinal association between frequent drinking and violence. Alcohol is a legal drug, and drinking is more commonly accepted by society than marijuana use, which is illicit. Thus, alcohol is seen as normative, whereas marijuana use and violence are not normative and are more likely to cluster in individuals with more deviant tendencies. Obviously, these findings apply to an inner-city adolescent sample and do not necessarily apply to frequent or heavy drinking and violence among adults.

Our findings differed somewhat from those for the older sample in terms of alcohol and violence relationships (White et al., 1999). In that study, White and colleagues found that the longitudinal associations between alcohol and

violence were slightly stronger than those between marijuana use and violence except in very early adolescence. The longitudinal associations between alcohol and violence remained significant when marijuana use as well as other risk factors were controlled. One reason that the findings from this study differed from the previous study may relate to cohort or period effects. The older sample experienced more violence and was in middle to late adolescence in 1993 during the peak of the violence epidemic in Pittsburgh, whereas the youngest sample was just entering adolescence (Fabio et al., 2003). The oldest sample came of age during the lowest rates of drug use in the early 1990s. In contrast to the oldest sample, the youngest sample is more involved in substance use and less involved in violence (White et al., 2001).

Differing results may also be due to the different age ranges used in the longitudinal analyses. The previous study examined behaviors at age 13 predicting behaviors at ages 14 to 18. This study examined behaviors at ages 11 to 14 predicting behaviors at ages 15 to 20. It is likely that developmental processes and temporal windows that fluctuate throughout adolescence shape the substance use–violence nexus. In the earlier study, race/ethnicity and hard drug use were not controlled for. In this study, both these factors were strongly related to violence and frequent marijuana use. Being African American was significantly related to engaging in violence as well as frequent marijuana use. We surmise that contextual effects may drive cultural differences in the associations between substance use and violence. We know that inner-city neighborhoods with a high minority concentration are plagued by violence. At the same time, a subculture of young African American males is using marijuana as their "drug of choice" instead of alcohol (Golub & Johnson, 2001). Thus, at the individual level, it may be hard drug rather than marijuana use that is the important predictor of violence.

Some limitations of the study should be considered. This study focused on a group of adolescents from one city. Therefore, the findings may not be generalizable to other areas of the country. Furthermore, we only included males in the study. Future research should also examine females. Our measure of violence can also be seen as a limitation. Because we focused on those who ever engaged in violence, those who may have committed violence only once are included with those who committed multiple acts of violence. It may be that associations between substance use and violence differ according to the degree or frequency of violent behavior, possibly in a dose-response fashion.

The strengths of this study stem from it being a community-based, longitudinal study with high follow-up rates and regular assessments with no gaps. Substance use and violence were measured prospectively, minimizing recall bias. The data are highly complete and collected at multiple waves, and infor-

mation about risk factors was gathered from multiple informants. Recent analyses of this dataset do not indicate selective attrition: Follow-up rates did not significantly differ according to initial high-risk status, race/ethnicity, socioeconomic status (SES), or baseline levels of alcohol, marijuana, or hard drug use. Further, substance use was based on frequency counts (rather than use/no use) and focused on the most frequent users.

The developmental relationships between substance use and violence are quite complex and are moderated by a host of individual (biological and psychosocial) and environmental factors. The nature of the substance use–violence relationship changes over the life course, and it is likely that the range and influence of risk factors also vary over time. It is also important to consider differences between bingeing, or acute episodic substance use, as opposed to patterns of chronic use. The developmental relationships between substance use and violence are further complicated by the fact that the prevalence and influence of risk factors also vary throughout development. In this study and the previous study, risk factors were measured at one point in time. It is possible that studies using time-varying covariates (e.g., changing levels of parental supervision or neighborhood quality) or more proximal risk factors (e.g., weapon carrying) would offer different findings as well.

Future research should explore the notion of alcohol consumption being more normative among Caucasian participants, in comparison to marijuana use being more normative among African American participants. Differential expectancies of the effects of alcohol or marijuana on violent behavior should also be considered. It is likely that different subcultures may adopt varying expectancies of the effects of substance use intoxication on aggressive behavior. Research on criminal careers can benefit from research about the persistence of violence, in terms of how substance use patterns are associated with chronic offending, desistance, and recidivism. Separate analysis by race/ethnicity can aid the development of culturally specific prevention and intervention programs for multiproblem youth. Finally, research should continue to identify factors that mediate or moderate the associations between substance use and violence.

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"Effects of Varying Marijuana Potency on Deposition of Tar and Delta-9 TCH in the Lung During Smoking"

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Effects of Varying Marijuana Potency on Deposition of Tar and Δ^9-THC in the Lung During Smoking

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MATTHIAS, P., D. P. TASHKIN, J. A. MARQUES-MAGALLANES, J. N. WILKINS AND M. S. SIMMONS. *Effects of varying marijuana potency on deposition of tar and Δ^9-THC in the lung during smoking.* PHARMACOL BIOCHEM BEHAV **58**(4) 1145–1150, 1997.—To determine whether smoking more, compared to less, potent marijuana (MJ) cigarettes to a desired level of intoxication ("high") reduces pulmonary exposure to noxious smoke components, in 10 habitual smokers of MJ, we measured respiratory delivery and deposition of tar and Δ^9-tetrahydrocannabinol (THC), carboxyhemoglobin (COHb) boost, smoking topography, including cumulative puff volume (CPV) and breathholding time, change in heart rate (ΔHR) and "high" during ad lib smoking of 0, 1.77, and 3.95% MJ cigarettes on 3 separate days. At each session, subjects had access to only a single MJ cigarette. On average, smoking topography and COHb boost did not differ across the different strengths of MJ, while THC delivery, as well as HR, were significantly greater ($p < 0.01$) and tar deposition significantly less ($p < 0.03$) for 3.95% than 1.77% MJ. Although individual adaptations in smoking topography for 3.95% compared to 1.77% MJ were highly variable, three subjects with the lowest 3.95% MJ:1.77% MJ ratios for CPV also displayed the lowest 3.95% MJ:1.77% MJ ratios for tar deposition. In vitro studies using a standardized smoking technique revealed a mean 25% lower tar yield from 3.95% than 1.77% MJ ($p < 0.05$), but no difference between 1.77% and 0% marijuana. Under the conditions of this study, we conclude that tar delivery is reduced relative to THC content in a minority of subjects, and this reduction appears to be due to a reduced intake of smoke (decreased CPV) and/or a reduced tar yield from the stronger MJ preparation. © 1997 Elsevier Science Inc.

Marijuana Δ^9-tetrahydrocannabinol (THC) Smoking topography Tar yield Tar deposition Lung Carboxyhemoglobin boost "High"

WE have previously shown that compared to tobacco smoking, marijuana smoking results in an approximately fourfold greater deposition of tar in the lung and a four- to fivefold larger boost of carboxyhemoglobin (COHb) in the blood when equivalent quantities of the two substances are smoked (12,16). These differential effects appeared to be mainly due to less filtration of marijuana than tobacco cigarettes, resulting in a relatively greater tar yield from marijuana (13), and the longer breathholding time following inhalation of the smoke of marijuana than that of tobacco, resulting in a greater fractional retention in the lung of the inhaled tar and a greater absorption of carbon monoxide (13,16). These findings suggest that, at least for equivalent weights of plant material smoked, marijuana joints might have a greater potential than tobacco cigarettes for adverse health effects related to the carcinogenicity and respiratory irritant effects of components in tar (6) and the reduced myocardial oxygen delivery (1) and reduced maternal and fetal tissue oxygenation caused (8) by an elevated COHb.

It has been hypothesized that the health hazards from toxic components in marijuana smoke could be reduced if habitual marijuana users smoked higher potency marijuana (4). This hypothesis assumes the following: 1) that smokers are able to "titrate" the amount of THC absorbed during marijuana smok-

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ing in a manner that will result in decreasing their cumulative puff volume of inhaled smoke when smoking a more potent compared to a less potent preparation, to achieve a given desired level of intoxication; and 2) that the yield of tar relative to Δ^9-tetrahydrocannabinol (THC) from marijuana preparations of different potency always decreases as the THC concentration of the preparation increases. To test this hypothesis and these assumptions, we evaluated the effects of varying THC concentrations in marijuana cigarettes (0, 1.77, and 3.95%) on the deposition of tar in the lung, carboxyhemoglobin boost, and subjective and physiological measures reflecting the bioavailability of THC in ten habitual smokers of marijuana.

METHODS

Subjects

We studied 10 male habitual marijuana smokers [mean age (± SD), 23.2 ± 2.3 years], who smoked an average of 12.7 ± 11.5 joints/week and reported a cumulative lifetime smoking history of 27.2 ± 46.5 joint-years (number of marijuana joints per day times the number of years of marijuana smoking). All were in good general health and had normal values for routine pulmonary function tests. None reported intravenous drug abuse or smoking illicit substances other than marijuana. Three were current tobacco cigarette smokers (14.0 ± 13.9 cigarettes/day) and four were ever-smokers of tobacco with a cumulative lifetime smoking history of 3.6 ± 1.1 pack-years (number of packs of cigarettes per day times the number of years of tobacco smoking). The study was approved by the UCLA Human Subject Protection Committee and the California Research Advisory Panel. All subjects signed an approved informed consent form prior to their participation in the study.

Study Protocol and Procedures

Each subject was studied on 3 separate days approximately 1 week apart after refraining from smoking tobacco for ≥1 h and marijuana for ≥6 h. During each study session, subjects smoked a marijuana cigarette (85 mm length × 25 mm circumference) containing either 0.000 ± 0.002% THC (mean weight 833 mg; range 808–864 mg), 1.77 ± 0.01% THC (mean weight 832 mg; range 789–924 mg) or 3.95% THC (mean weight 734 mg, range 687–774 mg), according to a crossover design. The order of assignment of the three different strengths of marijuana to each subject was randomized and subjects were masked to the assignment. All marijuana cigarettes were prepared from Mississippi-grown Mexican marijuana and were supplied by the National Institute on Drug Abuse; the 0% THC preparation was prepared by ethanol extraction. Marijuana cigarettes were stored at 4°C to minimize chemical degradation and were maintained in a humidifier at 60% humidity and 21°C for 24 h before the study to reduce harshness.

Subjects were asked to smoke each marijuana cigarette ad lib but were specifically instructed to stop smoking once they had achieved their desired level of intoxication ("high"). Peripheral venous blood was withdrawn anaerobically immediately before and 2 min after each cigarette was smoked for measurement of the percentage of COHb saturation using a CO-oximeter (Model 282, Instrument Laboratory, Lexington, MA). Immediately prior to smoking at 2, 5, 15, 30, and 45 min after smoking, heart rate was measured electrocardiographically and subjects were asked to rate their level of intoxication on a scale of 0 to 10, with 10 representing the greatest "high" they had ever achieved.

Smoking topographic measures were determined, as previously described (16). Briefly, the volume and number of puffs and the interpuff interval were measured using a 00 Fleisch pneumotachygraph (resistance 0.0068 cm H_2O; linear from 5 to 100 ml/s) connected through a differential pressure transducer (Model 282 MP54-3, Validyne, Northridge, CA) (range ± 2 cm H_2O) to a 12-channel oscilloscopic recorder with a differential integrator-computer and a rapid infrared writer attachment (Honeywell Simultrace Recorder, Model VR-12, White Plains, NY). The pneumotachygraph was connected through 1-cm diameter Tygon tubing (length 70 cm) to the distal end of a glass cylinder (diameter 5 cm; length 12 cm) that contained two 1-cm diameter ventilation ports and was sealed at its proximal end by a rubber stopper. The marijuana cigarette was held in a small plastic holder inserted through the rubber stopper. During a puff, the ventilation ports were occluded by rubber stoppers so that the entire volume of air drawn through the cigarette could be measured by the pneumotachygraph. Between puffs, the ventilation ports were uncovered to prevent extinction of the cigarette or accumulation of carbon monoxide. The volume of smoke and air inhaled into the lungs ("inhaled volume") in association with each puff was measured using inductive plethysmography (Respitrace-Plus, NonInvasive Monitoring Systems, Miami Beach, FL). During calibration maneuvers, inhaled volumes calculated from inductive plethysmography agreed with measurements obtained by spirometry within ±10%. The amount of time the inhaled smoke was retained in the lungs ("breathholding time") was calculated as the interval between the times corresponding to one-third of the maximum inhaled volume and two-thirds of the maximum volume exhaled following breathholding.

The amount of inhaled insoluble smoke particulates (tar) was measured by a previously described proportional smoke-trapping device (10) that was connected to the plastic cigarette holder at the proximal end of the puff-volume measuring apparatus (1). From the plastic cigarette holder, mainstream smoke was diverted into two parallel pathways, one containing one capillary tube and a Cambridge filter pad ("high-resistance" pathway) and the other containing seven parallel capillary tubes ("low-resistance" pathway). The filter pad trapped the smoke that passed through the high-resistance pathway. The tar (including THC) trapped by the filter was extracted with methanol. The tar content (total insoluble particulate matter) was analyzed by means of a spectrophotometer (wavelength 400 nm). THC concentrations were determined by injecting dilutions of the methanol wash into a Waters high performance liquid-chromatograph outfitted with a diode array detector according to modifications of ElSohly et al. (2). Ion pair technology was employed using a Beckman ultrasphere C18 column, a water:acetonitrile mobile phase of 15:85, and isocratic flow of 2 ml/min. Ultraviolet detection was performed at 220 nm with standards obtained from Alltech, Inc. (San Jose, CA). Because a constant fraction of the tar (approximately 12.5%) was retained in the filter over a wide range of puff volumes and flow rates, the actual quantity of inhaled tar, as well as inhaled THC, could be calculated by multiplying the amount of particulates and THC trapped in the Cambridge filter pad in the high-resistance pathway by the term ([1 ÷ 0.125] − 1), or 7 (10). At the end of the period of breathholding after each puff, subjects exhaled the smoke into a megaphone device, the distal end of which (4.5-cm diameter) was fitted with another Cambridge filter pad attached to a vacuum system (5,16) to trap the exhaled particulates. Following methanol extraction, the latter were also quantitated by spectrophotometry and the ex-

haled THC by HPLC (3) as detailed earlier. The amount of tar or THC retained (deposited) in the lung was calculated by subtracting the amount of exhaled from the amount of inhaled tar or THC.

The amount of tar delivered to the lung from different strengths of marijuana cigarettes is dependent not only on smoking technique but also on the actual tar yield of the cigarettes, which could vary with the potency of the preparation. We, therefore, measured the amount of tar in mainstream smoke generated from five 0%, five 1.77%, and five 3.95% marijuana cigarettes under standardized smoking conditions using a syringe with a 50-ml puff volume, 2-second duration and 30-s interpuff interval to uniform butt lengths of 25 mm. All the tar in the mainstream smoke was captured in a Cambridge filter interposed between the syringe and the cigarette and measured spectrophotometrically after methanol elution, as described above.

DATA ANALYSIS

For each subject, topographic measurements (puff volume, interpuff interval, inhaled volume, breathholding time) were averaged for each cigarette smoked. These mean values, as well as the number of puffs, cumulative puff volume (the product of the mean puff volume and the number of puffs for each cigarette), butt length, and the amounts of inhaled and retained tar and THC were averaged for all 10 subjects for each potency of marijuana smoked. COHb "boost," peak changes in heart rate from baseline and peak subjective ratings of degree of intoxication after smoking each strength of marijuana were also averaged for all subjects. In addition, for each subject, each measurement variable was expressed as a ratio of that variable determined in relation to smoking 3.95% marijuana to that determined for 1.77% marijuana; these ratios served as indicators of the relative pattern for each subject of smoking active marijuana of two different strengths. The Hotelling's T^2 test, a multivariate test for within-subject differences in repeated measures models, was used to determine the significance of differences in smoking patterns, delivery, and deposition of particulates and THC, and the "boost" in COHb and change in heart rate among the different strengths of marijuana cigarettes (9). Multiple comparisons were then performed using paired t-tests, where appropriate. Because the subject's levels of "high" were based on an ordinal scale, these data were analyzed for differences between the THC concentrations using Friedman's nonparametric two-way analysis of variance (7). Differences for all tests were considered significant for p values <0.05. Statistical analyses were performed using SAS (11) and BMDP (2) software.

RESULTS

Smoking topography, pulmonary deposition of tar and THC, COHb boost, and psychophysiologic responses to smoking all showed similarly wide variability across subjects for each strength of marijuana. The extent of this variability is illustrated for cumulative puff volume, breathholding time, tar deposition, and THC retention in Fig. 1, which shows the individual values for these variables for each type of marijuana preparation smoked.

Mean values (±SE) for cumulative puff volume (CPV), inhaled volume (Vol_I), breathholding time, butt length, amount of tar and THC retained in the lung, COHb boost, peak change in heart rate, and peak level of intoxication for each potency of marijuana smoked are shown in Table 1. As expected, both "active" marijuana preparations (1.77% and 3.95% THC) delivered significantly more THC, $F(2, 8) = 51.7$, $p < 0.001$; Hotelling's T^2, to the lung and resulted in a significantly greater change (increase) in heart rate, $F(2, 8) = 24.0$, $p < 0.001$; Hotelling's T^2, than the "inactive" (0% THC) preparation, although neither active preparation elicited a significantly greater "high" than "inactive" marijuana ($p = 0.12$; Freedman nonparametric two-way ANOVA). No differences in any of the measured smoking topographic variables [cumulative puff volume; average puff volume, number of puffs, or interpuff interval (data not shown); inhaled volume; breathholding time; butt length], nor in COHb boost, were noted across the different potencies of marijuana. On the other hand, despite the lack of any mean difference in smoking pattern for the different strengths of marijuana, the average amount of tar delivered to and retained in the lung from the most potent preparation (3.95% THC) was significantly lower than that from both the 0% THC and 1.77% THC preparations ($p < 0.03$). Moreover, the THC delivered to and retained in the lung from 3.95% marijuana was significantly greater than that deposited in the lung from 1.77% marijuana ($p < 0.001$); this difference is reflected in the significantly greater heart rate increase ($p < 0.01$) following the more potent "active" preparation.

The mean percent of inhaled (delivered) tar that was not exhaled and was thus deposited in the respiratory tract was comparable across the different strengths of marijuana (80.7 ± 2.1%, 86.9 ± 3.2%, and 83.6 ± 2.4% for the 0, 1.77, and 3.95% preparations, respectively). Likewise, the average percent of inhaled (delivered) THC that was retained in the lung was similar for the 0, 1.77, and 3.95% potencies (74.1 ± 5.0%, 83.6 ± 3.8%, and 76.5 ± 4.5%, respectively). Consequently, the differences between the amounts of tar (or THC) delivered to the lung between any two strengths of marijuana were similar to the differences between the amounts of tar (or THC) de-

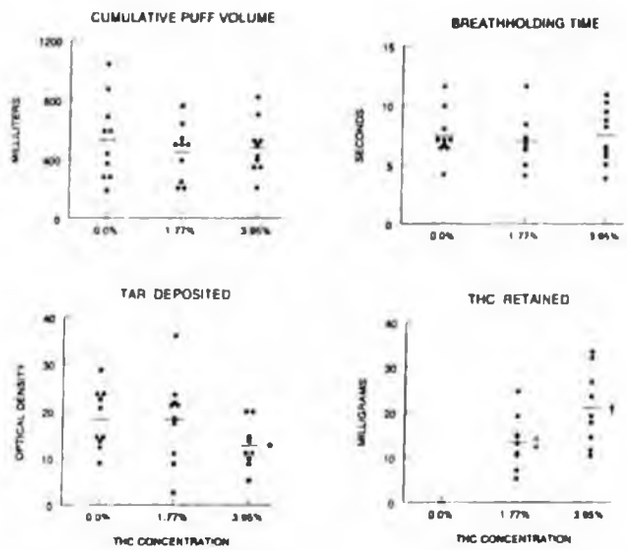

FIG. 1 Individual values for cumulative puff volume (ml) and breathholding time (s) and for amount of tar [optical density (O.D.) units] and amount of THC (mg) deposited in the respiratory tract for 0.0, 1.77, and 3.95% marijuana. Horizontal lines represent mean values. *$p < 0.03$ (compared with 1.77% and 0% THC); †$p < 0.01$ (compared with 1.77% and 0% THC); ‡$p < 0.001$ (compared with 0% THC).

TABLE 1

MEAN VALUES (±SE) FOR SMOKING TOPOGRAPHY, TAR, AND THC DEPOSITION IN THE LUNG, BLOOD CARBOXYHEMOGLOBIN BOOST, AND PSYCHOPHYSIOLOGIC RESPONSES TO THC DETERMINED DURING AND AFTER SMOKING MARIJUANA CIGARETTES OF DIFFERENT THC CONCENTRATION

	TAR O.D.	THC mg	BHT sec	CPV ml	Vol_t liters	Butt length mm	COHb %	High (0–10)	ΔHR min^{-1}
0% THC	18.9	0.1	7.5	534	2.52	16.7	2.6	3.0	6.2
	(2.1)	(0.0)	(0.6)	(87)	(0.28)	(4.3)	(0.5)	(0.7)	(1.6)
1.77% THC	19.9	13.4*	7.0	447	2.17	19.3	2.0	4.3	30.2*
	(2.6)	(2.0)	(0.6)	(5.9)	(0.33)	(4.7)	(0.4)	(0.7)	(3.8)
3.95% THC	13.6†‖	21.0*‡	7.5	479	2.11	19.0	2.0	6.0	39.0*‡
	(1.5)	(2.8)	(0.7)	(57)	(0.20)	(7.2§	(0.3)	(0.6)	(4.3)

Definition of abbreviations: Tar = respiratory tar deposition; O.D. = optical density units; THC = respiratory retention of Δ^9-tetrahydrocannabinol; BHT = breathholding time; CPV = cumulative puff volume; Vol_t = inhaled volume of smoke and air; COHb = carboxyhemoglobin saturation; ΔHR = change in heart rate from pre-smoking baseline.

*Significantly different from 0% THC; $p < 0.001$.

†Significantly different from 0% THC; $p < 0.02$.

‡Significantly different from 1.77% THC; $p < 0.01$.

§Significantly different from 1.77% THC; $p < 0.03$.

posited (retained) in the lung between the same two potencies of marijuana.

The ratio of values for the variables shown in Table 1 for 3.95% marijuana to those for 1.77% marijuana were calculated for each subject and averaged across all subjects. The distributions of the individual values for most of these ratios across the 10 subjects are illustrated in Fig. 2. Deviations of these ratios from 1.0 would imply a difference between the more and less potent "active" marijuana preparation with respect to smoking technique, delivery of smoke contents to the lung or the physiological effects of such delivery. The broad range of these ratios, which straddled 1.0 for all variables except the amount of THC delivered to and retained in the lung, reflects the large degree of variability across subjects in differential smoking technique and in subjective and physiological responses to THC between the two strengths of marijuana (Fig. 2). On average, ratios of values for smoking pattern, including cumulative puff volume, breathholding time, and inhaled volume, were close to 1.0. On the other hand, ratios for THC deposition, change in heart rate and "high" were always or mostly above 1.0, while ratios for tar deposition were mostly less than 1.0.

The individual tar yields determined using a standardized, syringe-simulated smoking technique for each of the five cigarettes of each strength that were tested are shown in Fig. 3.

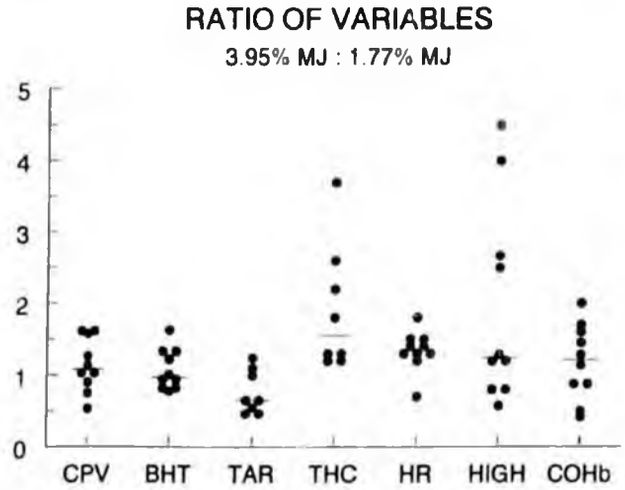

FIG. 2. Individual ratios of values for cumulative puff volume (CPV), breathholding time (BHT), respiratory tar deposition (TAR), respiratory retention of THC (THC), heart rate increase over presmoking baseline (HR), level of intoxication (HIGH) and carboxyhemoglobin boost (COHb) determined for 3.95% marijuana to those determined for 1.77% marijuana (3.95% MJ:1.77% MJ).

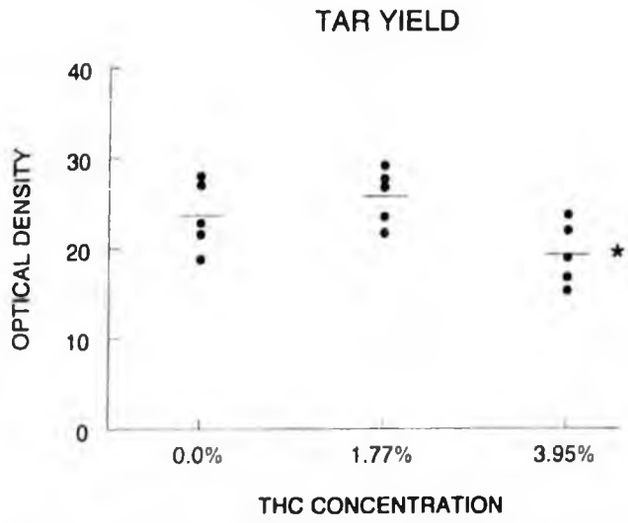

FIG. 3. Individual values for amount of tar (O.D.) in mainstream smoke generated from five 0.0%, five 1.77% and five 3.95% marijuana cigarettes using a syringe with a 50-ml puff volume, 2-s duration and 30-s interpuff interval to butt lengths of 25 mm. Horizontal lines represent mean values. *$p < 0.05$ (compared with 1.77% and 0% THC).

The average tar yield from the 3.95% marijuana cigarette was 19.3 ± 1.6 (SEM) optical density (O.D.) units, which was significantly lower ($p < 0.05$) than the tar yields from both the 1.77% preparation (25.2 ± 1.4 O.D.) and the 0% preparation (23.5 ± 1.6 O.D.).

DISCUSSION

The major findings from this study are that, in a small number of healthy, habitual marijuana smokers asked to smoke different strengths of marijuana to a desired level of intoxication, the amount of tar delivered to and deposited in the lung from the most potent marijuana preparation tested was significantly reduced compared to that of less potent preparations, despite the lack of demonstrable overall differences in smoking topography, including cumulative puff volume, across the different strengths of marijuana (Table 1). In contrast, no difference in COHb boost was observed between more and less potent marijuana cigarettes, while THC delivery and lung retention were significantly greater for 3.95% than 1.77% marijuana, as reflected in a significantly greater heart rate increase ($p < 0.01$) following the 3.95% than the 1.77% preparation (Table 1).

Differences in THC delivery and the related physiological responses to smoking marijuana of different strengths were found despite instructions to the subjects to smoke only to their desired level of intoxication. Possible reasons for the observed differences in THC delivery are 1) that subjects were generally unable to "titrate" THC delivery to achieve a uniform "high" from the 1.77 and 3.95% marijuana cigarettes; or 2) that their desired level of intoxication was greater than that which could be achieved with the weaker of the two active marijuana preparations under the conditions of the experiment, in which they were constrained to smoking only a single marijuana cigarette. In favor of the former possibility is that maximum levels of intoxication were not attained in the majority of subjects (7 of 10) until at least 5 min, and in some subjects (4 of 10) as long as 15 min, after completion of smoking, thus compromising their ability to self-titrate intake of smoke (and thus THC) based on levels of "high" perceived during active smoking. On the other hand, it is still possible that adjustments could be made during smoking with the expectation of delayed peak "highs" based on previous experience. The alternative possibility, namely that the single 1.77% preparation was insufficient, even if consumed to the maximum extent tolerable, to produce the desired level of intoxication, appears inconsistent with the finding that mean butt lengths of the smoked 1.77% and 3.95% marijuana cigarettes were nearly identical (19.3 mm and 19.0 mm, respectively). On the other hand, in 3 of the 10 subjects, butt lengths of the 1.77% marijuana cigarette were substantially shorter than those of the 3.95% preparation and, in 2 additional subjects, both preparations were nearly completely consumed (butt lengths 2–4 mm). Therefore, the possibility remains that in this subset of subjects the weaker of the two active preparations was insufficient to yield the desired level of intoxication, even when smoked to a relatively short butt length, in the absence of access to more than one marijuana cigarette.

The observation that the amount of tar deposited in the lung tended to be reduced for 3.95% marijuana compared to 1.77% marijuana (Table 1 and Fig. 1) is difficult to explain solely on the basis of differences in smoking topography, because smoking topography, including the variables that have been found to correlate best with the amount of tar delivered to and retained in the lung (cumulative puff volume and breathholding time) (13) were, on average, nearly identical for both the higher and lower strengths of active marijuana. Smoking marijuana down to a longer butt length would be expected to decrease tar delivery partly due to the increased filtration through the longer shaft of the cigarette (14); because average butt lengths were similar for the two active strengths of marijuana that were studied, however, this factor could not have accounted for the generally lower tar delivery from the more potent cigarette. On the other hand, considerable interindividual variability was observed in the 3.75:1.77% marijuana ratios both for tar delivery and deposition and for cumulative puff volume and breathholding time (Fig. 2). For the most part, those subjects who exhibited lower cumulative puff volumes when they smoked 3.95% marijuana than 1.77% marijuana also deposited lower amounts of tar in their lungs when they smoked the more potent preparation. A similar relationship between breathholding time and respiratory tar delivery for the two active strengths of marijuana was not observed. These observations suggest that, at least in some subjects, the reduced tar delivery to the lung from the higher potency marijuana preparation might be accounted for, at least in part, by adjustments in smoking technique that result in a lower cumulative puff volume.

Reduced tar delivery from more potent marijuana cigarettes could also occur if the actual tar yield from stronger preparations were reduced relative to that from the same quantity of weaker preparations, when smoking technique was standardized. To evaluate this possibility, we measured the amount of tar in mainstream smoke generated from the different strengths of marijuana cigarettes using a standardized in vitro smoking technique. As shown in Fig. 3, the average tar yield from the 3.95% marijuana cigarette was significantly lower ($p < 0.05$) than the tar yields from both the 1.77% and the 0% preparations. Consequently, a reduced tar yield from stronger preparations of marijuana might contribute, at least partly, to less delivery of tar to the lung. On the other hand, no difference was noted between the tar yields of the 0 and 1.77% preparations, so that a linear relationship between the potency of a marijuana cigarette and its tar yield was not apparent over the entire range of potencies (0.00–3.95% THC) of the preparations that we tested. Data from a recent preliminary Australian study on the relative yields of condensed particulate matter (tar) and THC from different samples of seized marijuana ranging in potency from 0.57 to 13.0 % (mean 3.42%; median 1.8%) (Hall, W., National Drug and Alcohol Research Centre, Kensington, Australia; Personal Communication) show a weak relationship between THC content and tar yield for preparations with THC concentrations ≤2.5% and inconsistently lower tar yields for the few preparations tested with THC concentrations >5%. Consequently, had we been able to evaluate the influence of smoking marijuana cigarettes with THC concentrations >5%, we might have found greater reductions in respiratory tar delivery than we demonstrated in the present study for 3.95% compared to 1.77% marijuana.

Mainstream smoke from marijuana or tobacco is a highly concentrated aerosol of liquid particles that is formed by complex chemical reactions, including hydrogenation, pyrolysis, oxidation, decarboxylation, dehydration, chemical condensation, distillation, and sublimation (15). The smoke aerosol is composed of a large variety of organic and inorganic chemicals dispersed in a gaseous medium of nitrogen, oxygen, hydrogen, carbon dioxide, carbon monoxide, and a number of volatile and semivolatile organic chemicals. The tar phase consists of total particulate matter minus water and contains a

number of constituents, including tumor initiators, carcinogens, and cocarcinogens that contribute to the health hazards of smoking. Several factors influence the tar yields of tobacco cigarettes (15) that might also be relevant to marijuana. These include plant genetics and growth conditions that affect chemical composition and physical properties of the leaf, moisture content, the curing and fermentation process, burning temperature, the quality of the cigarette paper (e.g., porosity), and the presence or absence of a filter. Which of these factors may be responsible for the apparently lower tar yield from more potent preparations of marijuana is unclear.

The mean percentage of inhaled tar deposited in the lung in the present study from marijuana cigarettes of different potency (80.7–86.9%) is similar to that previously reported from our laboratory from 0.00 and 1.24% marijuana cigarettes (84.4–86.1%) and higher than that deposited from tobacco cigarettes (64.0%) (16). The greater percentage deposition of inhaled tar from marijuana than tobacco cigarettes is attributable to the longer breathholding time characteristic of marijuana smoking compared to tobacco smoking (13,16). The similarity in mean breathholding times observed in the present study during the smoking of marijuana cigarettes of different strengths (Table 1) is consistent with the comparability in mean percentage of delivered tar that was deposited in the lung across the different potencies of marijuana.

In summary, in a small number of habitual marijuana users studied during the smoking of single marijuana cigarettes of varying potency up to a maximum THC concentration of 3.95%, adjustments of smoking topography to the different strengths of marijuana were highly variable between subjects. Under the conditions of the experiment (limited maximum potency of marijuana and a limit of a single cigarette), smokers generally appeared unable to titrate THC delivery to achieve a uniform "high," so that the level of intoxication and heart rate were often more increased after smoking cigarettes of higher than lower potency. Tar delivery from 3.95% marijuana was reduced relative to that from 1.77% marijuana in 3 of 10 subjects, and the reduction in tar delivery appeared to be related to reduced intake of smoke (lower cumulative puff volume) in these few subjects, as well as to the reduced tar yield during combustion of the stronger marijuana preparation. COHb boost was not affected by the potency of the marijuana smoked. We conclude that, compared to lower potency marijuana cigarettes, stronger preparations appear to lead to a modest reduction in exposure of the lung to tar in some smokers but not to carbon monoxide. We did not assess the influence of varying THC content on the respiratory delivery of volatile constituents other than carbon monoxide in the gas phase of marijuana smoke, some of which are known to be biologically hazardous. Although it is possible that relatively reduced exposure to carcinogenic components in the tar phase of marijuana from smoking cigarettes with a higher THC content might reduce the carcinogenic risk of marijuana smoking, the true health implications of these findings are as yet unclear.

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"The Limited Relevance of Drug Policy: Cannabis in Amsterdam and San Francisco"

Craig Reinarman, Peter Cohen, and Hendrien Kaal
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The Limited Relevance of Drug Policy: Cannabis in Amsterdam and in San Francisco

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Objectives. We tested the premise that punishment for cannabis use deters use and thereby benefits public health.

Methods. We compared representative samples of experienced cannabis users in similar cities with opposing cannabis policies—Amsterdam, the Netherlands (decriminalization), and San Francisco, Calif (criminalization). We compared age at onset, regular and maximum use, frequency and quantity of use over time, intensity and duration of intoxication, career use patterns, and other drug use.

Results. With the exception of higher drug use in San Francisco, we found strong similarities across both cities. We found no evidence to support claims that criminalization reduces use or that decriminalization increases use.

Conclusions. Drug policies may have less impact on cannabis use than is currently thought. (*Am J Public Health.* 2004;94:836–842)

There is a trend among Western democracies toward liberalization of cannabis laws. (Cannabis includes both marijuana and hashish.) In 1976, the Netherlands adopted de facto decriminalization. Under Dutch law, possession remains a crime, but the national policy of the Ministry of Justice is to not enforce that law. After 1980, a system of "coffee shops" evolved in which the purchase of small quantities of cannabis by adults was informally tolerated and was then formally permitted in shops that were licensed.[1–3] During the 1990s, Switzerland, Germany, Spain, Belgium, and Italy shifted their drug policies in the Dutch direction. Portugal decriminalized cannabis in 2001, and England similarly reclassified cannabis in 2004. Canada and New Zealand are currently considering cannabis decriminalization. These shifts constitute the first steps away from the dominant drug policy paradigm advocated by the United States, which is punishment-based prohibition.[4–6]

Moving in the opposite direction, the United States has stiffened criminal penalties for drug offenses and has increased arrests for cannabis offenses. Since 1996, voters in 8 states and the District of Columbia have passed medical-marijuana initiatives, but the federal government has resisted implementation. In 2001, 723 627 people were arrested for marijuana offenses.[7] In 2002, the Drug Enforcement Administration began raiding medical-marijuana organizations,[8] and the White House Office of National Drug Control Policy launched a campaign against marijuana.[9,10]

Such policies are designed to deter use. The core empirical claim made by criminalization proponents is that, absent the threat of punishment, the prevalence, frequency, and quantity of cannabis use will increase and will threaten public health.[11–16] The question of whether deterring use enhances public health was beyond the scope of our study, but we did examine the proposition that drug policies affect user behavior and deter use. It is possible that the causal arrow points the other way—that user behavior affects laws and policies, which has been the case with alcohol policies in some countries.[17] However, the Marijuana Tax Act of 1937, which first criminalized cannabis, predated widespread cannabis use in the United States and had clear political origins.[18–21] In the Netherlands, de facto decriminalization of cannabis was first forged in the late 1960s, when use was spreading among the youth counterculture. But Dutch policymakers decided that cannabis use was unlikely to lead to deeper deviance and that criminalization could lead to greater harm to users than the drug itself.[3] In neither country, then, was user behavior the effective cause of laws or policies.

The presumed effects of cannabis policies have been explored by those who are critical of criminalization in the United States[22] and by those who are skeptical of Dutch decriminalization.[23] However, until now there have been no rigorously comparative studies of user behavior designed to assess whether criminalization constrains use or whether decriminalization increases it. Our study compared the career use patterns of representative samples of experienced cannabis users in 2 cities with many similarities but with different drug-control regimes—Amsterdam, the Netherlands (decriminalization), and San Francisco, Calif (criminalization).

San Francisco was selected as the US comparison city not because it is representative of the United States but because it is the US city most comparable to Amsterdam. Both cities are large, highly urbanized port cities with diverse populations of slightly more than 700 000. They are financial and entertainment hubs for larger regional conurbations, and they have long been perceived within their home countries as cosmopolitan, politically liberal, and culturally tolerant.

Law enforcement officials in San Francisco are not as zealous about enforcing marijuana laws as law enforcement officials are in most other US cities. Nonetheless, San Francisco is embedded in the drug policy context of criminalization, which is a markedly different drug policy context than that of Amsterdam. Buying and selling cannabis are permitted in Amsterdam in 288 licensed "coffee shops,"[24] and public use is permitted, whereas in San Francisco, buying, selling, and public use of marijuana remain criminal offenses. In Amsterdam, there is neither proactive nor reactive policing of use or low-level sales, although police do enforce regulations against coffee shops' advertising, selling to minors, and creating public nuisances.

In San Francisco, there is strong proactive and reactive policing of sales, and there is moderate reactive policing of use.

These differences in drug policy context are palpable to users. San Francisco students are suspended from schools and are placed in treatment for marijuana use. San Francisco users risk citations, fines, and arrests if they are detected buying, possessing, or using marijuana. In Amsterdam, users face none of these risks. The use and sale of other illicit drugs sometimes used by cannabis users is proactively policed in San Francisco. In Amsterdam, police occasionally engage in reactive policing of complaints about open use or sale of other drugs, but they do not proactively patrol in search of these offenses.

METHODS

We required not merely a random sample of cannabis users but a random sample of users who had enough experience (defined as at least 25 episodes of use during their lifetimes) to answer questions about career use patterns. In Amsterdam, recruitment of users began as part of a drug-use prevalence survey of the general population. This survey was administered to a random sample that was obtained from Amsterdam's Municipal Population Registry. The overall response rate was 50.2%, which yielded a sample of 4364.[25] (The response rate was slightly below the 55% response rate of a 1990 iteration of the survey. Sampling details and an extensive response/nonresponse study can be found in Sandwijk et al.[24] or at http://www.cedro-uva.org/lib.) Comparisons of responders with nonresponders and with known city demographic data indicated no need for weighting. All respondents who reported having used cannabis at least 25 times (n=535; 12.3%) were asked to participate in an in-depth interview about their cannabis use. Of these 535 experienced users, 216 (40.5%) were interviewed in 1996.[26]

This modest response rate necessitated a check of representativeness. We compared the 216 users who responded with the 319 who did not on 12 demographic and drug-use prevalence variables. Respondents had slightly higher levels of formal education and slightly higher past-year prevalence of cannabis use,[26,27] but otherwise, they showed no differences compared with nonrespondents and thus were reasonably representative of experienced cannabis users in the general population. Homeless and institutionalized persons were not interviewed for either survey.

Beginning in 1997, the Amsterdam survey of experienced cannabis users was replicated in San Francisco, where there is no population registry. To remain consistent with Amsterdam, we first drew an area probability sample by randomly selecting census tracts, blocks, buildings, households, and adults within households. We administered a brief prevalence survey containing demographic and drug-use prevalence questions. Unlike the Amsterdam prevalence survey, which was an extensive study in its own right, the brief prevalence survey in San Francisco was principally designed to generate a random representative sample of experienced cannabis users.

The overall response rate of the San Francisco prevalence survey was 52.7%, which yielded a sample of 891.[28] Of these respondents, 349 reported that they had used cannabis 25 or more times (39.2% of the population sample and 3 times the prevalence found in the Amsterdam sample) and were asked to participate in the in-depth interview; 266 (76.2%) respondents were ultimately interviewed in depth about their career use patterns. As a check on their representativeness, respondents were compared with nonrespondents on 10 demographic and drug-use prevalence variables. No statistically significant differences were found.

The Dutch questionnaire was translated for use in San Francisco. Non-English-speaking Asian Americans were excluded because of the prohibitive costs of translating instruments and training interviewers in the many Chinese and other Asian languages found in San Francisco. This exclusion was not consequential, because national prevalence studies show that illicit drug use among Asian Americans is the lowest of any ethnic group.[29] Also, non-English speakers are mostly elderly and are thus least likely to be cannabis users. However, the instruments were translated into Spanish, and bilingual interviewers conducted interviews when necessary. Homeless and institutionalized persons were not interviewed.

RESULTS

Age at Onset, First Regular Use, and Maximum Use

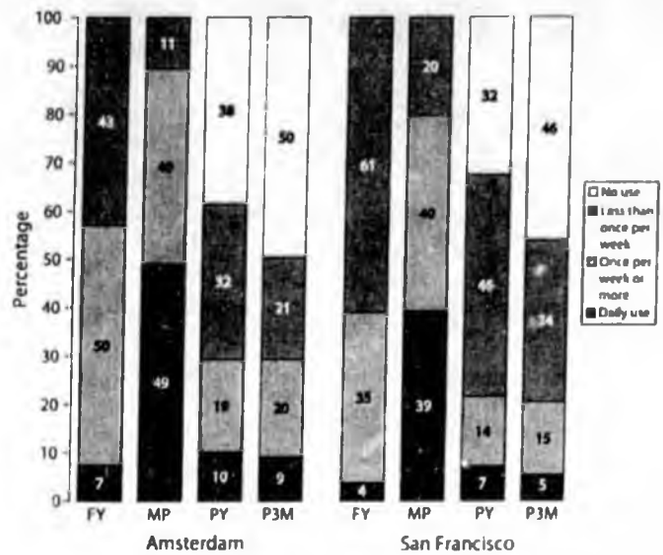
The mean age at onset of cannabis use was nearly identical in both cities: 16.95 years in Amsterdam and 16.43 years in San Francisco. The mean age at which respondents commenced regular use (≥once per month) also was nearly identical: 19.11 years in Amsterdam and 18.81 years in San Francisco. The mean age at which respondents in both cities began their periods of maximum use was about 2 years after they began regular use: 21.46 years in Amsterdam and 21.98 years in San Francisco. Clear majorities in both cities reported periods of maximum use of 3 years or less.

Cannabis Use Patterns Over Time

We asked about the frequency and the quantity of use and the intensity and the duration of intoxication. To assess how these dimensions of use may have changed over time, we asked about each for 4 periods: first year of regular use (≥once per month), maximum-use period, past year (12 months before the interview), and past 3 months (3 months before the interview).

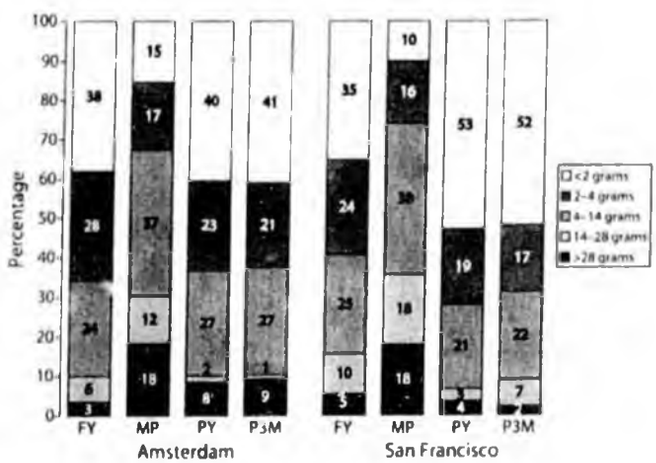
Frequency of use. Figure 1 shows the frequency of reported marijuana use for these 4 periods; the overall pattern is similar across both cities. During first year of regular use, strong majorities reported use of cannabis once per week or less, whereas small percentages reported daily use. Frequency increased during the period of maximum use but declined sharply thereafter. Amsterdam respondents reported more frequent use than did San Francisco respondents during their first year of regular use ($t=4.019$; $df=479$; $P=.000$) and during their period of maximum use ($t=2.979$; $df=479$; $P=.003$). When the maximum-use period was compared with the past year, daily use declined from 49% to 10% in Amsterdam and from 39% to 7% in San Francisco. This decline was even greater for the past 3 months.

The basic trajectory of frequency of use across careers was parallel in both cities. Most users reported a maximum-use period of 2 to 3 years, after which the vast majority sharply reduced their frequency of use or stopped al-



Note. FY = first year of regular use (≥ once per month); MP = maximum-use period; PY = past year; P3M = past 3 months.
[a]All respondents.

FIGURE 1—Frequency of cannabis use for 4 periods, by city (%).[a]



Note. FY = first year of regular use (≥ once per month); MP = maximum-use period; PY = last year; P3M = past 3 months.
[a]Respondents who still used at time of survey, for past year and past 3 months.

FIGURE 2—Average quantity of cannabis used per month (%).[a]

together. Roughly three fourths of the respondents in each city reported that they had used cannabis less than once per week or not at all in the year before the interview.

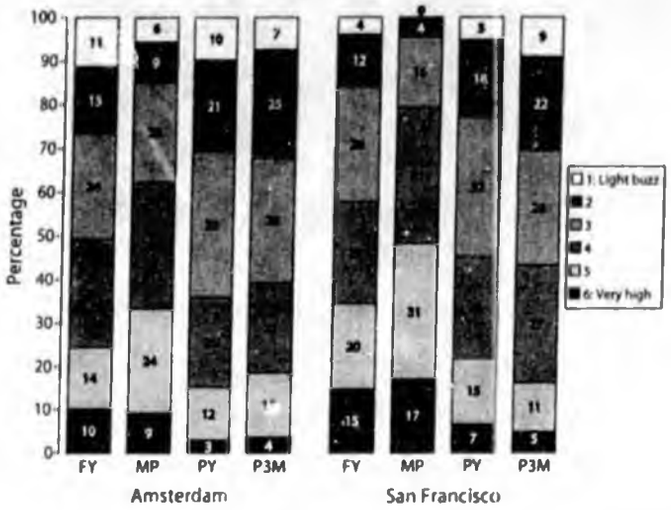
Quantity of use. Figure 2 shows that in the first year of regular use, few respondents in either city consumed large quantities of cannabis. Only 3% in Amsterdam and 5% in San Francisco used 28 grams (approximately 1 ounce) during an average month. Amsterdam respondents used significantly smaller quantities than did San Francisco respondents during this period. When the 2 smallest categories were combined, two thirds in Amsterdam (66%) and slightly less in San Francisco (59%) were found to have consumed 4 or fewer grams per month during their first year of regular use. More than one third used less than 2 grams per month during their first year of regular use—38% in Amsterdam and 35% in San Francisco.

Quantities consumed during maximum-use periods were larger and very similar across the cities. About two thirds of respondents consumed an average of 14 or fewer grams per month—69% in Amsterdam and 64% in San Francisco. Less than 1 in 5 respondents in each city (18%) consumed an average of 28 grams per month or more during their maximum-use periods.

During the year before the interview, consumption among those who still used cannabis declined sharply. Clear majorities used 4 or fewer grams per month, although this proportion was smaller in Amsterdam (63%) than in San Francisco (72%) ($t = 2.207$; $df = 297$; $P = .028$). About 1 in 3 respondents in each city reported no use. Overall, the patterns were parallel in both cities; quantities used increased from first regular use through maximum use but then quantities used declined steadily or use ceased altogether over the course of the respondents' careers.

Intensity of intoxication. Respondents were asked to estimate "how high or how stoned you generally got" when they consumed cannabis. Some recalled this occurence with greater consistency than did others, but all of them were able to make basic ordinal distinctions between more- and less-intense highs. To increase reliability of respondents' estimates, we displayed a 6-point scale ranging from "light buzz" (1) to "very high" (6) and asked them to select the number that best summarized their highs during each period.

Figure 3 shows that respondents in both cities generally increased the intensity of their highs during periods of maximum use but moderated their highs thereafter (past-year and past-month figures exclude those who had quit). Amsterdam respondents were significantly more likely than San Francisco respondents to report milder intoxication during the first year of regular use and during maximum-use periods: mean scores for the first year were 3.5 in Amsterdam and 3.9 in San



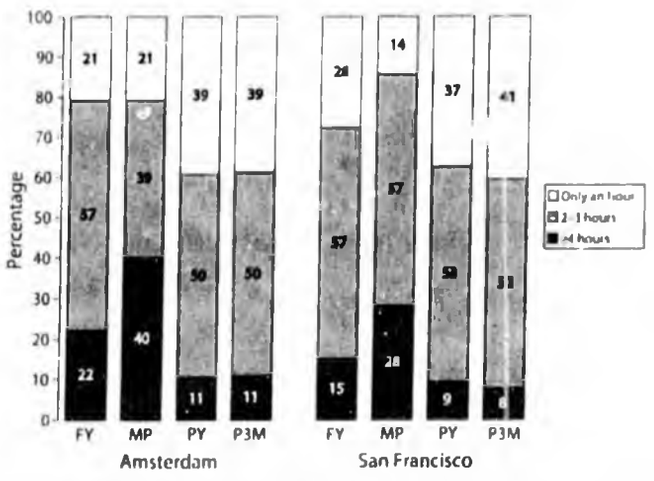
Note. FY = first year of regular use (≥ once per month); MP = maximum-use period; PY = past year; P3M = past 3 months.
[a]Respondents who still used at time of survey, for past year and past 3 months.

FIGURE 3—Intensity of intoxication during typical occasion of cannabis use (%).[a]

Francisco ($t = -3.180$; $df = 476$; $P = .002$), and these scores rose for maximum-use periods to 3.9 and 4.4, respectively ($t = -4.932$, $df = 413$; $P = .000$).

The same pattern was found for the more recent periods, although the mean scores declined. The proportion of respondents who chose 6 (very high) remained small and was between 3% and 7% in both cities. For highs experienced during the past year, Amsterdam respondents were again more likely to report milder intoxication ($t = -2.233$; $df = 310$; $P = .026$). For the past-3-month periods, majorities in both cities reported milder highs of 1 to 3 on the 6-point scale. In short, respondents in both cities reported less intoxication with use over the course of their careers.

Duration of intoxication. We also asked "about how long" respondents were high during a typical occasion of cannabis use. Reported durations were correlated with frequency and with quantity but were not a function of frequency and quantity alone. Here, too, we found a tendency toward moderation over the course of users' careers in both cities. Figure 4 shows that Amsterdam respondents reported highs of somewhat longer duration than reported by respondents in San Francisco during the first year of regular use ($t = 2.329$; $df = 476$; $P = .020$). (One reviewer noted a divergence between San Francisco respondents, who reported more intense highs during 3 of the 4 periods, and Amsterdam respondents, who reported highs of longer duration during 1 period. Because we found no reason to suspect that either sample played up or played down their responses to any of the questions, this divergence may indicate culture-specific consumption styles or cultural grammars of intoxication.[30,31]) However, during the other 3 time periods there were no significant differences: in each city, a clear majority of users regulated their ingestion so that highs lasted 2 to 3 hours or less. Substantial minorities in each city reported being high for 4 or more hours during maximum-use periods, but these proportions dropped sharply after those periods. Of those who used cannabis during the 3 months before the interview, 89% in Amsterdam and 93% in San Francisco reported being high for 2 to 3 hours or less.



Note. FY = first year of regular use (≥ once per month); MP = maximum-use period; PY = past year; P3M = past 3 months.
[a]Respondents who still used at time of survey, for past year and past 3 months.

FIGURE 4—Duration of high during a typical occasion of cannabis use (%).[a]

Overall Career Use Patterns

We also asked respondents to characterize their overall career use patterns. We presented a typology of trajectories[12] and asked them to identify the 1 that "best describes" their cannabis use over time (Table 1).

Two career use patterns were dominant in both cities. Pattern 4—gradual increased use followed by sustained decline—was the most common (49.4% of the combined sample). The second most common was Pattern 6—wide variation over time (24.4% of the combined sample). Patterns 1, 2, 3, and 5 were each selected by only 6% to 8% of the com-

TABLE 1—Trajectories of Overall Career Use

Pattern	Amsterdam, No. (%)	San Francisco, No. (%)
1: declining	17 (7.9)	18 (6.8)
2: escalating	13 (6.0)	17 (6.4)
3: stable	24 (11.1)	5 (1.9)
4: increase/decline	104 (48.1)	133 (50.4)
5: intermittent	7 (3.2)	25 (9.5)
6: variable	51 (23.6)	66 (25.0)
Total	216 (100.0)	264 (100.0)

Note. $\chi^2 = 24.047$; $df = 5$; $P = .000$. Pattern names listed as shown to respondents.

TABLE 2—Prevalence of Other Illicit Drug Use, Lifetime and During the Past 3 Months

	Amsterdam ($n = 216$)		San Francisco ($n = 264$)		Significance $\chi 2$	
	LTP	P3MP	LTP	P3MP	LTP	P3MP
Cocaine	48.1	9.3	73.2	7.5	*	NS
Crack	3.7	0.5	18.1	1.1	*	*
Amphetamines	37.5	1.9	60.4	4.5	*	NS
Ecstasy	25.5	9.3	40.0	6.4	*	NS
Opiates	21.8	0.5	35.5	2.7	*	*

Note. LTP = lifetime period; P3MP = past 3 months; NS = not significant.
*Too few cases in cells to compute statistical test.
*$P < .001$.

bined sample. Pattern 3—stable use from the beginning onward—was selected significantly more often by Amsterdam respondents (11.1%) than by San Francisco respondents (1.9%), whereas Pattern 5—intermittent use (many starts and stops over time)—was selected significantly more often by San Francisco respondents (9.5%) than by Amsterdam respondents (3.2%).

These findings are consistent with findings on frequency and quantity of use and intensity and duration of intoxication, and they have important public health implications. Claims that cannabis produces addiction or dependence[13–15] lead one to expect that many experienced users would report Pattern 2—escalation of use over time. But this pattern was reported by only 6% in both cities, which means that 94% of respondents had overall career use patterns that did not entail escalation across careers.

Other Illicit Drug Use

Another important question about the effects of drug policies concerns the use of other illicit drugs. The "separation of markets," in which lawfully regulated cannabis distribution reduces the likelihood that people seeking cannabis will be drawn into deviant subcultures where "hard drugs" also are sold is one public health objective of Dutch decriminalization.[1–3] The reduction of cannabis use and thereby the reduction of the extent to which it serves as a "gateway" to "harder" drugs is one public health objective of US criminalization.[11,12,14,16]

Users who had ingested cannabis 25 times or more during their lifetimes were far more prevalent in San Francisco than in Amsterdam, and the same was true for users of other illicit drugs. Table 2 shows a significantly lower lifetime prevalence of other illicit drug use in Amsterdam than in San Francisco. During the 3 months before the interview, prevalence of crack and opiate use also were significantly higher in San Francisco, but cocaine, amphetamine, and ecstasy use were not significantly different. Thus, rates of discontinuation—the decline from lifetime prevalence to prevalence during the past 3 months—were somewhat higher in San Francisco for cocaine, amphetamine, and ecstasy; however, rates of discontinuation were high (64%–98%) for all drugs in both cities.

DISCUSSION

Proponents of criminalization attribute to their preferred drug-control regime a special power to affect user behavior. Our findings cast doubt on such attributions. Despite widespread lawful availability of cannabis in Amsterdam, there were no differences between the 2 cities in age at onset of use, age at first regular use, or age at the start of maximum use. Either availability in San Francisco is equivalent to that in Amsterdam despite policy differences, or availability per se does not strongly influence onset or other career phases.

We also found consistent similarities in patterns of career use across the different policy contexts. Although a few significant differences were found in some dimensions of use during some career phases, the basic trajectory was the same in both cities on all dimensions of use: increasing use until a limited period of maximum use, followed by a sustained decrease in use over time or by cessation. It is significant, from a public health perspective, that clear majorities of experienced users in both cities never used daily or used large amounts even during their peak periods, and that use declined after those peak periods. Furthermore, both samples reported similar steady declines in degree and duration of intoxication. Only 6% in each city reported escalation of use over time.

We expected differences in drug policies to affect the duration of cannabis-use careers and the rates of cessation. Criminalization is designed to decrease availability, discourage use, and provide incentives to quit. Decriminalization is said to increase availability, encourage use, and provide disincentives to quit. Thus, we expected longer careers and fewer quitters in Amsterdam, but our findings did not support these expectations. Cannabis careers ranged from 1 to 38 years, and 95% of respondents in both cities reported careers of 3 years or longer. The mean career length was slightly greater in San Francisco (15 years) than in Amsterdam (12 years), but this finding was mostly because of the somewhat higher mean age in the San Francisco sample (34 years vs 31 years). Similarly, nearly identical proportions of respondents in each city had quit by the time they were interviewed—33.8% in Amsterdam and 34.3% in San Francisco.

If drug policies are a potent influence on user behavior, there should not be such

strong similarities across such different drug control regimes. Our findings do not support claims that criminalization reduces cannabis use and that decriminalization increases cannabis use. Moreover, Dutch decriminalization does not appear to be associated with greater use of other illicit drugs relative to drug use in San Francisco, nor does criminalization in San Francisco appear to be associated with less use of other illicit drugs relative to their use in Amsterdam. Indeed, to judge from the lifetime prevalence of other illicit drug use, the reverse may be the case.

Our study has limitations and should be replicated in other cities over longer periods. While our findings share the limitations of all self-report studies (e.g., vague or selective memory, over- or understatements of fact), we attempted to minimize these limitations by means of carefully worded questions, extensive pretesting, and use of multiple measures. The questionnaire is available under *questionnaire* at http://www.cedro-uva.org/lib/cohen.canasd.html. Our comparable samples and measures helped isolate the effects of drug policies, but "all else" is not necessarily "equal." Cultural and social conditions in the United States are different from in the Netherlands; therefore, cannabis use might increase if the United States were to adopt a Dutch approach. Further studies that examine prevalence before and after policy shifts would be illuminating, although previous studies of the impact of marijuana decriminalization among 11 US states during the 1970s found no increases.[33–36]

One hypothesis for future research is that with a widely used drug like cannabis, the informal social controls that users develop as part of their culture[30,31,37–39] have more powerful regulatory effects on their behavior than do formal social controls such as drug policies. This possibility emerged from responses to questions about the circumstances respondents found appropriate for cannabis use. In both cities, relaxation was the most common purpose of use, and majorities from both cities reported that they typically used cannabis with friends and at social gatherings. Majorities in both cities most often mentioned work or study as situations in which use was inappropriate. In both cities, 69% reported negative emotional states as unsuitable for cannabis use, and 80% reported having advised novices about the virtues of moderation.

CONCLUSIONS

These data suggest that most experienced users organize their use according to their own subcultural etiquette—norms and rules about when, where, why, with whom, and how to use—and less to laws or policies. When experienced users abide by such etiquette, they appear to regulate their cannabis use so as to minimize the risk that it will interfere with normal social functioning. This pattern suggests that if formal drug policies are based on the folk (informal) drug policies users themselves already practice, drug policies may achieve greater relevance. ■

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Contributors

C. Reinarman assisted in conceiving the study and analyzing the data. H.L. Kaal composed the figures and the tables that form the core of the data analysis. P.D.A. Cohen proposed the study, led its conceptualization, designed and supervised the data analysis, and assisted with writing the article.

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Human Participant Protection

This protocol was approved by all relevant institutional review boards and funding agencies.

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"Long-term effects of exposure to cannabis"

Leslie Iversen

Current Opinion in Pharmacology, 2005, 5:69-72

ELSEVIER

Long-term effects of exposure to cannabis

Leslie Iversen

The long-term use of cannabis, particularly at high intake levels, is associated with several adverse psychosocial features, including lower educational achievement and, in some instances, psychiatric illness. There is little evidence, however, that long-term cannabis use causes permanent cognitive impairment, nor is there is any clear cause and effect relationship to explain the psychosocial associations. There are some physical health risks, particularly the possibility of damage to the airways in cannabis smokers. Overall, by comparison with other drugs used mainly for 'recreational' purposes, cannabis could be rated to be a relatively safe drug.

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Abbreviations
THC Δ^9-tetrahydrocannabinol

Introduction

Cannabis is the most commonly used illicit drug. In many countries, more than 50% of young people have used it at least once and it is widely perceived as relatively safe. Many people believe that there are genuine medical uses for cannabis-based medicines and it seems likely that such products will gain official approval in several Western countries. Concurrently, there is a move towards relaxation of the criminal penalties associated with the recreational use of cannabis — ranging from the down-grading of criminal penalties in the UK to the possibility of full legalization in Canada and Switzerland. In light of these changes in attitude, it is timely to consider again the adverse effects associated with long-term cannabis use over a period of years, as no drug can ever be considered completely safe.

Effects on cognition

Several studies have addressed the question of whether severe deficits in cognitive function develop in chronic heavy users of cannabis, or in animals treated for prolonged periods with the drug. Most reports have shown that there are deficits in the performance of complex cognitive tasks in long-term cannabis users, although there is little evidence that these are qualitatively or quantitatively more severe than those seen after acute drug use [1].

More controversial is the question of whether long-term cannabis use can cause irreversible deficits in higher brain function that persist after drug use stops. Human studies are fraught with difficulties, as described in detail by Earleywine [1]. Indeed, many studies have suffered from poor design. One confounding factor in human studies is that comparisons have to be made between groups of drug users versus non-users; however, it is usually impossible to compare the baseline performance of these groups before cannabis use to see if they are properly matched. Pope *et al.* [2], for example, tested 69 early-onset heavy cannabis users (who began smoking before the age of 17) in a battery of neuropsychological tests after a two-week period of abstinence. The group performed significantly worse than late-onset users or controls, but also displayed a lower verbal IQ. When the data were adjusted for this, all differences between early-onset users and others ceased to be significant.

It is not sufficient to identify a group of cannabis users and simply to test them after stopping cannabis use. One study, for example, recruited 63 current heavy users who had smoked cannabis at least 5000 times in their lives and 72 control subjects [3]. The subjects underwent a 28-day washout from cannabis use, monitored by urine assays. At days 0, 1 and 7, the heavy users scored significantly below control subjects on a battery of neuropsychological tests, particularly in recall of word lists. However, by day 28, there were no differences between the groups in any of the test results, and no significant association between cumulative lifetime cannabis use and test scores. The fact that drug-induced effects on cognitive performance can persist for up to a week after stopping the drug (perhaps because of the persistence of Δ^9-tetrahydrocannabinol [THC] in the body, or because of a subtle withdrawal syndrome) means that many earlier studies that did not allow a sufficiently long washout period might be invalid.

One way of assessing cognitive function is to measure IQ. Fried *et al.* [4] tested the effects of cannabis use in a group of 70 young people by subtracting each person's IQ score at nine years of age (before drug use) from their score at age 17-20 years. Current cannabis use was found to be significantly correlated in a dose-dependent manner with a decline in IQ scores. However, no such decline was seen

in subjects who had formerly been heavy cannabis users and had stopped taking the drug. The authors concluded that cannabis does not have a long-term effect on global intelligence.

This general conclusion was also supported by a review of the 40 published studies that met adequate criteria, which failed to detect any consistent evidence of persisting neuropsychological deficits in cannabis users — although some studies reported subtle impairments in the ability to learn and remember new information [5].

Cannabis and psychiatric illness

There has been a long-standing concern that cannabis use might precipitate mental illness in some users. It is clear that an acute schizophrenia-like psychosis can occur in response to a high dose of cannabis [6•], but whether cannabis use can cause persistent psychiatric illness in people who had not previously shown psychotic symptoms remains contentious. A recent re-analysis of the results of a large scale study of >50 000 Swedish men (age 18–20 years) conscripted into the Swedish army between 1969 and 1970 suggested that those who had used cannabis >50 times before the age of 18 years had a 6.7-fold increased risk of developing schizophrenia in later life [7]. A review of this and four other longitudinal cohort studies also concluded that early cannabis use might be a causal factor for schizophrenia-like illness in later life [8••]. However, the interpretation of such studies is fraught with many difficulties, as reviewed by Macleod *et al.* [9••]. These authors highlighted that proof of a causal relationship is subject to many confounding factors. When known confounding factors were applied to the Swedish army data, for example, the odds ratio was reduced from 6.7 to 3.1 [7]. This, in turn, suggests that other residual unidentified confounding factors are also likely to exist. The published studies show that the existence of 'prodromal' symptoms of psychosis clearly increased the risk of subsequent psychiatric illness in cannabis users [8••]. This factor was adequately controlled for in only one of the five published longitudinal studies [10]. In this New Zealand cohort, even when those exhibiting prodromal symptoms of psychosis were eliminated, those who started cannabis use by age 15 years (but not those who started later) showed a fourfold increase in the risk of developing schizophrenia-like illness by age 26 years. However, the number of subjects involved was small (there were 26 15-year old cannabis users, of whom three developed mental illness) so the statistical power of this study was limited. Degenhardt *et al.* [11] sought to test the hypothesis of a causal relationship between cannabis use and schizophrenia by a careful examination of the incidence of schizophrenia in Australia during the past 30 years. Although the prevalence of cannabis use had increased markedly during this period, there was no evidence of a significant increase in the incidence of schizophrenia. The question of whether cannabis use can precipitate psychiatric illness in a vulnerable minority of previously well people remains unanswered. One could equally argue that a tendency to psychotic illness might increase the likelihood of early cannabis use [9••]. It is possible that cannabis may precipitate schizophrenic illness earlier in vulnerable people who exhibit 'schizophreniform' tendencies. Such a conclusion is supported by the results of a study of 122 newly admitted schizophrenia patients in the Netherlands, which showed a strong association between cannabis use and the age of onset of the first psychotic episode in men, with users experiencing their first psychotic episode 6.9 years earlier than non-users [12].

Other studies have explored the association between cannabis use and depression. One longitudinal study in Australia reported that daily use of cannabis by teenage girls (but not boys) led to an approximately twofold increased risk for depression/anxiety in later life [13]. A review of other studies of this type suggested that heavy cannabis use may increase depressive symptoms in some users, but whether this represents a causal relationship is again unclear [14].

Psychosocial sequelae of cannabis use

Apart from the potential risk of mental illness, there has been a long standing concern that adolescent use of cannabis could lead to reduced educational achievement and reduced motivation — sometimes referred to as an 'amotivational syndrome' [1].

Cherek *et al.* [15] attempted to assess this experimentally in a study in which human participants earned money by responding on a complex lever-pressing schedule. There was a significant reduction in the number of responses, time spent and money earned when the subjects were re-tested while smoking cannabis, indicating a drug-induced reduction in motivation.

Various longitudinal studies have sought to establish the relationship between cannabis use and subsequent educational achievement. A study of 1265 New Zealand children [16] showed that cannabis use was dose-dependently related to an increased risk of leaving school without qualifications, failure to enter university and failure to obtain a university degree. A similar conclusion was reached in reviews of other published studies of this type [9••,17]. The review by Macleod *et al.* [9••] was particularly comprehensive; the authors studied 48 published longitudinal studies on the use of cannabis, of which 16 were considered to provide the most robust evidence. Their conclusions for cannabis use were, firstly, a consistent association with reduced educational achievement; secondly, a consistent association with use of other drugs; thirdly, an inconsistent association with psychological problems of various types; and finally, an inconsistent association with antisocial or other

problematic behaviours. They concluded that "Available evidence does not support an important causal relation between cannabis use and psychosocial harm, but cannot exclude the possibility that such a relation exists".

Whatever the nature of the association, it seems clear that long-term heavy cannabis use carries a variety of negative attributes. A case control study compared 108 heavy-use long-term cannabis users, who had on average smoked 18 000 times, with 72 age-matched controls who had smoked cannabis <50 times [18••]. The heavy-use cannabis smokers reported significantly lower educational attainment and lower income than did controls. When asked to rate the subjective effects of cannabis on cognition, memory, career, social life, physical and mental health and various quality-of-life measures, a large majority of heavy-use cannabis smokers reported negative effects of their drug use.

Cannabis and substance dependence

Although it was previously thought that cannabis was not a drug of addiction, it is now recognized that cannabis use can lead to substance dependence in perhaps as many as 10% of regular users, according to the internationally accepted DSMIV definition of 'substance dependence' [6•]. In both animals and humans, a clear withdrawal syndrome can be identified [6•]. In rodents, chronic administration of THC or synthetic cannabinoids leads to downregulation and desensitization of cannabinoid CB_1 receptors in the brain [19]. This might partly explain the tolerance that develops in both animals and humans on repeated use of the drug. In regular cannabis users, abstinence leads to a withdrawal syndrome characterized by negative mood (irritability, anxiety, misery), muscle pain, chills, sleep disturbance and decreased appetite. A placebo-controlled study showed that these symptoms were significantly reduced by oral administration of THC, suggesting that the withdrawal syndrome and underlying substance dependence were related to effects of THC on the cannabinoid CB_1 receptor, rather than to any other component of herbal cannabis [20].

Other potentially toxic effects of long-term cannabis use

Some of the most serious adverse effects of smoked cannabis are on the respiratory system. Although little progress has been made recently in quantifying such risks, warnings continue to be issued about the potential for long-term damage or even malignancy in the airways [21]. It is known that lung macrophages isolated from cannabis smokers exhibit impaired anti-bacterial activity, and one experimental study showed that this might be caused, in part, by reduced expression of inducible nitric oxide synthase and decreased production of nitric oxide [22]. A review of the evidence for immunosuppressant effects of cannabis concluded that, with the exception of the effects of cannabis smoking on broncho-alveolar immunity, there is no evidence that cannabis causes any other serious immunosupression in users [23]. The authors suggested that the effects on lung macrophages might be related to the ability of cannabis in animal studies to cause a shift from Th1 to Th2 cytokine production.

With increasing use of cannabis, there remains a concern that cannabis use during pregnancy might impair foetal development. Reviews of data from humans, however, suggest that such effects are minimal for cannabis users when compared with the well-documented adverse effects of tobacco or alcohol use [24,25•]. Nevertheless, treatment of pregnant rats with high doses of THC did lead to significant reductions in expression of neural adhesion molecule L1 in the foetal brain — a key protein for brain development [26].

Conclusions

A review of the literature suggests that the majority of cannabis users, who use the drug occasionally rather than on a daily basis, will not suffer any lasting physical or mental harm. Conversely, as with other 'recreational' drugs, there will be some who suffer adverse consequences from their use of cannabis. Some individuals who have psychotic thought tendencies might risk precipitating psychotic illness. Those who consume large doses of the drug on a regular basis are likely to have lower educational achievement and lower income, and may suffer physical damage to the airways. They also run a significant risk of becoming dependent upon continuing use of the drug. There is little evidence, however, that these adverse effects persist after drug use stops or that any direct cause and effect relationships are involved.

In contrast, cannabis might have beneficial effects in some medical indications. There is considerable literature obtained from animal studies to suggest that cannabis has analgesic effects [27]. Until recently, however, there has been a dearth of controlled clinical studies to validate such effects in patients. This has now changed, with the publication in the past two years of a number of double-blind placebo-controlled trials showing the effectiveness of cannabinoids in relieving chronic neuropathic pain [28,29] or pain associated with multiple sclerosis [30••, 31]. The largest of these trials involved 630 multiple sclerosis patients and showed significant pain relief after 15 weeks of treatment with either pure THC or cannabis extract [30]. It seems likely that medicinal cannabis will re-enter the Pharmacopoeia.

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"The good and the bad effects of trans-delta-9-tetrahyrdocannabinol on humans"

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Review

The good and the bad effects of (−) *trans*-delta-9-tetrahydrocannabinol (Δ^9-THC) on humans

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Abstract

This review analyses the therapeutic usefulness of Δ^9-tetrahydrocannabinol and its potential to induce adverse reactions on humans. During the last 30 years an enormous amount of research was carried out resulting in the disclosure of the cannabinoid system in Central Nervous System, with its CB_1 and CB_2 receptors, and the agonist anandamide. Under the clinical point of view, Δ^9-THC produces some therapeutic benefits which are beyond reasonable doubt. Thus, the effects on nausea/emesis due to cancer chemotherapy, as appetite promoter, on some painful conditions and on symptoms of multiple sclerosis are clearly demonstrated.

Δ^9-THC is not devoid of ill effects. On the cognitive domain it impairs the human capacity to discriminate time intervals and space distances, vigilance, memory and the performance for mental work. On the psychic area Δ^9-THC may induce unpleasant reactions such as disconnected thoughts, panic reactions, disturbing changes in perception, delusions and hallucinatory experiences. However, the long term effects on the psyche and cognition are not known as there are no reports of prolonged use of Δ^9-THC. Actually, it has been proposed by WHO that Δ^9-THC should be rescheduled to schedule IV of the United Nations Convention on Psychotropic Drugs, as it does not constitute a substantial risk to public health and its abuse is rare if at all.

Keywords: Δ^9-THC; Dronabinol dependence; Abstinence; Multiple sclerosis; Nausea and vomiting; Appetite promoter

Contents

In an interesting review article on the history of cannabis use as a medicine—*The Forgotten Medicine*—by Aitken and Mikuriya (1980), two quotations deserve attention: "in 1890 Dr J. Russel Reynolds, Physician in Ordinary to Queen Victoria wrote: Indian hemp, when pure and administered carefully, is one of the most valuable medicines we possess;" and "quote from the Egyptian Government's Annual Report on Narcotics, 1944: Cannabis is a thoroughly vicious drug, deserving the odium of civilized people"

Very few drugs, if any, have such a tangled history as a medicine. In fact, prejudice, superstition, emotionalism and even ideology have managed to lead cannabis to ups and downs concerning both its medicinal properties and its toxicological and dependence-inducing effects. However, several breakthroughs occurred during the last 50 years and, consequently, the situation is now settled, at least partially, in that cannabis and its main active principle Δ^9-THC may actually be valuable medicines and the plant cannabis is not a 'thoroughly vicious drug'.

Delta-9-tetrahydrocannabinol, or 6a, 7, 8, 10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6*H*-dibenzo[*b*,*d*]-pyran-1-ol, is a substance possessing several stereochemical variants. One of them is (−)-*trans*-delta-9-tetra-hidrocannabinol, also called dronabinol or Δ^9-THC.

It was isolated, identified and synthesized in the 1960s (Gaoni and Mechoulam, 1964). The identification of several other cannabinoid compounds were also achieved in

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the following years. Among them the isomer Δ^8-THC which is, however, less potent than Δ^9-THC (Karniol and Carlini, 1973).

Almost three decades later, cannabinoid receptors in the brain were described (for reviews see Howlett, 1995; Childers and Breivogel, 1998; Pertwee, 1997, 1999), their cloning were achieved (Rinaldi-Carmona et al., 1996) and anandamide, the endogenous cannabinoid, was isolated and identified (Devane et al., 1992; Mechoulam et al., 1998a; Martin et al., 1999). Several analogs of anandamide were synthesized and structure-activity relationships were established (Mechoulam et al., 1998b).

All accomplishments concerning the chemistry of marihuana constituents and the description of an endogenous cannabinoid system were accompanied by a great deal of research on cannabinoid pharmacology and opened up opportunities to resume clinical research with these substances, mainly Δ^9-THC.

1. Beneficial effects (therapeutic effects) of Δ^9-THC

Much of the research carried out more recently in several countries dealt with old therapeutic folk uses of marihuana (Consroe et al., 1975; Mechoulam and Carlini, 1978; Mechoulam et al., 1984), such as the possible anti-epileptic and hypnotic properties of Δ^9-THC and cannabidiol, the latter a non-hallucinogenic cannabis constituent (Cunha et al., 1980; Carlini and Cunha, 1981). Other therapeutic indications such as anti-emetic, as antispasmodic, as analgesic, in glaucoma, as hypnotic, in asthma, in epilepsy, as appetite stimulant, as anxiolytic, and in Tourette syndrome, deserved also pre-clinical and clinical studies (Nakano et al., 1978; Ilaria et al., 1981; Musty, 1984; Sethi et al., 1986; Ashton, 1999; Ashton, 2001; Williamson and Evans, 2000; Söderpalm et al., 2001; Robson, 2001; Müller-Vahl et al., 2002).

For a few therapeutic indications Δ^9-THC produce beneficial clinical results that are beyond reasonable doubt (for review articles see Formukong et al., 1989; Mechoulam et al., 1998a; Williamson and Evans, 2000; Robson, 2001; Grotenhermen and Russo, 2002; Iversen, 2003). In the present review article four of them will be approached, namely, the (Δ^9-THC) effects on nausea/vomiting, on appetite, on pain and on symptoms of multiple sclerosis.

One such clinical indication refers to the anti-emetic effect in cases of chemotherapy-associated nausea and emesis. The first randomized, double-blind placebo-controlled trial was that of Sallan et al. (1975) showing that Δ^9-THC was more effective than placebo in controlling nausea/vomiting of cancer patients receiving chemotherapy. The control of emesis afforded by Δ^9-THC far exceeds that provided by prochlorperazine (Orr et al., 1980); it abolishes totally or partially the nausea and vomiting refractory to standard anti-emetic agents in 72% of patients (Lucas and Laszlo, 1980).

Poster et al. (1981) reviewed seven well-controlled studies on the subject; in six of them Δ^9-THC was a superior anti-emetic compared to control agents. These authors also concluded that toxic effects were manageable and suggested that THC use represents a major advance in anti-emetic therapy. In a more recent review (Tramèr et al., 2001) on the anti-emetic effect of cannabis compounds, involving 1366 cancer patients participating in 30 randomized studies, it was shown that cannabinoids act slightly better than alizapride, chloropromazine, haloperidol, domperidone, metoclopramide, prochlorperazine and thiethylperazine in crossover trials. These patients selected cannabinoids for future chemotherapy (Tramèr et al., 2001). Very successful treatment for nausea and vomiting was also reported by Musty and Rossi (2001). These authors examined the reports obtained from six American States, which conducted clinical trials on 748 cancer patients who smoked marihuana, and 345 patients who used oral Δ^9-THC. Both treatments promoted, respectively, 70–100% and 76–88% relief from nausea and vomiting.

The beneficial effects of Δ^9-THC on nausea/vomiting are partially counterbalanced by the adverse reactions reported by the patients such as drowsiness, apprehension and anxiety, dry mouth, etc. It is possible that such undesirable side effects may be minimized by simultaneous administration Δ^9-THC and cannabidiol, as observed in healthy subjects (Karniol et al., 1974; Zuardi et al., 1982).

Another clinical indication that is well established refers to the appetite promoter effect of marihuana and of cannabinoids (Hollister, 1971; Mechoulam and Carlini, 1978; Mattes et al., 1994). It is a clinical fact that HIV patients are prone to severe weight loss due to anorexia (Clebowski et al., 1989); Δ^9-THC improved appetite in these patients, and consequently brought also a betterment of their nutritional status and of other symptoms such as improving mood and decreasing nausea (Struwe et al., 1993; Beal et al., 1995, 1997). The anorexia-cachexia associated with cancer may also be counteracted by Δ^9-THC (Ekert et al., 1979; Gorter, 1991; Plasse et al., 1991). In fact, the promotion of appetite in marihuana smokers is a well-known fact (Foltin et al., 1988); therefore it is not surprising that Δ^9-THC has been considered as an effective appetite stimulant drug in cancer patients (Regelson et al., 1976).

An interesting corollary of these findings is the recent demonstration of the potent anorectic effect in obese animals of the substance SR 141716, an antagonist of the cannabinoid receptor CB_1 (Colombo et al., 1998; Mechoulam and Fride, 2001; Cota et al., 2003; Vickers et al., 2003).

It has also been shown in rats that cannabinoid antagonists may prevent the relapse of cocaine use (De Vries et al., 2001; Piomelli, 2001) and the self-administration of methamphetamine (Vinklerová et al., 2002).

According to Grotenhermen (2002a) the effects of cannabinoids on painful conditions of several aethiologies are relatively well confirmed. In fact, several recent review articles analysed anedoctal reports and controlled clinical trials on the analgesic effect of Δ^9-THC and other cannabinoids in painful conditions such as cancer, damaged nerves, migraine, post-operative pain, spinal cord injury, dental pain, phantom limb pai etc. (Noyes et al., 1975; Formukong et al., 1989; Ashton, 1999; Williamson and Evans, 2000; Robson, 2001; Holdecroft, 2002; Vaughan and Christie, 2002). The very ancient use of marihuana smoking as a headache and migraine medicament, reviewed by Russo (1998, 2001), adds support to the contention that Δ^9-THC and other cannabinoids are indeed active in alleviating pain.

In general, all the reports and trials analysed in the above mentioned reviews acknowledge that Δ^9-THC does indeed have analgesic properties which, according to some authors, approximately matches that of codeine. However, side effects such as sedation, dizziness, ataxia, blurred vision, tachycardia, psychological disturbances as anxiety and fear near panic states, may limit its use. Nevertheless, it also should be taken into consideration that these side effects are not life threatening as those from opiates, which also produce an array of adverse reactions.

Recently, Campbell et al. (2001) reviewed 20 randomized control led trials, nine from those being analyzed; a total of 222 patients participated in five trials on cancer pain, two on postoperative pain and two on chronic non-malignant pain. They concluded that the analgesic effects of cannabinoids were as effective as 50–120 mg of codeine.

The effects of *Cannabis sativa* L. on muscle spasticity, tremors, and neuropathic pain are known since at least the 19th century; in fact, famous physicians of that time, such as W. O'Shaughnessy in India and J.R. Reynolds in England (the personal physician of Queen Victoria), were enthusiastic prescribers of Indian Hemp (Aitken and Mikuriya, 1980; Robson, 2001; Grinspoon and Bakalar, 1993). Near 150 years later, Consroe et al. (1997), through interviews with 112 multiple sclerosis (MS) patients, confirmed the striking improvement (according to the patient's reports) afforded by cannabis smoking on MS symptoms such as the relief of chronic pain, night-time spasticity, tremor, impaired balance and trigeminal neuralgia associated with the disease.

Results obtained with clinical trials employing Δ^9-THC in MS patients are consistent with the claims of the Consroe's respondents (1997). Thus, Petro and Ellenberger (1981); Clifford (1983); Ungerleider et al. (1987); Meinck et al. (1989); Maurer et al. (1990); Brenneisen et al. (1996), reported that MS patients receiving Δ^9-THC presented improvements in tremor, ataxia, spasticity, nocturia and in well-being; adverse reactions as disphoria, headache, dry mouth, a 'high' sensation were also described.

On the other hand, at least two studies did not confirm these beneficial effects. In one of them (Killenstein et al., 2002) Δ^9-THC not only was unable to reduce spasticity, but also worsened the MS patients global impression; Greemberg et al. (1994), on the other hand, found that marihuana smoking further impaired the posture and balance in MS patients.

However, any possible doubts that might exist on whether or not Δ^9-THC is an useful medicine for MS symptoms, were removed by the results obtained in four very recent randomized, double-blind, placebo-controlled trials (Anonymous, 2002a, b). In these studies, 344 patients suffering from MS and neuropathic pain received a cannabis extract containing Δ^9-THC and cannabidiol (CBD) as its principal components; the medicine was delivered by mean of a spray into the mouth. The four studies evaluated the effects of the Δ^9-THC/CBD mixture on, respectively; neuropathic pain (66 patients), chronic refractory pain due to MS (70 patients), general symptoms of MS (160 patients), and pain due to brachial plexus injury (48 patients). In all the four studies a statistically significant improvement in the symptomatology and an excellent safety profile were obtained which could in part be due to the self-titration of the dose by the patients (Anonymous, 2002b). A first detailed study on this striking beneficial effect of Δ^9-THC/CBD mixture on the multiple sclerosis symptomatology has been published very recently (Wade et al., 2003): 24 patients obtained great relief from pain; bladder control, muscle spasms and spasticity were also improved. Side effects were predictable and well tolerated.

This lack of side effects could also be due to fact that cannabidiol is able to block anxiety and other ill effects of Δ^9-THC (Karniol et al., 1974). In conclusion it can be said that the statement by Drs Hare and Chrystie (1892) more than 100 years ago ('Cannabis is very valuable for the release of pain, particularly that depending on nerve disturbances; it produces sleep, it gives great relief in paralysis and tends to quiet tremors...') was finally proved to be correct.

2. Adverse effects of Δ^9-THC

Cannabis sativa L. was and is the most used drug by human beings for hedonistic purposes (UNODC, 2003). And even so, until the recent past, it was not considered as a potent inducer, if at all, of dependence in humans, this being due to the way dependence was defined in the past (Swift and Hall, 2002). However, with the adoption of the DSM-III and other similar criteria to define dependence, there have been recent reports stating that a certain proportion of chronic marihuana users may become dependent (Anthony et al., 1994; Budney et al., 2001; Swift et al., 2001a, b). Another point deserving attention is the very low incidence of ill effects under chronic use. For example,

Russo et al. (2002) described four patients who participated in a Compassionate Investigational New Drug (IND) Program of the American FDA, smoking standardized, heat-sterilized quality-controlled low grade marihuana cigarettes, for 11–27 years. Aside from mild changes in pulmonary function observed in two patients, no other physiological and neurological disturbances were found.

When the subject comes to Δ^9-THC, the dependence issue becomes clearer. Due to the enormous progress in chemistry, pharmacology, toxicology and clinical pharmacology of Δ^9-THC, leading to its clini ' usefulness, the United Nations in 1991 changed the status of Δ^9-THC, by removing it from Schedule I (use only for research purposes) and placing it in Schedule II (medical use allowed under strict control of production, trade and stocks) of the 1971 Convention on Psychotropic Drugs. Abstinence symptoms, after being exposed to rather large doses of Δ^9-THC (80–210 mg/day) were observed in humans participating in clinical laboratory experiments (Jones et al., 1981; Haney et al., 1999). However, according to the WHO Expert Committee on Drug Dependence, abuse of Δ^9-THC is rare (WHO, 2003); thus, from 103 countries responding a WHO questionnaire, only two indicated some abuse of Δ^9-THC: Denmark and USA. Actually, the United States informed that only three cases of Δ^9-THC abuse during the 1992–1994 period were reported by the American Association of Poison Control Centers. In this context it is rather interesting that anandamide has little if any capacity to induce abstinence symptoms and physical dependence in rats (Aceto et al., 1998).

Based on these facts, the WHO Expert Committee on Drug Dependence further considered that the abuse liability of Δ^9-THC does not constitute a substantial risk to public health and proposed that Δ^9-THC should be rescheduled to schedule IV of the United Nations 1971 Convention on Psychotropic Substances (WHO, 2003).

Δ^9-THC does not cause prominent physical changes in users; some degree of dry mouth, blurred vision and ataxia may be reported, and objectively, an increase in heart rate occurs (Carlini et al., 1974).

Δ^9-THC may adversely affect the psyche, cognition and the psychomotor performance of humans. Examples of acute effects on cognitive functions are: impairment and even loss of the capacity to discriminate or to produce time and distance intervals (Karniol and Carlini, 1973; Carlini et al., 1974; for review see Grotenhermen, 2002b). Thus, volunteers receiving 5–20 mg of Δ^8 or Δ^9-THC delivered through inhalation perpetrated gross errors when producing a time interval of 60 s; this unwanted effect was present up to at least for 20 min after the cannabinoids aspiration (Karniol and Carlini, 1973). Other ill effects are a decrease of vigilance, of the ability to inhibit responses and to perform arithmetic tasks (for reviews see Leweke, 2002; Iversen, 2003).

Among the psychic effects of acute administration of Δ^9-THC are feelings of well being, relaxation and anxiolysis; users may also suffer unpleasant reactions, such as disconnected thoughts, panic reactions, feelings of depersonalization, disturbing changes in perception, delusions and hallucinatory experiences (for reviews see Campbell et al., 2001; Leweke, 2002).

The long-term effects of Δ^9-THC on the psyche, cognition and brain structures of human beings are not yet, known, as there are not reports of prolonged use of Δ^9-THC. Thus, there is no mention in the scientific literature of an 'motivational syndrome' caused by the cannabinoid; furthermore it is worth mentioning that even for chronic marihuana use there is no conclusive evidence for the occurrence of this syndrome (Hall and Solowij, 1997; Hollister, 1998; Solowij and Grenyer, 2002; Iversen, 2003).

Similarly, there are no data in scientific literature reporting neuropathological changes in the brain of Δ^9-THC users; actually, such changes have not been convincingly demonstrated in the brain of marihuana users (for review see Iversen, 2003).

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6.

THE HEALTH AND PSYCHOLOGICAL EFFECTS...

"The health and psychological effects of cannabis use"

Wayne Hall, et al.
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Glossary

Term	Definition
Acute effects	The immediate, short-term effects of using a drug
AIDS	Acquired Immune Deficiency Syndrome
Allogenic lymphocytes	Cell types that induce distinct immune responses from an organism
AMA	Australian Medical Association
Amotivational syndrome	A pattern of behaviour characterised by a lack of motivation, energy and initiative
Analgesic	A drug which reduces pain
Anandamide	A natural cannabinoid found in the brain
Anorexia	Significant loss of weight, which can affect HIV patients
Antagonist	A substance that blocks the positive effects of a drug
Anti-emetic	A drug that reduces nausea and vomiting
ARGT	Australian Register of Therapeutic Goods
Asphyxiation	Choking, suffocation
BMA	British Medical Association
Burden of disease	The effect that a disorder has upon society measured by the years of life lost and amount of disability it causes
Cachexia	Significant loss of lean body mass such as skeletal muscle, which can affect cancer and HIV patients
Cannabinoids	Chemicals that act upon the same receptor sites in the brain as THC
Cannabis	All forms of the product of the *cannabis sativa* plant
Carcinogen	A substance that causes cancer
Cardiac arrhythmias	Irregular heart rhythms that can be fatal
Cardiomyopathy	General term for diseases of the heart muscle
CB1 and CB2	Two types of receptors found in the cannabinoid system
CBD	Cannabidiol, a cannabinoid without the psychoactive effects of THC
CD&SA	The Canadian Controlled Drug and Substances Act

Cerebrovascular disease	Atherosclerosis of the arteries in the brain that can lead to stroke: damage caused in the brain by blood clot or other obstruction interrupting the flow of blood and hence of oxygen to the brain
Chronic effects	The longer-term effects of drug use that may occur if drug use is continued over months or years
Cisplatin	Drug used to treat prostate bladder, ovary, head and neck cancers
Cohort	Any designated group of persons who have been exposed to some event (e.g. use of cannabis)
Cohort study	A study design in which people who have and have not been exposed (e.g. to cannabis) are followed up to see how many develop a disease
COPD	Chronic obstructive pulmonary disease
Coronary atherosclerosis	A disease in which deposits of cholesterol and fats form block the arteries that supply the heart muscle. It may lead to a 'heart attack'
Cross-over study design	Study in which participants received two or more treatments without their knowledge to see whether they respond differently to them
Cross-sectional study	A study design in which the health status and risk factors of a sample are assessed at one point in time e.g. a survey
DAWN	The US Drug Abuse Warning Network
DEA	The US Drug Enforcement Administration
Dependence (drug)	A disorder in which persons experience loss of control over drug use, and continue to use the drug despite the problems it causes them (see pp 75-76 for criteria)
DHHS	The US Department of Health and Human Services
Dopamine	A chemical that acts as a neurotransmitter in the brain
Double blind study	A study in which neither the patient nor the treating physician know whether the patient is receiving an active or placebo drug
Dronabinol	Synthetic THC, which is taken orally in a capsule with sesame oil
Dysphoria	Unhappy mood (as opposed to euphoria)
Emesis	Nausea and vomiting
Emetogenic	Causing vomiting and nausea

Endogenous cannabinoids	Cannabinoids that naturally occur in the brain, such as anandamide
Epidemiological research	Research that studies the occurrence of disease or risk factors for disease in the general population
Epilepsy	A disorder in which abnormal brain electrical activity causes seizures
Experimental study	A study design in which exposure to a key factor is under the researcher's control, e.g. when two groups of people are randomly assigned to receive a drug or a placebo
F&DA	The Canadian Food and Drugs Act
FAS	Foetal alcohol syndrome
FDA	The US Food and Drug Administration
Foetal alcohol syndrome (FAS)	Condition that results from a foetus being exposed to alcohol; it is marked by decreased alertness, hyperactivity, intellectual disability, motor problems, heart defects and facial abnormalities
Glaucoma	A disease caused by raised intra-ocular pressure that, if untreated, can cause blindness
Histopathological	Abnormality of the structure of bodily tissues
HIV	The Human Immunodeficiency Virus which causes AIDS
Humoral	Pertaining to the blood or the fluids of the body
Huntington's disease	A movement disorder caused by a dominant gene, producing pathological brain changes, including in areas controlling movement
Hypertension	High blood pressure
Hypomania	A condition in which people are energetic and have elevated mood
Illicit drugs	Drugs which adults are prohibited from using by law
Immunosuppressive	Anything (e.g. a drug, radiation, viral infection) that suppresses the functioning of the body's immune system
INCB	The United Nations' International Narcotics Control Board
IND	A program of the FDA that allows patients with serious or life-threatening diseases to use experimental drugs
IOM	Institute of Medicine, US

IOP	Intra-ocular pressure; pressure within the eyeball
Longitudinal study	A synonym for a cohort study
Lower brainstem	Areas of the brain including the cerebellum that control movement and respiration
Marijuana	Leaves and flowering tops of the *cannabis sativa* plant
Ma. inol	The trade name for dronabinol
Metabolites	Chemical products of a drug that are produced when it is processed in the body
Mitogens	Substances that induce cell transformations
MS	multiple sclerosis
mutagen	an agent or substance that induces genetic mutation in cells
Nabilone	A synthetic drug that has similar effects to THC
Narcotic	A legal term for drugs prohibited by international drug treaties that includes opioids, cocaine and cannabis
NCR	The Canadian Narcotic Control Regulations
NDA	An investigational New Drug Application, one step in the process in the US for approving drugs for medical use
Negative symptom	In schizophrenia, absence of a behaviour ordinarily seen in 'normal' people, such as initiative
NIDA	The US National Institute on Drug Abuse
n-of-1 clinical trial	Trial in which a single patient receives a drug and a placeb and their behaviour is measured under double blind conditions
NORML	The US National Organization for Reform of Marijuana Legislation
Odds ratio	A ratio of the odds of disease in persons who are and are not exposed to some factor. It measures the strength of the association between the factor and the disease
ONDCP	The US Office of National Drug Control Policy
Organic symptoms	Symptoms that are ascribed to physical (organic) causes
Pancreatitis	Acute or chronic inflammation of the pancreas
Parkinson's disease	A movement disorder that results from damage to area of the brain involved in movement control

Pharmacopeia	A book containing a list of products used in medicine, with descriptions, tests for purity and identity, and dosages
Placebo	An inactive drug that is indistinguishable in appearance from the active drug with which it is being compared
PLWHA	Association for People Living With HIV/AIDS
Positive symptoms	In schizophrenia, presence of a behaviour not seen in 'normal' people, such as hallucinations and delusions
Premorbid	A person's behaviour or personality prior to the onset of an illness
Prevalence	The number of cases of an illness or disease that are present in the total population in a specified period of time e.g. a year
Prodromal	In schizophrenia, symptoms that precede the onset of the illness
Prospective study	A synonym for a cohort study
Psychoactive drug	A drug that affects feeling, memory and thinking
Psychomotor	Having to do with voluntary movement
Psychostimulants	Drugs that have stimulating effects and increase psychomotor activity
Psychotomimetic drugs	Drugs that produce symptoms of psychosis, such as visual hallucinations, delusions and distorted perception
R&D	Research and development
RACP	Royal Australian College of Physicians
Randomised controlled trial	A clinical trial to evaluate a treatment in which participants are randomly assigned to receive an active drug or a placebo
RCT	Randomised controlled trial
Relative risk	A ratio of the rate of disease among persons exposed to a factor (e.g. cannabis use) and the rate among those who are not exposed
Resorption	To absorb again (from the Latin meaning 'to suck back')
Retrospective study	A study design in which exposure to a risk factor (e.g. drug use in adolescence) is determined retrospectively (e.g. by asking an adult about their drug use in early adolescence)
SAP	The Canadian Special Access Program

SCOST	House of Lords Select Committee on Science and Technology
Stress-diathesis model	A model of schizophrenia in the disorder is precipitated among vulnerable individuals (those with the diathesis) by life stressors
Temporal lobe	An area on either side of the brain that is involved in memory and emotion
Teratogen	A substance that produces abnormalities in a foetus during its development in the uterus
TGA	The Australian Therapeutic Goods Administration
THC	Delta-9-tetrahydrocannabinol, the principal psychoactive ingredient of cannabis
Titrate	To measure the dose of a drug against its effects
Tourette's syndrome	A movement disorder that results from damage to area of the brain involved in movement control
Toxic psychotic disorder	A psychosis caused by high doses of a drug or other substance
TPP	The Canadian Therapeutic Products Programme
Viscous	A substance that is sticky or glutinous

Executive summary

This review of the health and psychological effects of cannabis updates an earlier review (commissioned by the National Task Force on Cannabis in 1992) in the light of recent research and reviews by the World Health Organization (1997) and the US Institute of Medicine (1999).

Assessing the health effects of cannabis

There are a number of reasons why it is difficult to evaluate the health risks of using cannabis or any drug. First, it is difficult to decide whether use of a drug causes an adverse effect on human health when there is a long interval between its use and the appearance of the adverse effect. It takes time for such adverse effects to develop and for research to identify them.

Second, there is a trade off between the rigour and relevance of different types of evidence when making causal inferences. The most rigorous evidence is provided by laboratory investigations using animals or cell preparations in a test tube in which known drug doses can be related to measured biological outcomes. The relevance of this evidence to human disease is uncertain. Epidemiological studies of relationships between drug use and human disease are of greater relevance but the increased relevance is obtained at the cost of reduced rigour. Doses of illicit drugs used over periods of years are difficult to quantify because of the varied dosages of blackmarket drugs and stigma in admitting to illicit drug use. Interpretation is complicated by the fact that regular cannabis users often also use alcohol, tobacco and other illicit drugs.

The criteria for causal inference that we use are the standard ones: (1) evidence that there is a relationship between cannabis use and a health outcome provided by one of the accepted types of research design (namely, case-control, cross-sectional, cohort, or experiment); (2) evidence provided by a statistical test or confidence interval that the relationship is unlikely to be due to chance; (3) good evidence that drug use precedes the adverse effect (e.g. from a cohort study); and (4) evidence either from experiment, or observational studies with statistical or other form of control, that it is unlikely that the relationship is due to some other variable which is related to both cannabis use and the adverse health effect.

In the trade-off between relevance and rigour, we give more weight to human clinical and epidemiological evidence. In the absence of human evidence, animal experiments raise a suspicion that cannabis use has an adverse effect on human health. The degree of suspicion is in proportion to: the number of studies; the consistency of results across different species; and the degree of expert consensus on the extent to which findings in animals predict adverse effects in humans considering current patterns of cannabis use.

Cannabis the drug

Cannabis is the name for preparations from the plant *Cannabis sativa*. Laboratory research on animals and humans has demonstrated that the primary psychoactive constituent in cannabis is delta-9-tetrahydrocannabinol, abbreviated as THC. THC is found in a sticky resin that covers the flowering tops and upper leaves in the female plant.

The cannabinoid receptor

Cannabis acts upon specific receptors or molecules in the brain and immune system. These receptors are found in areas of the brain that underlie the psychoactive and other effects of cannabis use. Two 'endogenous' or naturally occurring molecules have been discovered in the brain and body which bind to the cannabinoid receptor and mimic the action of THC. These discoveries promise to improve our understanding of the role played by the cannabinoid system in the brain and explain the mechanism of action of cannabis.

Forms of cannabis

The concentration of THC varies between the three forms of cannabis: marijuana, hashish and hash oil. Marijuana is prepared from the dried flowering tops and leaves of the plant. Its potency depends upon the growing conditions, the genetic characteristics of the plant and the proportions of leaves and 'heads'. The flowering tops have the highest THC concentration, with potency decreasing through the upper leaves, lower leaves, stems and seeds. The concentration of THC in marijuana containing mostly leaves and stems may range from 0.5 to 5%, while heads of the 'sinsemilla' variety may have THC concentrations of 7 to 14%. The THC content of cannabis seized in the USA in the past two decades has increased although not to the extent sometimes claimed in the media.

Hashish or hash consists of dried cannabis resin and compressed flowers. The concentration of THC in hashish generally ranges from 2% to 8%. Hash oil is a highly potent and viscous substance obtained by extracting THC from hashish (or marijuana) with an organic solvent. The concentration of the THC in hash oil is generally between 15 and 50%.

Routes of administration

Cannabis is often smoked in a hand-rolled 'joint', like a cigarette. Tobacco is often added to assist burning. Hashish may also be mixed with tobacco and smoked as a joint, but it is probably more frequently smoked in a pipe. A water pipe known as a 'bong' is a popular way of smoking all cannabis preparations because the water cools the hot smoke before it is inhaled and less of the drug is lost through sidestream smoke. A few drops of hash oil may be applied to a cigarette or a joint, to the mixture in the pipe, or the oil may be heated and the vapours inhaled. Cannabis smokers often inhale deeply and hold their breath for several seconds to ensure maximum absorption of THC by the lungs.

Hashish may also be eaten in cooked or baked foods. When swallowed the onset of the psychoactive effects of THC is delayed by about an hour and the 'high' is of lesser intensity although it may last several hours longer. It is easier to achieve the desired level of intoxication by smoking than swallowing cannabis since the effects are more immediate. THC is insoluble in water, so it is rarely injected.

Dosage

A typical joint contains between 0.5 and 1.0 g of cannabis plant matter and between 5 and 150 mg of THC. Between 20% and 70% of the THC is found in the smoke that reaches the lungs; the rest is burnt and lost in sidestream smoke. Only 5% to 24% of THC in the joint reaches the bloodstream when cannabis is smoked.

Only a small amount of cannabis (delivering 2 to 3 mg of THC) will produce a brief high in an occasional user, and a single joint may be enough for two or three such individuals. A heavy cannabis smoker may use five or more joints per day, while heavy users in Jamaica, for example, may consume up to 420 mg THC per day.

Metabolism of cannabinoids

Different methods of using cannabis lead to differing absorption, metabolism and excretion of THC. When smoked, THC is absorbed from the lungs into the bloodstream within minutes. It is first metabolised in the lungs, and then in the liver where it is transformed to a number of metabolites. The first of these, 9-carboxy-THC, is detected in blood within minutes of smoking. When swallowed, THC takes 1 to 3 hours to enter the bloodstream, delaying the onset of psychoactive effects. Another major metabolite, 11-hydroxy-THC, which is 20% more potent than THC and penetrates the brain more rapidly than THC, is found in high concentrations after being swallowed.

THC and its metabolites account for most of the subjective effects of cannabis. Peak blood levels of THC are usually reached within 10 minutes of smoking, and decline to about 5-10% of their initial level within an hour. This rapid decline reflects the rapid conversion of THC to its metabolites and the distribution of THC to fatty tissues, including the brain.

THC and its metabolites are highly fat soluble, so they may remain in the fatty tissues of the body for long periods of time. THC and its metabolites accumulate in the body because of their slow rate of clearance They may be detected in the blood for several days and traces may persist for several weeks. THC may be stored in body fat for more than 28 days.

Detection of cannabinoids in body fluids

Cannabinoid levels in the blood vary between individuals and depend on the dose received and the individual's history of cannabis use. Blood levels of THC may range between 0 to 500 ng/ml, depending on the potency of the cannabis and the time since smoking. The detection of THC in blood above 10 to 15 ng/ml is evidence of recent use, although it is difficult to be precise about how recent. A more precise estimate of time since last use is provided by the ratio of THC to 9-carboxy-THC. Similar blood concentrations of THC and this metabolite indicate that cannabis has been used in the past 20-40 minutes and so suggest a high probability of intoxication, although this is less clear in regular users.

Cannabis intoxication impairs skills required to drive a motor vehicle, so it would be desirable to have a measure of cannabis intoxication similar to the breath test for alcohol intoxication. The major obstacle is the lack of a simple relationship between blood levels of THC (and its metabolites) and degree of psychomotor impairment.

Storage of THC

With repeated frequent dosing of cannabis THC accumulates in fatty tissues in the human body where it may remain for considerable periods of time. The health significance of this storage is unclear. The storage of cannabinoids *would* be serious cause for concern if THC were a highly toxic substance that remained physiologically active while stored in body fat. THC is not a highly toxic substance and it is inactive while stored in fat. Stored cannabinoids could conceivably be released into blood producing a 'flashback', although this is likely to occur very rarely, if at all.

Increasing potency of cannabis?

It has been claimed that the medical literature underestimates the adverse health effects of cannabis because it is based on research conducted on less potent forms of cannabis than have become available in the past decade. The evidence suggests that the average potency of cannabis has increased but not to the extent often claimed. Changes in patterns of cannabis use, with earlier age of first use and more regular use of more potent forms of cannabis, have probably been more important in increasing average dose of THC than any increase in the THC content of cannabis plants.

Patterns of cannabis use

In Australia in 1998, 40% of adults reported that they had used cannabis at some time in their lives. Cannabis is usually smoked in Australia in a water pipe or joint. Survey data from European countries generally shows lower rates of use than in Australia, Canada and the USA. The highest rates of use in Europe are in the United Kingdom, Denmark and France.

In Australia most young people have tried cannabis at some time in their lives. Regular cannabis use is much less common, with most cannabis users using intermittently and discontinuing their use. Males are more likely than females to have ever used cannabis and to have used in the past year or past month. Rates of use are highest in young adults in their early 20s. The natural history of cannabis use, documented in longitudinal studies conducted in the USA, is for use to begin in the mid to late teens, to reach a maximum in the early 20s and to decline in the mid to late 20s. A minority of cannabis users continue to use the drug into their 30s. Cannabis use substantially decreases after marriage and parenthood.

Only a small proportion of cannabis users use the drug for several years or more. The daily or near daily use pattern over a period of years is the pattern with the greatest risk of experiencing adverse health and psychological consequences. Daily cannabis users are more likely to be male and less well educated; they are also more likely to regularly use alcohol and to have experimented with a variety of other illicit drugs including amphetamine and other psychostimulants, hallucinogens, sedatives and opioids.

Acute psychological and health effects

The main reason people use cannabis is to get 'high' that is, to experience euphoria, relaxation, and perceptual alterations, and the intensification of ordinary sensory experiences, such as eating, watching films, and listening to music. The 'high' may be accompanied by infectious laughter and talkativeness. Cognitive effects include impaired short-term memory and a loosening of associations. Motor skills and reaction time are also impaired.

The most common unpleasant effects of cannabis are anxiety, panic reactions, and depressive feelings. These are most common among users who are unfamiliar with the drug's effects, and by patients who have been given THC for therapeutic purposes. Experienced users may occasionally report these effects after swallowing cannabis, as the desired dose is harder to estimate, with the result that the effects may be more pronounced and last longer than those experienced after smoking cannabis. These effects can be managed by reassurance and support. Psychotic symptoms such as delusions and hallucinations may be experienced but only rarely and following very high doses.

A few minutes to a quarter of an hour after cannabis is smoked or swallowed, THC increases heart rate by 20% to 50%. This may last for up to three hours. Blood pressure is increased while the person is sitting and decreases on standing. In healthy young users these cardiovascular effects are unlikely to be of any clinical significance because tolerance develops to the effects of THC, and young, healthy hearts will only be mildly stressed. These effects may pose more of a risk to patients with heart disease.

The acute toxicity of cannabis, and cannabinoids generally, is very low. There are no cases of fatal cannabis poisoning in the human medical literature. Animal studies indicate that the dose of THC required to produce 50% mortality in rodents is extremely high by comparison with other pharmaceutical and recreational drugs. The lethal dose also increases as one moves up the phylogenetic tree, suggesting that the lethal dose in humans could not be achieved by smoking or swallowing cannabis.

Psychomotor effects and driving

Cannabis intoxication impairs a wide range of cognitive and behavioural functions that are involved in driving an automobile or operating machinery. The effects are generally larger, more consistent and more persistent in tasks that require sustained attention. Recreational doses of THC produce similar performance impairments in laboratory tests and standardised driving courses to Blood Alcohol Concentrations of between 0.07% and 0.10%.

It is difficult to estimate how these impairments affect the risk of being involved in motor vehicle accidents. Studies of the effect of cannabis on driving performance on the road have found only modest impairments because cannabis intoxicated drivers drive more slowly, and take fewer risks, than alcohol intoxicated drinkers. Cannabis users seem to be more aware of their psychomotor impairment than alcohol users.

There is currently no controlled epidemiological evidence that cannabis users are more likely than non-users to be involved in motor vehicle or other accidents. This contrasts

with alcohol use where case-control studies show that persons intoxicated by alcohol are over-represented among accident victims.

Cannabinoids are found in between 4% and 37% of blood samples of motor vehicle accident victims but these findings are difficult to evaluate for the following reasons. First, we do not know whether persons with cannabinoids are over-represented among accident victims because we do not know how often cannabinoids are found in the blood of persons who are *not* involved in accidents. Second, cannabinoids in blood indicate recent use but they do not necessarily mean that the driver was intoxicated at the time of the accident. Third, 75% of drivers with cannabinoids in their blood also have high blood alcohol levels, making it difficult to separate the effects of cannabis on accident risk from those of alcohol.

Household survey data suggest that cannabis users are 2 to 4 times more likely to be represented among accident victims than non-cannabis users. Cannabis users who also use alcohol are even more highly over-represented among the victims of motor vehicle accidents. The separate effects of alcohol and cannabis on psychomotor impairment and driving performance are approximately additive.

The effects of chronic cannabis use

Cellular effects and cancers

There is weak evidence that THC can alter cell metabolism and DNA synthesis in the test tube. There is stronger evidence that cannabis *smoke* produces mutations in cells in the test tube and in live animals, and hence is a potential cause of cancer. Cannabis smoke contains many of the same carcinogenic substances as cigarette smoke. If cannabis smoking causes cancer it is most likely to be cancers of the lung and upper aerodigestive tract that are maximally exposed to cannabis smoke.

Aerodigestive tract cancers have been reported among young adults who have been daily cannabis users and a case-control study has found an association between cannabis smoking and head and neck cancer. A prospective cohort study of 64,000 adults did not find an increased incidence of head and neck or respiratory cancers but it found increased rates of prostate cancer. The relative youth of the participants, and their low rates of regular cannabis use, may have reduced the ability of this research to detect an increase in respiratory cancers. Further studies are needed to clarify the issue.

There is much weaker evidence for an increased risk of cancers among children born to women who smoked cannabis during pregnancy. Three studies of very different types of cancer have reported an association with maternal cannabis use. None of these was a planned study of the role of cannabis use in these cancers so a replication of their results is required. There have not been any increases in the rates of these cancers that parallel increased rates of cannabis use over the past three decades.

Immunological effects

Cannabinoids impair cell-mediated and humoral immunity in rodents and reduce resistance to infection by bacteria and viruses in animals. Cannabinoid receptors are

expressed in cells of the immune system in animals and humans although the significance of this for immune function is unclear. Cannabis smoke also impairs the functioning of alveolar macrophages, the first line of the body's immune defence system in the lungs. The clinical relevance of these findings is uncertain because the doses required to produce these effects have been very high, and extrapolation to the doses used by humans is complicated by the fact that tolerance may develop to these effects.

The limited experimental and clinical evidence in humans suggests that the adverse effects seen in animals are not replicated in humans. There is no conclusive evidence that cannabinoids impair immune system function in humans, as measured by T-lymphocytes, B-lymphocytes or macrophages, or immunoglobulin levels. There is suggestive evidence that THC impairs T-lymphocyte responses to mitogens and allogenic lymphocytes.

The clinical and biological significance of these possible effects in chronic cannabis users is uncertain. There is no epidemiological evidence of increased rates of disease among chronic heavy cannabis users, and several large prospective studies of HIV-positive homosexual men have found that cannabis use does **not** increase the risk of progression to AIDS.

Reproductive effects

Chronic administration of THC disrupts male and female reproductive systems in animals, reducing testosterone secretion, and sperm production, motility, and viability in males, and disrupting the ovulatory cycle in females. It is uncertain whether cannabis use has these effects in humans because of the inconsistency in the limited literature on human males, and the lack of research in the case of human females. There is uncertainty about the clinical significance of these effects in normal healthy young adults.

It is likely that cannabis use during pregnancy impairs foetal development, leading to smaller birthweight, perhaps as a consequence of shorter gestation, and probably by the same mechanism as cigarette smoking. There is no clear evidence that cannabis use during pregnancy increases the risk of birth defects as a result of exposure of the foetus to cannabis in the uterus.

There is some evidence that infants exposed to cannabis in the uterus may show transient behavioural and developmental effects during the first few months after birth. These effects are small by comparison with those caused by tobacco use during pregnancy, and have not been observed in all studies.

The cardiovascular system

The changes that cannabis causes in heart rate and blood pressure are unlikely to harm healthy young adults, but they may be less benign in patients with hypertension, cerebrovascular disease and coronary atherosclerosis, in whom cannabis smoking may pose a threat because it increases the work of the heart. The seriousness of these effects will be determined as the cohort of chronic cannabis users of the late 1960s enters the age of maximum risk for atherosclerosis in the heart, brain and peripheral blood vessels. These effects could be life threatening in patients with heart disease.

The respiratory system

Regular cannabis smoking impairs the functioning of the large airways and causes symptoms of chronic bronchitis such as coughing, sputum, and wheezing. Given that tobacco and cannabis smoke contain similar carcinogenic substances, and that tobacco smoke has adverse effects on the respiratory system, it is likely that chronic cannabis use also increases the risks of respiratory cancer. There is evidence that chronic cannabis smoking produces histopathological changes in lung tissues of the type that precede the development of lung cancer. Concern about the possibility of cancers caused by chronic cannabis smoking has been raised by case reports of cancers of the aerodigestive tract in young adults with a history of heavy cannabis use. A recent case-control study has provided the first evidence of an increased risk of aerodigestive tract cancers among cannabis smokers.

Gastrointestinal system

There is no human or animal evidence that cannabinoids adversely affect liver function. Animal studies show that cannabinoids affect intestinal motility and delay gastric emptying but this is of little significance. The most interesting gastrointestinal effect of cannabis is its potential therapeutic use to reduce nausea and stimulate appetite in cancer and AIDS patients.

Psychological effects of chronic cannabis use

Motivational effects

The evidence that chronic heavy cannabis use produces an amotivational syndrome consists largely of case studies. Controlled field and laboratory studies have not found evidence for such a syndrome, although their value is limited by the small sample sizes and limited sociodemographic characteristics of participants of the field studies, the short periods of drug use, and the youth, good health and minimal demands made of the volunteers in the laboratory studies. If there is such a syndrome, it is a relatively rare occurrence, even among heavy, chronic cannabis users. The phenomenon may be better explained as the result of chronic intoxication in dependent cannabis users.

A dependence syndrome

There is good evidence that a cannabis dependence syndrome (as defined in DSM-IV) can occur in heavy chronic users of cannabis. Regular cannabis use produces tolerance to the effects of THC and some users report withdrawal symptoms on cessation of use. There is clinical and epidemiological evidence that *some* heavy cannabis users experience problems controlling their cannabis use, and continue to use despite adverse personal consequences of use.

Surveys in the USA and Australia show that cannabis dependence is the most common form of drug dependence after alcohol and tobacco. The risk of developing dependence is about: one in ten among those who ever use the drug; between one in five and one in three among those who use cannabis more than a few times; and around one in two among those who become daily users. The prevalence of drug-related problems may be low by comparison with those of alcohol dependence and there is likely to be a high rate of remission of cannabis dependence without formal treatment. Treatment should

probably be based on the same principles as treatment for other forms of dependence, although this issue is also in need of research.

Cognitive effects

The weight of evidence suggests that long term heavy use of cannabis does not produce severe impairment of cognitive function like that observed in heavy alcohol users. There is evidence that it may produce more subtle cognitive impairment in the higher cognitive functions of memory, attention and organisation and integration of complex information. This evidence suggests that the longer cannabis is used, the more pronounced will be the cognitive impairment. It remains to be seen whether the impairment can be reversed after an extended period of abstinence.

Psychotic disorders

There is suggestive evidence that heavy cannabis use can produce an acute toxic psychosis during intoxication with symptoms of confusion, amnesia, delusions, hallucinations, anxiety, agitation and hypomania. The evidence comes from laboratory studies of the effects of THC on normal volunteers and clinical observations of psychotic symptoms in heavy cannabis users which seem to resemble those of other toxic psychoses and which remit rapidly following abstinence.

There is less support for the hypothesis that cannabis use can cause a psychosis which persists beyond the period of intoxication. There is suggestive evidence that chronic cannabis use may precipitate a psychosis in vulnerable individuals. This is only suggestive because in the best study conducted to date, the use of cannabis was not documented at the time of diagnosis, cannabis use may have been confounded by amphetamine use, and there were doubts about whether the study could distinguish between schizophrenia and acute drug-induced psychoses. The relationship is unlikely to be causal, because the incidence of schizophrenia has either remained stable, and possibly declined, while cannabis use has increased among young adults.

Effects on adolescent development

Cross-sectional and longitudinal studies of adolescents in the 1970s and 1980s indicate that chronic heavy cannabis use may adversely affect adolescent development in a number of ways. Interpretation of this evidence is complicated by the fact that many of the indicators of adverse development which have been attributed to cannabis use precede its use, and make it more likely that a young person will use cannabis. These include minor delinquency, poor educational performance, nonconformity, and poor adjustment.

The gateway hypothesis

Among American adolescents in the 1970s and 1980s the typical sequence of initiation into drug use was that the use of alcohol and tobacco preceded the use of cannabis, which in turn, preceded the use of hallucinogens, amphetamine, and the later use of heroin and cocaine. Generally, the earlier the age of first use, and the greater the involvement with any drug in the sequence, the more likely a young person was to use the next drug in the sequence.

The explanation of cannabis' role in this sequence remains controversial. The evidence for the hypothesis that cannabis use has a pharmacological effect that increases the risk of using later drugs in the sequence is not strong. More plausible hypotheses are that it reflects a combination of: th early recruitment into cannabis use of nonconforming and deviant adolescents who are likely to use alcohol, tobacco and illicit drugs; a genetic vulnerability to become dependent on a range of substances; and socialisation of cannabis users within an illicit drug using subculture which increases the exposure, opportunity, and encouragement to use other illicit drugs.

Adolescent psychosocial outcomes

In cross-sectional surveys of young people, cannabis use is related to failing to complete a high school education and job instability in young adulthood. The complication is that those who are most likely to use cannabis have lower academic aspirations and poorer school performance *before* using cannabis than those who do not. When these differences are taken into account, the relationship between cannabis use and educational and occupational performance is much more modest. Even so, the adverse effects of cannabis and other drug use upon educational performance are important because they further impair poor performance, and level of education affects choice of occupation, level of income, choice of mate, and quality of life.

There is also suggestive evidence that heavy cannabis use has adverse effects upon family formation, mental health, and involvement in drug-related (but not other types of) crime. In the case of each of these outcomes the apparently strong associations revealed in cross-sectional data are much more modest in longitudinal studies which statistically control for associations between cannabis use and other variables which predict these adverse outcomes.

Therapeutic Effects of Cannabinoids

There is reasonable evidence that THC is an effective anti-emetic agent for patients undergoing cancer chemotherapy. It was as effective as the drugs widely used in the late 1970s and early 1980s when most of the research was conducted but THC does not appear to be as effective as newer anti-emetic drugs.

There is reasonable evidence that THC and cannabis are effective in treating AIDS-related wasting. There is suggestive evidence that cannabinoids are useful as anti-spasmodic, and anti-convulsant agents that warrants further clinical research. There are other potential therapeutic uses which require more pharmacological and experimental investigation, such as, the use of cannabinoids as analgesics or antispasmodics in disorders such as multiple sclerosis.

THC and other cannabinoids have not been widely used therapeutically or investigated in clinical trials. This is because in the United States where most cannabis research has been conducted, clinical research on cannabinoids has been discouraged by regulation and the fact that THC, the most therapeutically effective cannabinoid, is the one that produces the psychoactive effects sought by recreational users. THC is also a naturally occurring substance that cannot be patented, which means that companies are unlikely to

conduct research into its medical uses. The discovery of a cannabinoid receptor and the cannabinoid-like substance anandamide may encourage more basic research into the therapeutic uses of natural and synthetic cannabinoids.

Overall evaluation of the health and psychological risks of cannabis use

Acute effects

The major acute adverse psychological and health effects of cannabis intoxication are:

- anxiety, dysphoria, panic and paranoia, especially in naive users;
- cognitive impairment, especially of attention and memory;
- psychomotor impairment, and possibly an increased risk of accident if an intoxicated person attempts to drive a motor vehicle;
- an increased risk of experiencing psychotic symptoms among those who are vulnerable because of personal or family history of psychosis; and
- an increased risk of low birth weight babies if cannabis is used during pregnancy.

Chronic effects

The most probable health and psychological effects of chronic heavy cannabis use appear to be:

- respiratory diseases associated with smoking as the method of administration, such as chronic bronchitis, and the occurrence of histopathological changes that may be precursors to the development of malignancy;
- an increased risk of cancers of the aerodigestive tract, i.e. oral cavity, pharynx, and oesophagus; and
- development of a cannabis dependence syndrome, characterised by an inability to abstain from or to control cannabis use.

The following **possible** adverse effects of chronic, heavy cannabis use remain to be confirmed by further research:

- a decline in occupational performance marked by underachievement in adults in occupations requiring high level cognitive skills, and impaired educational attainment in adolescents; and
- subtle forms of cognitive impairment, most particularly of attention and memory, which persist while the user remains chronically intoxicated, and may or may not be reversed by prolonged abstinence from cannabis.

High risk groups

A number of groups can be identified as being at increased risk of experiencing some of these adverse effects.

Adolescents

- Adolescents with a history of poor school performance whose educational achievement may be reduced by chronic intoxication with cannabis; and
- Adolescents who initiate cannabis use in the early teens who are at higher risk of progressing to regular cannabis use, to developing dependence on cannabis, and to using other illicit drugs.

Women of childbearing age

- The babies of women who continue to smoke cannabis during pregnancy may have lower birth weight.

Persons with pre-existing conditions

Persons with a number of pre-existing diseases who smoke cannabis are probably at an increased risk of exacerbating symptoms of their diseases. These include:

- Individuals with cardiovascular diseases, such as coronary artery disease, cerebrovascular disease and hypertension;
- Individuals with respiratory diseases, such as asthma, bronchitis, and emphysema;
- Individuals with schizophrenia; and
- Individuals who are dependent on alcohol and other drugs who are probably at an increased risk of developing dependence on cannabis.

Comparing the health risks of alcohol, tobacco and cannabis use

Comparing the adverse health effects of cannabis with those of alcohol and tobacco, reminds us of the health risks of two widely used psychoactive drugs. Cannabis shares a route of administration with tobacco smoking, and its effects resemble those of alcohol, which is also used for its intoxicating and euphoric effects.

Acute effects

Alcohol: The major risks of acute cannabis use are similar to the acute risks of alcohol intoxication in a number of ways. First, both drugs produce psychomotor and cognitive impairment. The impairment produced by alcohol increases risks of various kinds of accidents, and the likelihood of engaging in risky behaviour, such as dangerous driving and unsafe sexual practices. It remains to be determined whether cannabis intoxication produces similar increases in accidental injury and death.

Second, there is good evidence that substantial doses of alcohol taken during the first trimester of pregnancy can produce a foetal alcohol syndrome. There is weak but inconclusive evidence that cannabis used during pregnancy may have similar adverse effects.

Third, there is a major health risk of acute alcohol use that is *not* shared with cannabis. In large doses alcohol can cause death by asphyxiation, alcohol poisoning, cardiomyopathy and cardiac infarct. There are no recorded cases of overdose fatalities attributable to cannabis.

Tobacco: The major acute health risks that cannabis share with tobacco are the irritant effects of smoke upon the respiratory system, the adverse effects of carbon monoxide and other components of smoke on the cardiovascular system and the stimulating effects of both THC and nicotine on the cardiovascular system, which can be detrimental to persons with cardiovascular disease.

Chronic effects

Alcohol: A number of the risks of chronic alcohol use may be shared by chronic cannabis use. First, heavy users of both drugs may develop a dependence syndrome in which they experience difficulty in stopping or controlling their use. There is strong evidence of such a syndrome in the case of alcohol and reasonable evidence in the case of cannabis. A major difference between the two is that it is uncertain whether a withdrawal syndrome reliably occurs after dependent cannabis users abruptly stop their cannabis use whereas the abrupt cessation of alcohol use in severely dependent drinkers produces a well-defined withdrawal syndrome which can in rare cases be fatal if untreated.

Second, there is reasonable clinical evidence that the chronic heavy use of alcohol can produce psychotic symptoms and exacerbate psychoses in some individuals. There is suggestive evidence that chronic heavy cannabis use may produce a toxic psychosis and precipitate psychotic illnesses in predisposed individuals. There is better evidence that it can exacerbate psychotic symptoms in individuals with schizophrenia.

Third, there is good evidence that chronic heavy alcohol use can indirectly cause brain injury—the Wernicke-Korsakov syndrome—with symptoms of severe memory defect and an impaired ability to plan and organise. With continued heavy drinking, and in the absence of vitamin supplementation, the drinker may develop severe irreversible cognitive impairment. Chronic cannabis use does not produce cognitive impairment of comparable severity. It may produce more subtle deficits in cognitive functioning that may or may not be reversible after abstinence.

Fourth, there is reasonable evidence that chronic heavy alcohol use impairs occupational performance in adults and educational achievements in adolescents. There is suggestive evidence that chronic heavy cannabis use produces similar, albeit more subtle impairments in occupational and educational performance of adults and adolescents.

Fifth, there is good evidence that chronic, heavy alcohol use increases the risk of premature mortality from accidents, suicide and violence. There is no comparable evidence for chronic cannabis use, although dependent cannabis users who frequently drive while intoxicated with cannabis possibly increase their risk of accidental injury or death.

Sixth, alcohol use has been accepted as a contributory cause of cancer of the mouth, tongue and throat in men and women. There is some evidence that chronic cannabis smoking may also be a contributory cause of cancers of the mouth, tongue, throat, oesophagus, and lungs.

Tobacco: The major adverse health effects shared by chronic cannabis and tobacco smokers are chronic respiratory diseases, such as chronic bronchitis, and probably, cancers of the aerodigestive tract. The increased risk of cancer in the respiratory tract is a consequence of the shared route of administration by smoking. Chronic cannabis smoking may also share the cardiotoxic properties of tobacco smoking, although this possibility remains to be investigated.

Public health impact

Studies of deaths, disease, economic costs and disease burden attributable to alcohol, tobacco and illicit drugs differ in the way that they rank the impact of alcohol, depending upon whether they include the mortality benefit of moderate alcohol use or not. They all agree, however, that *on current patterns of use,* alcohol and tobacco are much more damaging to public health in developed societies than cannabis, which makes no known contribution to deaths and a minor contribution to morbidity.

These estimates cannot be used to predict what would happen if there was a major change in the prevalence of cannabis use, as may happen if cannabis were to become as freely available and as heavily promoted as alcohol and tobacco. All that can be said with confidence is that if the rate of cannabis use increased to the levels of cigarette smoking and alcohol use, its adverse impact on public health would increase. It is impossible to say precisely by how much.

1 Introduction

This monograph updates a review of the health and psychological effects of cannabis that was undertaken in 1993 at the request of a National Task Force on Cannabis. The Task Force commissioned this review because there had not been an international review of the health and psychological effects of cannabis since one was published in 1983 by the Addiction Research Foundation and World Health Organization (1). Since our review was published (2) the World Health Organization (3) and the US Institute of Medicine (4) have published reviews of the research that has been undertaken on the health effects of cannabis use. This review updates the earlier review in the light of recent research and authoritative reviews with the aim of providing as accurate and objective an analysis of the health risks of cannabis as the evidence allows. It also makes clear which issues remain uncertain.

1.1 Making causal inferences

We have used standard criteria in making causal inferences (5) about the health effects of cannabis. These require that the following conditions are met: that there is an association between cannabis use and an adverse health outcome; that chance is an unlikely explanation of the association; that cannabis use preceded the health outcome; and that plausible alternative causal explanations of the association can be excluded.

Evidence of an association between cannabis use and a health outcome is provided by a relationship between cannabis use and the health outcome observed in a case-control, cross-sectional, cohort, or experimental study. These study designs differ in the ease and expense with which they can be conducted and in the strength of the inference that they warrant about the association between cannabis use and the health outcome under study.

Evidence is required that chance is an unlikely explanation of any relationship observed between cannabis use and a health outcome. 'Unlikely to arise by chance ' is conventionally taken to mean that it is an event that would occur less than once in twenty trials (5% of the time). In the biomedical sciences, statistical tests and confidence intervals are used to evaluate the plausibility of this hypothesis.

If cannabis use is a cause of an adverse health effect then cannabis use should precede the health effect. Cross-sectional and case-control studies which assess cannabis use and health status at the same time often do not enable us to decide which came first, the cannabis use or the health outcome. This is a problem when age at which a health outcome first appears (e.g. school failure, schizophrenia) is around the age at which cannabis use begins, namely, late adolescence and early adulthood. The strongest evidence that cannabis use precedes the health effects would be provided by a cohort study or an experiment. In the former the researcher observes that cannabis use precedes the health effect while in the latter the experimenter would ensure by design that it did so.

The alternative explanation of an association between cannabis use and a health outcome that is the most difficult to exclude is that the association reflects an unmeasured variable that is the cause of both cannabis use and the health outcome. In cross-sectional surveys of high school-aged adolescents, for example, cannabis users perform more poorly at school than non-cannabis users (6). An 'obvious' explanation of this association is that cannabis use is a cause of poor school performance. An equally plausible hypothesis is that low intellectual ability or learning difficulties are causes of both poor school performance and cannabis use (7, 8).

Experiments in which persons were randomly assigned to use cannabis or not would provide the best way of ruling out such 'common causes'. Random assignment would ensure that adolescent cannabis users did not differ prior to using cannabis use from adolescents who did not. Hence, any later differences in educational performance could be attributed to cannabis use rather than to pre-existing differences in ability. For obvious reasons this option is not available. It is impossible for ethical and practical reasons to randomly assign individuals to cannabis use except when studying acute and innocuous health effects of use. It would be unethical to force some adolescents to use cannabis, and impractical, even if ethical, to prevent those who were assigned not to use cannabis from doing so.

Experiments using laboratory animals are the next best option to human experiments on some of the health effects of chronic cannabis use. In such studies, mice, rats, or monkeys are randomly assigned to receive either high doses of cannabis or placebo for substantial parts of their lives. The rates of various health outcomes (e.g. cancers, immunological changes, reproductive effects) are then compared between the experimental and control animals. This strategy has limited application in studying the psychological effects of chronic cannabis use because there are no animal models for mental illness, poor school performance, and personal adjustment. Even when animal models are available there are problems in extrapolating results across species which are compounded by the fact that humans and animals use different routes of administration (e.g. oral and injected in animals versus smoked in humans), different forms of cannabis (pure THC in many animal studies versus smoked cannabis plant in human use), and very different doses of THC (high doses in animals vs. long-term, low dosing of crude THC in cannabis products that are smoked by humans).

When a suitable animal model does not exist, and when randomisation of human subjects is impractical or unethical, epidemiological methods are used to rule out common causes in human studies. These use statistical methods to estimate the effect that cannabis use has on a health outcome, after adjusting for the effects of any differences between cannabis users and non-users that may affect the outcome (e.g. personal characteristics and life experiences before using cannabis). If the relationship persists after statistical adjustment, then confidence is increased that it is not attributable to the variables for which statistical adjustment has been made. This approach has been used, for example, in longitudinal studies of the effects of adolescent cannabis use on psychosocial outcomes (7–9).

1.2 An overall evaluation of causal hypotheses

A single research study, no matter how well done, does not permit us to decide whether cannabis use is a cause of an adverse health outcome. Causal hypotheses are evaluated in the light of a body of research using criteria of the sort outlined by Hill (10). These criteria are not sufficient for establishing that an association indicates a causal relationship since it is possible to be mistaken about a causal inference when the criteria have been met. But generally, the more of the criteria that are met, the more likely the association is to be causal.

Strength of association: the stronger a relationship is the better our ability to predict that cannabis use and a health effect co-occur. Stronger relationships are generally more deserving of trust than weaker ones that the relationship is less easily explained as artefacts of measurement or sampling.

Consistency: relationships which are consistently observed by different investigators, in different populations, using varied measures and research designs, are more credible than relationships which are not. The persistence of a relationship despite differences in sampling and research methods makes it unlikely that it can be explained by these factors.

Specificity exists when cannabis use is strongly associated with the outcome, and the health outcome is rare in non-cannabis users. This is a desirable but not a necessary condition. If there is specificity we can be more confident that there is a causal relationship but its absence does not exclude the possibility of a causal relationship.

Biological gradient refers to the existence of a dose-response relationship between frequency and duration of cannabis use and the likelihood of the health outcome. Satisfaction of this criterion is desirable but not necessary because there may be other patterns of relationship between cannabis use and the outcome, e.g. a threshold effect, an 'all or none', or a curvilinear relationship.

Biological plausibility: If there is no known mechanism that would explain a relationship, then we have grounds for scepticism. But if we have good evidence of association from well controlled studies, biological implausibility is not a compelling reason for rejecting a causal relationship: it may mean that existing theories are wrong, or that we need new theories to explain previously unknown phenomena.

Coherence means that the relationship is consistent with the natural history and biology of the condition. This too is desirable but not necessary: it is desirable if we have independent information that we can trust but its absence is not fatal since the other knowledge with which it is inconsistent may be in error.

1.3 Acute health effects

It is easier to make causal inferences about the acute effects of any drug (e.g. its effects on mood or thinking) than it is to make inferences about the health effects of its chronic use. It is clear in these cases that. Drug use precedes the effect; drug use and the effect typically occur closely together in time; and if the effects are not dangerous, they can be reliably reproduced in a substantial proportion of people by administering the drug under controlled conditions. All these conditions apply to the acute psychoactive effects of cannabis that are sought by recreational cannabis users (such as euphoria and relaxation). They also apply to the more common unpleasant or dysphoric effects, such as anxiety, panic and depression.

It can be more difficult to decide whether relatively rare acute experiences (such as flashbacks and psychotic symptoms) are caused by cannabis use. It may be uncertain whether these are: rare events that occur coincidentally with cannabis use; unusual effects of cannabis use that occur at much higher than usual recreational doses or that require some form of personal vulnerability; caused by other drugs which may have been taken with cannabis; or the result of interactions between the cannabis and other drug use.

1.4 Chronic effects

Causal inferences about the effects of chronic cannabis use become more difficult the longer the interval between starting to use it and the occurrence of the adverse health effects. If it takes a long time for adverse effects to develop, it may take longer for a suspicion to be raised about the relationship between cannabis use and the adverse outcome. In the case of tobacco, for example, it took three hundred years to discover that it caused cancer and heart disease and new health hazards of tobacco smoking continue to be discovered (11). The longer the time interval between cannabis use and the health consequence, the more alternative explanations of the association that there are to be excluded.

In making causal inferences about the chronic health effects of cannabis use we have a trade off between rigour and relevance in the available evidence. The most *rigorous* evidence is provided by laboratory investigations using experimental animals or preparations of animal cells and micro-organisms in which very large drug doses are administered over a substantial period of the organisms' lives. The relevance of such research to human disease, however, is often problematic.

Epidemiological studies of relationships between cannabis use and human disease are the most *relevant* in evaluating the human health effects of cannabis but this relevance is obtained at the expense of reduced rigour. Assessing exposure to cannabis and excluding alternative explanations of associations between cannabis use and health outcomes can be difficult in such studies. Uncertainty about the interpretation of human epidemiological studies affects interpretations of both 'positive' studies that find relationships between cannabis use and health outcomes and 'negative' studies which fail to find relationships.

A major problem in interpreting 'positive' epidemiological studies is that cannabis users are more likely to use alcohol and tobacco that are known to adversely affect health. Generally, the heavier the cannabis use, the more likely it is that the person uses alcohol and tobacco, as well as illicit drugs like amphetamine, hallucinogens, cocaine, and heroin (7, 12, 13). This makes it difficult to be confident that adverse health effects found in cannabis users are caused by their cannabis use (14).

A different problem arises when interpreting studies that fail to find any adverse health effects of chronic cannabis use. In the case of immunological effects, for example, the limited epidemiological evidence suggests that there are no adverse immunological effects of chronic heavy cannabis use in humans (2). Does this mean that THC has few, if any, immunological effects in humans or have the studies lacked the sensitivity to detect any such effects in humans? The answers to this question depends upon the likely magnitude of any such effects, their relationship to cannabis dose, frequency and duration of use, and the ability of studies with small sample sizes to detect them (15).

1.5 Comparing health effects of different drugs

Comparisons are often made between the public health impact of cannabis use and that of alcohol and tobacco. This impact is assessed by examining the number of individuals whose health is adversely affected by each type of drug and the severity of the health consequences for these individuals.

The major obstacle to making such comparisons is the paucity of information on the health effects of long-term cannabis use. It is nonetheless still useful to make comparisons of the adverse health effects of cannabis with those of alcohol and tobacco. These comparisons simply indicate whether or not cannabis shares the known adverse health effects of alcohol and tobacco. The reason for selecting these drugs are that they are widely used psychoactive drugs with which cannabis shares a route of administration in the case of tobacco, and which, in the case of alcohol, is also used for its intoxicating and euphoric effects. They therefore provide a useful standard of comparison when appraising the health risks of cannabis use.

1.6 An outline of the monograph

The remainder of this monograph reviews the literature on the health and psychological effects of cannabis in the following way. Chapter 2 describes 'cannabis as a drug'. It deals with the main preparations of cannabis that are used, the way in which they are typically used and the pharmacology of its major psychoactive ingredient, tetrahydrocannabinol or THC.

Chapter 3 describes the patterns of cannabis use in Australia and other developed societies, including the USA, Canada, and countries of the European Union. It describes sex and age differences in patterns of use and the natural history of cannabis use from adolescence into adulthood.

Chapter 4 describes the acute effects of cannabis. These include the positive psychological effects sought by recreational users as well as the adverse psychological effects some users experience. It also reviews evidence on the possible contribution that cannabis intoxication makes to motor vehicle accidents.

Chapters 5, 6 and 7 discuss the evidence on the adverse health effects of chronic cannabis use. Chapter 5 considers evidence on the effects of cannabis use on cellular functioning and the risks of users developing cancers. It also reviews evidence on the effects of cannabis use on immunological functioning in users. Chapter 6 discusses the possible reproductive effects of cannabis use. Chapter 7 considers the possible adverse effects that cannabis smoking may have on the respiratory, cardiovascular and gastrointestinal systems.

Chapters 8, 9 and 10 review research on adverse psychological effects that have been attributed to chronic cannabis use. These include the effects of cannabis use on motivation and the risk of developing dependence on the drug (chapter 8). Chapter 9 considers the possibility that people who use cannabis regularly over a period of years may develop cognitive impairment. Chapter 10 discusses evidence on the contribution that cannabis use may make to the precipitation and exacerbation of schizophrenia and other psychoses.

Chapters 11 and 12 consider the possible consequences of adolescent cannabis use. These chapters deal with evidence on societal concerns about the impact that adolescent cannabis use may have on the likelihood of using other illicit drugs (chapter 11) and on psychosocial outcomes, such as school performance, delinquency and mental health (chapter 12).

Chapter 13 considers the evidence on the therapeutic benefits of cannabis and cannabinoids. Chapter 14 concludes by comparing the adverse health effects of cannabis with those of alcohol and tobacco.

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2 Cannabis the drug

2.1 The cannabis plant

Cannabis preparations are obtained from the plant *Cannabis sativa,* which occurs in male and female forms. The cannabis plant contains more than 60 cannabinoids, that is, substances that are unique to the plant. The one that is primarily responsible for the psychoactive effects that are sought by cannabis users is delta-9-tetrahydrocannabinol or THC (1–3), which is found in a resin that covers the flowering tops and upper leaves of the female plant. Most of the other cannabinoids are either inactive or only weakly active, although they may interact with THC (2, 4).

The most common cannabis preparations are marijuana, hashish and hash oil. Marijuana is prepared from the dried flowering tops and leaves of the plant. Its potency depends upon the growing conditions, the genetic characteristics of the plant, the ratio of THC to other cannabinoids, and the part of the plant that is used (5). The flowering tops have the highest THC concentration with much lower concentrations in the leaves, stems and seeds. Varieties of cannabis cultivated for hemp fibre usually contain very low levels of THC. Cannabis plants may be grown to maximise their THC production by the 'sinsemilla' method in which only female plants are grown together (5).

The concentration of THC in marijuana may range from 0.5% to 5% while the 'sinsemilla' variety may contain 7% to 14% THC (6). The potency of marijuana preparations being sold in the USA has probably increased during the past several decades (6) although it has not increased 30 fold, as has been claimed in the popular media (7).

Hashish or hash consists of dried cannabis resin. It may be light brown to almost black and contain between 2% to 8% of THC. Hash oil is obtained by extracting THC from hashish (or marijuana) in oil. Its colour may range from clear to pale yellow/green, through brown to black. The concentration of THC in hash oil typically varies between 15% and 20% (8).

2.2 Routes of administration

Cannabis is typically smoked as marijuana in a hand-rolled cigarette or 'joint' which may include tobacco to assist burning. A water pipe or 'bong' is an increasingly popular way of using all cannabis preparations in Australia (7). Hashish may be mixed with tobacco and smoked as a joint or smoked in a pipe, with or without tobacco. Because hash oil is extremely potent a few drops may be applied to a cigarette or a joint, to the mixture in a pipe, or the oil may be heated and the vapours inhaled. Whatever preparation or method of smoking is used, smokers typically inhale deeply and hold their breath to ensure maximum absorption of THC by the lungs.

The oral route of administration may also be used. Hashish may be cooked in foods and eaten. In experimental research, THC dissolved in sesame oil is swallowed in gelatine capsules. In India, cannabis may be consumed in the form of 'bhang', a tea brewed from the leaves and stems of the plant.

Cannabis does not lend itself to injection because THC does not dissolve in water (Iversen, (3). Crude solutions of cannabis can be injected intravenously but they contain very little THC. They are more likely to include undissolved particles and substances that can cause severe pain and inflammation at the site of injection. Iversen has suggested that the inability to inject cannabis preparations was one of the reasons why its therapeutic use declined at the end of the nineteenth century.

Survey data on patterns of cannabis use in Australia indicates that all but a handful of cannabis users smoke cannabis (7). This is for a good reason because, as Martin and Cone have argued, the chemistry and pharmacology of cannabis dictate that it be smoked (2). Given the preponderance of smoking as the route of administration, the reader should assume that unless otherwise stated the method of ingesting cannabis is smoking.

2.3 Dosage

A 'typical' cannabis joint consists of between 0.5 and 1.0 g of cannabis that contains between 5 and 150 mg of THC (i.e. between 0.5% and 5% THC). The amount of THC delivered to the lungs in the smoke varies between 20% and 70% (2, 9); the rest is burnt or lost in sidestream smoke. The fraction of THC in the joint that reaches the user's bloodstream varies between 5% and 24% (mean 18.6%) (10). For all these reasons, it is difficult to estimate the typical dose of THC that is received when cannabis is smoked.

An occasional user only requires a small amount of smoked cannabis (e.g. 2 to 3 mg of absorbed THC) to experience a brief, pleasurable high, but a heavy cannabis smoker may consume five or more joints per day. Heavy cannabis users in Jamaica may consume up to 420 mg THC per day (11). In human laboratory research on the effects of cannabis, THC doses of 10, 20 and 25 mg have been defined as low, medium and high doses (12, 13).

2.4 Metabolism of cannabinoids

The way that cannabis is used affects the absorption, metabolism and excretion of THC. When cannabis is smoked, THC is absorbed within minutes into the bloodstream from the lungs. Orally administered THC is absorbed much more slowly, taking 1 to 3 hours to enter the bloodstream and produce its psychoactive effects (2).

After smoking, THC is metabolised first in the lungs and then in the liver where it is transformed into a number of metabolites (2). The metabolite 9-carboxy-THC is detectable in blood within minutes of smoking cannabis. It is not psychoactive. Another major metabolite is 11-hydroxy-THC. It is marginally more potent than THC and crosses

the blood-brain barrier more rapidly. It is found in very low concentrations in the blood after smoking and at higher concentrations after oral use (9). THC and its metabolites account for most of the psychoactive effects of cannabis (2).

Peak blood levels of THC occur within 10 minutes of smoking and decline to 5% of 10% of their initial level within an hour (2). The decline in THC reflects the conversion of THC to its metabolites. THC and its metabolites are highly fat soluble and concentrate in lipid-rich tissues, including the brain (14, 15). They may remain in the fatty tissues of the body for considerable periods of time, being slowly released into the bloodstream. This slows the elimination of THC from the body (2).

Research using sensitive detection techniques suggests that the half-life of THC in chronic users is 4 days on average (16, 17). Because of the slow clearance, THC and its metabolites accumulate in the body with repeated administration. Its slow release from fatty tissues into the bloodstream means that THC and its metabolites may be detectable in blood for several days. Traces of THC may persist for several weeks.

2.5 Detection of cannabinoids in body fluids

Plasma levels of THC in cannabis users vary between 0 and 500 ng/ml, depending on the THC content of the cannabis and the time since its use. Blood levels of THC may decline to 2 ng/ml an hour after smoking a low potency cannabis cigarette but it may take 9 hours to reach the same level after smoking a high potency cannabis cigarette. Such levels may persist for several days in chronic users because of the slow release of accumulated THC.

The detection of THC in blood above 10-15 ng/ml generally indicates 'recent' use of cannabis but it is not possible to estimate precisely how recent. A more precise estimate of the time of consumption is provided by the ratio of THC to 9-carboxy-THC. When the levels of 9-carboxy-THC are substantially higher than those of THC, cannabis was smoked more than half an hour ago, if the smoker was a naïve user (9, 13). Background levels of cannabinoids (particularly 9-carboxy-THC) in regular users make it difficult to estimate time since use.

Cannabinoid levels in urine are a weak indicator of recent cannabis use (18). In general, the more cannabinoid metabolites in urine, the more recent the use but it is impossible to be precise about how 'recent' (9). Only minute traces of THC are found in urine because most of the THC is excreted as metabolites in faeces and urine (19). 9-carboxy-THC can be detected in urine within 30 minutes of smoking. This and other metabolites may be detected for several days in first time or irregular cannabis users but regular users may continue to excrete metabolites for weeks and possibly months (20, 21).

Studies of cannabinoids in saliva have found that THC can be stored for at least 28 days (22). Measurement of cannabinoids in saliva may reduce the time frame for 'recent' use from days and weeks to hours because they reflect the presence of residual THC in the mouth after smoking (9, 23, 24). Salivary THC levels are correlated with subjective intoxication and heart rate (25).

Unlike alcohol where psychomotor impairment is correlated with blood alcohol level, there is no simple relationship between levels of THC (or its metabolites) in blood and impairment (18, 26). This is for two reasons: the delay between experiencing the subjective high and the appearance of THC in the blood; and large variations between different people in the level of intoxication experienced at the same blood level of THC. A consensus conference of forensic toxicologists concluded that there was not sufficient evidence for blood concentrations of THC to define a legal basis for driving a motor vehicle while under the influence of cannabis (27).

2.6 Two special concerns

2.6.1 Storage of THC

There is good evidence that with repeated dosing of cannabis at frequent intervals, THC can accumulate in fatty tissues in the human body where it may remain for considerable periods of time (Ashton (18) and see above). The storage of cannabinoids *would* be serious cause for concern if THC were a highly toxic substance which remained physiologically active while stored. THC is not a highly toxic substance and it is unlikely to have active effects while stored in body fat because it acts in receptors that are not present in body fat. One *potential* health implication of THC storage is that the release of stored cannabinoids into blood may produce unexpected symptoms of cannabis intoxication. The release of stored THC has been suggested as an explanation of 'flashback experiences' (e.g. Negrete (28); Thomas (29)). Such experiences have been rarely reported by cannabis users (e.g. Edwards (30)), and their significance is complicated by the fact that those who have reported these experiences have often used other hallucinogenic drugs.

2.6.2 Increases in the potency of cannabis

Cohen (31) claimed that research underestimates the adverse health effects of cannabis because it was largely based upon studies conducted when cannabis users used less potent forms of cannabis (0.5% to 1.0% THC) than later became available in the USA in the 1980s (3.5% THC in 1985–1986). This claim has been repeated often in the popular and scientific media (18, 32), usually asserted rather than shown and often supported by anecdotal reports of samples of cannabis containing high percentages of THC. An alleged 'thirty-fold' increase in potency has contributed to recent concerns about the health effects of cannabis in Australia (7).

There are two different interpretations of this claim: (i) that the average THC content of cannabis plants has increased; and (ii) that the average THC content of cannabis products consumed by users has increased by 10–30 times (7).

The USA is the only country that has regularly collected data on the THC content of cannabis plants over the past several decades. Claims that this data indicated that the THC content of cannabis in the USA had increased between three to seven-fold from the early 1970s to the mid 1980s have been challenged by data from independent laboratories, and because such claims relied on the assumption that the samples from the middle 1970s were representative of cannabis consumed at that time. More recent data have failed to show a 10–30 fold increase in the THC content of seizures between 1984

and 1998. At most this series shows a small increase in THC content from 3.3% in 1980 to 4.4% in 1998 (6, 33). Recent data published on the THC content of cannabis seized in New Zealand over the past 20 years has not shown any increase in average THC content (34).

2.7 Cannabinoid biology

Research during the 1990s has clarified the ways in which cannabinoids act in the human body and brain (35, 36). This research has identified 'cannabinoid receptors' and 'endogenous cannabinoids'. Cannabinoid receptors are the molecular sites in the brain and body at which the active components of cannabis, such as THC, act (36). Endogenous cannabinoids are substances that naturally occur in the human brain and body that, like THC, act on cannabinoid receptors in the brain. These include anandamide (37) and 2-arachidonyl-glycerol (2AG) (38, 39).

Two types of cannabinoid receptors, CB_1 and CB_2 have been identified. The CB_1 receptor that is found primarily in the brain is responsible for the psychological effects of THC (40). The CB_2 receptor is found in the immune system but its precise role remains unclear. CB_1 and CB_2 receptors belong to a large group of receptors found in the membranes of nerve cells that are involved in chemical signalling between nerve cells. Cannabinoid receptors have been found in the nervous system of lower vertebrates, including chickens, turtles and trout (41). This suggests that these receptors were present early in evolution, and their conservation implies that they serve an important biological function in many species including mammals (2).

The distribution of CB_1 and CB_2 receptors in the brain, immune and reproductive tissues is consistent with many of their therapeutic and recreational effects (38, 39). CB_1 cannabinoid receptors in the brain are most concentrated in brain systems that are involved in controlling mood, motor function, memory formation, food intake, pain modulation, immune, and reproductive functions).

Cannabis disrupts short-term memory in humans (see Chapter 4). This effect is consistent with an abundance of CB_1 receptors in the hippocampus, the brain region most closely associated with memory (3, 39). A high density of CB_1 receptors in the basal ganglia and cerebellum is consistent with the observation that cannabinoids interfere with coordinated movement (2). Cannabis has very little acute effect on respiratory function in humans (42, 43), which is consistent with the observation that the lower brainstem area has few cannabinoid receptors. The absence of cannabinoid receptors in the lower brainstem also explains why high doses of THC are rarely lethal (3).

2.8 Summary

Cannabis is derived from the *cannabis sativa* plant. THC is the constituent of cannabis that produces the psychoactive effects sought by recreational users. Different forms of cannabis (marijuana, heads, hash and hash oil) vary in their potency. Cannabis is

predominantly smoked in a joint or in a water pipe because this is the most efficient way to deliver THC quickly to the bloodstream and brain. THC and its metabolites can be detected in blood and urine but there is no simple relationship between these levels in blood or urine and the degree of intoxication or psychomotor impairment. THC acts on brain receptors ('cannabinoid receptors') that are also acted upon by substances that occur naturally in the brain ('endogenous cannabinoids'). Cannabinoid receptors are found in brain regions involved in control of mood, memory, and motor performance, all of which are affected by cannabis.

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3 Patterns of cannabis use

3.1 Measuring cannabis use

Most information about cannabis use is collected by surveying the general population and high school and university students. These surveys typically ask each person whether he or she has used cannabis: at any time in their lives (lifetime use), in the past year (past year use), and in the past month. Rates of weekly and daily cannabis use are low in most populations, so surveys typically only report whether the person has used cannabis in his or her lifetime or in the past year.

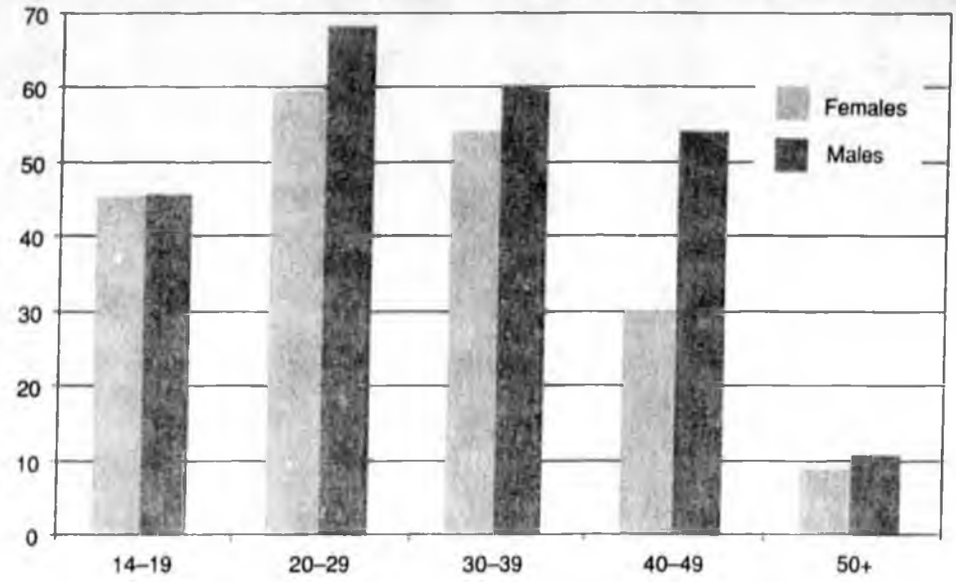
There is good evidence that carefully designed surveys provide valid information on self-reported cannabis use. O'Malley, Bachman, and Johnston (1), for example, showed that self-reported drug use in three waves of interviews of high school seniors was as reliable as self-reports of other behaviour. They have also shown that although some older adults later under-report drug use in adolescence and early adult life, under-reporting of cannabis use is quite low (2, 3). Most importantly, any small biases in self-reported cannabis use are fairly constant over time, meaning that we can be reasonably confident about *trends* in drug use from surveys (4, 5).

3.2 Cannabis use in Australia

Cannabis is the most widely used illicit drug in Australia. In 1998 39% of adults aged 15 and older reported that they had used cannabis at some time in their lives (6). Men were more likely to have used cannabis than women at all ages (44% of males vs. 35% of females) (7). Rates of cannabis use were highest among young adults: 45% of 14–19 year olds and 64% of 20 to 24 years olds reported lifetime cannabis use. Rates declined steadily with age (see Figure 1). The low rates of lifetime cannabis use among adults over the age of 50 years reflects the beginning of widespread cannabis use among young Australian adults in the early 1970s (7).

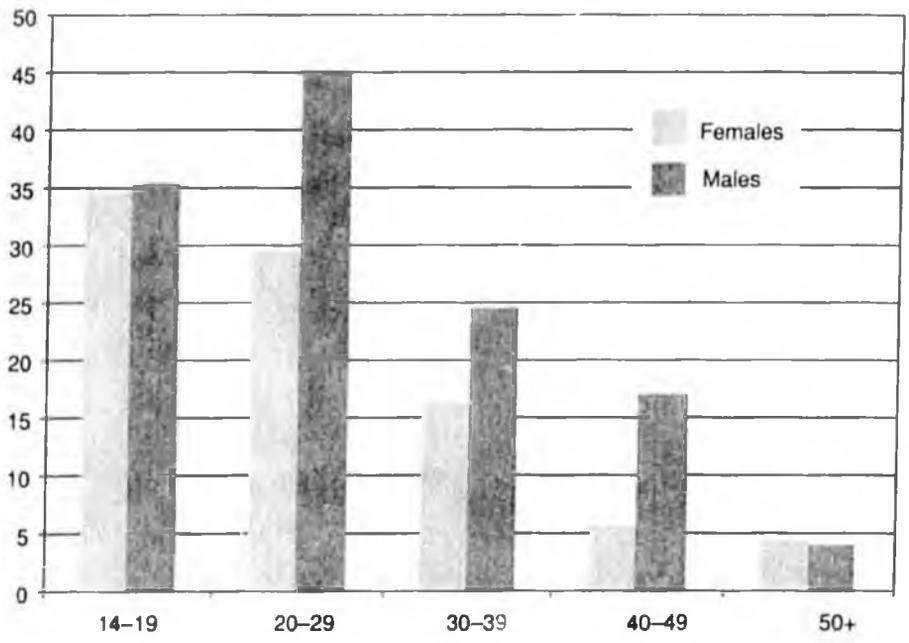
Most cannabis use is not regular. In the 1998 survey, three quarters of women and two thirds of men who had ever used cannabis either had not used in the past year or had used less than weekly (6). The proportion of users who became weekly users was 7% of women and 15% of men. Weekly cannabis use was most common among those aged 20 to 24 years, declining steeply thereafter (8).

Figure 1: Prevalence of lifetime cannabis use by age and gender, 1998 NDS survey



The rate of cannabis use in the past 12 months was 18% in the 1998 NDS. This was an increase on rates of use in previous household surveys, which found rates of 12 to 13% (9). Current use of cannabis was more common among males (21%) than females (15%) (Figure 2) but there was no difference in the youngest age group. The prevalence of current cannabis use was highest among 14–19 year olds (35%) and 20–29 year olds (37%). This is consistent with previous NDS surveys (8).

Figure 2: Prevalence of 12-month cannabis use by age and gender, 1998 NDS survey



The 1996 Australian School Student's Alcohol and Drugs Survey found that 36% of students aged 12–17 had used cannabis (10). Earlier studies of drug use among school aged youth in various Australian states conducted in the early 1990's reported rates of cannabis use between 25 to 30% (8). The 1996 school survey results suggest that there was an increase in the use of cannabis among youth during the 1990s, a finding that is supported by the NDS household surveys. The most recent national school survey found a small decline in rates of recent cannabis use among school students between 1996 and 1999 (11).

Australian cannabis users were more often males, who were under 35 years of age and more likely to be unemployed than non-users. While persons with higher education levels are more likely to have tried cannabis at some time in their lives, persons with lower levels of education are more likely to be regular users (9). Current cigarette smokers are more likely to smoke cannabis than non-smokers, and regular drinkers are more likely than occasional or non-drinkers, to be regular users of cannabis (12). Cannabis in Australia is most typically smoked, and the types of cannabis most commonly used are heads and leaf (9). The preferred mode of administration among younger users is a bong and to a lesser extent, a pipe; older users are more likely to smoke joints (13).

Surveys of drug use in the general population were not conducted in Australia until the mid 1980s. However, throughout the 1970s some market research companies included questions on cannabis use in other surveys (14). These show an increase in cannabis use in all age groups between 1973 and 1984. Among 20 to 29 year olds, for example, 23% reported having used cannabis in 1973 while the figure increased to 39% in 1984. The sharp increase in the rates of cannabis use between the 1984 market research survey and the 1985 national household survey may reflect greater anonymity given to respondents in the 1985 survey, and the different settings in which these questions were asked (in an 'omnibus' survey of consumer attitudes in 1984 and a special purpose survey about drug use and drug-related issues in 1985). There has been an increase in the percentage of Australians who report having ever tried cannabis in the NDS household surveys from 28% in 1985 to 39% in 1998.

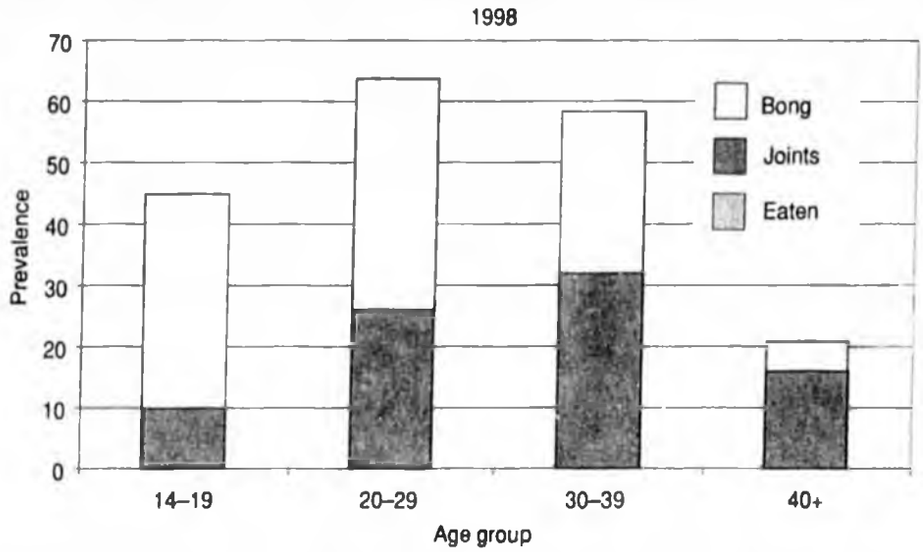
3.2.1 Changing patterns of cannabis use

Younger cannabis users now use more potent forms of cannabis at an earlier age. The 1998 NDS data show a decline in the age of initiation among younger cannabis users. One in five cannabis users (21%) born between 1940 and 1949 had initiated cannabis use by age 18, compared to 43% of those born in 1950–59, 66% of those born 1960–69 and 78% of those born in 1970–79 (15).

Earlier initiation of cannabis use increases the chances that these users will become daily or nearly daily cannabis users (16, 17). This, in turn, increases the risks of becoming dependent on cannabis and experiencing problems as a result of their use (16, 18). Levels of consumption among some adolescent cannabis users can be very high. For example, 40% of a sample of NSW juvenile offenders reported smoking 40 or more 'cones' of cannabis a week (19).

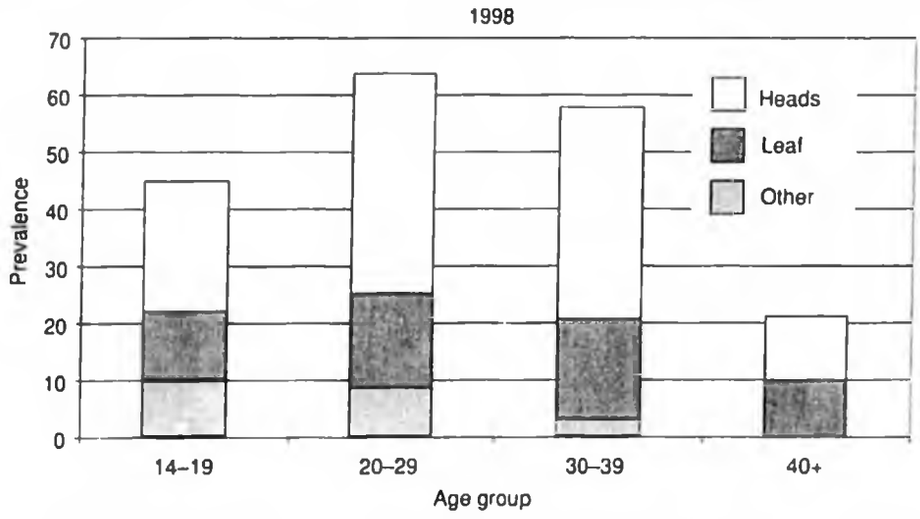
The greater expense of cannabis heads also encourages regular users to smoke them in waterpipes or 'bongs' in the belief that this maximises the delivery of THC. In the 1998 NDS Survey just over half of all persons who had used cannabis in the last year smoked 'heads' (57%) using bongs (56%). Younger users were more likely than older users to prefer bongs or pipes to joints (Figure 3) and heads to leaf, with the opposite trend in older users (Figure 4).

Figure 3: Prevalence of preference for different methods of using cannabis by age group



Source: National Drug Strategy Household Survey, 1998; Social Science Data Archives

Figure 4: Prevalence of preference of use of cannabis products according to age group



Source: National Drug Strategy Household Survey, 1998; Social Science Data Archives

All these changes in patterns of use—earlier initiation of cannabis use, greater use of more potent cannabis products such as heads, and the use of waterpipes—have probably increased the amount of THC consumed by regular cannabis users, while the concentration of THC in cannabis products has increased only marginally.

3 Cannabis use in the United States

In the United States two major surveys of illicit drug use have been undertaken since the early 1970s. The National Household Survey on Drug Abuse (sponsored by the National Institute on Drug Abuse) has surveyed household samples of adults throughout the U.S. since 1972. Since 1975, the 'Monitoring The Future' project has surveyed nation-wide samples of high school seniors, college students and young adults each year (2, 3).

3.3.1 NIDA Household Survey

NIDA has surveyed approximately 9000 persons aged 12 years and older in randomly selected households throughout the U.S. every two to three years since 1972. Since 1991, the survey has been conducted annually with a sample of over 30,000 participants (20).

In 1999, one third (35%) of the national sample reported that they had tried cannabis, 9% had used in the past year, and 5% reported that they were current users (Table 1) (21). Lifetime use increased from 11% among those aged 12 to 17 years to 59% among those aged 26 to 34 years before declining to 25% among those over the age of 35 years. Rates of discontinuation of use were high: more than two thirds of men and three quarters of women who had use cannabis at some time in their lives had not used it in the last year. Monthly cannabis use was uncommon. It was more common among men (9%) than women (6%) and most common among those aged 12 to 17 years (11%).

The NIDA Household survey series from 1974 to 1990 showed that rates of cannabis use increased throughout the 1970s, peaked in 1979, declined steadily throughout the 1980s to reach their lowest level in 1990, before increasing again in 1992.

Table 1: Prevalence of cannabis use (US National Household Survey on Drug Abuse, 1999)

	Lifetime	Past 12 months	Past month
12–17 years	18.7	14.4	7.7
18–25 years	46.8	24.8	14.8
26 + years	34.7	5.4	3.0
Total	34.6	8.9	5.1

Table 2: Trends in past month cannabis use (US National Household Survey on Drug Abuse 1974–1999)

Age	1974	1976	1977	1979	1985	1988	1990	1992	1995	1996	1999
12–17	12.0	12.3	16.6	16.3	13.2	8.1	7.1	5.3	10.9	9.0	7.7
18–25	25.2	25.0	27.4	38.0	25.3	17.9	15.0	13.1	14.2	15.6	14.8
26+	2.0	3.5	3.3								3.0
26–34				20.8	23.1	14.7	10.9	11.4	8.3	8.4	
35+				2.8	3.9	2.3	3.1	2.5	2.8	2.9	

3.3.2 The Monitoring The Future project

In this series of surveys, the prevalence of cannabis use has been estimated among secondary school students, college students and young adults. Since 1975 approximately 15,000 high school seniors have been surveyed. The college students and young adults who are surveyed each year represent a sample of those who were originally surveyed as high school seniors (about 14%) and have been followed up every two years. Since 1991 national samples of 8th and 10th grade students have also been annually surveyed.

In the 1999 survey, lifetime cannabis use increased with each higher age group but use in the past year reached a plateau in the 18 (last year of high school) to 28 year age group (Table 3). Daily use peaked at age 18, with 6% of high school seniors and 4.4% of 19 to 28 year olds reporting daily cannabis use. This is much lower than the 11% of high school seniors in the peak year of 1978 who used cannabis.

Table 3: Prevalence of cannabis use in the 1999 US Monitoring the Future Survey

	Lifetime use	12 month use	Past month use	Past month daily use
8th grade (14 years)	22.0	16.5	9.7	1.4
10th grade (16 years)	40.9	32.1	19.4	3.8
12th grade (18 years)	49.7	37.8	23.1	6.0
College	50.8	35.2	20.7	4.0
19–28 years	54.6	27.6	15.6	4.4

Because of high rates of daily cannabis use in the late 1970s, in 1982 more questions were asked about the duration of daily use. In 1982, 21% of the 12th graders reported that they had smoked cannabis daily for a month a more. This fell to 8% by 1992. Daily use has been consistently higher among males than females, and among those not planning to attend college. More than half of those who were daily users by age 18 began this pattern of heavy use by age 16. In 1993, 3% of all American 12th graders surveyed reported that they had smoked cannabis daily for two years or more on a continuous basis.

There have been rises and falls in cannabis use among American adolescents since 1975. Among 18 year olds, lifetime prevalence peaked at 65% in 1980, then fell by nearly half by the early 1990s. Use in the past year peaked at 51% in 1979 and fell to 22% by 1992. The rate of discontinuing use increased among those who had ever used cannabis (Table 4, third column), with less change in rates of discontinuation among those who had used

it 10 or more times. Most of those who ceased cannabis use had not had a great deal of experience with cannabis. The time trends in cannabis use were different from those of other drugs, suggesting that the changes in cannabis use reflected factors specific to that drug. Although most users of other illicit drugs also had used cannabis, trends in the use of other illicit drugs were independent of the cannabis-use trends.

Table 4: Trends in cannabis use among those in Year 12 (US Monitoring the Future Study, 1999)

	Lifetime use	12 month use	Discontinuation rate among those who had used cannabis	
			Ever	10 times +
1975	47	40	15	4
1980	60	49	19	5
1985	54	41	25	8
1990	41	27	34	12
1992	33	22	33	11
1993	45	36	20	8
1995	42	35	17	5

After more than a decade of declining rates of cannabis use among American secondary students, the 1992 and 1993 surveys reported that cannabis use rose sharply among 8th, 10th and 12th graders, and to a lesser extent among college students and young adults. There was an increasing initiation rate and a higher rate of continued use.

Johnston and colleagues have argued that changes in beliefs about the risks of cannabis use were responsible for the reduction in use between 1979 and 1991 and for the rise in use since 1992. They reported a strong negative correlation over time between the rates of cannabis use and the perceived risk of using cannabis and peer disapproval of use (e.g. (2, 3, 22). Between 1992 and 1996, a decrease in perceived risk, and a smaller decrease in personal disapproval of cannabis use, preceded an increase in rates of use (23).

3.3.3 The natural history of cannabis use

Bachman et al (24) have examined patterns of cannabis use from adolescence into adulthood in the Monitoring the Future data. They analysed data from 14 successive cohorts of high school seniors and college students who were followed from age 18 to 35 to assess the effect of major life transitions (such as entering college, entering full time employment, marrying and having children) on rates of use of cannabis in the past 30 days.

They found a steady decline in cannabis use from the early and mid 20s to the early 30s. The pattern for cannabis was similar to that for alcohol; it differed from tobacco use which was much more persistent. Major role transitions explained a substantial part of these changes. Use increased among those entering college but their use only caught up

with that of students who did not enter college (who used cannabis more often in high school than those who went on to college). Bigger decreases in use were seen in males and females on marriage and during pregnancy. Entering the military had a large impact on cannabis use, probably reflecting drug-testing before entry to service (4).

These findings have been confirmed in a detailed study of a single cohort of high school students that was followed from early adolescence into the middle adulthood (25, 26). This study also found that cannabis use peaked in the early 20s and declined steadily through the 20s and into the 30s. The decline was explained by the increasing societal responsibilities of marriage, children and employment. Use persisted in those who: did not enter conventional marriage (e.g. remained single or cohabited); did not enter college; and who were unemployed (see Chapter 8 below).

3.4 Cannabis use in Canada

A national telephone survey was conducted in Canada in 1994 by Health and Welfare Canada on 12,155 persons aged 15 years and older (27). Overall, 28% of the sample reported that they had used cannabis at some time in their lives, with males more likely to have used cannabis than females in all age groups. Rates of use in the past year declined with age from a high of 26% among those aged 15 to 17 years to 1.4% among those aged 45 to 54 years and 1% among those aged 55 to 64 years. Most users discontinued their use

There have been school surveys conducted in a number of Canadian provinces since the early 1970s. Adlaf and Smart (28) reviewed survey results in six of the ten provinces where surveys had been conducted between the early 1970s and the late 1980s. The most consistent trend was an increase in the prevalence of cannabis use during the 1970s followed by a sharp decline during the 1980s.

Since 1977 Ontario has conducted a series of surveys of students in grades 7, 9, 11 and 13 (corresponding to ages 10 through 19 years old) with sample sizes of between three and five thousand. The prevalence of cannabis use during the previous 12 months declined from 32% in 1979 to 14% in 1989. Declines were also reported for nine other drug types including tobacco and alcohol. Rates of illicit drug use were lower in Ontario than in the neighbouring United States. The size of the decline in rates of annual cannabis use was greater than for other substances (28). The Ontario surveys also found, like the U.S. surveys, that the perceived health risks of cannabis use increased as rates of use declined (28). Since the beginning of the 1990s there has been an increase in rates of cannabis use in the past year among Ontario high school students, from 12% in 1991 to 29% in 1999 (29). Comparison of trends in cannabis use in Canada has found the same pattern as reported in the USA, namely, a decline throughout the 1980s, followed by an increase in the early 1990s (30).

3.5 Cannabis use in Europe

Few European countries have undertaken regular community or high school surveys of cannabis and other illicit drug use. Those that have done so (e.g. Denmark, France, the Netherlands, Switzerland, and the United Kingdom) all reported increases in rates of cannabis use in the early 1990s (31). In all cases, the prevalence of current use was substantially less than lifetime use, indicating that most users stopped their use. Rates of current use were highest among those aged 15 to 24 years.

The Pompidou Group (32) examined illicit drug use among high school students in Belgium, France, Greece, Italy, Netherlands, Portugal, and Sweden (using a sample from the USA as the comparison). The study found that the rates of use of almost all illicit drugs were two or more times higher in the US sample. In the European samples, cannabis had been used at least once by between 10% and 36% of the older student population, and had been used in the past 30 days by between 3% and 14% of the European students as against 19% of the US students. Cannabis was used on a near daily basis by 1% or less of European samples compared with 3% in the US.

In 1992 in the Netherlands, a large national survey of drug use was undertaken involving over 10,000 students aged 10–18 years (33). About one third of males and one fifth of females had used cannabis at some time in their lives. Data from three national school surveys in 1984, 1988 and 1992 showed large increases in use between 1988 and 1992, particularly among males.

In 1997 the European Monitoring Centre on Drugs and Drug Addiction (EMCDDA) reported rates of lifetime cannabis use among adults and adolescents in household surveys in 9 countries and among high school students in 14 countries (34). Rates of lifetime use among adults varied from a high of 31.3% in Denmark to a low of 3.6% in a German mail survey. Rates among young adults varied between a high of 43% in Denmark to a low of 6% in Germany. Rates of use in the past year were available in fewer countries because of the low prevalence of this pattern of use, with rates varying between 1% in Sweden (for all illicit drugs combined) to a high of 21% in the United Kingdom (34). The school surveys showed higher rates of lifetime use, with a range between 41% in the United Kingdom and a low of 3% in Spain (34).

Smart and Ogborne (35) have recently analysed survey data on illicit drug use among students in 36 countries circa 1995. Most of these countries were European and developed industrialised societies. The highest rates of lifetime use of cannabis were in Britain. The rate was 53% in Scotland, followed by 41% in the United Kingdom and 33% in Wales. Then followed the USA (32%), Australia (31%) and the Netherlands (22%). Table 5 shows estimates produced by the EMCDDA in 2000.

Table 5: Prevalence of cannabis use in recent surveys in European countries

	Lifetime use (young adults)	12-month use (young adults)	Lifetime use (all adults)	12-month use (all adults)
Belgium	9.2	3.6	5.8	1.5
Denmark	43.0	6.0	31.3	3.3
Finland	17.5	6.3	9.7	2.5
France	25.7	8.9	16.0	4.7
E Germany	7.8	4.5	4.2	2.3
W Germany	20.1	7.8	13.4	4.5
Greece	19.7	8.8	13.1	4.4
Ireland	-	-	6.4	-
Netherlands	27.3	9.8	18.1	5.2
Spain	31.8	14.2	22.2	7.6
Sweden	16.0	2.0	13.0	1.0
United Kingdom	42.0	23.0	25.0	9.0

Taken from EMCDDA (2000)

These data suggest that, with the exception of the United Kingdom and Denmark, rates of cannabis use by young people in Europe is probably much lower than that in the USA. This has been confirmed in the recent European School Survey Project on Alcohol and Drugs (EPSAD) (36) which used the Monitoring the Future instrument to survey drug use in 95,000 year 10 school students in 30 participating countries. It found that the average rate of lifetime cannabis use in Europe was much lower (17%) than in the USA (41%). Rates in individual countries ranged between 1% in Romania and 35% in the Czech Republic, France and the United Kingdom (36).

3.6 Cannabis use in other regions

There is limited survey data on rates of cannabis use in other parts of the world (37). Surveys have been reported from different countries but their results have often been reported in ways that make it difficult to compare rates. In many cases these data provide only crude rates of cannabis use, survey methods are poorly reported, and it is sometimes unclear whether rates are lifetime or recent cannabis use (37). The limited data from developing countries in Africa, the Caribbean, Asia and South America suggest that rates of cannabis use are much lower in these countries than in Europe and English-speaking countries (37).

3.7 Correlates of cannabis use

Age: First use of cannabis typically begins in the teens and the heaviest rates of use occur in the early 20s. Rates of cannabis use remain relatively high during the early 20s but declines thereafter. Chen and Kandel (26) found that the majority of young adults who experimented with cannabis had done so by age 18 and Bachman et al (24) have found that rates of use decline steadily from the mid 20s into the early 30s.

Gender: Rates of cannabis use in the lifetime, the past year and the past week are consistently higher among males than females (2, 3, 8, 28). Daily use and long-term daily use are much more common among males (2, 3).

Income: A positive relationship has been found between income in adolescence and early adult life and cannabis use (9), with those earning more money more likely to report cannabis use. In the United States, Johnston (22) also reported that daily cannabis use correlated positively with income and hours worked on a paid job.

Socioeconomic Status: The relationship between cannabis use and socioeconomic status (SES) is weak. Higher rates of cannabis use are sometimes found among lower SES individuals but in the past two decades there has been no relationship between parent's education and cannabis use among 12th grade students in the United States, with the exception that the group with lowest parental education had slightly lower cannabis use than the others (2, 3). That difference may be better explained by differences in income during adolescence rather than by social class.

Ethnicity: Information on the relationship between ethnicity and cannabis use is limited. Ethnic differences in one country may not generalise to others and small sample sizes often make ethnic comparisons unreliable. Even in the very large Monitoring the Future survey, samples from several years have to be combined to make reliable comparisons between the three largest ethnic groups (2, 3, 38). These show that African-American students have lower rates of use in all grades than White or Hispanic students. Hispanics, on the other hand, tend to have the highest rates of use in the early grades, before the rates of school drop-out increase.

Availability: In general, and all other things being equal, the more freely available a drug is, the higher its use in the population. This hypothesis has been broadly supported in the case of alcohol consumption, where the larger the number of licensed outlets and the longer the hours of trading, the higher the levels of community alcohol consumption and alcohol-related problems (39, 40). There is very little evidence to rigorously test this hypothesis in the case of cannabis use. Self-reports from surveys on how easy it is to obtain cannabis (2, 3) have shown very little change over long periods of time for cannabis in the USA.

3.8 Summary

Patterns of cannabis use have been most extensively studied in developed societies such as the USA, Canada, Australia and some European countries. The limited data in Europe shows lower rates of use than in Australia, Canada and the USA. The highest rates are in the United Kingdom, Denmark and France. The limited data from developing countries suggest that Africa, the Caribbean, Asia and South America have much lower rates of cannabis use than Europe and English-speaking countries.

The USA, which has systematically collected survey data on cannabis and other drug use since 1975, has documented long waves of cannabis consumption among young people. Rates of cannabis use increased through the 1970s in the USA, peaked in 1979 and

declined throughout the 1980s until 1991. Rates of use increased sharply in 1992 and have continued to increase throughout the 1990s with a leveling out in the late 1990s. A rising trend in cannabis use during the early 1990s has been reported in Australia, Canada, the Netherlands, Norway and Sweden. The 'natural history' of cannabis use in studies conducted in the USA is for use to start in the mid to late teens, reach its maximum in the early 20s and decline in the mid to late 20s. A minority of cannabis users continue to use into their 30s. Marrying and having children substantially reduce rates of cannabis use.

A substantial minority of young people in Europe, North America and Australia (and during some periods in the USA and Australia, the majority) have tried cannabis at least once in their lives. Rates of regular cannabis use are much lower. Most cannabis users discontinue their use. Lifetime and recent cannabis use are higher among males than females, and highest among young adults in their early 20s.

3.9 References

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4 The acute effects of cannabis

4.1 Psychological effects

The effects of cannabis depend upon the dose received, the mode of administration, the user's prior experience with cannabis, any concurrent drug use, and the 'set and setting'—the user's expectations, attitudes towards the effects of cannabis, their mood state, and the social setting in which it is used (1). The main reason why most young people use cannabis is to experience a 'high': mild euphoria, relaxation and perceptual alterations, including time distortion, and the intensification of ordinary experiences, such as eating, watching films, listening to music, and engaging in sex (1, 2). When used in a social setting, the 'high' may be accompanied by infectious laughter, talkativeness, and increased sociability.

Cognitive changes include impaired short-term memory and attention. These make it easy for the user to become lost in pleasant reverie and difficult to sustain goal-directed mental activity (3, 4). Motor skills, reaction time, motor coordination and many forms of skilled psychomotor activity are impaired while the user is intoxicated (1, 4).

Some users report unpleasant experiences after using cannabis. These include anxiety, panic, a fear of going mad, and depression (5–7). These are often reported by users who are unfamiliar with the effects of cannabis (7), and by some patients given THC for therapeutic reasons (8). More experienced users may report these effects after swallowing cannabis because its effects may be more pronounced and of longer duration than they usually experience after smoking. These effects can be prevented by preparation of users about the effects they may experience and they can be managed by reassurance and support (5, 7). Psychotic symptoms, such as delusions and hallucinations, are very rare experiences that may occur at very high doses of THC, and perhaps in susceptible individuals at lower doses (5–7) (see Chapter 10 below).

4.2 Physical effects

The most immediate effect of smoking cannabis is to increase the heart rate by 20% to 50% within a few minutes to a quarter of an hour of smoking cannabis (9–11). Changes in blood pressure also occur. These depend upon posture: blood pressure is increased while the person is sitting, and decreases while they are standing. A sudden change from lying down to standing up may produce postural hypotension and a feeling of 'light-headedness' and faintness that is often the earliest indication of intoxication in naive users (12). In healthy young users these cardiovascular effects are unlikely to be of any clinical significance (11). They may amplify anxiety if the cannabis-induced palpitations and feeling faint are misinterpreted as symptoms of serious misadventure.

4.2.1 Toxic dose levels

THC is the component of cannabis that has the highest toxicity in animals. The cause of death is cessation of breathing or the heart, if breathing is assisted (13). Because tolerance develops to its effects, the toxic dose of THC depends upon the amount by which a dose exceeds the customary dose (14). Laboratory studies in humans of daily dosing of high levels of THC over weeks have demonstrated tolerance to mood effects, heart rate changes, decrease in skin temperature, increased body temperature, and impaired performance on psychomotor tests (15).

There are no reported cases of human deaths attributed to cannabis toxicity (16, 17). With many drugs the toxic dose gets smaller as one moves from mice, rats, monkeys and dogs to humans. With THC, by contrast, humans are probably much *less* susceptible to the acute toxicity of THC than animals. For example, the dose of THC which kills 50% of animals when administered intravenously is 40 mg/kg in the rat but it is 130 mg/kg in the dog and monkey (13). Extrapolation from the animal evidence suggests that the lethal human dose of THC is at least as high as, and probably higher than, that observed in the monkey. This means that the estimated toxic dose of THC in humans is so large, e.g. 4000 mg (18), that it is unlikely to be easily achieved by recreational users.

4.3 Psychomotor effects

A major societal concern about cannabis intoxication is that it may impair the psychomotor performance of automobile drivers, increasing the risk of accidents in cannabis users who drive a car while intoxicated. Individuals who drive while intoxicated with alcohol are dangerous to others in proportion to how intoxicated they are (19). It has been more difficult to decide whether cannabis intoxication impairs psychomotor performance in a similar way to alcohol.

4.3.1 Effects of cannabis on psychomotor tasks

Simple reaction time is not reliably affected by cannabis (20, 21). In choice reaction time tasks, in which the response is conditional upon the occurrence of a stimulus in the presence of another discriminant stimulus (such as the pitch of a tone), reaction time is usually slower after using cannabis (22, 23).

The performance of concurrent tasks is almost always adversely affected by cannabis, although the effects on the component tasks are not always consistent (24–28). In studies of concurrent tasks subjects are asked to do one task which requires continuous attention, typically tracking, while discriminating between significant stimuli that occur sporadically and non-significant stimuli that occur more frequently.

4.3.2 Effects of cannabis on simulated driving and flying

In simulated driving tasks subjects use skills similar to those involved in driving a car under laboratory conditions which have been designed to emulate the performance characteristics of a car. These simulations have two major advantages (29): cannabis users can be tested after taking large doses of cannabis, and they can be placed in simulated emergency situations which test their level of impairment. It would be unethical to do either of these things on the road. The difficulty with simulator studies lies in achieving fidelity to the conditions of on-road driving.

Smiley (29, 30) who critically reviewed research on the effects of cannabis on simulated driving has argued that the early studies which showed fewer effects than later studies suffered because of their unrealistic car dynamics. Later studies that used more realistic driving simulators have shown impairments of lane control after cannabis use. Some of the studies have also shown reductions in risk-taking as manifested in slower speeds, and maintenance of a larger distance from the car in front in following tasks (30).

A smaller number of simulator studies have been done on the effects of cannabis on flying skills. Janowsky et al (31) found substantial increases in errors in keeping the plane at the proper altitude and heading during a simulated flight after pilots had taken cannabis. Yesavage et al (32) originally reported that a simulated flying task was impaired up to 24 hours after smoking cannabis but this study did not include a control group. A later study with a control group (33) failed to replicate this result and only found an effect 1 to 4 hours after smoking. A third study that also included a control group (34) failed to show impairments in performance up to 24 hours after smoking cannabis. Although much has been made of the original findings (despite the failure to replicate them), the effects were very small and of uncertain significance for flying safety. Jones (35) has argued that the use of cannabis by pilots 24 hours before flying may be more an indicator of poor judgement than a risk because of residual psychomotor effects of cannabis.

4.3.3 Effects of cannabis on driving on road courses

A number of studies have been done on the effects of cannabis on driving cars around off road courses. These studies have found that cannabis has modest effects by comparison with alcohol. An early study by Hansteen et al (36) showed that a moderate dose of alcohol (approximately 0.07 BAC) or THC (5.9 mg) impaired driving on a traffic-free course, with driving speed decreased after using cannabis but not alcohol. Smiley et al (37), using a different type of course, found that reaction time to signal stimuli was increased by a combination of cannabis and alcohol. Klonoff (38) studied driving on a closed course, and in city traffic, after a placebo and two doses of smoked cannabis (4.9 and 8.4 mg THC). Driving on the closed course was impaired by both doses. Driving in traffic, however, was not significantly affected. Sutton (39) also found that cannabis had little effect on actual driving performance.

Peck et al (40) recorded performance on a range of driving tasks on a closed circuit on four occasions after the administration of placebo, up to 19 mg of smoked THC, 0.84 g/kg of alcohol, and the combination of both drugs. On most individual and derived composite measures, cannabis impaired performance. The effects of cannabis on driving performance were less than those of alcohol.

A recent series of on road studies by Robbe and colleagues (41, 42) found modest impairment of driving skills after cannabis on actual driving on either a driving course without traffic, on a highway or in urban traffic. They found that drivers were aware of their intoxication after using cannabis and took steps to minimise its impact on their driving by slowing down (41).

The effects of cannabis use on on-road driving have been smaller than the effects of intoxicating doses of alcohol (29, 30). Cannabis use has consistently made drivers slow down (30). This contrasts with the typical increase in speed when drivers are intoxicated

by alcohol. The compensatory behaviour of cannabis users may explain the comparatively small effects of cannabis intoxication in on road driving studies. For ethical reasons on road studies have not been able to test the response of cannabis-intoxicated drivers to emergency situations in which there is less opportunity to compensate for impairment. The few studies which have simulated this situation (e.g. by measuring reaction to other tasks while driving) have shown that cannabis use impairs emergency decision-making (29, 30).

4.3.4 Studies of cannabis use and accident risk

It is unclear whether cannabis use increases the risk of being involved in motor vehicle accidents. Surveys (42, 43) have found that the majority of cannabis users have driven after using cannabis, despite being aware of impairment (38, 44). But epidemiological studies of accident fatalities and injuries have not definitively shown that cannabis users are more likely to be involved in motor vehicle or other accidents. This contrasts with the role of alcohol intoxication in accidents where case-control studies have shown that persons with blood alcohol levels indicating intoxication are over-represented among accident victims by comparison to drivers who are not involved in accidents (45). The lack of the evidence in the case of cannabis reflects major difficulties in obtaining the necessary evidence to assess its role (19).

There are a substantial number of studies of the prevalence of cannabinoids in the blood of drivers who have been involved in motor vehicle accidents (see Chesher (19) and McBay (46) for reviews). Studies of accident fatalities tested post-mortem have found that 4% to 37% of blood samples contained cannabinoids, most often in combination with blood alcohol levels (BAC) indicative of intoxication (e.g. (47–49). An Australian study of 1045 fatalities (50, 51) found cannabinoids in the blood of 11% of drivers, 35% of whom also had BACs indicative of intoxicating doses of alcohol. Similar findings have been reported in studies of Californian motorists tested on suspicion of impairment by the Highway patrol (52) and in a prospective study of trauma patients (53).

These findings are difficult to evaluate for a number of reasons. First, it is not clear that drivers with cannabinoids are over-represented among accident victims because we do not know how many drivers who have not been involved in accidents have cannabinoids in their blood (54). Finding a rate of 35% of accident victims with cannabinoids in their blood may seem high but so is the rate of cannabis use among young males, the group who are most likely to be involved in motor vehicle accidents (53). Second, the presence of cannabinoids in blood levels does not necessarily mean that a driver was intoxicated by cannabis at the time of an accident (55) (see Chapter 2 above). Third, it is difficult to attribute an accident to cannabis when drivers with cannabinoids in their blood also have high blood alcohol levels (19, 46).

'Culpability analysis' has been developed to address these issues (54). In these analyses, a researcher decides which driver was 'culpable' for an accident using information about the circumstances of the fatal crash but excluding information on their alcohol and drug use. Drivers with no alcohol or other drugs in their blood are used as the control group to see whether cannabis and other drugs increase driver culpability. A common problem with these analyses is that the culpability of drug-free drivers is often high. This makes it difficult to detect an increase in culpability among drivers with alcohol, cannabis and other drugs in their blood.

Most culpability analyses have shown increased culpability among drivers with intoxicating levels of alcohol in their blood (19, 56). Drivers who have only had cannabis present have been in the minority because most also have intoxicating doses of alcohol (19, 56). There has been no evidence of an additive effect of alcohol and cannabis in these analyses despite the fact that laboratory studies suggest that the impairments produced by alcohol and cannabis are additive (19). These findings have been replicated in two Australian studies that used culpability analysis to examine the role of cannabis in fatal (51) and non-fatal motor accidents (50, 57, 58). There was a strong relationship between alcohol level and culpability in each study but neither study found any relationship between THC and culpability.

A different approach has been used by Gieringer (59), who estimated the proportion of drivers who might be expected to have blood and urine samples positive for cannabinoids from US household surveys. He estimated that cannabis users were 2 to 4 times more likely to be accident victims than non-cannabis users. Cannabis users who also used alcohol were even more likely to be over-represented among the victims of motor vehicle accidents.

4.3.5 Other epidemiological data on accidental injury

There is other suggestive evidence that cannabis use may increase the risk of accidents. Two surveys of self-reported accidents among adolescent drug users found a relationship between self-reported cannabis use and involvement in accidents. Cannabis smokers were approximately twice as likely to report being involved in accidents than non-cannabis smokers (60, 61).

Two studies of deaths among cannabis users provide suggestive evidence of an association between cannabis use and accidents (62, 63). Andreasson and Allebeck reported mortality over 15 years among 50,465 Swedish military conscripts. They found that men who had smoked cannabis 50 or more times by the age of 18 had an increased risk of premature death (Relative Risk (RR) = 4.6). Motor vehicle accidents accounted for 26% of these deaths and 7% were other accidents (e.g. drownings and falls). The increased risk was no longer statistically significant after statistical adjustment for antisocial behaviour and alcohol and other drug use in adolescence (62).

Polen et al (63) compared health service use by 450 people who did not use cannabis, and 450 persons who were daily smokers of cannabis only, who were screened by Kaiser Permanente Medical Centers between July, 1979 and December, 1985. They found an increased use of medical care by cannabis-only smokers for accidental injury over one to two years of follow-up, with cannabis users who were the heaviest alcohol users showing the highest rates of use. Sidney et al (64) reported death rates after 10-years among 65,171 members of the Kaiser Permanente Medical Care Program aged between 15 and 49. The sample comprised 38% who had never used cannabis, 20% who had used less than six times, 20% who were former users, and 22% who were current users. Regular cannabis users had a slightly increased rate of premature death (RR = 1.33) but this was explained by increased deaths caused by AIDS in men, probably because cannabis use was more common among male homosexuals than male heterosexuals.

4.4 Summary

The major adverse acute effects of cannabis use are anxiety and dysphoric experiences in a substantial minority of cannabis users. The risks of fatal overdose are very small, with no deaths reported in the medical literature.

Cannabis adversely affects the performance of a number of psychomotor tasks in a way that is related to dose and the difficulty of the task. The acute effects on psychomotor performance of cannabis in doses used recreationally are similar to but smaller than those of intoxicating doses of alcohol. Alcohol and cannabis also differ in their effects on user's willingness to take risks when driving. Persons intoxicated by cannabis engage in less risky behaviour than persons intoxicated by alcohol because they seem to be more aware of their impairment.

It has been difficult for technical and ethical reasons to decide whether the impairment produced by cannabis intoxication increases the risk of motor vehicle accidents. There is reasonable evidence from studies of cannabinoid levels in accident victims, and the few epidemiological studies, to suggest that driving after using cannabis probably increases the risk of motor vehicle accidents. The increased risk may be of the order of 2 to 4 times but it is difficult to rule out the possibility that it is the result of the combined use of cannabis and alcohol.

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5 Cellular and immunological effects of cannabis use

5.1 Is cannabis a potential cause of cancer?

Cannabis could be a cause of cancer if the cannabinoids it contains (or substances produced when it is burnt) produce genetic mutations in the user's somatic cells (such as those in the lung) (1). There is only weak evidence that THC is 'mutagenic' in this sense. THC can produce changes in cellular processes in animal cells in the test tube (2) but these changes probably delay or stop cell division rather than produce cellular changes that may lead to cancer (1).

There is no evidence that THC and other cannabinoids produce mutations in microbial tests of mutagenicity, such as the Ames test (1, 3). There is inconsistent evidence on whether cannabinoids produce breaks in chromosomes (3) but if they do, these changes are unlikely to cause cancers (1) because chromosomal abnormalities are more likely to kill the affected cell than to produce malignant transformation and proliferation (1). A recent study in rats and mice found no evidence that THC caused cancer (4).

Cannabis ***smoke*** is mutagenic in the test tube, and hence is potentially a cause of cancer (i.e. carcinogenic) (1, 3, 5). Cannabis smoke produces chromosomal aberrations, is mutagenic in the Ames test (6) and causes cancers in the mouse skin test (1). The fact that it is cannabis *smoke* that is carcinogenic (6) suggests that any cancers caused by cannabis smoking are most likely to occur in organs that receive long term exposure to cannabis smoke and the tars it contains, such as the lung, the upper aerodigestive tract (mouth, tongue, oesophagus) and the bladder (1).

5.2 Is cannabis smoking a cause of aerodigestive tract cancers?

There are good reasons for suspecting that cannabis may cause cancers of the lung and the aerodigestive tract (the oropharynx, nasal and sinus epithelium, and the larynx). First, tobacco is a cause of respiratory cancer (7) and cannabis smoke contains many of the same cancer-causing substances as tobacco smoke (8). Second, chronic cannabis smokers show many of the pathological changes in lung cells that precede the development of cancer in tobacco smokers (9, 10).

Third, cancers of the upper aerodigestive tract have been reported in young adults who have been chronic cannabis smokers (11–15). In many cases these were also cigarette smokers and alcohol consumers but Caplan and Brigham reported two cases of cancer of the tongue in men aged 37 and 52 years (12), neither of whom smoked tobacco or consumed alcohol. A history of long-term daily cannabis use was their only shared risk factor. These reports raise a suspicion but provide limited support for the hypothesis that

cannabis use is a cause of upper respiratory tract cancers. They do not compare rates of cannabis use in cases and controls, cannabis exposure has been assessed retrospectively and in the knowledge that the user has cancer; and they do not control for confounding factors such as alcohol and tobacco use.

Two recent controlled studies have produced inconsistent results. Sidney et al (16) studied cancer incidence during an 8.6 year follow up of 64,855 members of the Kaiser Permanente Medical Care Program (KPMCP). Study participants were asked about cannabis use during medical screening between 1979 and 1985. Their average age at entry was 33 years and they were followed until: death, a diagnosis of cancer or HIV/AIDS, exit from the KPMCP or 31 December 1993 (a mean of 8.6 years). At study entry 38% had never used cannabis, 20% had used it less than 6 times, 20% were former users, and 22% were current cannabis users. Data were collected from a cancer registry and the California mortality data system.

There were no more cases of cancer among those who had ever used cannabis or who were current cannabis users than among those who had not used cannabis at study entry. There were more tobacco-related cancers among tobacco smokers (regardless of cannabis use) but no more among cannabis smokers. Males who had ever smoked cannabis had an increased risk of prostate cancer (RR = 3.1) and so did males who were current cannabis smokers (RR = 4.7) (16).

Zhang et al (17) compared rates of cannabis use among 173 persons with primary squamous cell carcinoma of the head and neck and 176 controls who were blood donors matched on age and sex from the same hospital. Cases were more likely to have used cannabis than controls (14% and 10% respectively), with an odds ratio for cannabis smoking of 2.6 after adjusting for cigarette smoking, alcohol use and other known risk factors. The cases with cancer smoked cannabis more often and for longer than the controls. The relationship between cannabis smoking and these cancers was stronger among adults under the age of 55 years (Odds Ratio (OR) = 3.1). There was a suggestion that cancer cases were more likely to smoke both tobacco and cannabis than controls (17).

How do we reconcile the negative findings of the Sidney et al study with that of Zhang et al? The persons studied by Sidney et al were too young (average age of 43 at follow up) to see many excess cases of cancer attributable to cannabis smoking. The chance of Sidney et al finding cancers was further reduced because only 22% were cannabis users at study entry.

There is as yet no evidence that regular cannabis smoking causes cancers of the lungs and lower respiratory tract of the type caused by cigarette smoking (10). Studies of respiratory cancers would be timely since cannabis users in the post-War birth cohorts are reaching the age of 60 years when the incidence of all cancers steeply increases. A longer follow-up of the Sidney et al cohort may reveal whether cannabis smoking causes respiratory cancers.

5.3 The public health impact of cancers caused by cannabis smoking

On current patterns of use, cannabis smoking will cause very few respiratory cancers, even if the risks of *daily* cannabis smoking are comparable to those of daily tobacco smoking (18). This is because in Western societies there are many more daily tobacco (25–30%) than daily cannabis smokers (1–3%) (19), most cannabis smokers stop in their mid to late twenties (20), and the 1% or less who smoke cannabis daily over decades typically smoke 1 to 3 cannabis cigarettes per day rather than 10 to 30 tobacco cigarettes a day (21). Among this minority of users, prolonged use of cannabis into the fourth and later decades may increase the risk of respiratory cancer, especially among tobacco smokers who also smoke cannabis.

5.4 Is cannabis smoking during pregnancy a cause of childhood cancers?

Cannabis smoking has also been linked to cancers in children born to mothers who used cannabis during their pregnancy. Three case control studies have examined cannabis use as a risk factor for childhood cancers, along with a range of other risk factors. There was no prior reason to expect cannabis use to be related to these cancers, as there was with respiratory cancers.

Maternal cannabis use and childhood cancer were associated in a case-control study of Acute Nonlymphoblastic Leukemia (ANLL), a rare form of childhood cancer (22, 23). The study was designed to assess the relationship between this childhood cancer and maternal and paternal environmental exposures to petrochemicals, pesticides and radiation. Maternal cannabis use was assessed before and during pregnancy as one of many variables to be statistically controlled when analyzing the relationship between ANLL and maternal and paternal environmental exposures.

A strong association was found between maternal cannabis use and ANLL. The mothers of cases were 11 times more likely to have used cannabis before and during their pregnancy than mothers of controls. The relationship persisted after statistical adjustment for other risk factors. An alternative explanation is that because reports of cannabis use were obtained after the diagnosis of the ANLL, mothers of children with ANLL may have been more likely to report cannabis use than were mothers of controls. The authors did find that the rate of cannabis use among the controls in this study was much lower than among controls in other studies. When the rate of cannabis use among controls was adjusted upwards there was a reduced but still significant three-fold increase in risk.

Two other case-control studies have reported an increased risk of rhabdomyosarcoma (24) and astrocytomas (25) in children born to women who reported using cannabis during their pregnancies. Neither planned to study the association between childhood cancer and maternal cannabis use. In each case, cannabis use was one of a large number of variables that were to be controlled for in statistical analyses of the relationship between the exposure of principal interest and the childhood cancer.

Trends in the rates of these cancers suggest that these studies may have produced chance results. There was no increase in the rate of any of these cancers between 1979 and 1995 (26). The rate of ANLL, for example, remained steady during this period (27). The same was true of soft tissue sarcomas (which include rhabdomyosarcomas) (28). Cancers of the brain (about 52% of which are astrocytomas) did increase in incidence between 1979 and 1995 (29) but in a way that is more likely to reflect improved diagnosis than maternal cannabis use. The rate of these cancers increased abruptly in 1985, after Magnetic Resonance Imaging became widely available in the USA, and remained stable thereafter (29).

5.5 Immunological effects

Tobacco smoking suppresses humoral and cell-mediated immunity so it is reasonable, given the similarities between cigarette and cannabis smoke (30), to expect that cannabis smoke suppresses immunity (2). Cannabinoid receptors are also expressed in some immune cells (Kamminski, 1998) so THC may influence the immune system. If cannabinoids have immunosuppressive effects then their therapeutic use may be limited in patients with impaired immune systems. This could preclude their use as anti-emetic agents in cancer chemotherapy and as appetite stimulants and mood enhancers in patients with AIDS.

There are difficulties in deciding whether cannabis impairs the immune system in humans. First, most studies have been conducted on whole animals and in animal and human cell cultures that have been exposed to cannabis smoke or cannabinoids. The relevance of these studies to humans is limited by the fact that they used very high oral doses of THC (31). Second, there have been very few epidemiological studies of immune system functioning and disease susceptibility in heavy chronic cannabis users (31).

5.5.1 Effects of cannabinoids on humoral immunity

The effect of cannabinoids on humoral immunity has been assessed by measuring their effect on animal and human B-cell responses to sheep red blood cells. Cannabinoids do not consistently alter B-cell functioning (32). While cannabinoids consistently impair the B-cell responses in mice, no such effects have been observed in humans, and the few positive studies have produced results that are within the normal range (32).

Antibodies have been formed to THC in animals (31) and there are clinical reports in humans that cannabinoids exacerbate allergies and that allergy to cannabinoids can develop in humans (31). Hollister (33), however, has argued that although a few persons may become truly allergic to cannabinoids it is more likely that these are rare allergic reactions that are due to contaminants (e.g. bacteria, fungi, moulds, parasites, worms, chemical) found in cannabis.

5.5.2 Effects of cannabinoids on cell-mediated immunity

Studies of the effects of cannabinoids on T-cells and macrophage numbers have been mixed, with some showing reductions (2) while others have not (34). The evidence is also mixed on the effect of cannabinoids on T-cell functioning. A number of the earliest

studies suggested that T-cells from chronic cannabis users were less responsive but later laboratory studies of chronic heavy dosing in humans (35) have failed to replicate these results. Studies exposing human T-cells to cannabinoids have also produced mixed results while animal studies have showed a decreased T-cell response (32).
In a review of the literature published in this field in the 1990s, Klein (31) concluded that THC affected the function of immune cells including lymphocytes, macrophages, and polynuclear cells in the test tube but relatively high drug concentrations were required, the effects were not related to psychoactivity, and they were reversible.

5.5.3 Effects of cannabinoids on host resistance

Studies in mice and guinea pigs have suggested that high doses (200 mg/kg) of THC reduce resistance to infection (36–39). A consistent finding in humans has been that exposure to cannabis ***smoke*** adversely affects alveolar macrophages, the immune cells in the respiratory system that comprise the first line of defence against micro-organisms which enter the body through the lungs (5). Studies of these cells in cannabis smokers have shown abnormalities (40), and exposure of alveolar macrophages to cannabis smoke impairs their ability to inactivate bacteria (5, 32), and a fungus (41). It is the noncannabinoid components of cannabis smoke that produce these effects (5).

5.5.4 The human significance of the immunological effects of cannabinoids

The animal evidence is reasonably consistent that cannabinoids impair cell-mediated and humoral immunity and several animal studies have found decreased resistance to a bacteria and virus. However, the doses required to produce these immunological effects in animals are much higher than the doses used by humans (1). Human users may also develop tolerance to any immunological effects of cannabinoids, which may reduce the small effects projected from animal studies. Given the large number of cannabinoid effects to which tolerance has been shown to develop it would not be surprising if this were also true of its immunological effects.

The limited human evidence is mixed. A small number of studies that suggest that cannabis use impairs immunity have not been replicated by others. Munson and Fehr (32) concluded that there was 'no conclusive evidence' that cannabinoids impaired functioning of T-lymphocytes, B-lymphocytes or macrophages, or reduced immunoglobulin levels in humans. There was 'suggestive evidence' of impaired T-lymphocyte functioning reflected in an impaired reaction to mitogens and allogenic lymphocytes (32). More recently, Wallace et al (42, 43) failed to find impairment of lymphocyte function in alveolar macrophages in cannabis smokers although they did find it in tobacco smokers.

The significance of these immunological impairments in chronic cannabis users is uncertain. There have been sporadic reports of ill health among chronic heavy cannabis users in Asia and Africa (32) but these reports are difficult to evaluate because of the confounding effects of poor living conditions and nutritional status (32). Three field studies of the effects of chronic cannabis use in Costa Rica (44), Greece (45), and Jamaica (46), failed to find any evidence of increased susceptibility to infectious diseases among chronic cannabis users. But less than 100 users were studied, a number which is too small to detect a small increase in the incidence of common infectious and bacterial diseases.

A recent study by Polen et al (47) compared health service utilisation by non-smokers and daily cannabis-only smokers enrolled in a health maintenance organisation. Their results provided suggestive evidence of an increased rate of treatment for respiratory conditions among cannabis-only smokers, although its significance is uncertain because infectious and non-infectious respiratory conditions were not separated. Further studies of this type may better assess how serious a risk chronic heavy cannabis smoking poses to the immune and respiratory systems (31).

5.6 Effects of cannabis on immunity in immunocompromised persons

Cannabis has been used by young adults in Western societies for over 30 years so the absence of epidemic infectious disease among these users makes it unlikely that cannabis smoking produces *major* impairments in the immune systems of users. The absence of such epidemics does not rule out the possibility that heavy cannabis use may impair immunity in ways that produce small increases in rates of common bacterial and viral illnesses (32). This could have escaped the notice of clinical observers.

Studies of the effects of cannabis use on patients with immune systems compromised by AIDS provide one way of detecting immunological effects of cannabis. If there were no effects in patients with compromised immune systems, it would be a reasonable to infer that there was little risk of immunological effects in recreational users.

A number of epidemiological studies of HIV positive homosexual men have examined the effects of cannabis and other drug use on progression to AIDS. Kaslow et al (48) studied progression to AIDS among 4,954 homosexual and bisexual men and found that HIV-positive cannabis users were *not* more likely to progress to AIDS and cannabis use was not related to immunological functioning. There was no relationship between cannabis use and progression to AIDS over six years in 451 HIV-positive men in the San Francisco Men's Health Study (49). The only study which found an association between cannabis and progression to AIDS was the Sydney AIDS Project in which 386 gay men were followed up over 12 months (50). This result may be at odds with the others because the study had a short follow up and many of the HIV positive cases may already have had AIDS (30).

A study of deaths in 64,855 HMO patients in California (51) did find an association between cannabis use and premature death from AIDS. Unmarried men had much higher rates of cannabis use than married men but in this study cannabis use was probably a marker for high-risk sexual behaviour rather than an independent risk factor.

5.7 Summary

Cannabis *smoke* is mutagenic (capable of inducing genetic mutation) and carcinogenic in animal tests and it contains many of the same carcinogens as tobacco smoke. It is therefore a potential cause of cancer in body cells that are chronically exposed to it, such as those of the aerodigestive and respiratory tracts.

There are case reports of aerodigestive tract cancers among relatively young adults who have been daily cannabis users. A case control study found an association between cannabis smoking and head and neck cancer but a large prospective study did not. The youth of the participants and the low rate of regular cannabis use in this prospective study reduced its ability to detect an increase in these cancers. Further follow-up and case control studies are needed to clarify the issue.

There is weaker evidence for an increased risk of cancers among children born to women who smoked cannabis during pregnancy. Three studies of very different types of cancer have reported an association with maternal cannabis use but none of these was a planned study of the role of cannabis use in these cancers so replication of their results is required. There is no evidence that the rate of any of these cancers has increased over the past few decades.

In animals THC in high doses can impair cell-mediated and humoral immunity and reduce resistance to infection by bacteria and viruses. The relevance of these findings to human health is uncertain because the doses that produce these effects in animals are very high, and tolerance probably develops to the effects on the immune system in human users. The limited evidence on the immune effects of cannabis in humans is conflicting; the small number of studies that have produced adverse effects have not been replicated. The studies that have produced evidence of adverse effects have reported small changes that are within the normal range.

There has not been any increase in rates of infectious disease among chronic heavy cannabis users. Given the duration of large-scale cannabis use by young adults in Western societies, the absence of such epidemics makes it unlikely that cannabis smoking produces ***major*** impairments in the immune system. It is more difficult to exclude the possibility that chronic heavy cannabis use produces minor impairments in immunity.

There are three prospective studies of HIV-positive homosexual men two of which indicated that continued cannabis use did ***not*** increase rates of progression to AIDS and one of which suggested that it did. A recent epidemiological study which compared health service utilisation by nonsmokers and daily cannabis smokers provided suggestive evidence of an increased rate of medical care use for respiratory conditions among cannabis smokers. The most sensitive test of any small immunological effects of cannabis may come from studies of the therapeutic usefulness of cannabinoids in immunologically compromised patients, such as those undergoing cancer chemotherapy, or those with AIDS.

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6 The reproductive effects of cannabis use

Studies conducted in the mid-1970s showed that animals given large doses of cannabis or THC during pregnancy had lower levels of the gonadal hormones (testosterone and oestrogen) that control reproduction (1–5). There were also case reports of breast development in young men who had a history of heavy cannabis use (6). A study by Kolodny et al (7) found that chronic male cannabis users had lower levels of testosterone, a lower sperm count and motility, and more abnormal sperm than controls. These observations raised concerns that the use of cannabis by young adults during the 1970s and 1980s would impair fertility in men and adversely affect pregnancy outcomes in women. Cannabinoid receptors are expressed by cells in the hypothalamus and pituitary that regulate sex hormone production (8) so it is possible that THC can affect the functioning of the reproductive system.

6.1 Effects on the male reproductive system

Male animals given large doses of cannabis, crude cannabis extracts, THC and other cannabinoids showed lowered testosterone levels, retarded sperm maturation, reduced sperm count and sperm motility, and increased rates of abnormal sperm (1, 5, 9, 10). Although the mechanisms for these effects were uncertain, it was likely that they were a direct effect of THC on the testis, and an indirect effect on the hypothalamic hormones that stimulate the testis to produce testosterone (5).

Human studies of the effects of cannabis on male reproductive function produced mixed results (9). The study by Kolodny et al (7), which reported reduced testosterone, sperm production, and sperm motility and increased abnormalities in sperm, was not replicated in a larger, better controlled study of chronic cannabis users. This study failed to find any difference in testosterone level at study entry, or after three weeks of daily cannabis use (11). The significance of the animal findings for human cannabis users are uncertain (2) because testosterone levels in human cannabis users have generally been within the normal range (12).

6.2 Effects on the female reproductive system

In animal studies cannabis and THC interfere with the hormones controlled by the hypothalamic-pituitary-gonadal axis in non-pregnant female animals (1), delaying oestrous and ovulation (9). There have been very few human studies of the effects of cannabis on the female reproductive system because of fears that cannabis use may produce birth effects in women of childbearing age (13). An unpublished study by Bauman (1980 cited by Nahas (3)) compared the menstrual cycles of 26 cannabis smokers with those of 17 controls and found a higher rate of anovulatory cycles among the cannabis users. Mendelson and Mello (14) failed to find that cannabis use affected the female sex hormones, or the duration of the cycle. Mueller, Daling, Weiss and Moore (15) reported a modest association (OR = 1.7) between cannabis use and

infertility in a case-control study of 150 women with primary anovulatory infertility and 150 controls. The relationship was strongest in women who had used cannabis *less* frequently. In the absence of any other human evidence, Bloch (1), the Institute of Medicine (2) and Murphy (9) have argued that the animal evidence suggests that cannabis use probably inhibits human female reproductive function but it is uncertain how large these effects are.

6.3 Foetal development and birth defects

The possibility that cannabis use during pregnancy may adversely affect pregnancy outcomes is raised by evidence that THC crosses the placenta in animals (1) and humans (16). This makes it possible that THC, and other cannabinoids, may interfere with the development of the foetus, that is, may act as teratogens.

In mice, rats, rabbits, and hamsters large doses of cannabis or THC can produce foetal resorption, growth retardation, and malformations (1). Growth resorption and growth retardation have been more consistently reported than birth malformations (17) and the doses that produce malformations have been very high (17). Birth malformations have been observed more often after the administration of crude cannabis extract rather than pure THC, suggesting that other cannabinoids may produce any teratogenic effects. It is also unclear whether these teratogenic effects can be attributed to THC or to reduced food intake caused by the large doses of cannabis that have been used (1, 17). Bloch (1) concluded that THC was unlikely to be teratogenic in humans and was, at most, 'weakly teratogenic' in rodents and rats.

6.3.1 Human studies

Epidemiological studies of the effects of cannabis use on human reproduction have produced mixed results for a number of reasons. First, adverse reproductive outcomes and heavy cannabis use during pregnancy are relatively rare. This means that unless cannabis use produces a large increase in the risk of abnormalities, very large sample sizes will be required to detect adverse effects of cannabis use on foetal development. Many of the studies that have been conducted to date have been too small to detect effects of this size (18–20).

Second, societal disapproval of illicit drug use during pregnancy may discourage honest reporting when women are asked about drug use during their pregnancy (21). If a substantial proportion of cannabis users are misclassified as non-users, any relationship between cannabis use and adverse outcomes will be attenuated, requiring even larger samples to detect it (22).

Third, women who use cannabis during their pregnancies differ from those who do not in a variety of ways that may affect the outcome of their pregnancies. Cannabis users are, for example, more likely to smoke tobacco and use alcohol and illicit drugs during their pregnancy. They are also likely to have lower income, poorer education levels and poorer nutrition, all of which predict an increased risk of poorer pregnancy outcomes (10, 20, 23). These make it difficult to confidently attribute any poor birth outcomes to cannabis use rather than to other drug use, or to poor maternal nutrition and prenatal care.

Given these difficulties, there is reasonable consistency (although not unanimity) in the finding that cannabis use in pregnancy is associated with slightly reduced birth weight (24–26), and length at birth (23). This relationship has been found in the best-controlled studies, and it has persisted after statistically controlling for potential confounding variables (24, 25). A recent meta-analysis of these studies found that regular cannabis smoking during pregnancy possibly reduced birth weight but results varied considerably between studies (27). The mean weight reduction of 48 g (for any cannabis use vs no cannabis use during pregnancy) was much smaller than that associated with tobacco smoking during pregnancy, namely, 200 g (27).

The relationship between cannabis use and birth abnormalities is less certain. Milman (28) reported several cases of children with features similar to the Foetal Alcohol Syndrome (FAS) born to women who smoked cannabis during pregnancy but did not use alcohol. Epidemiological studies have largely not reported an increased rate of congenital abnormalities among children born to women who used cannabis during pregnancy (23, 25, 26, 29).

One study reported a five-fold increase in the rate of children with FAS-like features born to women who reported using cannabis (29). This finding was puzzling because there was *no* relationship between self-reported alcohol use and the 'foetal alcohol syndrome'. An additional study reported an increase in the crude rate of birth abnormalities among children born to women who reported using cannabis but this result was no longer statistically significant after adjustment for confounders (30). The study by Zuckerman et al is the most convincing study that failed to find an effect. A large sample of women was studied, among which a substantial proportion reported cannabis use that was verified by urinalysis. There was a low rate of birth abnormalities among the cannabis users, and no suggestion that their rate was higher than that in the controls.

6.4 Post-natal development

The most extensive research on the effects of cannabis use during pregnancy on the post-natal development of the child comes from the Ontario Prospective Prenatal Study (OPPS). This study assessed developmental and behavioural abnormalities in children born to women who reported using cannabis during pregnancy (31–39). A sample of 698 mothers were asked about their drug use during pregnancy and their children were measured on the Brazelton scales after birth and neurologically assessed at one month. In subsequent studies, these children were assessed using standardised scales at six and twelve months and throughout their childhood and into their adolescence (31).

The initial OPPS studies reported a developmental delay shortly after birth in the infants' visual system, and an increased rate of tremors and startle among the children born to cannabis users (31). The effects found at birth faded by one month, and there were no differences in performance on standardised tests of ability at six and twelve months. Small effects were again reported at 36 and 48 month follow ups (40) but these were not found at 60 and 72 months (41). These results are suggestive of a transient developmental impairment occurring among children who had experienced a shorter gestation and prematurity. It seems unlikely that the tests used in later follow-ups were

insensitive to the effects of prenatal cannabis exposure because they showed adverse effects of tobacco smoking during pregnancy on behavioural development at 60 and 72 months (40, 41).

The results of studies that ha attempted to replicate the OPPS findings have been mixed. Tennes et al (23) conducted a prospective study of the relationship between cannabis use during pregnancy and postnatal development in 756 women, a third of whom reported using cannabis during their pregnancy. The children were assessed shortly after birth using the same measures as Fried (20) and a subset were assessed at one year of age. There were no differences in behavioural development after birth between the children of women who did and did not use cannabis and there were no differences at one year. More recently, Day et al (42), have followed up children at age three born to 655 women who were asked about their substance use during pregnancy. They found a relationship between the mothers' cannabis use during pregnancy and the children's performances on memory and verbal scales of the Stanford-Binet Intelligence Scale at age three. A later follow up at age six did replicate the OPPS findings of increased impulsivity and impaired attention among children whose mothers had smoked cannabis during their pregnancy (43).

Fried and Smith (31) concluded after reviewing the literature that the effects of 'prenatal exposure to marihuana are subtle' and 'considerably moderated by other risk factors'. There were 'limited (if any) effects upon foetal growth and central nervous system functioning' and little evidence of effects on growth and behaviour during the toddler stage. They argued that there was suggestive evidence for subtle effects after the age of three in impulsivity, attention and problem solving, the significance of which needed to be clarified by further research.

A more sceptical view was expressed in a recent meta-analytic review of the effects on foetal development of maternal use of cocaine, a drug with a much greater reputation for foetal toxicity than cannabis (44). Frank et al concluded that, after controlling for exposure to tobacco and alcohol, there were no effects of prenatal cocaine use on physical of behavioural development to age six.

6.5 Summary

High doses of THC use disrupt the male and female reproductive systems in animals. THC interferes with hormones controlling reproduction, reducing testosterone secretion, sperm production, motility, and viability in males, and interfering with the ovulatory cycle in females. It is uncertain whether these effects occur in humans, given the high doses used in animal studies, the inconsistency of findings in studies of human males, and the fact that the effects observed in the positive human studies are still within the normal range.

Cannabis use during pregnancy probably leads to lower birthweight, although the decrease is much smaller than that produced by tobacco use. Cannabis use during pregnancy is unlikely to be a *major* cause of birth defects but it is possible that cannabis use during pregnancy produces a small increase in the risk of birth defects as a result of

exposure of the foetus in utero. There is suggestive evidence that infants whose mothers smoke cannabis during their pregnancy may experience behavioural and developmental effects during the first few months after birth and possibly in the longer term. These effects, if they exist, are likely to be smaller than comparable effects of alcohol use and tobacco smoking during pregnancy.

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7 Cardiovascular, respiratory and gastrointestinal effects

7.1 Cardiovascular effects of cannabis

One of the most consistent effects of cannabis in humans and animals is to increase heart rate (1–3). This change parallels the subjectively experienced 'high' and is related to the amount of THC in the blood (3, 4). Healthy young adults are only mildly stressed by these cardiovascular effects of cannabis (5).

An increased heart rate is most obvious in occasional cannabis users because regular users become tolerant to this and other effects of THC (4). Tolerance occurs within 24 hours in laboratory studies and even large amounts of cannabis may have little effect on heart rate (1, 2, 6–9). Tolerance to these effects has also been observed in field studies of chronic heavy cannabis users in Costa Rica (10), Greece (11), and Jamaica (12). These studies failed to find any adverse effects of cannabis on heart function.

7.1.1 Effects on patients with cardiovascular disease

Patients with ischaemic heart disease, hypertension, and cerebrovascular disease who use cannabis (13, 14) may experience cardiac arrhythmias, chest pain, and myocardial infarction (or heart attack). Because THC has analgesic effects it may mask chest pain, delaying treatment. Cannabis smoking also increases the level of carboxyhaemoglobin in the blood, decreases oxygen delivery to the heart and increases the work of the heart (4). Patients with cerebrovascular disease may experience strokes caused by changes in blood pressure and patients with hypertension may experience exacerbations of their disease for the same reason.

A number of laboratory studies have found that smoking cannabis cigarettes adversely affects patients with heart disease. Aronow and Cassidy (15) compared the effect of smoking a cannabis and a placebo cigarette on heart rate and the time required to induce chest pain in an exercise tolerance test. Heart rate increased by 43%, and the time taken to produce chest pain halved after smoking a cannabis cigarette. Aronow and Cassidy (16) compared the effects of smoking a single cannabis cigarette and a high nicotine cigarette in 10 men with heart disease, all of whom were cigarette smokers. Smoking cannabis produced a 42% increase in heart rate, compared with a 21% increase after smoking the tobacco cigarette. Exercise tolerance time was halved after smoking a cannabis cigarette by comparison with a tobacco cigarette. These findings have been confirmed by Gottschalk and colleagues (17).

7.1.2 Significance of cardiovascular effects

It seems unlikely that healthy young adults who occasionally smoke cannabis develop heart disease as a result of their cannabis smoking. Most of these cannabis users discontinue their use by their late 20s (18, 19). A recent study (20) provides support for predictions that adverse cardiovascular effects may occur in a minority of chronic

cannabis users who continue to use cannabis into their late 40s and early 50s, the age of highest risk for heart disease (21).

Mittleman et al reported a case-crossover study of the possible role that smoking cannabis may play in triggering an acute myocardial infarction (heart attack) (20). They asked 3882 patients who had had a myocardial infarction in the previous 4 days about their use of marijuana in the hour before it occurred, and compared this with their typical frequency of use. Only 3.5% of all patients, and 12.5% of those under the age of 44 years, had smoked cannabis in the previous year but it increased the risk of a myocardial infarction 4.8 times in the hour after use. The risk dropped rapidly after the first hour, as expected from the effects that THC and carbon monoxide from smoking have on heart function. The effect of smoking cannabis was smaller than the effect of cocaine use observed in earlier studies (a 24 fold increase). Mitteleman et al estimated that a 44-year-old adult who used cannabis daily would increase their annual risk of an acute cardiovascular event by 1.5% to 3%. They concluded that: 'smoking marijuana is a rare trigger of acute myocardial infarction' that 'may pose a health risks to patients with coronary heart disease and perhaps to individuals with multiple coronary risk factors' (p. 2808). The significance of this contribution may rise as the proportion of older adults who smoke cannabis increases.

7.2 Effects on the respiratory system

It is likely that regular cannabis smoking adversely affects the respiratory system (22). Cannabis smoke is similar to tobacco smoke, and contains a higher proportion of particulate matter and more of some carcinogens (e.g. benzpyrene) than tobacco smoke (22, 23). The inhalation of cannabis smoke therefore deposits carcinogenic substances on lung surfaces. Cigarette smoking is a cause of bronchitis, emphysema, and cancers of the lung, oral cavity, trachea, and oesophagus (24). Although tobacco smokers smoke many more cigarettes than cannabis smokers, cannabis smokers typically inhale more deeply, and hold their breath for longer, thereby depositing more particulate matter in the lung (22).

7.2.1 Chronic bronchitis and obstructive pulmonary disease

Convincing evidence that chronic cannabis use may impair lung function and cause symptoms of respiratory disease comes from a series of studies conducted by Tashkin and his colleagues since the mid 1970s (22). One of their early studies evaluated the effects of heavy daily cannabis smoking on respiratory function. The subjects were young male cannabis smokers who were studied in a closed hospital ward where they were allowed free access to cannabis for 47 to 59 days. There was a significant decrease in the function of large and medium-sized airways during the study and the degree of impairment was related to the number of cannabis cigarettes smoked, suggesting that the quantity of inhaled irritants was the important factor.

Tashkin and his colleagues (25) subsequently studied cannabis only smokers (MS, n = 144), cannabis and tobacco smokers (MTS, n = 135), tobacco only smokers (TS, n = 70), and non-smoking controls (NS, n = 97). These subjects were followed to study changes in lung function, signs and symptoms of respiratory disease, and histopathological changes that precede the development of cancer.

At baseline Tashkin et al (25) found more symptoms of bronchitis (such as cough, bronchitic sputum production, wheeze and shortness of breath) in all types of smokers (MS, MTS, TS) than non-smokers. Cannabis and tobacco smokers did not differ in the rates of these symptoms. Lung function tests showed poorer functioning and greater abnormalities in small airways among tobacco smokers whereas cannabis smokers had poorer large airways function than non-cannabis smokers.

Follow up studies of this conort have shown different effects of cannabis and tobacco smoking on lung function (26). The first follow up study two to three years after the baseline study retested almost half of these subjects, most of whom were in the same smoking categories as at baseline. At both baseline and follow up, cough, sputum, and wheeze were more common in smokers than among nonsmokers. There was no significant change in the respiratory status of any of the smoking groups over time when those individuals who ceased smoking were excluded. The same was found when the subjects were followed up 3 to 4 years after first assessment. In addition, the group that smoked both cannabis and tobacco showed both types of damage found in those who only smoked cannabis or tobacco.

Tashkin and colleagues (27, 28) studied the histopathology of the lungs in a sample of their cohort. Fligiel et al (27) compared the bronchial morphology of 30 males who were heavy smokers of cannabis-only with those of 17 cannabis and tobacco smokers 15 tobacco only smokers and 11 nonsmoking controls. All subjects who smoked had more severe abnormalities than nonsmokers. Many of these were more common in cannabis smokers, and they were most marked in men who smoked cannabis and tobacco. These abnormalities occurred at a younger age in cannabis than tobacco smokers, despite the fact that the cannabis smokers smoked less than a quarter as many 'joints' as the tobacco smokers smoked cigarettes.

Additional research (29, 30) suggests a number of reasons why cannabis smoking may be more toxic to the respiratory system than tobacco smoking. Laboratory studies show that cannabis smokers inhale a larger volume of smoke than tobacco smokers (40% to 54% more). They also inhaled more deeply and held their breath about four to five times longer than tobacco smokers. As a result, they retained more particulate matter, and absorbed three times more carbon monoxide, than tobacco smokers (29).

Other studies have replicated some of the findings of Tashkin and colleagues. Bloom et al (31) examined the relationship between smoking 'nontobacco' cigarettes and respiratory symptoms and respiratory function in the general population. Their sample comprised 990 individuals aged under 40 years who were followed up in a prospective community study of obstructive airways disease. The proportion who said that they had ever smoked a 'non-tobacco' cigarette was 14% (the same as the rate of cannabis smoking in general population surveys at the time), 9% were current and 5% ex-smokers of 'non-tobacco' cigarettes. On average non-tobacco cigarettes were smoked 7 times per week for 9 years. Non-tobacco smokers were more likely to have smoked tobacco and they inhaled more deeply than tobacco only smokers.

Non-tobacco smokers reported more cough, phlegm, and wheeze, regardless of whether they smoked tobacco or not. They also had poorer respiratory function. Those who had never smoked had the best functioning, followed in order of decreasing function by

current cigarette smokers, current non-tobacco smokers, and current smokers of tobacco and non-tobacco cigarettes. Non-tobacco smoking alone had a bigger effect on respiratory function than tobacco smoking alone, and the effects of both types of smoking on respiratory function was additive.

Sherril et al (32) have reported follow up data on respiratory symptoms and respiratory function in this sample. Rates of non-tobacco use declined over time, as did the quantity of cannabis that was smoked per week. At each follow-up non-tobacco smokers were twice as likely to report chronic cough, chronic phlegm and wheeze than non-smokers. The rate of reported symptoms increased with the number of non-tobacco cigarettes smoked per week and with the length of time that non-tobacco cigarettes were smoked. Non-tobacco smokers showed impairment on all indices of respiratory function.

Taylor et al (33) studied symptoms of respiratory disease and respiratory function in 1037 young New Zealand adults who were followed from birth until age 21. They compared symptoms of respiratory disease and respiratory function in those who were: cannabis dependent, cigarette smokers and non-smokers of tobacco and cannabis. Tobacco smokers had a higher rate of chronic bronchitis, wheeze and cough than non-tobacco smokers and the rate of these symptoms increased with the number of cigarettes smoked per day. Cannabis dependent subjects had higher rates of wheezing, shortness of breath, chest tightness and morning sputum production than non-smokers, after taking account of tobacco use. Among cannabis dependent subjects the effects in cannabis users were similar to those in tobacco smokers of 1–10 cigarettes/day. A higher proportion of cannabis dependent subjects had impaired respiratory function and the adverse effects of tobacco and cannabis smoking on respiratory function were additive.

7.2.2 Respiratory cancers

As discussed in detail in Chapter 5, there is evidence that cannabis *smoke* is mutagenic and carcinogenic and a potential cause of cancer in body cells that are regularly exposed to it, such as those of the aerodigestive and respiratory tracts. There are case reports of aerodigestive tract cancers among relatively young adults who have been daily cannabis users. A case control study has found an association between cannabis smoking and head and neck cancer (34). The only prospective cohort study to date has not found evidence of increased incidence of head and neck or respiratory cancers, although it found evidence of increased rates of prostate cancer. The relative youth of the participants and the low prevalence of regular cannabis use in the latter study reduced its ability to detect an increase in respiratory cancers. There is also evidence that the lungs of chronic cannabis smokers show changes in gene expression that appear to be precursors of cancer in tobacco smokers (35). Further follow ups of the Sidney et al cohort (36), and additional case control studies, are needed to clarify the issue (see Chapter 5).

7.3 Effects on the gastrointestinal system

Studies in experimental animals have not found any evidence that THC causes liver damage (37–39). Liver weight was reduced but this may have been caused by reduced food consumption because very high doses of THC were used. There is no human evidence that the chronic use of cannabis disturbs liver function (4).

Anecdotal evidence suggests that cannabis increases appetite ('the munchies' or 'hash hungries') (40–42). Cannabinoids reduce food and water intake in animals (4) but experimental studies in humans provide some support for the anecdotal reports (43–45). THC in the synthetic form of dronabinol (Marinol) has been shown to produce weight gain when used to treat nausea and vomiting caused by cancer chemotherapy. A similar weight gain was reported when used in patients with HIV infection. There are now objective data to support these anecdotal reports, and these suggest that THC has a potential therapeutic use as an appetite stimulant.

7.4 Summary

Smoking cannabis increases heart rate and affects blood pressure but there is no evidence that these effects have a permanently deleterious effect on the normal cardiovascular system. These effects are less benign in patients with hypertension, cerebrovascular disease and coronary atherosclerosis in whom THC may increase the work of the heart. The seriousness of these effects in persons with cardiovascular disease will be determined as persons who initiated cannabis use in the late 1960s enter the risk period for cardiovascular disease.

Cannabis smoking causes chronic bronchitis and impairs functioning of the large airways and produces pathological changes in lung tissues that may be precursors of lung cancer. Case studies and a case-control study suggest that cannabis may cause cancers of the aerodigestive tract. Additional studies of these cancers are a high priority.

There appears to be little or no human or animal evidence that cannabinoids affect liver function. The most interesting gastrointestinal effect of cannabis is its therapeutic use in reducing nausea and stimulating appetite in cancer and AIDS patients.

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8 Effects on motivation and the risk of dependence

8.1 Motivational effects

Chronic daily cannabis use has been reported to impair motivation in users in Egypt and the Caribbean (1). Young cannabis users in the USA in the early 1970s who were apathetic, withdrawn, lethargic and unmotivated (2, 3) were said to suffer from an 'amotivational syndrome' (3, 4). It is difficult in these cases to disentangle the effects of chronic cannabis use from those of poverty, poor education and pre-existing psychiatric disorders (5–7).

The effects of cannabis use on motivation were assessed in a number of field studies of chronic cannabis users in Costa Rica (8), Jamaica (9) and the USA (10). Rubin and Comitas (9), for example, found that Jamaican farmers who regularly smoked cannabis worked harder but less efficiently after using cannabis. A study of Costa Rican cannabis smokers produced mixed evidence on the effect of chronic cannabis use on job performance. Carter et al (8) compared 41 heavy cannabis users (10 cannabis cigarettes per day for ten or more years) with 41 nonusers of cannabis matched on age, marital status, education, occupation, and alcohol and tobacco use. The nonusers were more likely: to have a stable employment history, to have been promoted and given pay rises, and to be in full-time employment. Users spent more of their incomes on cannabis and were more likely to be in debt. Among users, however, those who had steady jobs or who were self-employed smoked twice as many cannabis cigarettes per day as those with more frequent job changes, or those who were chronically unemployed.

A follow up study of long-term cannabis users in the USA suggests that the amotivational syndrome is rare among long-term cannabis users. Halikas et al (10) assessed symptoms of the amotivational syndrome in 100 regular cannabis users six to eight years after they were first studied. Only three individuals had ever experienced amotivational symptoms in the absence of depression and their use did not differ from that of other cannabis users.

Laboratory studies of long-term heavy cannabis use have also failed to clearly show that cannabis impairs motivation (5). Early studies conducted by the LaGuardia Commission (11) reported deterioration in behaviour among prisoners given daily doses of cannabis over a period of some weeks but these reports were based upon uncontrolled observation. A study using standardised measures of performance failed to observe such effects (11). In this study 10 casual and 10 heavy cannabis smokers were observed in a laboratory over a 31-day study period. For 21 of these days subjects were given access to as many cannabis cigarettes as they earned by performing a simple task. All subjects earned the maximum number of points allowed per day throughout the study and their output was not affected by cannabis use. Providing similar access to alcohol in heavy drinking subjects in the same setting profoundly disrupted performance. Similar results were reported in a study by Campbell (12) in which young cannabis users were given

high doses of cannabis. They showed no gross behavioural changes, no social deterioration, and no alterations in intellectual functioning but their productivity was reduced when they were given 30 mg of THC per day, a dose that many subjects found unpleasant.

Schwenk (13) has recently reviewed evidence on the relationship between cannabis use and job performance in laboratory studies, surveys, observational studies, anthropological studies and studies of drug testing. He concluded that the associations between cannabis use and poor job performance in laboratory studies and surveys were small. Schwenk argued that these results were more consistent with the hypothesis that there was a relationship between the characteristics of cannabis users and poor job performance rather than with the hypothesis that cannabis use was a cause of poor job performance.

The amotivational syndrome remains contentious because of differences of opinion about the value of clinical observations and controlled studies. Those who accept the existence of the syndrome appeal to the small number of cases fitting the description of an 'amotivational syndrome' (14). Sceptics are more impressed by the unsupportive field and laboratory studies. If there is an amotivational syndrome, it is a relatively uncommon consequence of prolonged heavy cannabis use. Research suggests that the features of the 'amotivational syndrome' can be better explained as symptoms of chronic cannabis intoxication in cannabis dependent users, thereby obviating the need to invent a new psychiatric syndrome (5).

8.2 Is there a cannabis dependence syndrome?

For much of the 1960s and 1970s cannabis was not regarded as a drug of dependence because it did not seem to produce tolerance or a withdrawal syndrome like that seen in alcohol and opioid dependence. Views changed in the late 1970s and early 1980s with the adoption of a broader conception of drug dependence (15). This new conception reduced the emphasis on tolerance and withdrawal and placed more emphasis on the compulsion to use, a narrowing of the drug using repertoire, rapid reinstatement of dependence after abstinence, and the high salience of drug use in the user's life. It was reflected in the Third and Fourth Revised Editions of the Diagnostic and Statistical Manual (DSM-III-R and DSM-IV) of the American Psychiatric Association (16, 17).

8.2.1 Drug dependence in DSM-IV

'The essential feature of Substance Dependence is a cluster of cognitive, behavioral and physiologic symptoms indicating that the individual continues use of the substance despite significant substance-related problems' (p.176) (16). A diagnosis of Substance Dependence is made if *three or more* of the following criteria occur at any time in the same 12-month period:

'1. tolerance, as defined by either of the following:

   a. need for markedly increased amounts of the substance to achieve intoxication or desired effect

   b. markedly diminished effect with continued use of the same amount of the substance

2. withdrawal, as manifested by either of the following:
   a. the characteristic withdrawal syndrome for the substance
   b. the same (or closely related) substance is taken to relieve or avoid withdrawal symptoms
3. the substance is often taken in larger amounts or over a longer period than was intended;
4. there is a persistent desire or unsuccessful efforts to cut down or control substance use;
5. a great deal of time is spent in activities necessary to obtain the substance (e.g., visiting multiple doctors, driving long distances), use the substance (e.g. chain smoking), or recover from its effects;
6. important social, occupational, or recreational activities are given up or reduced because of substance use;
7. the substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.' (16).

8.2.1 Cannabis tolerance and withdrawal: experimental evidence

Cannabis users can develop tolerance to the effects of THC and they can experience withdrawal symptoms under certain conditions. Tolerance to many of the behavioural and physiological effects of THC has been demonstrated in humans and animals (18–23). The precise mechanisms are unknown but they probably involve changes in cannabinoid receptor function (20, 24).

Jones and Benowitz (25) studied the effects of 210 mg dose of oral THC per day given in a fixed dosing schedule to healthy male volunteers with extensive histories of cannabis use. Over the 30-day study, the positive effects of intoxication declined and there was a recovery in social, cognitive and psychomotor performance. Georgotas and Zeidenberg (19) also reported tolerance to the subjective effects of cannabis in humans.

Early case reports of cannabis withdrawal symptoms in humans have been supported by abstinence symptoms in laboratory studies (18, 21, 26). Studies in clinical and non-clinical samples of long-term cannabis users have reported withdrawal symptoms, such as anxiety, insomnia, appetite disturbance and depression (27–30).

Jones and Benowitz (25) abruptly withdrew regular cannabis users after two weeks on high doses of oral THC. Within six hours, they complained of 'inner unrest' and after 12 hours they reported 'irritability, insomnia, and restlessness' that were also observed by staff. These symptoms were correlated with THC dose and frequency of use, and were reduced after using cannabis (22). Georgotas and Zeidenberg (19) reported similar symptoms during the first week of abstinence in subjects who had received 210 mg of smoked cannabis a day for four weeks. Recent laboratory studies by Haney et al (31, 32) have reported withdrawal symptoms at much lower doses of THC given orally and by smoking. The most common symptoms were anxiety, depression and irritability.

Kouri and Pope (33) reported a controlled prospective study of withdrawal symptoms among chronic cannabis users who were assessed daily on various withdrawal symptoms while in a hospital ward for 28 days. Their ratings of mood, anxiety, depression and irritability were compared to those of two control groups of abstinent former heavy cannabis users and non-users of cannabis. During the course of the 28 days the chronic cannabis users showed decreases in mood and appetite and increases in irritability, anxiety, physical tension, and physical symptoms, and their scores on the Hamilton Depression and Anxiety scales increased. These appeared within 24 hours and were most marked in the first 10 days although the increase in irritability and physical tension persisted throughout the 28-day observation period.

Research using the cannabinoid antagonist SR 141716A (which immediately reverses the effects of THC) has shown that a withdrawal syndrome can be produced in rats, mice and dogs that have been maintained on THC (34, 35). The antagonist produces compressed and accentuated symptoms that are much more dramatic than the milder and more prolonged symptoms that occur under usual conditions of human use (36). The relatively long half-life and complex metabolism of cannabis may also result in a less intense withdrawal syndrome than drugs such as opiates (24).

8.2.2 Epidemiological studies of cannabis dependence

The Epidemiological Catchment Area (ECA) study estimated the rates of cannabis abuse and dependence in US population in the early 1980s (37). It found that 4.4% of the US population had a diagnosis of cannabis abuse or dependence according to DSM-III criteria. A third of those with lifetime cannabis abuse or dependence (38%) reported problems with cannabis use in the last year. Men had a higher risk of cannabis dependence than women, with the highest risk among 18 to 29 year olds. (38).

The most common symptoms reported by those who were cannabis dependent were: requiring larger amounts (21%), having psychological (21%) or social (17%) problems attributed to cannabis, and inability to reduce use (8%). Few reported health problems (5%) or withdrawal sickness (3%) (39). Surveys using similar methods to the ECA have produced similar estimates of the rate of cannabis dependence in Canada and New Zealand (40–42).

The National Comorbidity Survey (NCS) conducted in the USA between 1990 and 1992 (43) found that 4.2% of adults met DSM-III-R criteria for cannabis dependence at some time in their lives. The proportion of people who had ever used cannabis who met criteria for cannabis dependence was 9%. This compared to 32% of nicotine, 23% of heroin, 17% of cocaine, 15% of alcohol and 11% of stimulant users who met criteria for dependence.

The Australian National Survey of Mental Health and Well-being (44) found that 1.7% of Australian adults met the International Classification of Diseases (ICD-10) (45) criteria for a diagnosis of cannabis dependence, and 0.1% met criteria for harmful use in the previous year. One in four (23%) of those who had used cannabis more than five times in the last year met criteria for cannabis dependence or harmful use.

8.2.3 Studies of long-term cannabis users

Studies of long-term cannabis users in Egypt (46), India (47), Germany (2), Greece (48), Costa Rica (8) and Jamaica (9) did not study symptoms of dependence other than withdrawal, which then defined dependence. Stereotyped use patterns, persistent desire to quit, tolerance, chronic intoxication, mild withdrawal and continued use despite problems were reported in the Egyptian, Indian and Jamaican studies but there were no withdrawal symptoms reported in the Costa Rican, Jamaican or Greek studies.

Kandel and Davies (49) described problems reported by a subset of daily cannabis users (aged 28–29 years) who were recruited in a large prospective study of 1,222 adolescents. The major adverse consequences of cannabis use reported were: cognitive deficits, reduced energy, depression, and, among males, problems with their spouse.

Recent Australian surveys of long-term cannabis users diagnosed a substantial proportion as cannabis dependent. Among 243 rural cannabis users, who had used cannabis several times a week for 19 years, 57% qualified for lifetime DSM-III-R and ICD-10 cannabis dependence diagnoses (30). The most common symptoms reported were: frequent intoxication during daily activities (73%) and a strong urge to use cannabis (75%). Few reported withdrawal symptoms (5%) or using cannabis to relieve withdrawal symptoms (20%), although 54% reported tolerance. Only 26% believed they had a problem with cannabis and only 9% had sought help to cut down or stop.

Among 200 young Sydney adults who had used cannabis at least weekly for 11 years, 92% met criteria for a DSM-III-R lifetime diagnosis of dependence and 40% were classified as severely dependent (29). Tolerance and withdrawal were reported by 78% and 76% respectively and use to relieve withdrawal symptoms by 39%. Most met criteria for cannabis dependence in the past year according to DSM-III-R (77%) and ICD-10 (72%) criteria. A follow-up of these users found that cannabis use and dependence symptoms were stable over a year (50). The majority (81%) of the follow-up sample met criteria for a dependence diagnosis during the last year on three measures of dependence.

8.2.4 Clinical populations

Cannabis dependent persons seek help with cannabis-related problems in Australia, the United States and Europe. The National Census of Clients of Australian Treatment Service Agencies (51, 52) found that the proportion of cases in whom cannabis was the *main* drug problem increased from 4% in 1990 to 7% in 1995. Between 1994 and 1998 cannabis was the primary drug of abuse for between 11% and 26% of clients of treatment agencies in the United States (53, 54). Cannabis was the primary drug problem for between 2% and 16% of clients attending treatment agencies in the European Union in 1998 (55).

A Swedish treatment program (56) reported that its clients typically complained of: unsuccessful attempts to stop or moderate use and frequent (often daily) intoxication, despite suffering adverse effects connected with their cannabis use. These included sleeplessness, depression, impaired concentration and memory, and blunting of emotions.

Stephens and colleagues (57) described the symptoms reported by 382 persons who sought help to cease cannabis use. These included: an inability to stop using (93%), feeling bad about using cannabis (87%), procrastinating (86%), loss of self-confidence (76%), memory loss (67%) and withdrawal symptoms (51%). Similar experiences have been reported among users in recent US (28, 58) and Australian studies of interventions for problem cannabis use (27). In the Australian study, among 180 long-term cannabis users seeking help, the most common symptoms were withdrawal and use to relieve withdrawal.

8.2.5 The risk of cannabis dependence

People who use cannabis daily over weeks to months are most likely to become dependent. Kandel and Davis (49) estimated that one in three daily cannabis users met DSM-III criteria for dependence. The risk of dependence among less frequent users of cannabis is lower (59). In the ECA study, 17% of those who used cannabis more than 5 times met DSM-III criteria for dependence at sometime in their lives (38). In the National Comorbidity Study (NCS), Anthony et al (43) estimated that the proportion of persons who had ever used alcohol, amphetamines, cannabis, cocaine, heroin, nicotine and sedatives who met DSM-III-R criteria for dependence on each drug at some time in their lives were: 32% for nicotine, 23% for heroin, 15% for alcohol and cocaine and 9% for cannabis.

These estimates suggest the following rules of thumb about the risks of cannabis dependence. For those who have ever used cannabis the risks of developing dependence is probably of the order of one chance in ten. Among those who use the drug more than a few times the risk of developing dependence is in the range of from one in five to one in three. As a rule, the more often cannabis has been used, and the longer it has been used, the higher the risk of dependence.

The following factors also predict a higher risk of regular involvement with cannabis: poor academic achievement, deviant behaviour in childhood and adolescence, nonconformity and rebelliousness, personal distress and maladjustment, poor parental relationships, earlier use, and a parental history of drug and alcohol problems (49, 60–62).

8.2.6 The consequences of cannabis dependence

The large gap between the ECA estimates of cannabis abuse and dependence in the community and the number of cannabis users who seek treatment suggests that many of these cases remit without treatment, as is true of alcohol abuse and dependence (63). Kandel and Davies (49) found that by age 28 to 29, less than 15% of daily cannabis users were still using daily, and Bachman et al have found that most regular cannabis users discontinued their use during the mid to late twenties (64).

Among the minority of regular cannabis users who are sufficiently troubled to seek help the major complaints are: a loss of control over their cannabis use, cognitive and motivational impairments which may interfere with work performance, lowered self-esteem and depression, and complaints by spouses and partners about their frequent

intoxication (see above). There is no doubt that some dependent cannabis users report impaired performance and a reduced quality of everyday life but more research is necessary to decide how common this is, and how impaired cannabis dependent persons are.

8.2.7 The treatment of cannabis dependence

Little research has been done on the sort of assistance that should be given to cannabis users who seek help to stop using cannabis (65). Although many users may succeed in quitting without professional help we need to assist those who are unable to stop on their own. It is not clear what type of treatment should be provided for dependent cannabis users who have repeatedly failed to stop using cannabis and seek help.

Roffman et al (66) reported one of the few randomised controlled trials comparing group based relapse prevention and social support. Subjects were 120 men and women (aged 32 with 16 years of cannabis use) who answered advertisements for help to stop using cannabis. One-month after treatment only 30% of their patients were still abstinent and by the end of a year only 17% were abstinent.

Stephens et al (67) recently reported another study of behavioural treatment for cannabis dependence in 291 subjects. Subjects were randomly assigned to one of three treatments: (1) a 14 session group based relapse prevention intervention (RPSG) similar to their earlier study but with more sessions; (2) an individualised advice (IAI) two session intervention using principles of motivational interviewing adapted from Miller's Drinker's Check-up; and (3) a delayed treatment condition (DTC) in which participants did not receive any treatment for four months.

At the four month follow up all three groups had reduced their cannabis use but the two treatment groups showed the largest reduction and did not differ from each another. In the treatment groups 37% were abstinent compared with only 9% in the delayed treatment group. The amount of cannabis use also declined by 70% in the treatment groups and by 30% in the delayed treatment groups. Abstinence rates declined over time but the two treatments did not differ at 7, 13 and 16 months after treatment. Twenty-two percent of participants were abstinent throughout the 16 month study and their abstinence was corroborated by partners and family members.

Budney, Higgins, Radinovich and Novy (68) reported a controlled comparison of three treatments for 60 cannabis dependent patients. They compared three treatments: motivational enhancement to quit (M), motivational enhancement plus behavioural coping skills (MBT), and MBT plus incentives to remain abstinent (MBTV). In the latter, vouchers for retail items were exchanged for urine samples that were negative for cannabinoids. The MBTV group had a longer period of continuous abstinence than the other two groups which did not differ from each other. By 14 weeks post-treatment fewer than 10% of participants had been continuously abstinent from cannabis.

Copeland, Swift, Roffman and Stephens (69) replicated the study by Stephens et al (67) in an Australian sample. They randomly assigned 229 cannabis dependent adults to three treatments: a six session cognitive behavioural intervention; a single session cognitive

behavioural treatment, and a delayed treatment control group who were offered treatment four months after the other two groups. Only 6.5% of all subjects (n = 11) were continuously abstinent during the 8-month follow up period and all of these were in the treatment groups. There were greater reductions in cannabis related problems and in dependence symptoms in the two treatment groups.

So far rates of continuous abstinence from cannabis have been low in the treatments tested, although there have been substantial reductions in rates of use and problems related to use. Nonetheless, much more research is needed before sensible advice can be given about the best ways to achieve abstinence from cannabis. In the absence of better evidence of treatment effectiveness, people offering treatment for cannabis dependence should avoid replicating experience in the treatment of alcohol dependence where inpatient treatment has been widely adopted in the absence of any evidence that it is more effective than outpatient forms of treatment (70, 71).

8.3 Summary

There is no compelling evidence for an amotivational syndrome among chronic cannabis users. Some heavy users do complain of impaired motivation but this pattern of behaviour is better explained as a symptom of chronic intoxication among persons who are cannabis dependent.

There is good evidence that a cannabis dependence syndrome can develop in some chronic cannabis users. These users develop tolerance, experience withdrawal symptoms on cessation of use, have problems controlling their cannabis use, and continue to use despite the experience of adverse personal consequences of use. Cannabis dependence is the most common form of drug dependence after alcohol and tobacco in the USA and Australia. The risk of developing dependence is about:: one in ten among those who ever use the drug; between one in five and one in three among those who use cannabis more than a few times; and around one in two among those who become daily users. Few cannabis dependent persons seek treatment, probably because many disorders remit without treatment. It is not clear as yet what advice should be given to the minority of dependent cannabis users who seek help to stop their use.

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9 The effects of cannabis use on cognitive functioning

Cannabis acutely impairs cognitive performance, so there is an understandable concern that its chronic use may cause longer lasting impairment of cognitive functioning. This possibility seemed to be supported by clinical observers in the USA during the early 1970s (e.g. Kolansky and Moore, (1, 2)) who reported that young adults who had used cannabis weekly or more often had 'poor attention span, poor concentration, confusion' (2). More recently, some long-term cannabis users seeking help to stop using cannabis have complained that their memory and thinking is impaired (3). The difficulty with these reports has been in ruling out alternative explanations, namely, that cognitive impairment preceded cannabis use or was the result of other drug use.

9.1 Cross-cultural studies

One research strategy has been to examine cognitive performance in heavy cannabis users in cultures with a tradition of heavy use. An early report by Soueif (4) illustrates the problems with this strategy. Soueif studied Egyptian male prisoners of whom 850 were hashish smokers and 839 controls. The hashish users performed more poorly than the controls on ten of sixteen measures of perceptual speed and accuracy, distance and time estimation, immediate memory, reaction time and visual-motor abilities (4–7). The findings were weakened because the two groups also differed in ways that may have affected cognitive performance, namely, the hashish users were less well educated and more likely to use opiates and alcohol (8).

In the late 1960s the National Institute on Drug Abuse (NIDA) commissioned three cross-cultural studies in Jamaica, Greece and Costa Rica to assess the effects of chronic cannabis use on cognitive functioning (among other things). It was assumed that any cognitive effects of chronic daily cannabis use should be apparent in users with a long-history of heavy cannabis use, a pattern of use that was common in these cultures.

Bowman and Pihl (9) reported two field studies of cannabis users in Jamaica who had been daily cannabis users for a minimum of 10 years (23 joints per day) while controls had no experience with cannabis. No differences were found between the users and nonusers in either study or when rural and urban samples were combined. Rubin and Comitas (10) reported similar findings in a study of 30 Jamaican cannabis users who had used for 17.5 years and 30 nonusers.

The Greek study (11, 12) compared 47 daily hashish users (who used for 23 years) with 40 controls matched for age, sex, education, demographic region, socioeconomic status and alcohol consumption. The groups did not differ in total IQ score on either the WAIS or Raven's Progressive Matrices but the controls obtained a higher verbal IQ score than hashish users and the users performed worse than controls on all but one of the subtests of the WAIS (13). Since subjects did not abstain from hashish before testing, it was not clear whether these differences were due to long-term hashish use, or the acute effects of the drug at the time of testing.

In the Costa Rican study (14), researchers compared 41 males who had used 10 cannabis joints per day for 17 years with matched controls on a test battery that assessed neuropsychological, intellectual and personality variables. The Costa Rican users did not differ significantly from controls on any test. Page, Fletcher and True (15) followed up this sample after 10 years, by which time they had used cannabis for around 30 years. No differences were detected on any of the original tests but there were significant differences on three new tests of sustained attention and short-term memory. They emphasised that these differences were 'quite subtle' and 'subclinical', with only a small number of subjects clinically impaired. It was also difficult to exclude the possibility that the differences were due to recent cannabis use, since 24 hour abstinence was requested but not verified.

A number of studies of long term Indian cannabis users have also reported cognitive impairment. Agarwal et al (16) studied forty subjects who had used bhang daily for about 5 years. A comparison of their scores with normative data found that 18% had memory impairment, 28% showed mild intellectual impairment (IQs less than 90), and 20% showed substantial cognitive disturbances on the Bender-Gestalt Visuo-Motor Test. Wig and Varma (17) substantially replicated these results and Mendhiratta, Wig and Verma's (18) found that 50 heavy cannabis users reacted more slowly and had poorer concentration and time estimation than 50 matched controls.

The cross-cultural studies of long-term heavy cannabis users provide equivocal evidence of cognitive impairment among long-term cannabis users. They have either failed to find any differences or have found modest cognitive impairment in persons with a long history of heavy cannabis use. Their negative results cannot be attributed to short duration or low intensity of cannabis use because these subjects had used cannabis for between 17 and 23 years, and the amount of THC consumed per day ranged from 20–90 mg in the Jamaican study to 120–200 mg in the Greek sample. The differences that were observed are difficult to interpret because users often had higher rates of polydrug use, poorer nutrition, poorer medical care, and higher rates of illiteracy than controls, all factors which may have biased these studies towards finding poorer performance among cannabis users. Many of these studies also failed to ensure that subjects were not intoxicated by cannabis at the time of testing.

9.2 Studies of Western cannabis users

Studies of the cognitive performance of North American cannabis users have generally been on college students with much shorter histories of cannabis use than the chronic users in the cross-cultural studies (19). It is therefore unsurprising that most of these studies have failed to find evidence of cognitive impairment in cannabis users (19). One study to which these criticisms do not apply is that of Schaeffer et al (20) who studied cognitive impairment in 10 heavy cannabis users in the United States who used cannabis daily for religious reasons. All were Caucasian and all had been born and educated in the USA. All had smoked between 30 and 60 gms of cannabis a day for over 7 years and they had *not* used alcohol or any other psychoactive substances. At the time of testing, all subjects had evidence of recent heavy cannabis use in their urine. Overall, their scores on the WAIS IQ test were in the superior to very superior range, and their scores on all other tests were within normal limits but with only 10 subjects the study had a limited capacity to detect cognitive impairment.

9.3 Laboratory studies of daily cannabis use

Another strategy for investigating the cognitive effects of chronic cannabis use has been to study the cognitive performance of persons who use cannabis daily over periods of weeks. These studies have controlled the quantity, frequency, and duration of cannabis use, as well as nutrition and other drug use, by observing subjects in a hospital ward while they use cannabis. All such studies have used pre- and post-drug observation periods. The sample sizes in these studies have been small and cannabis has been used from 21 to 64 days.

Dornbush et al (21) administered cannabis containing 14 mg THC to 5 regular cannabis users for 21 days. They were tested before and 60 minutes after using cannabis on short-term memory and digit symbol substitution. Performance on the short-term memory test decreased on the first day of drug administration but gradually improved until by the last day of the study it had returned to baseline. Performance on the digit symbol substitution test was unaffected by cannabis but improved with time as a result of practice.

Mendelson, Rossi and Meyer (22) studied the effects of 21 days of cannabis use on 20 healthy, young male subjects who smoked as much cannabis as they wanted to. Short-term memory was impaired during intoxication but there was no impairment of performance before or after cannabis smoking. Similar failures to detect cognitive effects have been reported in three other studies (23–25).

9.4 Controlled laboratory studies of chronic cannabis users

Research studies in the late 1980s and 1990s improved upon the earlier studies of chronic cannabis users by using control groups, verifying abstinence from cannabis before testing, and quantifying the quantity, frequency and duration of cannabis use (Solowij, 1998). More effort was also made to relate specific cognitive processes to quantity, frequency and duration of cannabis use.

A study by Block and colleagues (26) addressed the concern that cannabis users had poorer cognitive ability than controls *before* they started using cannabis. Block et al matched their user and nonuser samples in their scores on the Iowa Tests of Basic Skills collected in the fourth grade of high school, ensuring that the two groups did not differ in intellectual abilities before they began using cannabis. Block and colleagues compared 144 cannabis users, 64 of whom were light users (less than 4 times per week for 5.5 years) and 80 heavy users (5 or more times per week for 6.0 years) with 72 controls aged 18-42. Twenty-four hours of abstinence was required prior to testing. The results showed that heavy cannabis users performed more poorly on tests of verbal expression and mathematical skills on the 12th grade Iowa test.

Solowij et al (27–29) studied the effects of long-term cannabis user's ability to exclude irrelevant stimuli when concentrating their attention on a task. Solowij assessed attentional processes in long-term cannabis users using a combination of performance

and brain event-related potential (ERP) measures as markers of underlying cognitive processes. She measured the amplitude and latency of ERP components that have been shown to reflect various stages of information processing.

Solowij et al (27) studied 9 cannabis users aged 19–40 who had used cannabis for 11 years for an average of 5 days per week. They were matched on age, sex, years of education and alcohol consumption with 9 controls who had either never used or had used cannabis fewer than 15 times in their lives. Subjects were excluded if they had a history of head injury, neurological or psychiatric illness, had used other drugs, or had high levels of alcohol consumption. The groups did not differ in premorbid IQ estimated by the NART score (30). Cannabis users were asked to abstain from cannabis and alcohol for 24 hours prior to testing and were urine tested to ensure that they did so.

Subjects performed an auditory selective attention task in which random sequences of tones varying in location, pitch and duration were presented through headphones while brain electrical activity (EEG) was recorded. They were asked to attend to a particular pitch presented in particular ear, and to respond to long duration tones by pressing a button. Cannabis users performed significantly more poorly than controls, with fewer correct detections, more errors and longer reaction times. They were less able than controls to filter out irrelevant information, suggesting that long-term cannabis use impaired the ability to efficiently process information.

In a second study Solowij et al (28, 29) assessed relationships between degree of impairment and the frequency and duration of cannabis use. Thirty-two cannabis users were divided into four groups of equal size (N = 8) defined by frequency (light: 2 or fewer times per week versus heavy: more than 3 times per week) and duration (short: 4 or fewer years of use versus long: 5 or more years of cannabis use). Subjects were matched to a group of nonuser controls (N = 16). The cannabis users performed worse than the controls and the greatest impairment was in the heavy user group. The long duration user group found it harder to ignore irrelevant stimuli than the short duration users and controls who did not differ. This impairment increased with the number of years of use but it was not related to frequency of use. There were no differences between groups defined on frequency of use on this measure. Speed of information processing was related to frequency of cannabis use but not to duration of use.

Solowij (31) assessed whether these ERP changes in long-term cannabis users persisted after extended abstinence from cannabis. She studied 32 former users who had used cannabis for a mean of 9 years and who had been abstinent for a mean of 2 years. She found some partial recovery of functioning: the speed of information processing was not reduced in the ex-users but their ability to ignore irrelevant stimuli remained impaired. The degree of impairment increased with the length of cannabis use and was unrelated to the length of abstinence.

Supportive evidence was provided by a NIDA funded study by Struve and colleagues of CNS changes in chronic cannabis users. This research found evidence of larger changes in EEG frequency, primarily in frontal-central cortex, in daily cannabis users of up to 30 years duration compared to short term users and nonusers (32). The results also

suggested that the EEG changes increased with the number of years of daily cannabis use. The major limitation of this research is that changes in frequency of EEG spectra have not been shown to be related to cognitive functioning.

This research group also assessed cognitive functioning (33–35) in subjects screened for current or past psychiatric and medical disorders and CNS injury. Daily cannabis users who had at least 3 years of use were compared to a group who had used daily for 6-14 years, a group who had used on a daily basis for 15 years or more, and a nonuser control group. Sample sizes averaged 15 per group. They reported a dose-response relationship between test performance and intensity of cannabis use, with controls performing best, followed by short term daily cannabis users, with the poorest performance in the very long-term group (33–35).

Pope and Yurgelun-Todd (36) compared the cognitive performance of heavy and light cannabis using college students. The heavy users (n = 65) had used for at least 2 years, on 28 of the past 30 days, and had cannabinoids in their urine. The light users (n = 64) had used no more than 3 days in the past month and had no cannabinoids in their urine. The authors used this design because they argued that infrequent users would 'differ less from heavy users on some possible confounding variables than would control subjects who had never used cannabis at all, while still differing sharply from heavy users on ... extent of recent cannabis use' (p 521).

Subjects were admitted overnight to a hospital ward to ensure that they were abstinent from cannabis at least 19 hours before being tested. The two groups did not differ on any social or demographic variables, except that heavy users came from more affluent families and scored more poorly on Verbal IQ and self-reported Scholastic Aptitude Tests. These differences were statistically adjusted for when comparing the two groups on the neuropsychological tests. The groups did not differ on tests of digit span, auditory sequential processing, the Stroop Test or the Wechsler Memory Scale. They differed on tests of attention (the Wisconsin test, the Benton VFT, and the CLVT) and these differences persisted when adjusted for differences in verbal IQ, self-reported SAT score and other drug use.

9.5 Epidemiological evidence

Lyketsos et al (37) reported a large-scale prospective epidemiological study of the effect of cannabis use on cognitive functioning. They followed up 1318 adults 11.5 years after they were assessed on the Mini Mental State Exam (MMSE) and assessed cognitive decline on the MMSE. They also inquired about use of cannabis, alcohol and tobacco. Their study came close to meeting the criteria for an optimum study specified by Pope et al (38), namely, it was a longitudinal study using a large sample of people from the general population who were assessed on cognitive performance and on cannabis and other drug use. Lyketsos et al found that the mean MMSE score declined by 1.2 points over 11.5 years and the decline was greater among older participants. There was, however, no relationship between cannabis use and the decline in MMSE score, and this lack of relationship persisted when adjustments were made for age, sex, education, minority status and use of alcohol and tobacco.

The Lyketsos et al study supports other evidence that cannabis use does not produce *gross* impairment of cognitive function but for a number of reasons it does not exclude the possibility that cannabis use causes more subtle cognitive impairment. First, only 57% of those initially interviewed were followed up and those lost to follow up had poorer MMSE scores at first assessment. Second, the MMSE is a screening test for gross cognitive impairment; it is not sensitive to small changes in cognitive functioning (39). Third, more than two weeks daily use at any of the three assessments qualified as 'heavy cannabis use'. Since cannabis use declines steeply with age (40) very few of this sample were likely to be daily cannabis users for any length of time.

9.6 Studies of neurotoxicity

Human studies of brain anatomy have generally failed to find signs of gross 'brain damage' after chronic use of cannabis (19, 41). The human studies of cognitive functioning suggest that cannabis may produce more subtle changes in brain function that existing methods of brain imaging are not sufficiently sensitive to detect (19). Wert and Raulin (41) proposed, that on the available evidence 'there are no gross structural or neurological deficits in marijuana-using subjects, although subtle neurological features may be present' (p.624).

9.7 Summary

The evidence suggests that long term heavy use of cannabis does not produce severe impairment of cognitive function like that observed in heavy alcohol users. There is some evidence that daily cannabis use over many years may produce more subtle impairment in memory, attention and the organisation and integration of complex information. This evidence suggests that these forms of cognitive impairment increase with the duration of cannabis use. It remains to be seen whether the impairment can be reversed by an extended period of abstinence.

Well controlled studies using sophisticated methods of investigation have failed to demonstrate gross structural change in the brains of heavy, long term cannabis users. These negative results are consistent with the evidence that any cognitive effects of chronic cannabis use are subtle, and hence unlikely to be manifest as gross structural changes in the brain.

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10 Cannabis use and psychotic disorders

There is reason to suspect that cannabis use may be a cause of psychotic disorders, i.e. mental illnesses in which sufferers experience hallucinations and delusions and show impaired reality testing. THC produces symptoms found in some psychotic disorders, namely, euphoria, distorted time perception, and cognitive and memory impairments (1, 2). In laboratory studies normal volunteers given high doses of THC have reported visual and auditory hallucinations, delusional ideas, thought disorder, and symptoms of hypomania (3, 4). A 'cannabis psychosis' has been reported by clinical observers in countries with a long history of heavy cannabis use, such as India and Egypt (1, 5).

We need to distinguish two hypotheses about possible relationships between cannabis use and psychosis (6). The strongest causal hypothesis is that heavy cannabis use can cause a 'cannabis psychosis', that is, a psychosis would not occur in the absence of cannabis use and in which the causal role of cannabis can be inferred from the symptoms and their relationship to cannabis use (being preceded by heavy cannabis use and remitting after abstinence).

A second hypothesis is that cannabis use can precipitate an episode of schizophrenia. According to this hypothesis, cannabis use is one factor among many others (including genetic predisposition and other unknown causes) that bring about schizophrenia, a psychotic disorder which becomes chronic in a substantial proportion of those who develop it.

If cannabis use can precipitate schizophrenia it is also likely that it can exacerbate the symptoms of the disorder. Even if cannabis use does not precipitate schizophrenia, its use may exacerbate symptoms of schizophrenia either directly, by affecting the dopaminergic system in the brain, or indirectly, by reducing compliance with, or interfering with the effects of, the neuroleptic drugs used to treat its symptoms.

In order to infer that cannabis use is a cause of psychosis in any of these ways we need evidence: that cannabis use and psychosis are associated; that chance is an unlikely explanation of the association; that cannabis use preceded the psychosis; and that plausible alternative explanations of the association can be excluded (7). As we will see, there is evidence that cannabis use and psychosis are associated, that chance is an unlikely explanation of the association, and that cannabis use often precedes psychoses. The most difficult task is excluding the hypothesis that the relationship between cannabis use and psychosis is due to other factors (e.g. other drug use, or a genetic predisposition both to develop schizophrenia and use cannabis).

10.1 'A cannabis psychosis'

Case reports of 'cannabis psychoses' (8–11) describe individuals who develop psychotic symptoms or disorders after using cannabis. Chopra and Smith (9), for example, described 200 patients who were admitted to a psychiatric hospital in Calcutta between

1963 and 1968 with psychotic symptoms following the use of cannabis. The most common symptoms 'were sudden onset of confusion, generally associated with delusions, hallucinations (usually visual) and emotional lability ... amnesia, disorientation, depersonalisation and paranoid symptoms' (p. 24). Most psychoses were preceded by the use of large doses of cannabis. Chopra and Smith argued that heavy cannabis use was not a sign of pre-existing disorders because a third of their cases had no prior psychiatric history, the symptoms were remarkably uniform regardless of prior psychiatric history, and those who used the most potent cannabis preparations experienced psychoses after the shortest period of use.

The findings of Chopra and Smith have received some support from other smaller case series that suggest that large doses of potent cannabis products can be followed by a 'toxic' psychotic disorder with 'organic' features of amnesia and confusion. These disorders have been reported from the Caribbean (12), New Zealand (13), Scotland (11), South Africa (10), Sweden (8), the United Kingdom (14) and the United States (15).

These disorders have been attributed to cannabis use for the following reasons: the onset of the symptoms followed closely the ingestion of large quantities of cannabis; the affected individuals often exhibited 'organic' symptoms, such as confusion, disorientation and amnesia; some had no personal or family history of psychoses before using cannabis; their symptoms rapidly remitted after abstinence from cannabis use, usually within several days to several weeks; recovery was usually complete with the person having no residual psychotic symptoms; and the disorder only recurred if the individual resumed cannabis use (16).

Sceptical author (2, 17) have criticized the poor quality of information in these studies on: cannabis use; its relationship to the onset of psychosis; the person's premorbid adjustment; and their family history of psychosis. They also emphasize the variety of clinical pictures of 'cannabis psychoses' reported by different observers. These weaknesses impair the value of these case series.

10.1.1 Controlled studies

A small number of controlled studies have been conducted over the past 20 years (18–22). Some studies have either compared persons with 'cannabis psychoses' with persons who have schizophrenia, or compared psychoses occurring in persons who do and do not have biochemical evidence of cannabis use prior to presenting for treatment. Their results have been mixed, in part because of the small sample sizes in studies that have failed to replicate positive findings, and because of variations in the research methods (16).

Several studies have examined the relationship between cannabis use and psychotic symptoms in the general population. Tien and Anthony (23) used data from the Epidemiologic Catchment Area study to examine the relationship between drug use and reports of one or more of 11 'psychotic experiences' during a twelve-month period (4 types of hallucinations and seven types of delusional belief). They compared 477 cases who reported one or more psychotic symptoms with 1818 controls who did not. Cases and controls were matched for age and social and demographic characteristics. Daily cannabis use was found to double the risk of reporting a psychotic symptom (after statistical adjustment for alcohol use and psychiatric diagnoses at baseline).

Thomas (24) reported the prevalence of psychotic symptoms among cannabis users in a random sample of people in a large city in the North Island of New Zealand. One in seven (14%) cannabis users reported 'strange, unpleasant experiences such as hearing voices' or 'becoming convinced that someone is trying to harm you or that you are being persecuted' after using cannabis.

The National Survey of Mental Health and Well-Being (NSMHWB) conducted in Australia in 1997 included a screening questionnaire for the presence of psychotic symptoms (25). Among those under 50 years of age who screened positive for a psychotic disorder, 8% (n = 27) met criteria for cannabis dependence in the past 12 months. This was 17% of all persons diagnosed with cannabis dependence (26). After adjusting for demographics, affective and anxiety disorders, smoking status and alcohol dependence, a diagnosis of cannabis dependence doubled the odds of reporting psychotic symptoms (27).

10.1.2 Overall evaluation

The hypothesis that there is a 'cannabis psychosis' is still contentious. In its favour are the equivocal evidence from the case series and the small number of positive controlled studies. Critics of the hypothesis emphasize the poor quality of the clinical judgments about aetiology, the poorly specified criteria used in diagnosing these psychoses, the dearth of controlled studies, and the striking variations in the clinical features of these 'cannabis psychoses'.

It is a plausible hypothesis that high doses of cannabis can produce psychotic *symptoms* but the evidence for a 'cannabis psychosis' as a specific clinical syndrome is much less compelling because the symptoms reported by different observers have been so mixed (28). If cannabis-induced psychoses exist, they are either rare or they only rarely receive medical intervention in Western societies. The total number of cases of putative 'cannabis psychoses' in the 12 case series reviewed in [illegible] (16) was 397 and 200 of these came from a single series collected over 6 years from a large geographic area in which heavy cannabis use was endemic (9).

10.2 Cannabis use and schizophrenia

10.2.1 Clinical studies

In case-control studies (29, 30), schizophrenic patients are more likely to have used psychotomimetic drugs such as amphetamines, cocaine, and hallucinogens than other psychiatric patients, normal controls or the general population (31). Variations in rates of use between studies reflect differences in the sampling of patients, with younger patients reporting higher rates than older persons with chronic disorders. Studies have also differed in the criteria for diagnosing schizophrenia and the manner in which substance use has been assessed (32).

Alcohol use, abuse and dependence are probably more common in the schizophrenic population than in the general population (33, 34) but findings on cannabis use have been more mixed (16). Generally, cannabis is the most commonly used drug after

alcohol and tobacco, and it is often used with alcohol (32, 35, 36). An Australian study of a clinical sample of persons with schizophrenia (37) has broadly confirmed the pattern of substance use and abuse in American studies, finding alcohol the most commonly abused substance (18% abuse or dependence in the past 6 months), followed by cannabis (13% abuse or dependence in the past 6 months).

The controlled clinical studies disagree about the correlates of substance abuse in schizophrenia. Most have found that young males are over-represented among cannabis users (16), as they are in the general community (38). In some studies, substance users have been reported to have an earlier onset of psychotic symptoms, a better premorbid adjustment, more episodes of illness, and more hallucinations (36, 39, 40) but other well controlled studies have failed to replicate some or all of these findings (41–43).

10.2.2 Population studies

Surveys of psychiatric disorders in the community have reported higher rates of substance abuse disorders among persons with schizophrenia. In the ECA study (44) nearly half of the patients identified as schizophrenic had a diagnosis of substance abuse or dependence (34% for an alcohol disorder and 28% for another drug disorder) (45). These rates were higher than the rates in the general population, namely, 14% for alcohol disorders (46) and 6% for drug abuse (44). Cuffel et al (42) reported that the most commonly used substances among persons with schizophrenia in the ECA study were: alcohol (37%) and cannabis (23%), followed by stimulants and hallucinogens (13%). The most common combination was alcohol and cannabis (31%). These findings have also been replicated in a similar survey in Edmonton, Alberta (47).

In the Australian National Survey of Mental Health and Well-Being (NSMHWB), cannabis use and a positive screen for psychosis were associated. Among those under 50 years of age who reported that they had received a diagnosis of schizophrenia, 12% met ICD-10 criteria for a cannabis use disorder in the past 12 months and 21% met criteria for an alcohol use disorder. After adjusting for other disorders and unemployment status, those who met criteria for ICD-10 cannabis dependence were 2.9 times more likely to report that they had been diagnosed with schizophrenia than those without cannabis dependence (26).

A high rate of cannabis use was also reported in the Low Prevalence Study (LPS) of psychoses in the Australian cities of Perth, Melbourne, Brisbane and Canberra (48). In this study persons with a suspected psychotic disorder were assessed by experienced clinicians using ICD-10 criteria, (48) including significant proportions who were not in domestic dwellings (which was a limitation of the NSMHWB sample) (26). One in four (24%) were daily cannabis users, 30% met lifetime criteria for alcohol abuse or dependence and 25% met lifetime criteria for cannabis abuse or dependence (48).

10.3 Explaining the association

One hypothesis is that cannabis use precipitates schizophrenic disorders in vulnerable persons. Its supporters cite the earlier age of onset of psychotic symptoms among persons with schizophrenia who use cannabis and reports that they have better premorbid adjustment, fewer negative symptoms, and a better treatment response (49).

A second possibility is that the association between cannabis use and an acute onset of schizophrenia is spurious. It may be, Arndt et al (39) argue, that schizophrenics with a better premorbid personality are more likely to be exposed to illicit drug use than persons with schizophrenia who are socially withdrawn. There is supportive evidence (50) that persons with acute onset psychoses usually have a better premorbid adjustment and a better prognosis. They also have greater opportunities to use cannabis and other illicit drugs than persons who are socially withdrawn.

A third possibility is that cannabis use is a consequence (rather than a cause) of schizophrenia. For example, cannabis and other drugs may be used to medicate the unpleasant symptoms of schizophrenia (51), such as depression, anxiety, lethargy, and anhedonia, or the unpleasant side effects of the neuroleptic drugs that are often used to treat the disorder (40).

10.3.1 Precipitation of schizophrenia

The most convincing evidence that cannabis use may precipitate schizophrenia comes from a 15-year study of cannabis use and schizophrenia in 50,465 Swedish conscripts (52). This study investigated the relationship between self-reported cannabis use at age 18 and receiving a diagnosis of schizophrenia in the next 15 years (as indicated by the Swedish psychiatric case register). Andreasson et al found that those who had tried cannabis by age 18 were 2.4 times more likely to be diagnosed with schizophrenia than those who had not. The more often cannabis had been used by age 18 the more likely they were to receive this diagnosis. The rate of a schizophrenia diagnosis was 1.3 times higher among those who had used cannabis one to ten times, 3 times higher among those who had used cannabis between one and fifty times, and 6 times higher among those who had used cannabis more than fifty times.

These risks were substantially reduced after statistically adjusting for variables that were related to the risk of developing schizophrenia, namely, having a psychiatric diagnosis at conscription, and having parents who had divorced (as an indicator of parental psychiatric disorder). Nevertheless, the relationship remained statistically significant. The risk of a diagnosis of schizophrenia was still 1.5 times greater for those who had smoked cannabis from one to ten times, and 2.3 times greater for those who had used ten or more times. Andreasson et al (52) and Allebeck (49) have argued that this indicates that cannabis use precipitates schizophrenia in vulnerable individuals.

A number of alternative explanations have been offered of the Swedish finding. First, there was a large gap between self-reported cannabis use at age 18 and the development of schizophrenia over the next 15 years (53). The diagnosis of schizophrenia was based upon a case register so there was no data on how many individuals were using cannabis at the time that their schizophrenia was diagnosed. Andreasson et al argued that cannabis use persisted because use at age 18 was strongly related to a diagnosis of drug abuse.

A second possibility is that schizophrenia was misdiagnosed. On this hypothesis, the higher rate of 'schizophrenia' among the heavy cannabis users was due to cannabis-induced psychoses that were misdiagnosed as schizophrenia (53). Andreasson et al (54) tested this possibility by examining 21 cases of schizophrenia among conscripts in the case register (8 of whom had used cannabis and 13 of whom had not). They found that

80% of these cases met the DSM-III requirement that the symptoms had been present for at least six months, thereby excluding the diagnoses of transient drug-induced psychotic symptoms.

A third hypothesis is that the relationship between cannabis use and schizophrenia is explained by the use of other drugs. Studies show (see chapter 5) that heavy cannabis users in late adolescence are more likely to use other illicit drugs, including amphetamine, which can produce an acute psychosis (55). Amphetamines were the most commonly used illicit drugs in Sweden during the late 1960s and early 1970s (56). On this hypothesis, amphetamine-induced psychoses would produce a spurious association between cannabis use and schizophrenia. The evidence that psychotic symptoms persisted beyond 6 months (54) also makes this an unlikely hypothesis.

A fourth hypothesis is that early cannabis use was a symptom of emerging schizophrenia. Andreasson et al (54) rejected this hypothesis, noting that the cannabis users who developed schizophrenia had better premorbid personalities, a more abrupt onset, and more positive symptoms than the non-users of cannabis. Moreover, there was still a dose-response relationship between cannabis use and schizophrenia among those who had no previous psychiatric history. The persuasiveness of this evidence depends upon whether a *failure* to identify a psychiatric disorder at conscription meant that no disorder was present.

A fifth hypothesis depends upon under-reporting of cannabis use at conscription. Andreasson et al (52) acknowledged that cannabis use was probably under-reported because this information was not collected anonymously. They argued, however, that under-reporting would *under*-estimate the relationship between cannabis use and schizophrenia. This is true if the schizophrenic and non-schizophrenic conscripts were equally likely to under-report. If, for example, pre-schizophrenic subjects were more candid about their drug use, then the apparent relationship between cannabis use and schizophrenia could be spurious (53). This seems unlikely, however, in view of the relationship between the *frequency* of cannabis use by age 18 and the risk of a schizophrenia diagnosis among heavy users.

10.3.2 Exacerbation of schizophrenia

Clinical reports suggest that schizophrenic patients who continue to use cannabis experience more psychotic symptoms (57), respond poorly to neuroleptic drugs (58), and have worse clinical outcomes than those patients who do not (59). These reports have been supported by controlled studies.

Negrete et al (60) conducted a retrospective study of the relationship between self-reported cannabis use and symptoms in the clinical records of 137 schizophrenic patients who had the disorder for at least six months. They found higher rates of hallucinations and delusions and more hospitalisations among patients who were cannabis users. These relationships persisted after statistical adjustment for age and sex. Similar findings have been reported by Cleghorn et al (61) who found that cannabis was the most heavily used drug, and drug abusers had higher rates of hallucinations, delusions and positive symptoms than those who did not abuse drugs. DeQuardo et al (62) reported similar findings in a retrospective study of 67 schizophrenic patients.

Jablensky et al (63) reported a two year follow-up of 1202 first episode schizophrenic patients enrolled in 10 countries as part of a WHO Collaborative study. They found that the use of 'street drugs', including cannabis and cocaine, was associated during the follow up period with more psychotic symptoms and hospitalisation. Martinez-Arevalo et al (64) reported in a study of 62 schizophrenic patients that those who used cannabis during a one-year follow up were more likely to relapse and comply poorly with drug treatment. Caspari (65) reported similar findings in a six year follow up study of 39 schizophrenic patients with a history of cannabis abuse and 39 schizophrenic patients without such a history.

Linszen et al (66) reported a prospective study of 93 psychotic patients whose symptoms were assessed monthly over a year. Twenty-four of these patients were cannabis abusers (11 were less than daily users and 13 were daily cannabis users). The cannabis users relapsed to psychosis sooner, and had more relapses in the year of follow up, than the patients who had not used cannabis. Daily users relapsed earlier, and more often, than the less than daily users who, in turn, relapsed sooner, and more often, than the patients who did not use cannabis. These relationships persisted after statistically controlling for premorbid adjustment, and alcohol and other drug use.

Two uncertainties remain. First, it may be that schizophrenia patients who do and do not use cannabis differ in premorbid personality, family history, and other characteristics. This explanation is unlikely in the WHO schizophrenia study (63) and the Linszen et al study (66), both of which used statistical methods to adjust for these confounders. The second difficulty is separating the contributions that cannabis and other drugs make to the exacerbation of schizophrenic symptoms. Heavy alcohol use is common among persons with schizophrenia, and the heavier their cannabis use, the more likely the person is to use psychostimulants and hallucinogens (32). Only Linszen et al statistically adjusted for the effects of concurrent alcohol and drug use. Our confidence that the effect is attributable to cannabis will increase with replications of the Linszen et al study.

10.3.3 Intervention studies

If cannabis use exacerbates schizophrenia then patients who reduce their cannabis use should have fewer symptoms and lower relapse rates. The major difficulty with testing this prediction is getting persons with schizophrenia to reduce their cannabis use. Dependence on alcohol and other drugs is difficult to treat (67), and persons with schizophrenia often have characteristics that predict a poor treatment outcome, namely, they lack social support, they may be cognitively impaired, they are often unemployed, and they may comply poorly with treatment (32, 68).

There are very few controlled outcome studies of substance abuse treatment in schizophrenia (69). Few of these have produced large enough benefits of treatment, or treated a large enough number of patients, to provide an adequate chance of detecting any positive impacts of abstinence on the course of disorders. The few that have been large enough (70) have not reported results separately by diagnosis. Better designed intervention studies should help to clarify the relationship between cannabis use and schizophrenia.

10.3.4 Self-medication

The evidence for the self-medication hypothesis (that persons with schizophrenia use cannabis to avoid unpleasant symptoms of the illness) is not very compelling. Persons with schizophrenia report that they use alcohol, cannabis and other illicit drugs for similar reasons to persons who do not have schizophrenia, namely, to relieve boredom, to provide stimulation, to feel good, and to socialize with peers (32, 37, 71, 72). The drugs that are most often used by schizophrenic patients are also those that are most readily available in the general population, namely, tobacco, alcohol, and cannabis.

In favour of the self-medication hypothesis is the evidence that some schizophrenic patients report using cannabis for its euphoric effects and to relieve negative symptoms and depression (e.g. (29, 40, 73)). Dixon et al (40), for example, surveyed 83 patients with schizophrenia who reported that cannabis reduced anxiety and depression, and increased a sense of calm, but at the cost of making them feel more suspicious.

Hamera et al (74) examined correlations over 84 consecutive days between self-reported psychotic symptoms, licit and illicit drug use, and medication use in 17 persons with schizophrenia. They found relationships between nicotine and prodromal psychotic symptoms and between caffeine use and symptoms of anxiety and depression but there were no relationships between psychotic symptoms and alcohol or cannabis use. This study does have limitations. The difficulty of the self-monitoring task probably selected patients who were more compliant than a representative sample of schizophrenics and they reported low rates of drug use. It is also possible that the time period of 84 days was too short to fully examine the relationship between drug use and major exacerbations of the illness.

10.4 Summary

Evidence supports the hypothesis that cannabis use exacerbates the symptoms of schizophrenia. This evidence comes from a number of retrospective and prospective studies that have controlled for confounding variables. This hypothesis is also biologically plausible: psychotic disorders involve disturbances in the dopamine neurotransmitter systems (75) and cannabinoids, such as THC, increase dopamine release (76).

It is also possible that cannabis use precipitates schizophrenia in persons who are vulnerable because of a personal or family history of schizophrenia. This hypothesis is consistent with the stress-diathesis model of schizophrenia (50, 77) in which schizophrenia is the result of stress acting upon a genetic 'diathesis' to develop schizophrenia. The only direct evidence for it comes from a study by McGuire et al (21) which reported that schizophrenic patients with a history of heavy cannabis use were 10 times more likely to have a family history of schizophrenia than persons with a psychosis who had not used cannabis.

It remains uncertain whether cannabis use can cause schizophrenia that would not have occurred in its absence (78). If it can, it is unlikely to account for more than a minority of cases. Most of the 274 conscripts in the Andreassen et al study who developed

schizophrenia had not used cannabis (54) and only 21 of those who did were heavy cannabis users. The *treated* incidence of schizophrenia has not increased during the 1970s and 1980s (79), despite very substantial increases in cannabis use among young adults in Australia and North America (38). Although there are complications in interpreting such trends (80), the debate has been about whether the incidence of schizophrenia has *declined* or remained *stationary* rather than *increased* (81).

10.5 References

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11 Is cannabis a gateway drug?

Adolescent cannabis use is an understandable concern to the community. This is because adolescents' decisions about whether or not to use drugs are not as informed as those of adults (1) and regular cannabis use may complicate the transition from childhood to adulthood by interfering with school performance, interpersonal relationships with parents and peers, and limiting important life choices, such as whom and when to marry, and what occupation to pursue (2, 3). Young people who start using cannabis in adolescence are more likely to become regular users and are therefore more likely to experience any adverse health effects caused by chronic cannabis use (e.g. (1, 3). Adolescence is also a time of risk-taking when the use of an intoxicant, such as alcohol or cannabis, while driving a car may increase the risk of accidental injury and premature death (1).

One concern about adolescent cannabis use has dominated the cannabis policy debate. This is that adolescent cannabis use may increase the chance that young people will use other more dangerous illicit drugs, such as cocaine and heroin (4–6). This is known as the 'gateway hypothesis'.

In deciding whether cannabis is a gateway drug the first question that needs to be answered is whether cannabis users are more likely to use other illicit drugs. If so, we need to ask whether the relationship is explained by other factors. One possibility is that individuals who use cannabis are more likely to use other illicit drugs for other reasons. We can test this by seeing whether rates of illicit drug use among cannabis users change when we take account of the characteristics of young people who are the most likely to use cannabis.

If there is a relationship between cannabis and other illicit drug use, we have to explain it. The two main explanations that feature in the public debate are: (1) that cannabis users are more likely to use other illicit drugs because of the pharmacological and other effects that cannabis has; and (2) that cannabis users are more likely to use other illicit drugs because the same black market supplies cannabis and other illicit drugs, so cannabis users are more likely to have access to other illicit drugs.

11.1 Is there a relationship between cannabis use and other drug use?

There is abundant evidence from surveys of adolescent drug use in the United States and elsewhere that *regular* cannabis use and the use of cocaine and heroin are associated (7). From the late 1970s to the 1990s in the United States, there was a strong relationship between regular cannabis use and the later use of heroin and cocaine. Kandel (8), for example, found that only 7% of American adolescents who had not used cannabis reported using another illicit drug. By contrast, 33% of those who reported using cannabis had used another illicit drug. Most (84%) daily cannabis users had done so and they had also used many more types of illicit drugs than their peers who had not used cannabis or who were not daily users of cannabis (8).

The same relationship has been observed in Australian surveys of drug use (9). In the 1993 National Campaign Against Drug Abuse (NCADA) survey of drug use in Australia, for example, even though 96% of cannabis users had *not* used heroin, the odds of using heroin were approximately 30 times higher among those who have used cannabis than those who had not (9). In the 1998 National Drug Strategy Household Survey, there was an even stronger relationship: those who reported that they had ever used cannabis were 78 times more likely to report having used heroin. The association is so strong because so few persons who have used heroin had not used cannabis (only 4 out of 276 in the 1998 survey).

Kandel and colleagues have described a typical sequence of involvement with licit and illicit drugs among American adolescents during the 1970s and 1980s. Almost all adolescents who have tried cocaine and heroin, had used alcohol, tobacco and cannabis in that order (10). Those who began to use alcohol and tobacco at an early age, and those who became regular smokers and drinkers, were the ones who were most likely to use cannabis. In turn, it was cannabis users who began use at an early age who were the most likely to become regular cannabis users and the most likely to use hallucinogens, amphetamines and tranquillisers. The heaviest users of these drugs were, in turn, more likely to use cocaine and heroin. Kandel and her colleagues have confirmed these results in longitudinal studies of adolescent drug use in this age cohort (11) and in later cohorts with high rates of crack cocaine use (12, 13).

Generally, the earlier the age at which a young person used any drug in the sequence, and the more regular their use of it, the more likely they were to use the next drug in the sequence (14–16). This sequence of drug involvement has largely been confirmed by other US researchers (7, 17). Longitudinal studies of drug use in Australia (18), Germany (19), New Zealand (20–23), and Sweden (24, 25) have broadly confirmed US findings on sequences of drug involvement and predictors of progression to cannabis and other illicit drug use.

11.2 Is the relationship between cannabis and other drug use spurious?

One explanation of the relationship between daily cannabis use and the use of other drugs is that it is due to the type of person who uses cannabis. According to this 'selective recruitment' hypothesis, the relationship is explained by the recruitment to cannabis use of deviant and nonconformist young persons who have a predilection to use a range of intoxicating drugs like alcohol, cannabis, cocaine and heroin (22). On this hypothesis, the order in which these drugs are tried simply reflects their availability and the societal disapproval of their use (7, 17). That is, alcohol and tobacco use precede cannabis use because alcohol and tobacco are readily available to adolescents, and cannabis use precedes heroin and cocaine use because cannabis is the much commonly used illicit drug and it is more readily available than cocaine and heroin. On this hypothesis, cannabis use is not a cause of the use of other illicit drugs. Rather, cannabis and other illicit drug use are common consequences of pre-existing social deviance and nonconformity (26, 27).

The selective recruitment hypothesis is supported by the substantial correlations between various types of nonconforming adolescent behaviour, including high school drop out, early sexual experience and unplanned pregnancy, delinquency, and alcohol and illicit drug use (28, 29). All of these behaviours are correlated with nonconformist and rebellious attitudes and antisocial conduct in childhood (30) and early adolescence (27, 28).

Regular cannabis users are more likely than their peers: to have a history of antisocial behaviour (23, 31); to be nonconformist and alienated (30–32); to perform more poorly at school (33–35); and to use drugs to deal with personal distress (30, 36). In general, the more of these risk factors that adolescents have, the more likely they are to use cannabis daily, and to use other illicit drugs (31, 37, 38).

The selective recruitment hypothesis can be tested in longitudinal studies by examining whether cannabis use still predicts the use of heroin and cocaine after statistically controlling for pre-existing differences between cannabis users and nonusers in social deviance and non-conformity (22). A number of studies have used this strategy to test the selective recruitment hypothesis.

Yamaguchi (39) tested whether the relationship between cannabis use and 'harder' illicit drug use persisted after statistically controlling for pre-existing adolescent behaviours and attitudes, interpersonal factors, and the age of initiation into drug use. They found that the relationship between cannabis use and the use of other illicit drugs was not explained by these factors or by friends' cannabis use. The same finding has emerged in several other studies (11, 40, 41). In these studies, the relationship between cannabis and heroin use has been reduced but not eliminated by statistically controlling for differences between users and non-users of cannabis.

O'Donnell and Clayton (40) have argued that this is strong evidence in favour of a causal connection between cannabis and heroin use. The strength of their argument depends on whether the most important characteristics of cannabis users have been statistically controlled for in these studies. It would be difficult to argue that this was true in the early studies. Kandel et al. (11), for example, were unable to measure the users' attitudes and family characteristics at the time of drug initiation. In the O'Donnell and Clayton (40) and Robins et al. (41) studies, deviance 'prior' to drug use was assessed retrospectively, with unknown validity. Baumrind (42) argued that 'in the absence of evidence of external validity' of these measures it is 'safer' to assume that the relationship between cannabis use and heroin use is spurious.

Two studies by Fergusson and Horwood (20, 22) address many of the weaknesses in the earlier studies. These report data from a prospective study of 990 New Zealand children who were followed from birth to age 21 years and assessed on a wide range of psychosocial variables that potentially explain the relationship between cannabis use and the use of other illicit drugs. These included: family background (socio-economic status, parental conflict and divorce, childhood sexual abuse, parental punishment and parental attachment); parental adjustment (parental alcohol and drug problems, criminality and illicit drug use); individual characteristics of the young person (gender, intelligence, novelty seeking); early adolescent development (cigarette smoking, frequency of alcohol

use, juvenile offending, school drop out, conduct problems and attitudes towards drug use); peer affiliations (peer use and problems with alcohol and other drug use); and personal history of risk taking. These factors were statistically controlled for in analyses of relationships between cannabis use and use of other illicit drugs.

Fergusson and Horwood (20) reported on the relationship between the use of cannabis by age 16 and the use of other illicit drugs by the age of 18 years. They found a strong relationship between the frequency of cannabis use by age 16 and development of a problem with cannabis, alcohol or other substances by age 18. Early cannabis users came from lower socio-economic status families with a history of parental conflict, parental criminality and alcohol and drug use and low parental attachment. They also had a personal history of conduct problems, low self-esteem, high novelty seeking, and high affiliation with delinquent peers. Adjustment for these factors reduced but did not eliminate the relationship between early cannabis use and the use of other illicit drugs.

Fergusson and Horwood (22) reported a later follow up of the cohort. They found that 69% of their sample reported using cannabis by age 21, and 26% had used one or more other illicit drugs, with 4% having used cocaine or an opiate. In 99% of cases, cannabis use preceded the use of other illicit drugs. They found a strong relationship between level of cannabis use at any age and the use of another illicit drug. Compared to those who had never used cannabis, the risk of using another illicit drug was around 4 times higher among those who had used cannabis once or twice, 12 among those who had used 3 to 11 times, 41 times higher among those who had used 12 to 49 times and 143 times greater among those who had used 50 times or more. The relationships were reduced but remained substantial when other psychosocial factors were controlled for statistically. Compared to non-users of cannabis, the risks (after statistical adjustment) were 3 greater for those who had used once or twice, 8 greater for those who had used 3 to 11 times, 21 greater for those who had used 12 to 49 times and 59 greater for those who had used for 50 times or more.

The results of the Fergusson and Horwood studies make it unlikely that selective recruitment wholly explains the relationship between cannabis use and other illicit drug use. But its findings do not, as Fergusson and Horwood acknowledge, rule out other explanations. Among these is the possibility that there is a shared genetic vulnerability to use and become dependent on cannabis and other illicit drugs.

Studies of alcohol, tobacco and other drug use in identical and non-identical twins indicate that there is a genetic vulnerability to developing dependence on alcohol (43), cannabis (44) and tobacco (45). More importantly, a component of the genetic vulnerability to dependence on these three drug classes is shared or common (46). So too are the shared family and environmental factors that influence alcohol and cannabis dependence (46). The contribution of genes to dependence on other illicit drugs is less certain because rates of use in these twin studies have been too low to provide a powerful test of this hypothesis. The hypothesis of common genes for regular use of cannabis and other illicit drugs has not been directly tested in any of the cohort studies, including that of Fergusson and Horwood. The identification of specific candidate genes for vulnerability to drug dependence will enable this hypothesis to be tested in future studies.

11.3 Explaining the association between cannabis and other drug use

If the association between cannabis and heroin use is not explained by pre-existing differences between cannabis users and nonusers, how might cannabis use 'cause' heroin and cocaine use? The two main competing explanations differ in whether they attribute the relationship to the pharmacological effects of cannabis or to the social context within which cannabis is obtained and used.

One hypothesis is that the pharmacological effects of cannabis use predispose regular cannabis users to use other intoxicating drugs (47, 48). Nahas (47) has hypothesised that 'the biochemical changes induced by marijuana in the brain result in a drug-seeking, drug-taking behaviour, which in many instances will lead the user to experiment with other pleasurable substances' (p xxiii).

Recent studies in animals (e.g. 49) have been interpreted as supporting a pharmacological explanation of the association between regular cannabis use and other drug use (50). These studies indicate that common biochemical pathways underlie the rewarding effects of cannabis, cocaine, heroin and nicotine (51). All these drugs appear to act on dopaminergic neurotransmitter systems that are involved in the 'reward centres' in an area of the midbrain, the nucleus accumbens (52). However, there is as yet no direct evidence from animal studies that administration of THC to animals increases their risk of using other illicit drugs (53).

Pharmacological explanations of the relationship between cannabis and other drug use also have difficulty explaining a number of facts about their relationship. First, there are relatively low rates of progression from cannabis use to the regular use of other illicit drugs; experimentation and discontinuation of cannabis use is the norm (54). Those heavy cannabis users who do use other illicit drugs also continue to use cannabis, as well as the new illicit drugs. As Donovan and Jessor (17) have noted: '...'harder' drugs do not serve as substitutes for 'softer' drugs. Rather, a deepening of regular substance use appears to go along with a widening of experience in the drug domain' (p. 548–549). This pattern of involvement is more consistent with a genetic vulnerability to drug dependence than the hypothesis that cannabis use is a stepping-stone to experimentation with other drugs.

Third, the pattern of progression in drug use among American adolescents in the 1970s was affected by drug availability (14). Among cohorts of heroin users in the 1950s and 1960s, cannabis use was confined to those geographic areas of the US in which it was readily available (5). Research on African-American adolescents also showed a variation in the sequence of drug use. In African-American communities cocaine and heroin were more readily available than hallucinogens so cocaine and heroin use often preceded the use of hallucinogens (14). Similarly, American soldiers in Vietnam used heroin before they used alcohol because heroin was cheaper and more freely available in Vietnam than was alcohol (since many of the American troops were under the legal drinking age of 21) (55).

The historical and geographical variations in sequences of drug use suggest sociological explanations of the use of heroin among heavy cannabis users. One hypothesis is that regular cannabis use predicts an increased use of other illicit drugs because regular cannabis users have an increased contact with other drug users and drug sellers and hence more opportunities to use other illicit drugs than peers who do not use cannabis regularly. Regular cannabis use thereby increases involvement in a drug using subculture which, in turn, exposes cannabis users to peers who have used other illicit drugs, who approve of such drug use, and who provide more opportunities to use other illicit drugs because of their increased availability within their social circle (5, 56).

Although plausible, there is little direct evidence on the drug subculture hypothesis. Goode (5) presented data from the late 1960s indicating that the number of friends who used heroin was a stronger predictor of heroin use than was frequency of cannabis use, arguing that the 'correlation between frequency of use and the use of dangerous drugs ... [is] the result of interaction and involvement with others who use' (p. 332). These observations have been supported by Kandel's (8) finding that the strongest predictor of continued cannabis use in early adulthood was the number of friends who were cannabis users.

Fergusson and Horwood's (22) analysis of the Christchurch Child Development Study was able to examine the contribution of affiliation with drug using peers to the relationship between cannabis and other illicit drug use. They included self-reported peer use of alcohol, cannabis and other illicit drugs in their statistical analyses. Their inclusion reduced but did not eliminate the relationship between cannabis and other illicit drug use, indicating that while peer drug use made a contribution to the association, it did not fully explain it.

The role of socialisation in a drug-using subculture and involvement in drug markets has not been directly tested in the important cohort studies (22). It is nonetheless a plausible hypothesis. Regular cannabis users are distinguished from non-users by their extensive social relationships with other drug users and often by buying and selling cannabis and other illicit drugs to finance their own drug use (5).

11.4 Summary

Research on adolescent use of cannabis and other illicit drug use has revealed a number of consistent findings about the relationship between cannabis and other illicit drug use. First, among American adolescents in the 1970s the use of alcohol and tobacco preceded use of cannabis, which in turn, preceded the use of hallucinogens and 'pills', and the use of heroin and cocaine. Generally, the earlier the age of initiation into drug use, and the greater the involvement with any drug in the sequence, the more likely a young person was to use the next drug in sequence. Similar sequences have been observed in a variety of societies, including Australia.

The explanation of the role of cannabis in the sequence of illicit drug use remains controversial. The relationship does not appear to be spurious. The hypothesis that the sequence of drug use represents a direct pharmacological effect of cannabis use upon the

use of later drugs in the sequence is not compelling. It also seems unlikely that the association between regular cannabis use and the use of other illicit drugs is *wholly* the result of shared risk factors or common causes. Selective recruitment of socially deviant adolescents to cannabis use, plays some role but it also does not explain the relationship. A shared genetic vulnerability to alcohol, tobacco and cannabis dependence is a plausible explanation that cannot be excluded on the available evidence.

If there is a causal relationship between cannabis and other illicit drug use the explanation is more likely to be a sociological than a pharmacological one. The fact that cannabis use predicts an increased chance of using other illicit drugs reflects a combination of: (1) the selective recruitment to heavy cannabis use of persons with pre-existing personality and attitudinal traits (possibly genetic in origin) that predispose to the use of other intoxicants; (2) their affiliation with drug using peers; (3) socialisation into an illicit drug subculture in which there is an increased opportunity and encouragement to use other illicit drugs; (4) increased access to opportunities to purchase and use other illicit drugs because of involvement in illicit drug markets as buyers and sellers; and possibly (5) a shared genetic vulnerability to use and become dependent on a range of different drugs.

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12 Effects on adolescent psychosocial development

There have been two dominant concerns about the effects of adolescent cannabis use on psychosocial development. One is that adolescent cannabis use may adversely affect educational outcomes. The other is that cannabis use may adversely affect other psychosocial outcomes, such as employment, involvement in crime, and mental health. The evidence relevant to these concerns is discussed in this chapter.

12.1 Adolescent cannabis use and educational performance

It is reasonable to suspect that adolescent cannabis use may impair educational performance and increase the chances that a student will discontinue their education (1). Cannabis use acutely impairs memory and attention and, if used regularly, it could impair learning and school performance, thereby increasing the chance of a student dropping out of school. If the adolescent's school performance was marginal to begin with, as research suggests it is among regular cannabis users, then cannabis use could increase the risk of school failure. Since high school education is so important to occupational choice, this potential effect of adolescent cannabis use could flow through the individual's life.

A number of cross-sectional surveys have examined relationships between cannabis use and educational attainment among school children and youth. The measures of educational outcome have only rarely included school grades and examination performances. Instead these studies have measured truancy and early school leaving, perhaps because confidentiality and privacy preclude access to school grades and performance in external examinations.

Resnick et al (2) reported that a low grade point average was associated with cannabis use in a national sample of 12,118 adolescents in the USA. Brook et al (3) reported that among 1,687 Colombian adolescents those who were dissatisfied with school were more likely to use cannabis. In an Australian study of 199 high school students aged 13–16 years, Jones and Heaven found that young people who were regular cannabis users had a more negative attitude toward school and a poorer record of school attendance than those who were not (4). Lifrak et al reported a negative correlation between cannabis use and scholastic competence for boys (but not for girls) in a sample of 271 seventh and eight grade students (5). Novins & Mitchell (6) also reported a significant association between poor school performance and cannabis use for males (but not females) in a sample of 1464 Native American adolescents.

A number of studies have shown that rates of cannabis and other illicit drug use are higher among young people who either no longer attend school or who are absent from school on any given day. For example, Lynskey et al (7) found that young people in the

Australian School Students' Alcohol and Drugs Survey who reported being away from school the day before the survey had higher rates of cannabis use than students who attended school on that day. Similarly, Fergusson, Lynskey and Horwood (8) found that truancy was more common among cannabis users in a sample of nearly 1,000 16 year old New Zealanders.

Mensch and Kandel (9) examined relationships between educational achievement and cannabis use in the US National Longitudinal Survey of Young Adults. They found that high school graduates reported significantly more cannabis use during adolescence than college graduates, even after controlling for socio-demographic factors, and differences in academic ability, self-esteem and delinquency. The value of this study was compromised by a reliance on retrospective reports of cannabis use, the reliability and validity of which have been questioned (10).

12.2 Explaining the relationship

Four broad explanations of the relationship between cannabis use and educational outcome need to be considered. The first and simplest explanation of the association is that early cannabis use causes poor educational outcomes. Kandel, Davies, Karus and Yamaguchi (11) argued that early cannabis use encourages continued use of the drug, and that cannabis and other illicit drug use encourages anti-conventional behaviours including early school leaving, delinquency, employment problems and difficulties in interpersonal relationships.

A second alternative explanation is that heavy cannabis use is a *consequence* of poor educational attainment. There is some support for this hypothesis in that poor educational performance is a risk factor that precedes cannabis use (12–16). The hypotheses that cannabis use is a cause of poor school performance and that poor school performance is a cause of cannabis use are not mutually exclusive. Both processes could be at work (17) if poor school performance increased the risks of using cannabis, which in turn worsened school performance.

A third possible explanation is that cannabis use and poor educational attainment are reflections of a common syndrome of problem behaviour (18). A wide range of problem behaviours in adolescence are manifestations of a common syndrome of problem behaviours (19).

The final possibility is that the associations between early cannabis use and poor educational outcomes are not causal but the result of common factors that increase the likelihood of both early cannabis use and poor educational performance. There is evidence that the risk factors and life pathways for early cannabis use overlap considerably with those for poor educational performance. These risk factors (see reviews by (15, 20, 21) include: the extent to which the norms and attitudes of the wider community encourage or discourage the use of drugs; social disadvantage and family dysfunction; individual factors including personality and an individual's propensity to violate norms; and the extent to which an individual affiliates with delinquent and drug using peers.

12.3 Longitudinal studies of cannabis use and educational outcomes

These four explanations can only be distinguished by prospective longitudinal studies in which a large representative group of young people is assessed over time on their cannabis use, educational attainment and other potentially confounding factors, such as family and social circumstances, personality characteristics and delinquency. These studies have the following strengths (22). First, they enable us to tell which comes first, cannabis use or poor educational performance. Second, they reduce the effects of bias in retrospective reports of cannabis use and behaviour. Third, they enable us to test causal hypotheses about cannabis use and educational outcomes by statistically adjusting for confounding variables. That is, they allow us to answer the question: do young people who use cannabis have poorer educational outcomes than those who do not, when we allow for the fact that cannabis users are more likely to perform poorly in school before they used cannabis?

Newcomb and Bentler (23) followed a sample of 654 high school students over 8 years to assess the impact of early substance use on educational outcomes at ages 19 to 24 years. They used statistical methods to examine the extent to which cannabis and other drug use were associated with adverse outcomes in young adulthood, after taking account of the effects of confounding factors. Their analyses indicated that early substance users were more likely to abandon a college education.

The results of this study have been supported by Fergusson, Lynskey and Horwood (24) who examined the extent to which cannabis use before the age of 15 years predicted regular drug use, criminal offending, poor mental health and reduced life opportunities at age 16, after adjusting for a range of potentially confounding factors. The sample consisted of 990 young people who had been followed from birth to age 16 years. They were assessed on cannabis use at age 15 and on cannabis use and a wide range of other health and psychological outcomes at age 16.

The ten percent of the sample who had used cannabis by the age of 15 had elevated risks of school problems at age 16. Specifically, 22.5% had left school before age 16 (the minimum school leaving age in New Zealand) compared with only 3.5% of those who had not used cannabis. The frequency of truancy between 15 and 16 years was also higher among those who had used cannabis before the age of 15 years (31.5%) than those who had not used cannabis (4.7%). The relationship between early cannabis use and early school leaving persisted after statistical adjustment for pre-existing differences between early cannabis users and their peers. In a later follow-up of the same birth cohort, Fergusson and Horwood (25) reported that those who had used cannabis before the age of 16 years were more likely to leave school without formal qualifications. This relationship also persisted after control for a wide range of confounding variables.

Duncan et al (12) examined the factors that predicted escalation of substance use in 664 adolescents who were assessed at three time points. They found that academic failure predicted higher levels of substance use (including cannabis use) at the initial time period. Deteriorating academic performance over the course of the study was also associated with increasing substance use.

Ellickson et al assessed cannabis use and a range of other factors in seventh graders who were followed up five years later (26). Cannabis use predicted early school leaving among Latino students, even after controlling for demographic variables, family structure, academic orientation and early deviance. Young Latinos who were heavy cannabis users were more likely to leave school before graduating. After controlling for these confounding factors, cannabis use did not predict early school leaving for Asians, Blacks or Whites.

Garnier, Stein and Jacobs (27) conducted a long-term prospective study of early high school drop-out. They reported that early school leaving was determined by multiple factors, which included adolescent drug use. They found that, after taking account of a range of other determinants of early school leaving, there was still a significant association between drug use assessed at age 17 years and early school leaving.

Krohn, Lizotte and Perez (17) reported that the use of alcohol and other drugs during adolescence increased the risks of precocious transitions to a range of adult roles, including leaving school early. They used longitudinal data from a sample of 775 high-risk adolescents studied from age 13 to 20 years. Early substance use, measured by frequency of alcohol, cannabis and other illicit drug use, predicted early school leaving for males but not for females.

Tanner, Davies and O'Grady (28) used data from the National Longitudinal Study of Youth to examine the influence of drug use (assessed between 14 and 17 years) on social outcomes assessed between the ages of 25 to 30 years. These included educational outcomes (highest grade completed, graduation from high school, college degree) and employment variables (occupational status, unemployment). They found that (after controlling for socio-demographic background, cognitive skill and educational expectations) early drug use predicted early school drop out, failure to graduate from high school and failure to obtain a college degree in males and females. Among males early drug use was also related to lower occupational status and unemployment.

Similar findings have been reported by Brook, Balka and Whiteman (29) in a sample of 1182 Puerto Rican and African American students who were followed over a five year period. Young people who reported using cannabis once a month or more often at age 14 were more likely to leave high school before completing 12th grade, even after controlling for a range of factors assessed at age 14. Young people who used cannabis at least monthly at age 14 were also more likely to report delinquency, other drug related problems, sexual risk taking and to have more friends who exhibited deviant behaviour.

In summary, a number of longitudinal research studies have generally shown that early cannabis use is a risk factor for poor educational outcomes and, in particular, early school leaving. A causal interpretation of the link between early cannabis use and subsequent educational performance has been supported by the fact that many of these studies have statistically controlled for a wide range of variables on which cannabis users and non-users differ. In these studies early cannabis use predicts an increased risk of early school leaving and making precocious transitions to adult roles by: engaging in early sexual activity (30), unplanned pregnancy during adolescence (17, 31), unemployment (25), and leaving the family home (17).

12.4 Explaining the association between cannabis use and early school leaving

In the better longitudinal studies statistical methods have taken account of a wide range of potential explanations of the association between cannabis use and early school leaving. Perhaps the most comprehensive effort was the study by Fergusson et al (24). Their results, and those of other studies, indicate that, even though statistical control substantially reduces the associations between cannabis use and early school leaving, a significant association remains.

It is still possible that the association between cannabis use and early school leaving arises from the effects of factors that were not measured in the studies, such as neighbourhood effects (32) and genetic vulnerability (33). The difficulty in making a causal inference is not peculiar to the relationship between cannabis use and early school leaving. A number of studies, for example, have found a relationship between cigarette smoking and early school leaving which remains after extensive statistical control for confounding factors (25, 26). There is no obvious biological explanation of the relationship so it is more likely to reflect uncontrolled factors that are associated with tobacco use and early school leaving. Although a similar possibility cannot be excluded with respect to cannabis, a number of explanations have been suggested of the relationship between cannabis use and early school leaving.

12.5 Does cannabis use produce an 'amotivational' syndrome?

Daily cannabis use over months and years has been reported to impair motivation and social performance in users in Egypt and the Caribbean (34) (see chapter 6). The existence of an 'amotivational syndrome' among chronic heavy cannabis users has not been supported by the results of a number of field studies conducted in societies where heavy cannabis use is widespread, including Jamaica (35) and Costa Rica (36) (see chapter 6). Evidence reviewed in chapter 6 suggests that an amotivational syndrome is rare, if it exists (37, 38) and 'it may be more parsimonious to regard impaired motivation as a symptom of chronic cannabis intoxication' (p.277) (39). Hence, it appears unlikely that 'amotivation' explains poor school performance.

12.6 Does cannabis use produce cognitive deficits?

A third explanation is that cannabis use causes cognitive impairment, which increases the likelihood of leaving school early. The evidence (as reviewed in chapter 8) indicates that long-term cannabis use does not produce marked impairments in thinking and memory that are as easily detected as those found in long-term heavy alcohol consumers (40). Solowij has argued that daily or near cannabis use over periods of three or more years does produce subtle impairment in selective attention in adults.

These deficits are of doubtful relevance to adolescent cannabis users because few would have used cannabis intensively or long enough to produce the effects found in adults.

The adults in the studies reviewed by Solowij, for example, used cannabis daily for an average of 10 years. By contrast, in the study reported by Fergusson and Horwood (25) the 'heavy' cannabis use group included those who had smoked cannabis on at least ten occasions. There is no evidence in the scientific literature on adults that such low levels of use are associated with any lasting cognitive impairment.

This does not mean that acute cognitive impairment is irrelevant in adolescents. Rather it suggests that any cognitive impairment in cannabis using adolescents is more likely to result from the *acute* effects of cannabis use rather than the effects of long-term use. If cannabis intoxication became an everyday occurrence in the life of an adolescent, their school performance would suffer, especially if it was poor to begin with.

12.7 Does early cannabis use lead to the precocious adoption of adult roles?

Fergusson and Horwood (25) have argued that the effects of early adolescent cannabis use on later development can be attributed to the social setting in which adolescents use cannabis, namely within a group of delinquent and substance using peers. Their views are in agreement with those of Kandel et al (11) who argued that early substance use sets in train a cascade of events that increases later psychosocial risk. On Fergusson and Horwood (25)'s hypothesis, the important causal factors is that cannabis use occurs in a peer group that rejects conventional values, such as high educational achievement and social conformity, and which instead encourages non-conformist behaviour and a premature transition to adulthood.

12.8 Other effects of adolescent cannabis use

12.8.1 Occupational performance

Among young cannabis users who enter the work-force the continued use of cannabis and other illicit drugs in young adulthood might impair job performance for the same reasons that it may impair school performance, namely, that chronic intoxication impairs cognitive and psychomotor performance. There is some support for this expectation in that cannabis users report higher rates of unemployment than nonusers (e.g. (41, 42) but this comparison is confounded by the different educational qualifications of the two groups.

Mensch and Kandel (9) examined cross-sectional relationships between alcohol, tobacco and cannabis use and performance in a range of occupations in a nationally representative sample of Americans. Apart from tobacco use there were only modest associations between cannabis use and occupation. There were very weak negative correlations between job satisfaction and tobacco smoking and cannabis use. Workers in occupations that were lacking in 'complexity, intellectual flexibility and variety' were more likely to smoke cannabis at work, perhaps because heavier cannabis users seek or are forced to accept less challenging jobs. Cannabis use and tobacco smoking were associated with 'lack of conformity or attachment to social institutions, such as having dropped out of school, having participated in delinquent activities, or not being married' (p 181).

Longitudinal studies have suggested that there is a relationship between adolescent cannabis use and job instability among young adults that is not explained by differences in education and other characteristics which precede cannabis use (e.g. (11). Newcomb and Bentler (23) examined the relationships between adolescent drug use and income, job instability, job satisfaction, and resort to public assistance in young adulthood, while controlling for differences between users and nonusers in social conformity, academic potential and income in adolescence. Their findings supported those of Kandel who found that adolescent drug users had a larger number of changes of job than nondrug users. Newcomb and Bentler conjectured that this reflects impaired work performance, or a failure of illicit drug users to develop responsible employment behaviour such as conscientiousness, thoroughness, and reliability.

Fergusson and Horwood (25) included unemployment for 3 months or more as one of their early outcomes in the follow up of their cohort at age 18 years. There was a relationship between how often cannabis had been used by age 16 and being unemployed for 3 months or longer. The rate of unemployment among those who had never used cannabis was 9.5% compared to rates of 18.9% and 37.5% among those who had used 1–9 times and 10 or more times respectively. After adjusting for covariates, the strength of the association was reduced but still significant (namely, 10.5%, 17.3% and 26.9% respectively). After adjustment for peer affiliations, the relationship was no longer statistically significant (12.2%, 13.4% and 14.6% respectively).

One longitudinal study (43) found more mixed evidence of an association between adolescent cannabis use in a sample of 785 young people followed from late high school in 1971–1973 until early adulthood in 1981. They found that adolescent cannabis use was weakly correlated with poor job performance, low job satisfaction or adverse job terminations. The correlations between cannabis use and these indices of job performance were 0.07, 0.07, and 0.17 respectively. These weak relationships between adolescent drug use and adult occupational performance were explained as the result of cannabis use persisting into adult life where it was associated with poor job performance, low job satisfaction, and adverse job termination.

12.8.2 Interpersonal relationships

There are good reasons for suspecting that cannabis use may adversely affect interpersonal relationships. Heavy adolescent drug use may produce a developmental lag, entrenching adolescent styles of thinking and coping which impair the ability to form adult relationships (1). There are also strong correlations between drug use and precocious sexual activity, and early marriage which in turn predicts a high rate of relationship failure (23).

Cross-sectional studies of drug use in young adults have indicated that a high degree of involvement with cannabis predicts a reduced probability of marriage, an increased rate of cohabiting, an increased risk of divorce or failed de facto relationships, and a higher rate of unplanned pregnancy and pregnancy termination (41, 42). These findings have been confirmed in analyses of the longitudinal data from a cohort of young adults (11).

Newcomb and Bentler (23) found similar relationships between drug use and early marriage in their analysis of the data from young adults in Los Angeles. Drug use in adolescence predicted an increased rate of early family formation in late adolescence and

of divorce in early adulthood. They interpreted this as evidence that: 'early drug involvement leads to early marriage and having children which then results in divorce' (p. 97). Newcomb and Bentler argued that this finding provided evidence for their theory of 'precocious development', according to which drug use accelerates development and drug users 'bypass or circumvent the typical maturational sequence of school, work and marriage and become engaged in adult roles of jobs and family prematurely without the necessary growth and development to enhance success with these roles ... [thereby developing] a pseudomaturity that ill prepares them for the real difficulties of adult life' (pp. 35–36).

12.8.3 Mental health

A number of cross-sectional studies of the association between cannabis use and poor mental health in young adults have produced mixed findings. The US National Longitudinal Alcohol Epidemiologic Survey (NLAES), a nationally representative survey of US adults (44) found that persons with DSM-IV major depression in the past 12 months were 6.4 times more likely to have DSM-IV cannabis abuse or dependence than those without major depression (6% vs. 1% respectively)(44).

A study of cannabis use and depressive symptoms did *not* find that frequency of cannabis use was associated with depression in young adult males (45). A weak association observed between early initiation of cannabis use and depression was not significant after controlling for educational attainment, marital status, and alcohol and tobacco use (45).

A study of male army draftees using cannabis but no other illicit drugs found that more problematic cannabis users had a higher rate of DSM-III-R psychiatric disorders and higher scores on the Beck Depression Inventory (BDI) (46). A study of adolescents cannabis users found that frequent users of cannabis had higher levels of depression on the Brief Symptom Inventory than abstainers or recreational users (47). 'Heavy' users were defined as those using cannabis at least 40 times *and at least one other illicit drug*.

Degenhardt et al. (48) examined relationships between cannabis use and mental health using data from the Australian National Survey of Mental Health and Well-Being (NSMHWB), a survey of a nationally representative sample of 10,641 Australian adults aged 18 years and over There was an association between cannabis use in the past 12 months and affective and anxiety disorders. Among those with cannabis dependence, 14% had an affective disorder and 17% had an anxiety disorder, compared with rates of 6% and 5% respectively in non-users. Heavier cannabis users also reported greater levels of psychological distress (as measured by Kessler's Psychological Distress scale).

The results of a number of longitudinal studies have provided more mixed evidence of the relationship between cannabis use and mental health. Kandel (41) found a cross-sectional study found an association between level of cannabis use and dissatisfaction with life, having consulted a mental health professional, and having been hospitalised for a psychiatric disorder (41). Longitudinal analyses of this cohort, however, found only weak associations between adolescent drug use and adult mental health; the strongest relationship was between cigarette smoking in adolescence and symptoms of depression in adulthood (11).

The cross sectional adult data in Newcomb and Bentler's (23) study also showed strong relationships between adolescent drug use and emotional distress, psychoticism and lack of a purpose in life. Emotional distress in adolescence predicted emotional distress in young adulthood but there were no relationships between adolescent drug use and adult emotional distress, depression and lack of a sense of purpose in life. Adolescent drug use predicted psychotic symptoms in young adulthood, and hard drug use in adolescence predicted increased suicidal ideation in young adulthood, after controlling for general drug use and earlier emotional distress. Newcomb and Bentler interpreted this as evidence that adolescent drug use 'interferes with organised cognitive functioning and increases thought disorganisation into young adulthood' (p 180).

Fergusson and Horwood (25) found a dose response relationship between frequency of cannabis use by age 16 and the likelihood of meeting DSM-IV criteria for an anxiety and depressive disorder and reporting a suicide attempt. These relationships were no longer statistically significant, however, after controlling for confounding factors.

Brook, Cohen and Brook (3) reported a longitudinal study of the relationship between alcohol, tobacco and cannabis use and mental health among 975 adolescents followed from age 13.7 years until 22.1 years in New York state. They found that early cannabis use predicted later antisocial behaviour after controlling for earlier antisocial behaviour. It did not predict an increased risk of anxiety and affective disorders. The strongest relationships between adolescent drug use and adult mental disorders were between cigarette smoking, illicit drug use (other than cannabis) and depression.

McGee, Williams, Poulton and Moffit (49) reported a longitudinal study of the relationships between cannabis use and mental health in a Dunedin, New Zealand, birth cohort between the ages of 15 and 21 years. They found that rates of cannabis use were higher among young people with mental disorders at 15, 18 and 21 years and that cannabis use was predicted by social disadvantage in childhood and low parental attachment. Cannabis use at age 15 did not predict mental health problems at age 18 but having mental health problems at age 15 (primarily alcohol dependence and conduct disorder) modestly predicted cannabis use at age 18. Cannabis use at age 18 also predicted alcohol dependence and conduct disorders at age 21. McGee et al argued that the lack of a relationship between cannabis use and anxiety and affective disorders suggests that cannabis use is not a form of 'self-medication in anxious and depressed individuals but rather reflects a 'willingness to contravene the law'.

12.8.4 Suicide

A small number of studies have examined the relationship between cannabis use and suicide among adolescents (see Hillman et al (50) for a review). Several have found an association but it remains unclear whether it is explained by other factors. An analysis of cross-sectional data from the US National Comorbidity Survey found an association between self-reported suicide attempts and the dependence on a number of drugs, including alcohol, sedatives, stimulants, cannabis, and inhalants (51). The risk for cannabis dependence was still significant after adjusting for socio-demographic factors and the presence of other psychiatric disorders, such as depression and alcohol dependence (odds ratio of 2.4,

Beautrais, Joyce and Mulder (52) reported a case-control study of the role of cannabis and other drug use in serious suicide attempts that resulted in hospitalisation. They compared rates of cannabis use among 302 consecutive hospital cases treated for serious suicide attempts with that in a random sample of 1,028 people in the community. They found that 16% of the suicide attempters had a cannabis use disorder (cannabis abuse or dependence) compared with 2% of the controls. Controlling for social disadvantage and having a diagnosis of depression or alcohol dependence substantially reduced the association but did not eliminate the association (reducing it from an odds ratio of 10 to 2).

The evidence from a small number of prospective studies is also mixed. Fergusson and Horwood (25) also found a dose response relationship between frequency of cannabis use by age 16 and the likelihood of reporting a suicide attempt, but it did not remain statistically significant after controlling for confounding factors. Patton et al (53) reported a longitudinal study on suicide attempts and self-harm in a cohort of 2066 Victorian secondary school students followed from age 15 to 16 to age 21. They found that cannabis was associated with self-harmful behaviour among females but not males, after controlling for depression and alcohol use.

Andreasen and Allebeck (54) reported an association between cannabis use and suicide deaths in their follow up of 50,465 conscripts. They found a fourfold increased risk of suicide among heavy cannabis users. A more detailed analysis of predictors of suicide in this cohort reported by Allebeck and Algulander (55) found that inpatient psychiatric hospitalisation by age 18 was the strongest predictor of suicide risk (OR = 11.3). Use of 'narcotics' (which includes cannabis) did not predict suicide independently of a psychiatric diagnosis (OR =1.3) but a diagnosis of alcohol dependence (OR = 4.3) and drug dependence (OR = 3.6) did.

12.8.5 Delinquency and crime

Cannabis and other illicit drug use are related to social nonconformity (2[illegible]6, 57) so it is unsurprising that there is a relationship between the extent of cannabis use and lifetime delinquency among adult drug users (41, 42), having been convicted of an offence, and having had a motor vehicle accident while intoxicated (41). Surveys of drug use in young people in the juvenile justice system also find high rates of regular cannabis use and a relationship between level of cannabis use and frequency of offending (58, 59).

Longitudinal studies reveal an interesting pattern of relationships between cannabis use and crime. Johnston et al. (60) analysed the relationship between drug use and delinquency in two waves of interviews of adolescent males. In their cross-sectional data, rates of delinquent activity increased steadily with increasing rates of drug use. However, analyses of changes in drug use and crime over time indicated that heavy drug users groups had much higher rates of delinquent acts *before* using drugs. The onset of illicit drug use (including cannabis) had little effect on delinquent acts, except among those who used heroin, whose rates of delinquency increased.

Newcomb and Bentler (23) reported a positive relationship between drug use and criminal involvement in adolescence, but found more mixed results in the relationship between adolescent drug use and criminal activity in young adulthood. Adolescent drug use predicted *drug* crime involvement in young adulthood; but after controlling for other

variables, it was *negatively* correlated with violent crime, and general criminal activities in young adulthood. Newcomb and Bentler argued that these negative correlations indicated that the correlation between different forms of delinquency in adolescence decreases with age, as criminal activities become differentiated into drug-related and non drug-related offences.

White (61) reported a follow up study of the relationship between cannabis use and delinquency in 1992 New Jersey youth followed from age 12 to age 18. He found modest correlations between cannabis use and delinquency at age 15 and age 18 and evidence that there were separate groups of adolescents who either engaged in cannabis use or in delinquent acts. These groups were distinguished by which of these two behaviours was most common among their immediate peers.

Fergusson and Horwood (25) included four measures of delinquency in their analysis of the consequences of adolescent cannabis use. These were: three or more violent offences, three or more property offences, arrested by police, and convicted of an offence in court by age 16. There was a dose-response relationship between each of these outcomes and frequency of cannabis use by age 16. This persisted after adjustment for covariates, suggesting that it was not wholly explained by the characteristics of adolescents who become regular cannabis users by age 16. It also persisted after adjustment for drug use and criminal behaviour in the users peer group, indicating that it was not explained by affiliating with delinquent and drug using peers.

Brook et al (29)'s longitudinal study of 695 African-American and 637 Puerto Rican youth in New York City also assessed self-reported violence towards others. They found that early cannabis use predicted a doubling of the risk of self-reported violence towards others, after adjusting for other covariates (but not for a history of delinquency and violence prior to using cannabis).

Arsenault, Moffit, Caspi and Taylor (62) reported a longitudinal study of the relationships between mental disorders and violence in a cohort of 961 youth studied from birth to age 21 in Dunedin, New Zealand. They assessed psychiatric disorders, including alcohol and cannabis dependence and asked about alcohol and other drug use prior to self-reported violence. Violence was assessed using self-report and police records of convictions for violence. They found that 7.6% of the sample reported engaging in violence in the past year and 4% had been convicted of violent offences. They found strong associations between self-reported and officially recorded violence and alcohol dependence, cannabis dependence and schizophrenia. Controlling for a history of conduct disorder in childhood (prior to using cannabis) substantially reduced the association between cannabis dependence and violence. The authors argued that the relationship reflected the heavy involvement of cannabis dependent and conduct disordered adolescents in the drug market where violence was used to resolve disputes.

12.9 Summary

Cross-sectional and prospective research indicates that young people who use cannabis are at increased risk of adverse psychosocial outcomes including criminal behaviour, poor mental health, impaired educational achievement and reduced life opportunities. The longitudinal studies suggest that a large part of these associations arise because the factors that predispose young people to use cannabis overlap with the factors that predict these outcomes. In ordinary language, the young people who are most likely to use cannabis in early adolescence are the same young people who were at greatest risk of using other drugs, engaging in delinquency, having poorer mental health, attempting suicide, and doing poorly at school *before they began to use cannabis*.

However, not all of the relationships between cannabis use and these poorer social outcomes can be wholly explained this way. There is evidence that early cannabis use further impairs the school performance of adolescents whose performance was poor before they began to use cannabis. It may also predict involvement in criminal behaviour after controlling for a history of conduct disorder, perhaps by exacerbating pre-existing anti-social behaviour. It may possibly increase the risk of suicide but this remains to be clarified by better designed studies.

Plausible mechanisms that may explain these associations have been suggested by Fergusson and Horwood (25), namely, that adolescents who are socially disadvantaged and have conduct problems as children are more likely to become early cannabis users, and early cannabis use increases the chances of an unconventional lifestyle. The latter occurs as a result of affiliating with delinquent and substance using peers and disengaging from conventional social roles such as completing education and obtaining a job. The acute effects of cannabis intoxication may also play a role by encouraging impulsive behaviour and impairing perceptions of risk among the minority of students who are daily cannabis users.

12.10 References

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13 Therapeutic uses of cannabis

Cannabis has had a long history of medical and therapeutic use in India and the Middle East (1–3), where it was used to treat pain, convulsions, spasm, nausea and to induce sleep. Cannabis was introduced to Britain in the mid-nineteenth century by O'Shaughnessy (4) who had used the drug while an Army surgeon in India (2, 3). He recommended its use for the relief of pain, muscle spasms, and convulsions occurring in tetanus, rabies, rheumatism and epilepsy (3). Cannabis was widely used as an analgesic, anticonvulsant and antispasmodic in Britain and the USA during the latter half of the nineteenth and the early part of the twentieth centuries.

Medical uses of cannabis declined after the turn of the twentieth century because natural cannabis preparations varied in potency and effectiveness. Cannabis was largely supplanted by pharmaceutically pure drugs, such as the opiates, aspirin, chloral hydrate, and the barbiturates, all of which could be given in standard doses to produce more predictable effects (2, 3). Many of these drugs could also be injected to provide rapid relief of symptoms whereas cannabis extracts had to be given orally (5). After the introduction of international drug control agreements in the early part of the 20th century, the medical use of cannabis preparations was discouraged by laws that treated cannabis as a 'narcotic' drug. Cannabis disappeared from the American pharmacopoeia in the early 1940s after the passage of the Marijuana Tax Act (1), although it continued to be used in Australia into the 1960s (6).

The isolation of THC in 1964 (7) occurred shortly before cannabis became widely used as a recreational drug by American youth. Its illegality and recreational use hindered pharmaceutical research, so the rediscovery of its therapeutic uses was serendipitous. Its value as an anti-emetic agent in treating nausea caused by cancer chemotherapy was discovered by young adults who had used cannabis recreationally while undergoing chemotherapy for leukemia (8).

From the mid 1970s until the early 1980s clinical research was undertaken on the therapeutic value of cannabis and cannabinoids. On the whole, however, this research was very thin and uneven, and, consequently, many of the claims for the therapeutic efficacy of cannabinoids rely on the reports of individuals who have derived medical benefit from its use (e.g. (1, 9). When cannabinoids and cannabis are advocated for medical uses it is primarily for relief of symptoms rather than to cure any underlying disease. The conditions for which cannabis is most commonly advocated are for symptomatic relief of nausea, vomiting, appetite loss, and chronic pain (10).

13.1 Cannabinoids as anti-emetic agents

Severe nausea and vomiting may prompt patients to discontinue life-saving chemotherapy and radiotherapy for cancer (10). Anti-emetic drugs (e.g. the phenothiazines) are effective in controlling nausea and vomiting in cancer patients

undergoing chemotherapy but a substantial minority of patients do not benefit from these drugs. The incomplete success of existing treatments prompted oncologists in the late 1970s and early 1980s to study the anti-emetic properties of cannabinoids (10).

One of the earliest trials studied the effects of THC on nausea and vomiting (11) in 22 patients with a variety of cancers, 20 of whose nausea and vomiting had proven resistant to existing anti-emetic drugs. Patients were randomly assigned to receive oral THC and placebo in one of four different orders. Outcome was assessed by patients' self-reports of nausea and vomiting after THC and placebo into three categories: complete response if there was vomiting after placebo but not after THC; partial response if there was a greater than 50% reduction in nausea and vomiting after THC compared to placebo; and no response if there was a less than 50% reduction in nausea and vomiting.

There were 29 trials, 14 of placebo and 15 of THC. There was no anti-emetic response in any of the 14 placebo trials. There were 5 successes, 7 partial responses, and 3 no responses in the 15 THC trials. Most patients (13/16) reported a 'high' after receiving THC, an experience which was correlated with the anti-emetic effect. The most common side-effect was sleepiness. Two patients experienced visual illusions and hallucinations and depression lasting several hours. Several patients reported that smoking cannabis had the same anti-emetic effects as oral THC.

A trial by Chang et al (12) largely supported the findings of Sallan et al (11). In this study 15 patients with osteogenic sarcoma receiving monthly high dose methotrexate therapy served as their own controls. They were assigned to receive three THC and three placebo trials in randomised order during six treatment sessions. If the patients vomited, the remaining doses of either THC or placebo were administered by smoking a cigarette. The effect of THC and placebo on vomiting and retching episodes were assessed by nursing staff who graded response into three categories: excellent (greater then 80% reduction after THC by comparison with placebo in each of these endpoints); fair (greater than 30% and less than 80% reduction), and no response (less than 30% reduction).

Eight patients had an excellent response, 6 a fair response, and one had no response. On all outcomes THC produced a statistically greater reduction in nausea and vomiting than placebo. There was a relationship between blood levels of THC and reports of nausea and feeling 'high'. Higher THC blood levels were achieved when cannabis was smoked than when THC was taken orally. There were few side effects, sedation being the most common (12/15 patients). Four patients experienced 5 dysphoric reactions in the course of 281 THC drug doses (2%). None of these lasted more than 30 minutes, and all were successfully managed by reassurance.

Since these early studies, a number of controlled clinical trials have compared the effectiveness of THC with a placebo or another anti-emetic drug (see (13–15) for reviews). Studies comparing oral THC with existing anti-emetic agents have had less consistent results than comparisons with placebo but the results have generally indicated that THC is as effective as the anti-emetic drug prochlorperazine (13, 15). The equivalence of THC and prochlorperazine was reported in one of the largest and best conducted studies (16).

Although cannabinoids showed *some* anti-emetic efficacy by comparison with prochlorperazine they typically failed to stop nausea in two thirds of patients. In one controlled study, THC produced complete control of emesis in only 13% of cases as against 47% who received metoclopramide. It achieved 'major control' of vomiting (two or fewer episodes) in 27% as against 73% in the comparator (10). The same has been true of the anti-emetic effects of nabilone and levonantradol (10).

Since these trials were conducted much more effective anti-emetic drugs than prochlorperazine have become available (10). These newer agents have dramatically reduced nausea and vomiting. The selective serotonin type 3 receptor agonists, such as ondansetron, have achieved complete control over nausea induced by cisplatin in 75% of cases and up to 90% for less emetogenic chemotherapy (10). Side effects include headache and constipation but these are generally well tolerated. These drugs have reduced the demand for THC as an anti-emetic drug.

13.2 Cannabinoids and HIV-related wasting

Cannabis has also been used therapeutically as an anti-nausea agent, an appetite stimulant and an analgesic in patients with HIV-related wasting (10). HIV/AIDS patients often experience nausea and weight loss, either while receiving antiviral drugs to suppress HIV, or as a direct effect of the AIDS-related diseases. Wasting syndrome in HIV/AIDS has been defined by the US Centers for Disease Control and Prevention as 'the involuntary loss of more than 10% of baseline average body weight in the presence of diarrhoea or fever of more that 30 days that is not attributable to other disease processes' (10).

In animal studies cannabinoids have been shown to act on brain centres that control appetite (17), supporting reports of benefits in patients with AIDS. Few controlled trials have been published on the effectiveness of cannabis or cannabinoids for this purpose. Oral THC has been shown to be of benefit in short-term trials (18, 19) and it has been registered for this purpose in the US. Some patients do not like dronabinol because of its psychoactive side effects, the difficulty in controlling their dose, the delayed onset of effects, and the prolonged effects when it is taken orally (10). There are anecdotal reports that smoked cannabis is effective for the treatment of HIV/AIDS-associated anorexia and weight loss (1, 20). There have not been any controlled studies on smoked cannabis but one is underway in California.

A major concern with HIV-infected patients smoking cannabis for medical purposes is that it might have immunosuppressive effects or infectious organisms in cannabis plant material may produce opportunistic infections. Recent epidemiological evidence does allay this concern to a degree in that a large prospective cohort study of HIV/AIDS in homosexual and bisexual men recently failed to find any relationship between cannabis use, or any other psychoactive drug use, and the development of clinical AIDS (21). Nonetheless, the immunosuppressive effects of THC and smoked cannabis need to be investigated in any research on the therapeutic uses of cannabinoids in the treatment of HIV-related wasting.

13.3 Cannabinoids as anti-glaucoma agents

Glaucoma is the leading cause of blindness in the United States, causing 300,000 new cases each year (22). It is caused by a gradual increase in pressure within the eye, intraocular pressure' (IOP). If untreated, IOP may damage the optic nerve, leading to blindness. Its incidence increases over the age of 35, especially among individuals who are short-sighted. Many drugs that reduce IOP have unwanted side-effects and patients may become tolerant to their therapeutic effects.

The effects of cannabis on IOP were discovered serendipitously by researchers and patients in the early and middle 1970s. Hepler and his colleagues (23–25) demonstrated that cannabis and oral THC substantially reduced IOP in normal volunteers and in patients with glaucoma (23–25). Subsequent research indicated that THC produced this effect (22).

Although there have been a number of case reports of the successful use of cannabis in the management of glaucoma (e.g. (1, 9), there have not been any controlled clinical studies of its effectiveness and safety. Although THC reduces IOP acutely there are doubts about its long-term effectiveness because tolerance develops to this effect (26). The US Institute of Medicine concluded that there was no evidence to support the use of THC in glaucoma (10). It argued that the effects of cannabis and THC on IOP are too short-lived, and the high oral doses that were required produced side effects that precluded its long-term use (10). The harmful effects of chronic cannabis smoking, it argued, outweighed its modest medical benefits. A cannabinoid drug with longer lasting effects on IOP and fewer psychoactive effects than THC could be of greater use (10).

13.4 Cannabinoids and epilepsy

Animal studies have provided some support for the historical use of cannabis preparations to control seizures in epilepsy, tetanus and rabies (3). Cannabidiol (CBD) appears to be a potent anticonvulsant in animals (27–29). There is very limited evidence on the therapeutic effects of cannabinoids in humans with epilepsy. There are a small number of case studies of individuals with epilepsy in which the use of cannabis appeared to enhance the anticonvulsant effects of more traditional anticonvulsant medication (e.g. (1, 30).

There is one randomised placebo controlled study of CBD in 15 patients whose epilepsy was not controlled by conventional anti-convulsants. Four of the eight patients who received CBD in addition to their usual anti-convulsant drugs were free of seizures throughout the study period, and three were improved. By contrast, only 1 out of 7 patients in the placebo condition showed any clinical improvement (31). Despite this suggestive evidence of efficacy there has been no further research on the anticonvulsant properties of CBD (3). This may be because more effective anticonvulsant drugs exist and pharmaceutical companies have no interest in marketing a naturally occurring substance that cannot be patented.

13.5 Cannabinoids and muscle spasticity

Muscle spasticity is the increased resistance to passive stretch of muscles. Involuntary contractions may occur which can be painful and debilitating. About 90% of MS patients eventually develop muscle spasticity, in the form of stiffness, spasms, cramps, aches or pain. Recent animal research has found that THC reduces both tremor and spasticity among diseased mice, suggesting that the cannabinoid system may be involved in control of these functions (32). A survey of 112 MS patients (33) supported the use of cannabis for MS, and some open studies have suggested it is of benefit (34–36).

Clinical studies have not supported the anecdotal evidence, but this may be due to the studies' limitations (10). The survey results suggest that it would be useful to investigate the potential therapeutic value of cannabinoids in relieving symptoms associated with MS (37). The regular use of *smoked* cannabis is not advisable in a chronic illness such as MS.

Muscle spasticity is also common among patients with spinal cord injuries, 60% of whom are younger than 35 years and need long-term care. As with MS, surveys of these patients suggest that cannabis reduces spasticity, nausea and insomnia. Carefully designed clinical trials of THC should be conducted, and have been proposed in the UK (38).

13.6 Cannabinoids and movement disorders

Movement disorders are caused by abnormalities in brain areas that control motor functions. They result in abnormal skeletal muscle movements in the face, limbs and trunk that may occur in patients with dystonia, Huntington's disease, Parkinson's disease and Tourette's syndrome (10). There is limited research that cannabis is useful for treating movement disorders.

There is some evidence that the muscle spasms or 'tics' experienced by patients with Gilles de la Tourette Syndrome are relieved by THC (e.g. (39). Since stress often transiently exacerbates movement disorders, the anxiety-relieving effects of cannabis or cannabinoids might help patients with movement disorders. However, regular cannabis smoking would be a risk for persons already suffering from chronic health conditions (10).

The evidence that cannabinoids have therapeutic effects in patients with movement disorders is largely anecdotal (e.g. (1, 40). Grinspoon and Bakalar (1), for example, presented four case histories of individuals with multiple sclerosis whose condition improved while they smoked cannabis, and deteriorated after they stopped smoking.

There has been one controlled study by Clifford (34) who examined the effects of THC on tremor in 8 patients (4 male and 4 female) with advanced multiple sclerosis. Five patients reported subjective benefit from THC and there was objective evidence of benefit in two of these cases. There was also evidence that their clinical condition deteriorated when they were given placebo and that it improved with the reinstatement of THC.

Grinspoon and Bakalar (1) also described several patients with paraplegia and quadriplegia who reported that cannabis use helped to reduce muscle spasm. The experiences of these individuals were supported by reports in a survey of 43 individuals with spinal cord injuries, 22 of whom reported that they used cannabis to control their muscle spasm.

One controlled trial has evaluated the effects of CBD on chorea in 19 patients with advanced Huntington's disease (41). In this study patients received CBD or placebo for six weeks under double blind conditions in a crossover design. There was no evidence of improvement in chorea on any of the clinical, self-report or motor measures.

13.7 Cannabinoids as anti-asthmatic agents

Smoked cannabis and oral THC dilate the bronchial tubes in normal persons and persons with asthma (42, 43), that is, they increase the lung's capacity to absorb oxygen. Tashkin and colleagues (43), for example, found that smoking a 2% THC cannabis cigarette produced a bronchodilator effect nearly equivalent to that of a clinical dose of isoproterenol, an anti-asthmatic medication.

A major obstacle to the therapeutic use of cannabinoids in asthma is the fact that oral THC produces a much smaller bronchodilator effect and after a substantial delay, than smoked cannabis (44). Attempts to give THC as an inhalant produce irritation and reflex bronchoconstriction (44). Smoking cannabis is the most dependable way of delivering an effective dose of THC but this is an inappropriate way to administer a drug to patients with asthma because it would also deliver other noxious substances that would nullify its therapeutic effects and increase the risk of other respiratory diseases, including cancer in the long-term (44). The unwanted psychotropic effects from cannabis smoking have also been a barrier to its use as an anti-asthmatic drug.

13.8 Cannabinoids as analgesics

Animal studies suggest that cannabinoids may be useful as analgesics. The CB_1 receptor acts on pathways that partially overlap with those affected by opioids like morphine but it acts through pharmacologically distinct mechanisms. This means that cannabinoids and opioids probably have different side effects and may have additive or synergistic analgesic effects.

The few controlled studies of the analgesic efficacy of cannabinoids in humans have been inconclusive. Three experimental pain studies in humans produced mixed results (45–47), but they were poorly controlled (10). More encouraging results have come from three clinical studies of the effects of cannabinoids in patients with severe cancer pain that was persistent and had resisted traditional analgesics (48–50). These studies, which were all double blind and placebo controlled, demonstrated that cannabinoids had analgesic effects equivalent to those of codeine, without its severe side effects, while improving mood, well–being, and appetite.

13.9 The limitations of anecdotal evidence

With the exception of its anti-emetic, anti-nausea and appetite stimulating effects, much of the case for the therapeutic uses of cannabis and cannabinoids is based upon anecdotal evidence. Such evidence is distrusted in clinical medicine. This is especially so in chronic conditions which have a fluctuating course of remission and exacerbation because it is difficult in these diseases to exclude alternative explanations of improvements in a patient's condition that follow their use of THC. It is difficult to exclude the possibility of simple coincidence: that is, THC preceded an improvement in the patient's condition that would have occurred in its absence. It is for these reasons that this review has relied upon evidence from controlled clinical trials in appraising the therapeutic uses of cannabinoids.

13.10 The risks of therapeutic cannabinoid use

For most people the primary adverse effect of acute cannabis use is impaired psychomotor performance. This makes it inadvisable for anyone under the influence of cannabis or THC to operate machinery that might put the user or others in danger, such as driving a car or operating equipment. Most people can be expected to show impaired performance of complex tasks, and a minority experience dysphoria. People who have psychiatric disorders (including substance dependence) may be vulnerable to cannabis dependence, and so sustained therapeutic cannabis use would be contraindicated for them. The short-term immuno-suppressant effects are not well established; if they exist, they are probably not large enough to preclude legitimate medical use. The US Institute of Medicine concluded that the acute effects of cannabis use were 'within the risks tolerated for many medications' (10).

The chronic effects of cannabis are of greater concern for medical use. They fall into two categories: the effects of chronic smoking, and the possibility of dependence on cannabis or THC. Cannabis smoke like tobacco smoke is a risk factor for cancer, lung damage, and poor pregnancy outcome. Smoked cannabis is therefore unlikely to be a safe medication for any chronic medical condition that requires daily use over a period of years. The risk of developing dependence on cannabis is highest in adolescents, particularly those with conduct disorders, and people with psychiatric disorders, or problems with substance abuse (10).

13.11 Obstacles to therapeutic cannabinoid use

Despite their comparative safety, and the evidence for the therapeutic effects of cannabinoids as anti-emetics and appetite stimulants, they have not been widely used clinically. Nor has pharmacological research developed synthetic cannabinoids for medical use. There are two main reasons for this. One is the lack of incentives for pharmaceutical companies to develop and market cannabinoid drugs; the other is the politics of recreational cannabis use.

13.11.1 The market outlook for therapeutic cannabinoids

The decision to develop and conduct clinical trials on a new drug is based upon a drug company's judgment that there is likely to be an adequate return on investment. The research and development costs of cannabinoids are likely to be similar to those of neuropharmaceuticals and anti-inflammatory drugs (10). In the case of the cannabinoids, there are the additional costs of meeting regulatory requirements for drugs derived from a prohibited plant.

The potential market for cannabinoids is determined by the current and projected number of patients who may use the drug, the sales of existing drugs for the indication, the availability of competing products, and the duration of disease (e.g. disease with an early age of onset and a need for long term use). Factors that affect market return include the company's ability to patent the drug, the availability of other forms of market protection, access to health insurance reimbursements, restrictions on access because of drug scheduling, social attitudes towards the drug, its adverse effect profile, and its interactions with other drugs. Naturally occurring substances such as THC cannot be patented; only newly synthesized or derived cannabinoid drugs can be patented.

13.11.2 The politics of therapeutic cannabinoids

Research on the therapeutic use of cannabinoids in the USA has become a casualty of the debate about the legal status of recreational cannabis use. For example, some of the groups advocating the therapeutic use of cannabis have also been proponents of cannabis legalisation (e.g. NORML), thereby fuelling the fears of opponents of cannabis use that success in the campaign for marijuana rescheduling will be the thin edge of a wedge to legalise cannabis. Other proponents of legalisation (e.g. 1) have argued for the legalisation of cannabis as a way of making cannabis available for therapeutic purposes.

On the other side of the argument are those opponents of cannabis use who fear that the admission that cannabis, or any of its constituents, may have a therapeutic use will send the 'wrong message' to youth. This has led to the denial that cannabinoids have any therapeutic effects, and to attempts to prevent all scientific inquiry into any such effects (Bernstein, 1989 cited (52) (p.395).

It is unfortunate that a connection has been forged between the debates about the legal status of cannabis as a recreational drug and the use of cannabinoids for therapeutic use. There is a world of difference between the use of controlled doses of a purified drug under medical supervision and the recreational use of crude preparations of a drug. In a rational world, clinical decisions about whether to use pure cannabinoid drugs should not be abrogated because crude forms of the drug may be abused by those who use it recreationally. We do not allow this type of thinking to deny us the use of opiates for analgesia. It should not deny patients access to any therapeutic uses of cannabinoids derivatives that may be revealed by pharmacological research.

13.12 Summary

The following provisional conclusions can be drawn on the therapeutic uses of cannabis. First, there is sufficient evidence that THC is an anti-emetic agent to justify it being made available in pure synthetic form to cancer and AIDS patients. In the light of the recent development of more effective anti-emetic agents, it remains to be seen how widely used THC will be for this purpose. Second, there is also reasonable evidence for the efficacy of THC in the treatment of AIDS-related wasting. Third, the suggestive evidence of the usefulness of cannabinoids as analgesic and anti-spasmodic agents warrants further pharmacological and experimental investigation, and perhaps clinical research into their effectiveness.

Despite the basic and clinical research work which was undertaken in late 1970s and early 1980s the cannabinoids have not been widely used therapeutically or extensively investigated. This seems largely attributable to the disincentives pharmaceutical companies have to develop cannabinoid drugs and the regulatory obstacles to their registration. The discouragement of therapeutic research also derives from the fact that THC, the most therapeutically effective cannabinoid, has the psychoactive effects sought by recreational users. The discovery of the cannabinoid receptor may help to overcome some of the resistance to research into the therapeutic uses of cannabinoids by holding out the prospect that the psychoactive effects of the cannabinoids can be disengaged from their other therapeutically desirable effects.

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14 A comparison of the health effects of cannabis with alcohol and tobacco

This chapter compares the most probable harms caused by cannabis use with those caused by alcohol and tobacco, two commonly used psychoactive substances in Western societies. A number of issues arise in comparing the health effects of cannabis with those of these two drugs. The first are difficulties in making causal inferences about the connections between cannabis use and the adverse health and psychological consequences which have been attributed to it (1). The second is lack of information about the risks of cannabis use for users. Both of these problems arise from the scarcity of epidemiological studies of the health risks of cannabis use by comparison with such studies of alcohol and tobacco use.

A third set of difficulties arise in measuring the public health impact of these risks. The methods used to date have typically involved comparisons of the numbers of deaths, persons years of life lost, and hospital bed days attributable to conditions caused by each type of drug (e.g. English et al, (2)). The most recent innovation has been to use a combination of Life Years Lost (YLL) and Disability Adjusted Life Years (DALYs) to estimate the total burden of disease attributable to alcohol, tobacco and illicit drug use (3, 4).

14.1 The probable adverse health effects of cannabis

The following are the major adverse health and psychological effects of acute and chronic cannabis use, classified by the degree of confidence in the relationship.

14.1.1 Acute effects

The major acute psychological and health effects of cannabis intoxication are:

- anxiety, dysphoria, panic and paranoia, especially in naive users;
- cognitive impairment, especially of attention and memory while intoxicated;
- psychomotor impairment, and probably an increased risk of accidental injury or death if an intoxicated person attempts to drive a motor vehicle or operate machinery;
- an increased risk of experiencing psychotic symptoms among those who are vulnerable because of a personal or family history of psychosis;
- an increased risk of low birth weight babies, and possibly of birth defects, if used during the first trimester of pregnancy.

14.1.1 Chronic effects

The major health and psychological effects of chronic cannabis use, especially daily use over many years, remain uncertain but the major **probable** adverse effects appear to be:

- respiratory diseases caused by smoking cannabis, such as chronic bronchitis, and changes in lung tissue that are precursors of malignancy;
- development of a cannabis dependence syndrome, characterised by an inability to abstain from or to control cannabis use;
- an increased risk of developing cancers of the aerodigestive tract, i.e. oral cavity, pharynx, and oesophagus.

The following are the major **possible** adverse effects of chronic, heavy cannabis use which remain to be confirmed by controlled research:

- subtle forms of cognitive impairment, most particularly of attention and memory, which persist while the user remains chronically intoxicated, and may or may not be reversible after prolonged abstinence from cannabis.
- a decline in occupational performance marked by underachievement in adults in occupations requiring high level cognitive skills, and impaired educational attainment in adolescents.

High risk groups

A number of groups are at increased risk of experiencing some of these adverse effects.

Adolescents

- Adolescents with a history of poor school performance whose educational achievement may be further limited by the cognitive impairments produced by chronic intoxication with cannabis;
- Adolescents who initiate cannabis use in the early teens are at higher risk of progressing to heavy cannabis use and other illicit drug use, and to the development of dependence on cannabis.

Women of childbearing age

- Babies born to women who continued to smoke cannabis may have a slightly lower birth weight.

Persons with pre-existing diseases

Persons with a number of pre-existing diseases who smoke cannabis are probably at an increased risk of exacerbating symptoms of their diseases. These include:

- individuals with cardiovascular diseases, such as coronary artery disease, cerebrovascular disease and hypertension;
- individuals with respiratory diseases, such as asthma, bronchitis, and emphysema;
- individuals with schizophrenia who are at increased risk of precipitating or of exacerbating schizophrenic symptoms;
- individuals who are or have been dependent upon alcohol and other drugs are probably at an increased risk of developing dependence on cannabis.

14.2 The implications of increased potency of cannabis

It has been claimed that a substantial increase in the average THC content of cannabis has 'made obsolete' much of what we once knew about the risks and consequences of cannabis use (5) because most of this was based on research on cannabis with low levels of THC. This argument is unconvincing for two reasons. First, as discussed in chapter 2, the evidence does not support claims that the average THC content of cannabis products has increased substantially in recent decades. Second, it is untrue that the research literature on the adverse health effects is based on studies of populations consuming cannabis with low levels of THC. The field studies in Costa Rica, Greece, Jamaica and Egypt examined very heavy, long term cannabis users and laboratory studies conducted in the USA involved subjects consuming 30 mg THC per day for periods of a month.

The claim about increased potency is popular because it appears to explain an apparent increase in the adverse effects of cannabis use. There probably has been some increase in the prevalence of some of these effects, most notably dependence, although this is uncertain because of limitations with the available data (6). There are, however, two more plausible alternative explanations for any increase in adverse effects of cannabis use: (1) cannabis markets have increased the availability of more potent forms of cannabis; and (2) changes in the patterns of cannabis use have increased the prevalence of harmful patterns of cannabis use (6).

The effect of using more potent cannabis products will depend upon the type of health effect in question, and the user's experience with cannabis. Higher average doses of THC will probably increase the risk of adverse psychological effects of cannabis use, an effect likely to be most obvious among naive or first time cannabis users. This effect may discourage further experimentation with the drug among these users. Risks of increased THC exposure among regular cannabis users possibly include an increased risk of accidents among those who drive while intoxicated, especially if cannabis use is combined with alcohol, and an increased risk of regular cannabis users developing dependence. If the THC content of the most commonly used cannabis products has increased, the net adverse effects of cannabis use may have marginally increased. Respiratory risks may be marginally decreased if cannabis smokers are able to titrate their doses of THC.

14.3 A comparison of the health risks of alcohol, cannabis and nicotine

We have used the following as authorities on the health risks of alcohol and tobacco: Anderson et al. (7); English et al (2); the Institute of Medicine (8); the International Agency for Research into Cancer (9); Mathers, Vos and Stephens (4); Roselle et al (10); and the Royal College of Physicians (11).

14.3.1 Acute effects

Alcohol

Some of the acute risks of cannabis use are similar to those of alcohol. Both drugs cause psychomotor and cognitive impairment, especially of memory and planning. In the case of alcohol these impairments increase the risks of motor vehicle and other accidents (2, 8). While cannabis intoxication probably increases the accident risks in hazardous situations, it remains to be determined whether it increases risky behaviour.

However, alcohol and cannabis differ in their relation to intentional injuries. First, alcohol intoxication is strongly associated with aggressive and violent behaviour. The relationship is complex, and the nature and extent of alcohol's causal role is controversial (12–14), but changes in the level of alcohol consumption appear to affect the incidence of violent crime (15–17). There is also increasing evidence that alcohol plays a role in suicide (18). Although cannabis and violence may be correlated among adolescents (see chapter 6), it remains to be clarified whether the relationship is causal because persons with a history of violence are more likely to become heavy cannabis users.

Second, substantial doses of alcohol taken during pregnancy can produce a Foetal Alcohol Syndrome (2). There is weak evidence that cannabis can adversely affect the development of the foetus when used during pregnancy (19), but there is no equivalent for cannabis of the foetal alcohol syndrome.

Third, acute alcohol use has one health risk that is not shared with cannabis. In large doses alcohol can cause death by asphyxiation, alcohol poisoning, cardiomyopathy and cardiac infarct. There are, by contrast, no recorded overdose fatalities from cannabis.

Tobacco

Cannabis and tobacco share acute irritant effects of smoke upon the respiratory system and THC and nicotine both stimulate the cardiovascular system. Smoking cannabis and tobacco can adversely affect persons with cardiovascular and respiratory diseases. In both cases, these effects arise from the fact that the drug is smoked.

14.3.2 Chronic effects

Alcohol

There are a number of risks of chronic alcohol use, which may be shared by chronic cannabis use. First, daily use of both increases the risk of developing dependence. There is strong evidence of such a syndrome for alcohol and reasonable evidence for cannabis. One difference is that withdrawal symptoms are mild in dependent cannabis users who abruptly stop using cannabis, whereas the abrupt cessation of alcohol use in severely dependent drinkers can produce a severe withdrawal syndrome that can be fatal in a small proportion of cases, if untreated (20).

Second, there is reasonable evidence that chronic heavy alcohol use can produce psychotic symptoms and psychoses in some individuals, either during acute intoxication or during withdrawal. There is suggestive evidence that chronic heavy cannabis use may

produce a toxic psychosis, some epidemiological evidence that heavy cannabis use may precipitate schizophrenia in individuals with a personal or a family history of psychiatric disorder, and stronger evidence that cannabis use worsens the course of schizophrenia.

Third, there is good evidence that chronic heavy alcohol use can indirectly cause brain injury—the Wernicke-Korsakov syndrome—with symptoms of severe memory defect and an impaired ability to plan and organise. With continued heavy drinking, and in the absence of vitamin supplementation, this injury may produce severe and irreversible cognitive impairment. Chronic cannabis use does not produce cognitive impairment of comparable severity. There is suggestive evidence that chronic cannabis use may produce subtle deficits in cognitive functioning that may or may not be reversed by abstinence.

Fourth, there is reasonable evidence that chronic heavy alcohol use impairs occupational performance in adults and educational achievement in adolescents. There is suggestive evidence that chronic heavy cannabis use produces similar, albeit less marked, impairments in the occupational and educational performance of adolescents and adults.

Fifth, there is good evidence that chronic, heavy alcohol use increases the risk of premature mortality from accidents, suicide and violence. There is no comparable evidence for chronic cannabis use, although it is likely that dependent cannabis users who frequently drive while intoxicated with cannabis would be at greater risk of accidental injury or death.

Sixth, alcohol use has been accepted as a contributory cause of cancer in various tissues and organs of the digestive system and breast cancer in women. There is suggestive evidence that chronic cannabis smoking may be a cause of cancers of the aerodigestive tract.

Seventh, heavy alcohol use is a major cause of liver cirrhosis and is also implicated in gastritis, high blood pressure, stroke, cardiac arrhythmias, cardiomyopathy, pancreatitis, and polyneuropathy. On the other hand, alcohol use is also associated with a reduction in the risk of heart disease that is of public health significance in societies with high rates of heart disease (18). No equivalent adverse or protective effects have been reported for cannabis. There is some evidence that THC may be therapeutically useful for appetite stimulation and as anti-emetics in patients undergoing cancer therapy.

Tobacco

The major adverse health effects shared by chronic cannabis and tobacco smokers are chronic bronchitis, and probably, cancers of the aerodigestive tract (i.e. the mouth, tongue, throat, oesophagus, lungs). The increased cancer risk is a consequence of the fact that both drugs are smoked. It is possible that chronic cannabis smoking also shares the cardiotoxic properties of tobacco smoking but this remains to be investigated. These respiratory risks could be avoided by a change to the oral route of administration which would also reduce but not eliminate the cardiovascular risks.

Tobacco smoking is associated with a wide variety of other chronic health conditions for which cannabis smoking has not so far been implicated. These include cancer of the cervix, stomach, bladder and kidney, coronary heart disease, peripheral vascular disease, and stroke, as well as cataracts and osteoporosis (2).

14.4 Comparing the magnitude of risks

Many of the quantitative risks of cannabis use can only be guessed at in the absence of studies of the dose-response relationship between cannabis use and adverse health effects. The following are guesstimates of the risks of cannabis use for the most probable adverse health effects. When in doubt we have assumed that the relative risks of cannabis use are similar to the risks of alcohol or tobacco.

Motor Vehicle Accidents: If we assume that driving while intoxicated with cannabis produces a comparable increase in the risk of accidents to that produced by driving while intoxicated with alcohol (say with a blood alcohol level of 0.05% to 0.10%), then the RR of an accident while intoxicated would be in the range of 2 to 4. The fact that alcohol and cannabis are often used in combination makes it difficult to estimate the relative risk of having an accident when using cannabis alone.

Respiratory Diseases: If we assume that a daily cannabis user who smokes 5 or more joints per day faces a comparable risk of respiratory disease to that of a 20 cigarette a day tobacco smoker, then the RR of developing chronic bronchitis would be 6 or greater for those who had ever smoked cannabis, and substantially higher among those who had been daily cannabis smokers over many years and those who also smoked tobacco (2). Recent research suggests that the risk of daily cannabis smoking is more like that of smoking 10–15 cigarettes per day (21), so the relative risks may be smaller.

Respiratory Tract Cancers: If we make the same worst case assumptions about daily cannabis smoking then the relative risks of various cancers of the respiratory tract would be of the order of: 5 for oropharyngeal cancer, 4 for oesophageal cancer, and 7 for lung cancer (2). Again these risks would be substantially higher among cannabis smokers who also smoked tobacco. The recent case control study of head and neck cancer suggested a relative risk of 2 for cannabis smoking, after adjustment for tobacco use (22).

Low Birthweight Babies: Making a worst-case assumption, a woman who smokes cannabis during pregnancy may double her chance of giving birth to a low birthweight baby (2). The average size of the effect is smaller than that for tobacco smoking (19).

Schizophrenia: This is one of the few health consequences for which there is a quantitative estimate of relative risk. If we use the estimated RR from the study by Andreasson et al (23) after adjustment for confounding variables, then an adolescent who had smoked cannabis 50 or more times by age 18 would have a 2 to 3 times higher risk of developing schizophrenia than an adolescent who had not used cannabis.

Dependence: The risk of cannabis dependence is estimated by the proportion of those who have ever used cannabis, or have had a history of daily use, who become dependent on the drug. The best estimates from US data in the late 1970s and early 1980s is that 10% of those who have ever used cannabis (24), and between 33% and 50% of those who have had a history of daily cannabis use, will become dependent on cannabis (see Hall et al (25)). The comparable risks among those who had ever used tobacco (32%), opiates (23%) and alcohol (15%) were higher than the risk for cannabis users (24).

14.5 Public health significance

14.5.1 Motor vehicle accidents

The epidemiological studies indicate that in its own right, cannabis makes at most a very small contribution to motor vehicle accidents, and so, on the whole, it may seem be a minor road safety problem by comparison with alcohol. Its public health significance for road safety may be in amplifying the adverse effects of alcohol in the majority of drivers who drive when intoxicated by alcohol and cannabis.

14.5.2 Respiratory diseases

Respiratory diseases, such as bronchitis, caused by cannabis smoking are likely to have greater public health significance than respiratory cancers. This is for two reasons. First, respiratory cancers require a greater length of exposure to cigarette smoke (15 to 20 years) than does chronic bronchitis. Second, there are very few cannabis users who use the drug for more than 5 years (26). On current patterns of use, cannabis smoking is more likely to produce respiratory disease than it is to cause premature deaths from cancers of the respiratory tract.

14.5.3 Respiratory tract cancers

Even if we make the worst case assumption that the risks of cancer are comparable among daily tobacco and cannabis smokers then cannabis smoking will make a small contribution to the occurrence of these cancers, on current patterns of use in developed societies (1). Only a minority of those who ever use cannabis become daily users, and a much smaller proportion of these use cannabis beyond their middle twenties by comparison with the high proportions of tobacco smokers who do so (26). Among this minority, concurrent cannabis and tobacco use may exacerbate the adverse respiratory effects of each.

14.5.4 Low birthweight babies

If cannabis smoking during pregnancy doubles the risks of a low birthweight baby, its public health significance will be much less than that of tobacco smoking, because the prevalence of cannabis use is much lower than that of tobacco smoking. The risks of a low birthweight baby will be higher among women who also smoke tobacco, as do many of those who smoke cannabis during pregnancy.

14.5.5 Schizophrenia

If the relationship between cannabis use and schizophrenia is causal, cannabis use would account for less than 10% of new cases of schizophrenia. Even this figure seems unlikely, however, since the incidence of schizophrenia has probably declined during the period when cannabis use among adolescents and young adults has increased (27).

14.5.6 Dependence

Cannabis dependence is potentially a more prevalent outcome than any of the other potentially adverse health effects of cannabis. On the ECA estimates, approximately 4% of the adult US population met diagnostic criteria for cannabis abuse or dependence in their lifetime and 2% in the past year. This compares with 14% who met diagnostic criteria for alcohol abuse and dependence at some time in their lives. This is a substantial proportion of the population but there may be a high rate of remission of symptoms in the absence of treatment.

14.6 Overall public health significance

Overall, the relative risks of adverse health effects for cannabis are small to moderate and the proportion of users who use regularly is much smaller than the proportions of alcohol and tobacco users who do so (28). In aggregate, then, the public health problems caused by cannabis *on current patterns of use* are modest compared with those of alcohol and tobacco.

A number of attempts have been made to directly compare the effects of alcohol, tobacco and illicit drugs on mortality, morbidity and societal costs. One of the earliest was an Australian study by Holman et al (29) which estimated the number of deaths, person years of life lost and number of hospital bed days that could be attributed to the use of alcohol, tobacco and illicit drugs. According to Holman et al, in Australia in 1986 there were 23,639 deaths attributable to these three classes of drugs. Of these 17,800 were attributed to tobacco, 5,360 to alcohol and 479 to illicit drugs, of which 289 (60%) were due to opiate use. There was a similar rank ordering of person years of life lost (92,023 for tobacco, 66,034 for alcohol and 16,438 for illicit drugs) and bed days (1,014,336 for tobacco, 1,009,591 for alcohol and 57,361 for illicit drugs). No deaths were attributed to cannabis use and cannabis made no contribution to morbidity. The authors concluded 'that apart from dependence, abuse and withdrawal, no other adverse health effect of cannabis is sufficiently substantiated or quantified to enable an analysis of resultant morbidity or mortality' (p. 377).

English et al (2) updated the Holman et al estimates of drug-caused mortality and morbidity in Australia in 1992. Unlike Holman et al, English et al included estimates of the protective effects of moderate alcohol consumption on mortality from cardiovascular disease. The inclusion of a protective effect for alcohol reduced the number of deaths attributed to alcohol from 5,360 in 1986 to 3,660 in 1992 and person years of life lost declined from 66,034 to 55,540. The contributions of tobacco and illicit drugs to mortality did not change much from the earlier estimates (18,290 and 488 respectively). Opiates were responsible for 92% of illicit drug deaths and no deaths were attributed to cannabis. Cannabis contributed to hospital bed days through treatment of cannabis dependence and abuse (1% of all bed days attributed to illicit drug use).

More recently, Ridolfo and Stevenson (30) updated the English et al estimates for Australia in 1998 using a different method to take account of the protective effect of alcohol on cardiovascular deaths. In their analysis alcohol produced a *net reduction* of 2371 deaths because the number of deaths averted by moderate alcohol use exceeded the number of deaths that alcohol caused. The number of deaths attributed to tobacco marginally increased from 18,290 to 19,019 and the number of deaths attributed to illicit drugs increased from 488 to 1,023 because of a substantial increase in the number of opioid overdose deaths.

14.6.1 Burden of disease estimates

A different approach to estimating the public health impact of alcohol, tobacco and cannabis was adopted in the Global Burden of Disease (GBD) Study (3, 33). In this study, an estimate of the years of life lost (YLL) as a result of the use of drugs was added to the disability caused by diseases to estimate the number of Disability-Adjusted Life-

Years (DALYs) for each type of drug use. This enabled an estimate of the proportion of global burden of disease that was accounted for by different types of drug use.

Murray and Lopez estimated that 3.5% of global DALYs was attributable to alcohol, 2.6% to tobacco, and 0.6% to illicit drugs (3). In six of the eight world regions, tobacco and alcohol outranked illicit drugs in DALYs. Illicit drugs outranked alcohol in the Middle Eastern region, and tobacco in the Latin American region. The authors caution that 'because of the great difficulty in reliably estimating prevalence of illicit drug use, and of reliably quantifying its health effects, the estimates for this risk factor may well be too low' (p. 310). The illicit drug that made the largest contribution to the global burden was heroin.

The Australian Burden of Disease and Injury (ABDI) (4) adapted the approach of Murray and Lopez to estimate the contribution that alcohol, tobacco and illicit drugs made to the burden of disease and injury in Australia. The ABDI study used the comprehensive data collected on mortality and morbidity in Australia which includes surveys of the health of nationally representative samples of Australians. Their findings differed from those of the GBD study in the rank ordering of alcohol and tobacco because the Australian study included an estimate of the burden of disease that was averted by moderate alcohol use. Tobacco accounted for 9.7% of the total burden of disease in Australia, alcohol accounted for 2.2% and illicit drugs for 1.8%. Among illicit drugs, the overwhelming majority of the burden was due to heroin dependence, which accounted for 1.2% of total burden. Cannabis dependence and abuse accounted for 0.2% of all disability. No deaths were attributed to cannabis use (4).

14.6.2 Summary of public health impact

Studies of mortality and morbidity and disease burden attributable to alcohol, tobacco and illicit drugs differ in their rankings of impact depending upon whether the mortality benefits of moderate alcohol use are included or not. They leave little doubt, however, that *on current patterns of use*, alcohol and tobacco are much more damaging to public health in developed societies than illicit drugs. Among illicit drugs, cannabis makes no known contribution to mortality and a minor contribution to morbidity and disability.

14.6.3 Predicting the effects of changes in the prevalence of cannabis use

These estimates of the public health impact of cannabis use are based on *current patterns of use*. They cannot be used to predict what would happen if there was a major change in the prevalence of cannabis use, as may happen if cannabis were to become as freely available and as heavily promoted as alcohol and tobacco. Although in principle, it may seem simple to predict the public health consequences of increased cannabis use (e.g. by multiplying its harms at present by the increased number of users), such a calculation would assume that the risks of cannabis use did not change with the characteristics of the user, or the legal regime under which the drug was used.

Both assumptions are questionable. Cannabis is likely to be used by a different population when its use is illegal and prevalence of use is lower than would be the case if it were legal and more people used it. This has been reported with alcohol, for example, with different patterns of alcohol consumption and alcohol-related problems in

'dry' (non-drinking) and 'wet' (high level of drinking) cultures. If adult cannabis use were legalised, it might also be easier to reduce some of these health risks, for example, by encouraging cannabis users to ingest rather than to smoke the drug, or by reducing the tar content of cannabis that is smoked. Decriminalising cannabis for adult use would probably also increase use by adolescents, the health effects of which would be very difficult to predict. Estimating the net effects of harm reduction efforts in adults and a likely increase in adolescent use is therefore difficult.

For these reasons we have not attempted to predict the health risks of cannabis use if it became as widely used as alcohol and tobacco. All that can be said with confidence is that if its rate of use increased to the levels of cigarette smoking and alcohol use, its adverse impact on public health would increase. It is impossible to say precisely by how much.

14.7 Summary

Cannabis use can harm health when it is used daily over years or decades. Considerable uncertainty remains about whether some of these effects are attributable to cannabis use alone or to tobacco and alcohol. There is too little data on the relationship between frequency, quantity and duration of cannabis use, and the risks of many of these effects. Using estimates of the known effects of alcohol and tobacco, the most probable adverse effects of chronic heavy cannabis use over a period of years are: the development of a dependence syndrome; an increased risk of motor vehicle accidents; an increased risk of chronic bronchitis; an increased risk of respiratory cancer; an increased risk of giving birth to low birth weight babies when used during pregnancy; and perhaps, an increased risk of developing schizophrenia among those who are vulnerable. Many of these risks are shared with alcohol and tobacco, which is unsurprising given that cannabis is an intoxicant, like alcohol, that is usually smoked, like tobacco.

On *current patterns of use*, cannabis poses a much less serious public health problem than alcohol and tobacco in Western societies. This is no cause for complacency as the public health significance of alcohol and tobacco are substantial, and the public health impact of cannabis would probably increase if the prevalence of heavy daily cannabis use were to approach that of heavy alcohol use, or that of daily cigarette smoking among adults.

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"An overview of cannabis potency in Europe"

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INSIGHTS

An overview of cannabis potency in Europe

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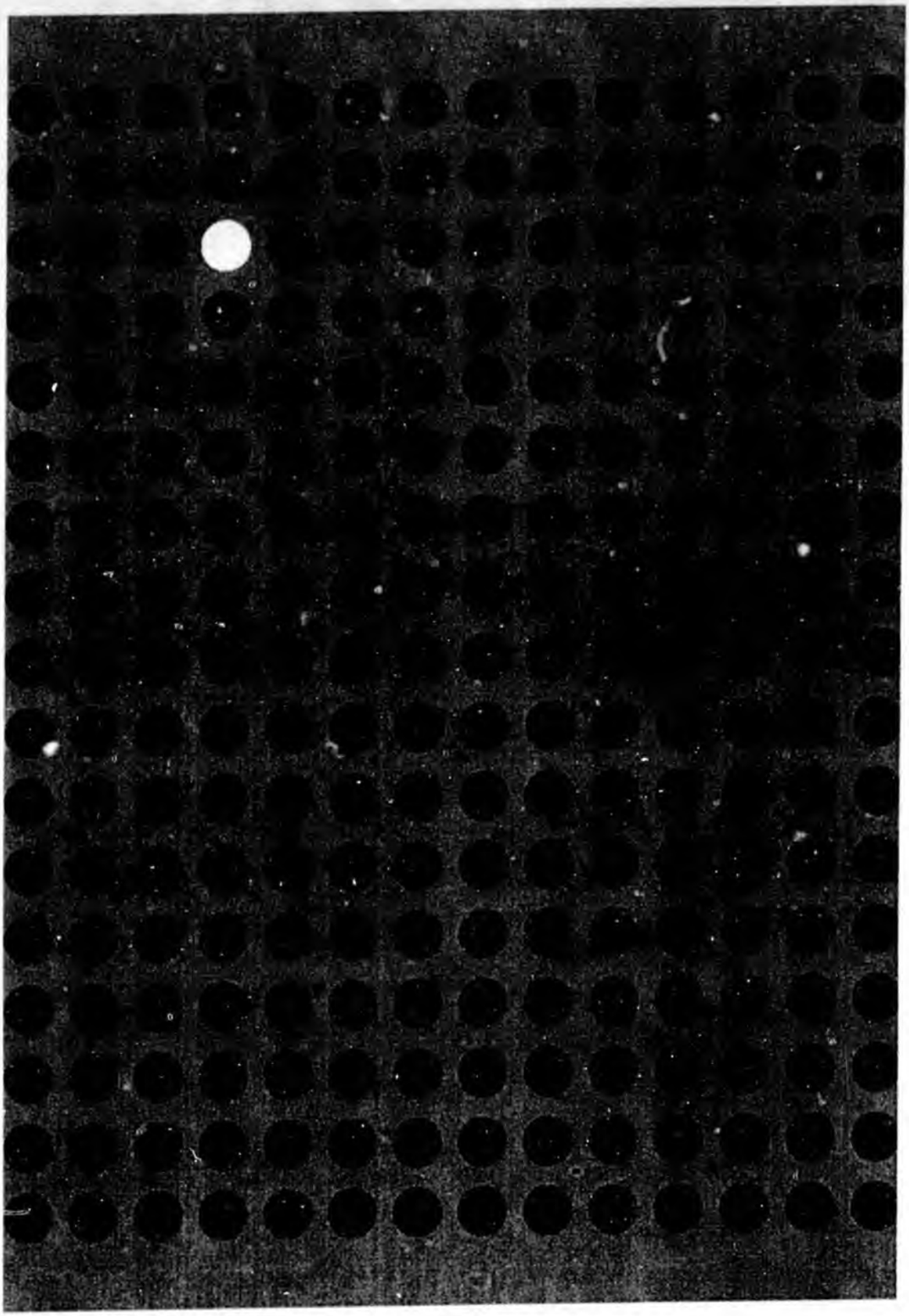

Foreword

Cannabis is the illegal substance most commonly used in all countries of the European Union, with many countries reporting lifetime experience of the drug by more than 20% of the general population.

Used mainly by young adults, but also by many schoolchildren, cannabis is a drug consumed by individuals during their formative years, at a time when they may be more vulnerable to the long-term harmful effects of drug use.

The increased use of cannabis during the past decade, during which more attention has also been given to the medicinal use of cannabis, has increased the profile of the drug. So too have legislative changes in some countries, and the more open debate on the costs and benefits of different drug control options. At the same time there is also a concern that cannabis is increasingly mentioned in connection with applications for drug treatment — and this is an issue that will be explored in detail in the Annual Report of the EMCDDA in 2004.

Comments in the media and elsewhere of a large increase in the potency of cannabis have raised concerns that the drug now available is much stronger than that available in the past. A much stronger drug might have implications for both the health and other problems resulting from the use of the drug and for the development of future policy options. However, the information on which the claims of greatly increased cannabis potency have been made is not always clear.

To establish a scientific basis on which to advise policy makers and practitioners in the drugs field, the EMCDDA commissioned an investigation into cannabis potency in Europe. The results of this study are presented here. Changes in the production and sourcing of cannabis products are documented. Information supplied through the Reitox national focal points are added to data from a wide variety of sources to enable a first overview of cannabis potency in Europe. This is discussed in the wider context of information from the United States, Australia and New Zealand, countries where there have also been media reports of increased cannabis potency.

As always when attempting to study illegal substances, the data are incomplete and the conclusions are qualified. Nevertheless, it is now possible to respond with facts and figures to questions about large increases in cannabis potency in

Europe. As the reader will discover, this is not a simple or straightforward issue. This report identifies a number of important questions that require further consideration if we are to understand the implications of changes in patterns of cannabis consumption in Europe. Nonetheless, we hope that the information and analysis contained in this edition of the EMCDDA *Insights* series will make a valuable contribution to a more informed debate about cannabis potency in Europe — and its potential impact.

Georges Estievenart
Executive Director
EMCDDA

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Preface

The cultivation of the hemp plant (*Cannabis sativa* L.) stretches back into antiquity. Although originally produced as a source of fibre, its value as a drug also has a long history. For most of this time, it is likely that little change occurred in the methods used to manufacture the traditional drug products, namely herbal cannabis (marijuana) and cannabis resin (hashish). Yet in the last decades of the twentieth century, interest in cannabis expanded considerably. This was partly driven by the ever-increasing drug use in many countries, some of which was stimulated by new intensive methods of cultivation. But there were other developments: the licensing of commercial cultivation in the EU for fibre production; a renewed interest in medicinal uses; and legislative changes often caused by a need for law enforcement agencies to focus on more dangerous substances. There was also concern about the rising frequency with which cannabis was mentioned in the context of the treatment demand indicator (EMCDDA, 2003), and this will be the subject of a separate publication by the EMCDDA in 2004.

In parallel with these changes, there has been a greater focus on the constituents of cannabis, and in particular the main principle: Δ^9-tetrahydrocannabinol (THC). Concerns were raised that the potency of cannabis (i.e. the THC concentration) may have increased so much that the illicit drug now bears little resemblance to the cannabis that was used only thirty years ago. A widely publicised example of this is the statement by the so-called 'drug czar' in the USA, published in the Washington Post, that "Parents are often unaware that today's marijuana is different from that of a generation ago, with potency levels 10–20 times stronger than the marijuana with which they were familiar" (Walters, 2002). In a similar vein, and even more recently, Professor John Henry of St. Mary's Hospital, London, commented on the apparent increase in association between cannabis and deaths recorded as accidents and suicides. He is quoted (Henry, 2004) as saying "until the early 1990s, there was less than one per cent tetrahydrocannabinol in most cannabis. Now the most potent form, skunk, contains up to 30 per cent". As a final example of this alarm, Ashton (House of Lords, 1998) stated that "... a typical 'joint' today may contain 60–150 milligrams or more of THC". However, the potency question is not new. Nearly twenty years ago, Cohen (1986) noted that "...material ten or more times potent than the product smoked ten years

ago is being used, and the intoxicated state is more intense and lasts longer". But Mikuriya and Aldrich (1988) pointed out that the cultivation of sinsemilla and its superiority to other forms of cannabis was well known to the British Government in India in the nineteenth century.

Cannabis in its various forms remains the most commonly used illicit drug in the EU, with many countries reporting lifetime prevalence rates in excess of 20 % of the general population (EMCDDA, 2003). The purpose of the present report is to examine the evidence for changes in the potency of cannabis products in Europe and whether any such changes are a cause for public concern. Comparisons are made with the situation in the USA, New Zealand and Australia, the only non-European countries to have made serious efforts to monitor the quality of cannabis over a number of years. Published data are often in the form of national annual averages. The report examines the types of cannabis consumed and their respective origins, analytical aspects such as sampling strategies, the effect of storage, and the laboratory methods used since these could all be major factors affecting such data.

Information was collected from the published and unpublished (grey) literature and interviews with colleagues in the United Kingdom and the Netherlands. In addition, a questionnaire (available from the EMCDDA on request) was sent via the Reitox focal points to the 25 EU Member States and Norway. Replies from thirteen countries were received, but not all were able to provide data on recent trends in the potency of cannabis products.

Although this review concentrates on matters relating to potency, there is a vast scientific literature devoted to cannabis. The following is not intended to be an exhaustive list of reviews: pharmacology (Ashton, 1998, 2001; Nutt and Nash, 2002), health and psychological effects (Hall et al., 2001), effects of chronic/heavy use (Van Amsterdam et al., 1996), psychiatric illness (Johns, 1998; Rey and Tennant, 2002), therapeutic uses (British Medical Association, 1997; Baardman, 2003), production of cannabis resin (Cherniak, 1995), forensic toxicology (Huestis, 1999), historical development (Booth, 2003), medicinal products (Clarke and Watson, 2000), social and criminal aspects (Plant, 1998a), metabolism and disposition (Hawks, 1982), forensic and legislative aspects (Phillips, 1998), analysis in biological materials (Raharjo and Verpoorte, 2004), global trends in seizures and consumption (UNODC, 1997/1998, 2003) and

epidemiology (Plant, 1998b). Single sources of useful information can be found in the books by Brown (1998) and Iversen (2000) and a British Parliamentary report (House of Lords, 1998). The World Wide Web provides yet further sources of information.

To maintain consistency in this report, the phrases 'herbal cannabis' or 'herbal' are used to describe what original authors may have referred to as 'marijuana', 'grass' or even 'leaf'. Cannabis described in the literature as 'flowering tops', 'nederwiet' or 'skunk' is taken to mean 'sinsemilla', particularly when grown by intensive indoor methods or when a contrast is made by the authors with the term 'seeded', which is here defined as 'imported'. Although imported cannabis can usually be distinguished from other forms, it is possible that in some published reports either no distinction was made, or some overlap between the two occurred. The term 'cannabis resin', or simply 'resin', is used in preference to 'hashish'. 'Cannabis products' or 'cannabis' is used in a generic sense to refer to plants, herbal cannabis, cannabis resin and hash oil. This report does not include any analysis of the potency of 'hemp', that is to say plants of the 'fibre-phenotype' with little THC content, which are grown for non-drug purposes. Certain recommendations on nomenclature are discussed in Chapter 6. The Glossary provides a fuller definition of these and other terms.

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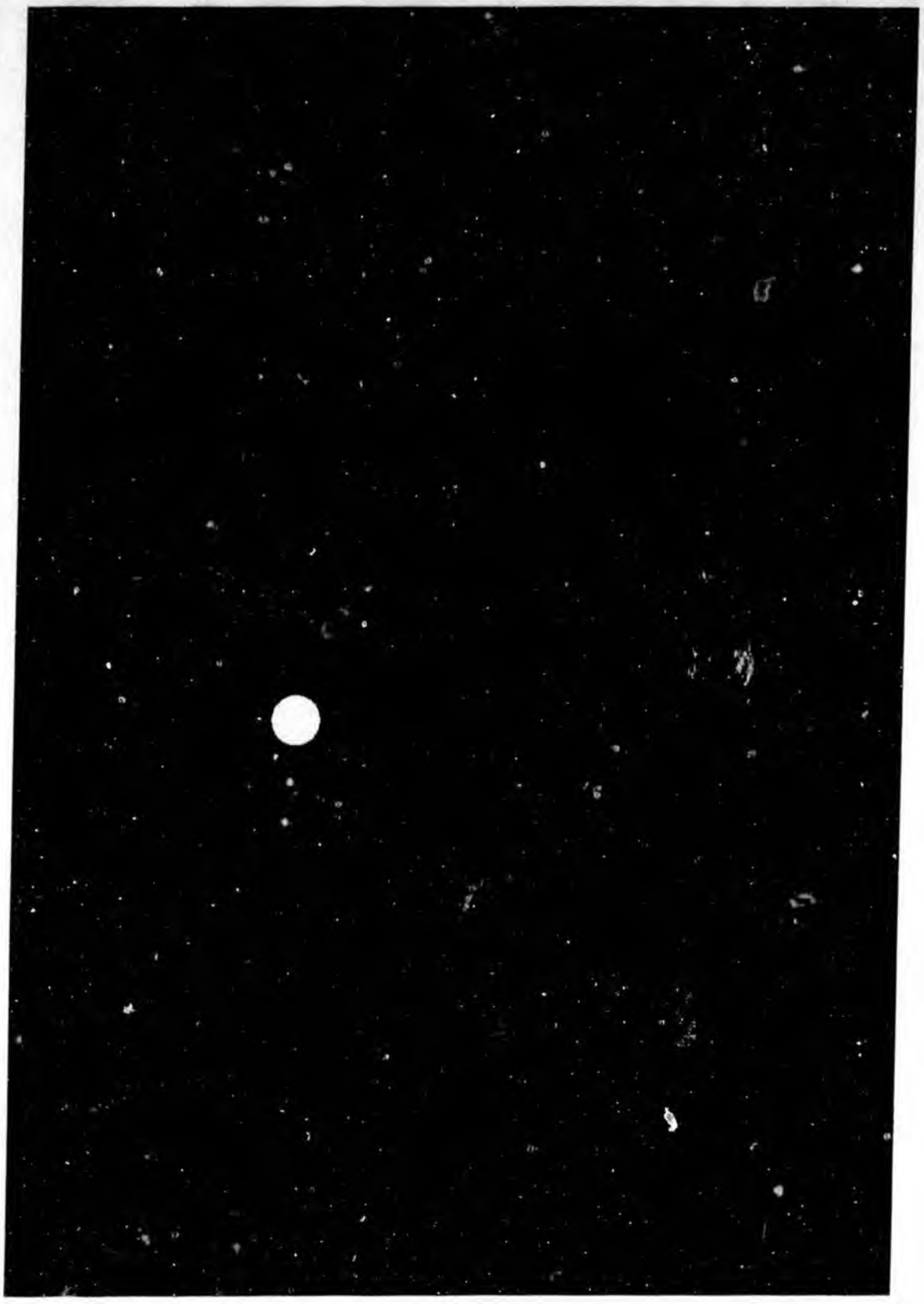

Executive summary

1. The potency of cannabis products (a term used in preference to purity) is equivalent to the Δ^9-tetrahydrocannabinol (THC) content. THC is the primary active constituent in cannabis.

2. Information on the potency of cannabis products in European countries was obtained from Standard table 14 of the EMCDDA-REITOX reporting system and by means of a questionnaire sent to experts. Information on THC levels in other countries (USA, New Zealand and Australia) was obtained from the published literature.

3. Herbal cannabis produced by intensive indoor methods (e.g. hydroponic systems with artificial lighting, propagation by cuttings and control of day length) usually has higher THC levels than imported material. Although the potency range of home-grown herbal cannabis may overlap with that of imported herbal cannabis, the average potency of home-grown herbal cannabis may be two or three times greater than that of imported herbal cannabis. The overall increases in potency that have occurred in some countries can be almost entirely attributed to the increased relative consumption of home-grown herbal cannabis.

4. Indoor cultivation of herbal cannabis occurs in all European countries. In the Netherlands, it is estimated that this product represents over half of the cannabis consumed, but for most European countries, imported products are more common.

5. The higher potency of herbal cannabis produced by indoor methods is a reflection of several factors: genetic (selected seed varieties and cultivation of female plants); environmental (cultivation technique, prevention of fertilisation and seed production); and freshness (production sites are close to the consumer and storage degradation of THC is avoided).

6. In the Netherlands, locally produced cannabis resin has particularly high THC levels, but this material is still uncommon in that country and almost unknown elsewhere.

7. Hash oil is uncommon in all countries.

8. The available data do not show any long-term marked upward trend in the potency of herbal cannabis or cannabis resin imported into Europe.

9. The countries of Europe fall into two clear groups according to whether herbal cannabis or cannabis resin is the most commonly consumed product. Of the countries for which information was available, cannabis resin was most common in Germany, Ireland, Portugal and the United Kingdom, whereas herbal cannabis was the most common product in Austria, Belgium, Estonia, Czech Republic and the Netherlands.

10. Information on potency trends and the relative consumption of different products in a particular country can be combined to give the overall trend in THC levels as perceived by the average user. Termed the effective potency, it is derived by weighting the potency of each product by its fractional share of the market and then summing the individual values. The effective potency in nearly all countries has remained quite stable for many years at around 6-8%. The only exception has been the Netherlands where, by 2001-2002, it had reached 16%.

11. In the United Kingdom, the amount of herbal cannabis or cannabis resin in cannabis cigarettes has shown no trend in the last twenty years.

12. Statements in the popular media that the potency of cannabis has increased by ten times or more in recent decades are not supported by the limited data that are available from either the USA or Europe. The greatest long-term changes in potency appear to have occurred in the USA. It should be noted here that before 1980 herbal cannabis potency in the USA was very low by European standards.

13. There are major differences in the market between the USA and Europe. In some European countries, cannabis resin, originating almost entirely from North Africa, is more common than herbal cannabis. Herbal cannabis imported into Europe originates from the Caribbean, Africa and the Far East. In the USA, herbal cannabis is either grown domestically or imported from Canada or Mexico, but cannabis resin is more rarely seen. As a consequence, direct comparisons between data in North America and Europe have questionable relevance.

14. There are major differences in the methods of consumption between the USA and Europe. In Europe, both forms are usually smoked in a mixture with tobacco. In the USA, cannabis is commonly smoked alone. These differences have important implications for the interpretation of experimental pharmacological investigations and the health effects of cannabis, particularly when comparisons are made between the USA and Europe.

15. The natural variation in the THC content between and within samples of herbal cannabis or cannabis resin at any one time and place far exceeds any long-term changes that may have occurred either in Europe or the USA. This natural variation is even greater when material from different geographical locations is examined.

16. As well as uncertainties caused by the oxidation of THC during storage and the problems of extracting (inhomogeneous) herbal or resinous material, there are analytical difficulties in the precise and accurate determination of THC. These measurement errors could also be sufficient to mask any small secular changes in potency.

17. If it is accepted that the cannabis resin imported into Europe is a fairly uniform substance that is rarely adulterated, originates mostly from North Africa and has shown no clear trend in potency for many years, then the considerable potency variations reported by different countries could suggest that there are high variations in sampling strategies and/or systematic errors in the quantitative analysis of THC in different laboratories/countries.

18. This study identifies a number of important areas that require attention if cannabis potency issues are to be properly evaluated. These include a need to:

    a. improve information gathering, analysis and dissemination;
    b. develop a consensus on nomenclature that can better identify different cannabis products;
    c. understand better the relative consumption of cannabis products in different markets and the extent and practice of domestic indoor cultivation;
    d. investigate the cannabis content of cannabis cigarettes;
    e. improve the monitoring of street prices;
    f. improve the standards of laboratory analysis, as well as data collection and data presentation at European level;

g. address information gaps that exist in understanding the relationships between potency, smoking behaviours and blood levels of THC in the European context;
h. investigate the extent to which high-potency cannabis results in increased dose exposure and any possible relationship to either chronic or acute health problems.

19. The conclusion of this report is that there have been modest changes in THC levels that are largely confined to the relatively recent appearance on the market of intensively cultivated domestically produced cannabis. Cannabis of this type is typically more potent, although it is also clear that the THC content of cannabis products in general is extremely variable and that there have always been some samples that have had a high potency. A clear need exists to develop monitoring systems that can assess the market share of different cannabis products and track changes over time. Currently this information is to a great extent lacking. This is important, as a concern exists that hydroponically produced cannabis grown in the EU may be increasing its market share.

20. An important point to note is that the possibility of additional public health problems caused by the use of high-potency cannabis as compared to cannabis products in general remains poorly understood. Nonetheless, a number of clear research questions are identifiable, that would shed light on this issue. These are discussed in the conclusions of this report.

21. This study has implications for both supply and demand side strategies, as well as to the possible costs and benefits of responding differentially to different cannabis products.

Chapter 1: Introduction

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The cannabis plant and derived products

The cannabis plant (*Cannabis sativa* L.) is an annual that will grow successfully to a height of 2-3 metres in a wide range of soils in both tropical and temperate climates. The leaves are compound with up to eleven separate serrated lobes. It is dioecious (plants are either male or female), and is the only known natural source of cannabinoids (see section *Cannabinoids*). The cannabinoids are found in resinous material, produced by glandular trichomes situated mostly around the flowering parts. Although some have suggested that there is a separate species (*Cannabis indica* Lam.), most authors consider the genus to be monospecific, but that considerable genetic diversity exists leading to wide phenotypic variability. Plants grown for drug use have traditionally been cultivated outdoors in hot climates. In temperate climates, and even when grown under glass, summers may not be long enough to allow full development of the flowering parts. Apart from the fibrous stem, which was once used for rope manufacture and is still used for other purposes, the two main drug products have been herbal cannabis and cannabis resin. Herbal cannabis is the dried flowering tops with or without variable amounts of leaves, stems and seeds. Cannabis resin is obtained by sieving or otherwise separating and compressing the flowering tops. Cannabis (hash) oil is a derived product made by solvent extraction of either herbal cannabis or cannabis resin. In the past ten to twenty years, a number of horticultural developments such as propagation by cuttings, hydroponics and artificial control of 'day' length have led to the widespread development of indoor cultivation of cannabis. Recent developments in cultivation and product quality have been discussed by Szendrei (1997/1998). The situation in the United Kingdom has been described by Bone and Waldron (1997/8).

Cannabinoids

The major active principle in all cannabis products is Δ^9-tetrahydrocannabinol (THC), the structure of which is shown in Figure 1. The unsaturated bond in the cyclohexene ring is located between C_8 and C_{10} in the more common dibenzopyran ring-numbering system. Although sometimes known as dronabinol (an international non-proprietary name), naturally occurring Δ^9-tetrahydrocannabinol exists in four isomeric forms and is not chemically identical to synthetic dronabinol. Two related

substances, Δ^9-tetrahydrocannabinol-2-oic acid and Δ^9-tetrahydrocannabinol-4-oic acid (THCA) are also present, sometimes in large amounts. Figure 1 shows one of the two positional isomers of THCA. During smoking, THCA is converted to THC, although other substances are also formed (A. Hazekamp, personal communication, 2004) and some is lost by evaporation. The active isomer Δ^8-THC, where the unsaturated bond in the cyclohexene ring is located between C_8 and C_9, is found in much smaller amounts. Other closely related substances that occur in cannabis include cannabidiol (CBD; Figure 1) and, in aged samples, cannabinol (CBN; Figure 1), both of which have quite different pharmacological effects to THC. Other compounds include the cannabivarins and cannabichromenes; they are all collectively known as cannabinoids.

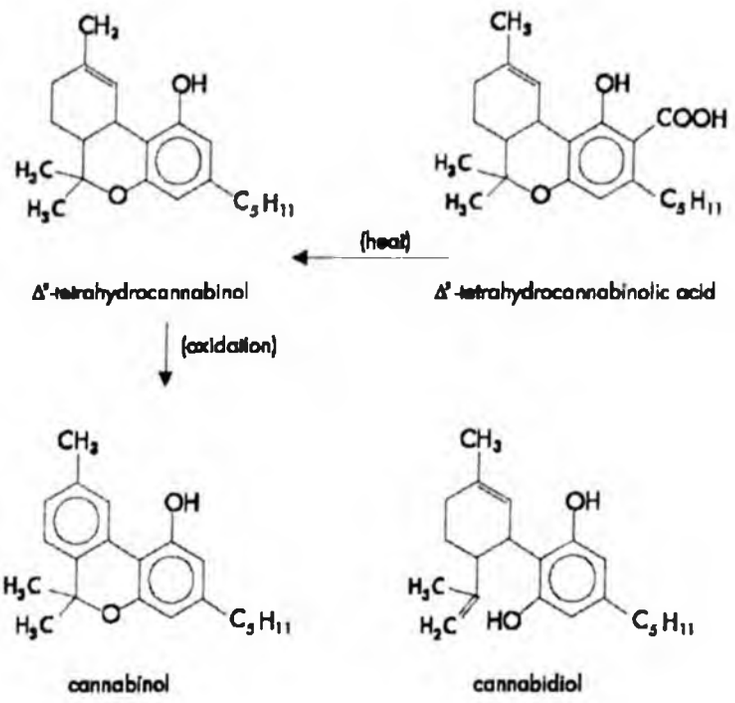

Figure 1: The structures of Δ^9-tetrahydrocannabinolic acid (THCA), Δ^9-tetrahydrocannabinol (THC), cannabinol (CBN) and cannabidiol (CBD).

The highest levels of THC occur around the floral parts of the unfertilised female plant, and this material is then described as sinsemilla (Spanish: without seeds). Fertilisation and the consequent seed production serves to reduce the level of THC. Much lower amounts are present in the leaves, and in male plants, whereas the stalk and clean seeds contain almost none. A distinction is sometimes made between cannabis plants for drug use and cannabis grown for fibre. Thus, cannabidiol is often absent in the former, but is usually found at levels exceeding 0.5% in the latter. As discussed by Maguire (2001), a useful parameter of distinction is the ratio [(% THC + % CBN)/% CBD]. If this is greater than 1.0 then the material is described as 'drug-phenotype' and if it is less than 1.0 it is 'fibre-phenotype'. In the light of the biological diversity of *Cannabis sativa*, these are simply extreme forms in a wide spectrum of different types.

Purity and potency

It is more informative, and indeed more scientifically correct, to talk of cannabis potency rather than cannabis purity. Purity is a concept that is best applied where there is a question of adulteration or dilution of an otherwise pure substance. In this sense, it is correct to refer to the purity of, say, powdered illicit drugs such as cocaine or amphetamine where cutting agents are normally added to the pure drug before it enters the retail market. Cannabis, however, does not represent a pure form of the active ingredient. The range of concentration of cannabinoids in cannabis also undermines the concept of cannabis purity. In addition, although it is alleged that cannabis resin sometimes contains inert fillers such as henna powder, herbal cannabis is rarely adulterated. For these reasons, it is not appropriate to use 'purity' when referring to cannabis. Reviews of the literature also show that 'cannabis potency', defined as the THC concentration, is the preferred term. The publication *Global Illicit Drug Trends* (UNODC, 2003) illustrates the ambiguity caused by the phrase 'purity levels' in relation to herbal cannabis and cannabis resin: values are either clustered around 1–10% and presumably reflect the THC content or they are much higher, typically above 50%, the interpretation of which is unclear, but could reflect some other concept of quality.

In the following report, the THC content of illicit herbal cannabis and cannabis resin only are considered. In the EU, cannabis (hemp) cultivated under licence for fibre contains less than 0.3% THC, and is essentially not usable as a drug. Although some data are available on the THC content of cannabis oil, the potency

is determined not only by the source material, but is also affected by its age, the efficiency of extraction and the extent to which the solvent has been removed. Furthermore, in Europe and elsewhere, hash oil accounts for a tiny fraction of the total quantity of cannabis products consumed. In the United Kingdom, the THC content of hash oil is typically in the range 25–45 % and appears to have shown no changes over the years (Baker et al., 1982; Gough, 1991; King, 2001). In the USA, during the period 1980–1997, a similar stability in the THC content of hash oil (typically 12–17 %) was reported (ElSohly et al., 2000).

A curious method of increasing the potency of cannabis was discussed by Segelman and Sofia (1973), whereby treatment of cannabis with boiling water removes unwanted soluble components, but not THC. On a weight basis, the THC concentration may be increased by around 30 %, although the absolute amount of THC has not changed.

Pharmacological aspects of high-potency cannabis

Cannabis is nearly always smoked. In Europe, it is often mixed with tobacco in a joint, also known as a reefer or spliff, but some is smoked in a water pipe (a bong). By contrast, in the USA, where little resin is consumed, cannabis is usually smoked alone. A recent trend in the USA is the smoking of 'blunts' (hollowed out cigars), which may be filled with 2–3 g of cannabis (DEA, 1999). Nearly all studies on the smoking of cannabis and its relation to potency have been carried out in North America, but it is clear that this research may not translate well into the European situation. Thus Matthias et al. (1997) found some evidence that those who smoke more potent cannabis are less exposed to noxious smoke components than those who use less potent forms. But in Europe, where a reefer cigarette typically contains only 100–260 mg of cannabis (Humphreys and Joyce, 1982; Buchanan and O'Connell, 1998; Bal and Griffin, 2001), much of the tar, carbon monoxide and other combustion products will derive from the concomitant tobacco.

Comparing the effects of marijuana cigarettes at three different potencies, Perez-Reyes et al. (1982) found no qualitative difference between the psychopharmacological effects of consuming large amounts of THC and those caused by consuming smaller amounts. Nevertheless, it is accepted that there is a dose–response curve (Miller et al., 1977). McBride and Thomas (1995) pointed out that psychosis attributed to 'skunk' (Wylie, 1995) is also common in users of 'normal' (or other types of) cannabis. If the potency of cannabis products has shown a marked increase, then it might be expected that the typical user would

need to consume less on a weight basis to achieve the desired effect. Given a choice, users preferred cigarettes with a higher THC content (Chait and Burke, 1994; Kelly et al., 1997). Ashton (1998) also argued that users would not titrate the dose of THC from cannabis in contrast to nicotine/tobacco smokers. However, Heishman et al. (1989) found that those smoking cigarettes with a higher THC content tended to have a lower inhalation rate than control subjects. Yet little research has been conducted, particularly in Europe, to answer a crucial question: Do those smoking high-potency cannabis have higher blood levels of THC?

Pharmacological studies are also compromised by a number of other factors. For example, while smoking is able to deliver a drug rapidly into the bloodstream and hence the brain, it is an inefficient process. Some THC will be destroyed by combustion or lost in the side-stream smoke, and the bioavailability of THC by this route is usually less than 50 % (Moffat et al., 2004). Based on the complete consumption of a cigarette containing 200 mg of cannabis, the amount of THC absorbed will be less than 10 mg in most cases. However, ingestion of cannabis in foods (e.g. spacecake) or infusions leads to an even lower bioavailability, largely because the gut poorly absorbs THC. Cannabis extracts do not lend themselves to injection because THC is practically insoluble in water. A further complicating factor is that some of the major metabolites of THC, such as 11-hydroxy-Δ^9-THC, have long half-lives and are themselves active.

Medicinal cannabis

In the Netherlands, herbal cannabis is available as a prescription medicine (Office of Medicinal Cannabis, 2004). Known as 'cannabis flos', one of the preparations has a nominal THC content of 18 % (±2.7 %) and is locally produced by the same intensive indoor methods that are used for illicit cultivation. It is indicated for multiple sclerosis, certain types of pain and other neurological conditions. Patients are advised to consume the cannabis by means of a hot water infusion. However, Hazekamp (personal communication, 2004) has found that, even in boiling water, the conversion of THCA to THC can take some hours and other by-products are formed. In the United Kingdom, an extract of cannabis is expected to be to licensed in 2004 to GW Pharmaceuticals Ltd. The product, to be known as Sativex, will be supplied in a nebuliser for sub-lingual application at a concentration of well below 1 % THC. Cannabis is not available for licensed therapeutic use in any other European country.

Chapter 2: Analytical aspects

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Quantification of THC

There are a number of problems beseting r .ıtative analysis of THC in cannabis products. Firstly, herbal cannabis, and to a esser extent cannabis resin, is an extremely inhomogeneous material. As well as the flowering tops of the female plant, where most of the THC is located, a sample may contain varying amounts of stalk, seeds and leaves, none of which contains much active drug. It is to be expected that even within a well-mixed single large batch of crude material and following removal of 'unwanted' matter, different aliquots could lead to quite different analytical results. Yet authors rarely publish information on such intra-sample variance.

Given that a suitably 'cleaned' sample has been obtained and that the THC has been efficiently extracted into a suitable solvent such as petroleum ether, then most laboratories proceed to use gas chromatography (GC), often with flame-ionisation detection (Raharjo and Verpoorte, 2004) to determine THC concentration. This has the merit that the naturally occurring precursor (THCA) is decarboxylated to THC, just as occurs during smoking. Cannabinoids can also be determined by high performance liquid chromatography (HPLC), a method suited to profiling ('chemical fingerprinting') and the separate measurement of THCA. To measure the total THC content by HPLC, the sample must be heat-treated before analysis (Kanter et al., 1979; Lehmann and Brenneisen, 1995; Rustichelli et al., 1998).

Other issues to arise in the analysis of THC concern the precision (reproducibility) and accuracy (closeness to the 'true' value) of the measurement process. Poortman van der Meer and Huizer (1999) claimed that in a series of proficiency tests organised in 1997 for 30–40 European laboratories, the relative standard deviation was about 29% whereas cocaine and amphetamine gave less than 5% and 8% respectively. This means that arourid one third of results for THC were either more than 29% greater or more than 29% below the mean value.
It is clear that even worse precision could be expected if the measurement error, caused by the sampling and extraction process noted above, were to be included.

As a reference standard, THC is usually only available from chemical suppliers in the form of an ethanolic solution and may be labelled, for example, as 'approximately 95%'. Not only could confusion arise if analysts assume the

concentration to be 100%, but Poortman-van der Meer and Huizer (1999), using the response of a flame-ionisation detector, found that one sample of a commercial THC solution had only 90% of the concentration of a different commercial solution. These authors recommended that THC quantification should be based on CBN or CBD as the internal standards and a correction made for the expected detector response from the effective carbon number of the respective substances. They claimed that this method had been used in Germany for the past ten years. It was also the method used by Maguire (2001) to study the cannabinoid content of (mostly fibre-type) cannabis in Ireland. However, as far as could be determined from the questionnaire responses, many laboratories in Europe continue to prepare standard dilutions of stock THC solution to construct calibration curves.

Finally, if precautions are not taken during analysis, THC can be lost from dilute solutions because of its propensity to adsorb onto unsilanised glass surfaces (Moffat et al., 2004). As this can affect both 'pure' reference material and extracts of cannabis products, it is a further source of error in THC determination.

Lability of THC in cannabis products and solutions

Atmospheric exposure of THC causes oxidation to CBN and other substances. In cannabis resin, Martone and Della Casa (1990) showed that, even when stored in the dark, the half-life of THC was often less than one year, and in some cases THC had disappeared almost completely within two years. In a block of resin, this could lead to variations in the THC concentration between the outside and the inside. The rate of THC decomposition in cannabis at room temperature was estimated as 17% per annum by Ross and ElSohly (1997/8). Since CBN is almost entirely absent from fresh cannabis, these authors suggest that the ratio CBN/THC could serve as a measure of the age of a sample. The relevance of this to questions of potency can be understood when it is realised that some imported products may have been harvested or manufactured many months before consumption or analysis. By contrast, and other things being equal, it is to be expected that domestic (i.e. local) production will lead to a fresher product containing more THC.

Natural variation of THC content in cannabis products

There is a wide range of variation in THC concentrations between different samples of a particular product, be that herbal cannabis or resin. Such variation is

often attributed to the quality of different geographical sources as well as the method of cultivation. Whether geographical profiling has any merit is a separate issue, but it is clear that even within a single geographical source, the potency may rise and fall in time. Figure 2 shows the variation in the THC content of herbal cannabis seized by customs in the United Kingdom in the period 1985-1986. Data were derived from Gough (1991) based on measurements at the Laboratory of the Government Chemist (LGC), and have been frequency-grouped according to the number of samples examined in that period. If this distribution had been based on the original individual THC measurements for each sample, then the spread of values would have been even greater. Thus the lowest and highest values in 1985-1986 were 0.9% and 12.2% respectively. Although not shown graphically here, the lowest and highest values found for cannabis resin in that same period were 0.5% and 26% respectively.

As a further example, the frequency distributions of the THC content of sinsemilla and imported herbal cannabis examined in the Forensic Science Service in 1996-1998 are shown in Figure 3 (King, 1998, 2000). During this period, there was no clear trend in the potency of herbal cannabis, but the inter-sample variance was large.

A difficulty faced by all sampling experiments is whether the materials examined are typical of the population. Even when samples are representative, the methods of chemical extraction are efficient and analysis is precise and accurate, it is still necessary to examine an appropriate number and derive the mean and other statistical parameters. This is particularly true of cannabis where, like many natural products, considerable diversity exists between individual samples. Thus, without knowing the lower value or the mean or even the sample size, statements such as were attributed to the situation in Switzerland (Anon, 2002), that cannabis contains up to 28% THC, are almost valueless. The comment (Henry, 2004) that "...the most potent form, skunk, contains up to 30 per cent" is equally unhelpful.

It is clear that cannabis users have constantly been exposed, in almost random fashion, to unexpectedly high and low amounts of THC in the course of their careers. Perhaps what is more significant is that the natural variation in THC content in both herbal cannabis and cannabis resin could far exceed any changes in the mean potency that may or may not have taken place over certain time-spans.

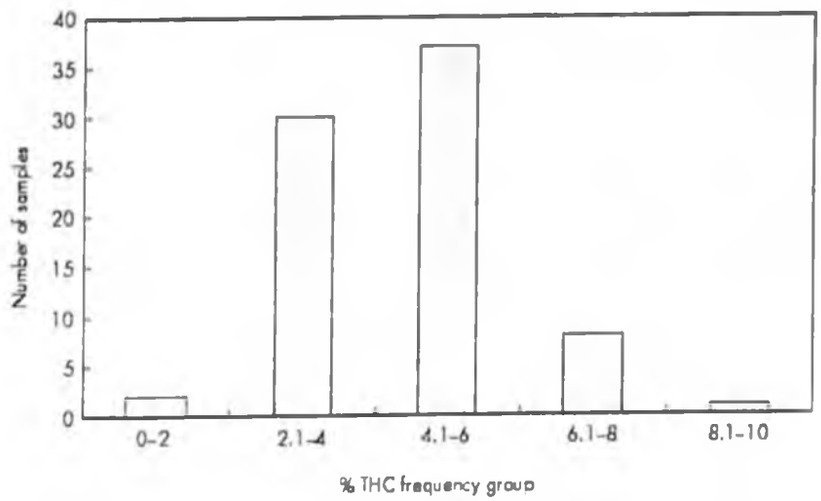


Figure 2: Variation in the mean THC content of imported herbal cannabis samples in the period 1985–1988, weighted by the number of samples from which each mean had been derived (Gough, 1991).

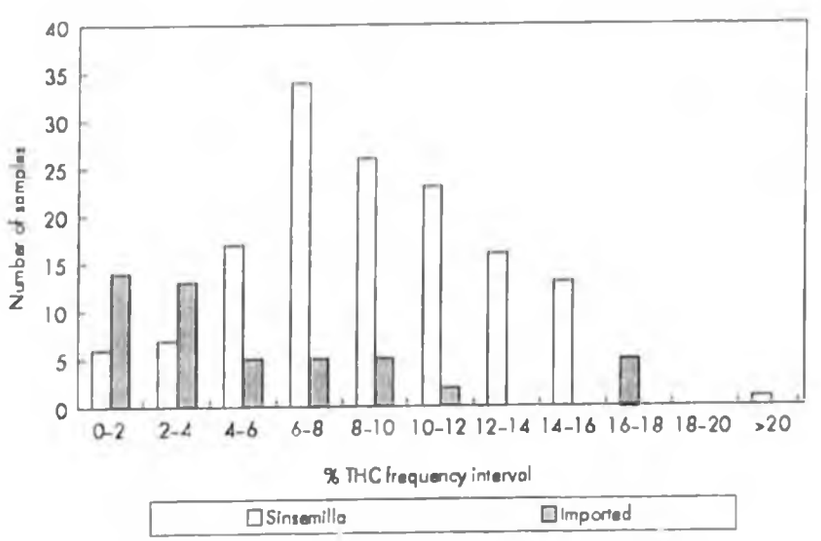
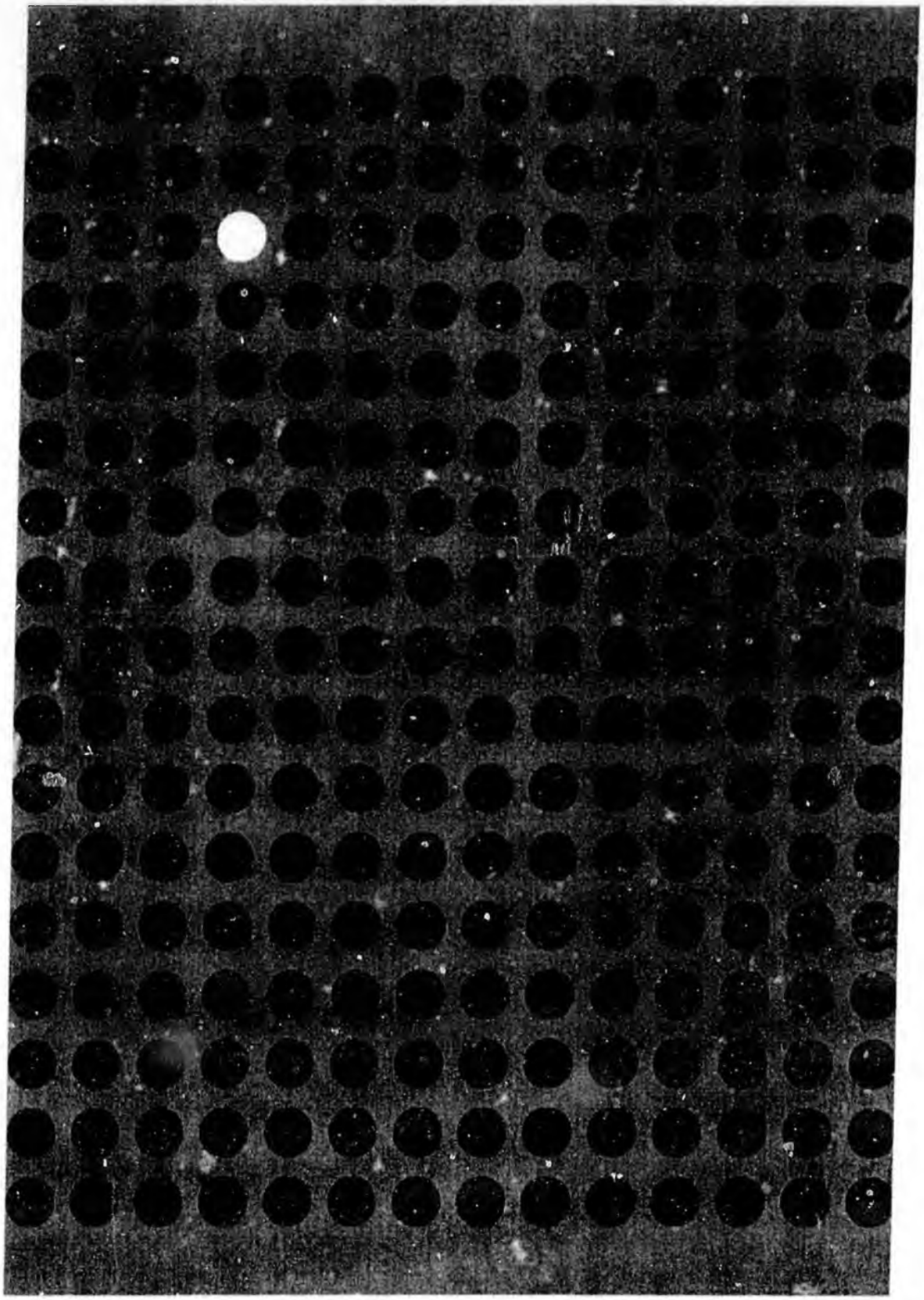


Figure 3: Frequency distributions of THC in herbal cannabis examined in the Forensic Science Service, UK (1996–1998)



Chapter 3: Trends in cannabis potency in Europe

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National reports to EMCDDA (Standard table 14)

Tables 1 and 2 show the mean national potency of cannabis 'leaf' (taken to be herbal cannabis) and cannabis resin respectively in Member States of the European Union and Norway for the period 1996–2001 as submitted to the EMCDDA by the Reitox national focal points in Standard table 14.

Table 1: Mean national potencies (% THC) of herbal cannabis at retail level in Standard table 14 submitted to the EMCDDA (European Union and Norway)

Country	1998	1999	2000	2001	2002
Belgium (i)	–	–	10.4	6.0	6.0
Czech Republic (ii)	–	–	11	11	12
Czech Republic (iii)	–	–	–	1.6	2.65
Germany (i)	–	6.0	6.4	8.6	8.4
Finland (i)	–	–	–	–	2
France (i)	–	–	2	2	8
Hungary (iii)	–	–	–	–	1.1
Italy (i)	8.3	16.9	6.3	5.8	5.5
Latvia (i)	–	–	–	–	1.5
Luxembourg (i)	–	–	–	–	8
Netherlands (i)	–	7.5	10.1	14.6	–
Netherlands (ii)	–	8.6	11.3	15.2	–
Netherlands (iii)	–	5.0	5.1	6.6	–
Norway (i)	–	–	–	–	8
Portugal (i)	1.6	–	–	5.2	3.1
Portugal (ii)	–	–	–	14.6	13.1
UK (i)	7.9	9.5	12.0	9.5	10.7

Notes: Standard table 14 provides herbal cannabis to be reported as (i) cannabis leaves; (ii) nederwiet; (iii) other grass. Data originally listed as '0' or '–' were ignored. Some countries gave separate values for those different forms of herbal cannabis, but all data were used when calculating annual means. Values shown as '<2' by France in 2000 and 2001 were taken as 2. UK refers strictly to England and Wales only. Data for the Netherlands refer to 1999–2000, 2000–2001 and 2001–2002 instead of 1999, 2000 and 2001.

Table 2: Mean national potencies (% THC) of cannabis resin at retail level in Standard table 14 submitted to the EMCDDA (European Union and Norway)

Country	1998	1999	2000	2001	2002
Belgium		-	7.1	13.6	9.7
Czech Republic		15	11.5	11.5	6.3
Germany	-	8.4	10.5	8.6	7.9
France	-	-	7.5	7.5	8
Hungary	-	-	-	-	2.0
Italy	4.9	8.5	8.8	11.2	13.9
Latvia	-	-	-	-	4.5
Luxembourg	-	3.5	8.0	7.1	-
Netherlands	-	12.6	12.8	20.6	-
Norway	-	-	-	5	8
Portugal	4.3	3.7	2.2	5.5	2.6
UK	7.3	2.6	18.1	7.4	-

Notes: Values for resin reported by France in 2000 and 2001 as "5 to 10" are shown above as 7.5. All data were used when calculating annual means. UK refers strictly to England and Wales only. Data for the Netherlands refer to 1999–2000, 2000–2001 and 2001–2002 instead of 1999, 2000 and 2001.

The EMCDDA Standard table 14 lists mean potencies of both herbal cannabis and cannabis resin by country. The original data, upon which the country means were based, were not available. For all years and countries combined, the mean potency values of herbal cannabis and cannabis resin were 7.7% and 8.2%, respectively. Since it is likely that the sample size and sampling strategy varies between countries, these overall mean values should be treated with some caution.

Caution is also required when analysing these data as they are limited to countries where data are available (under-representation of Eastern European countries) and might, for some of them, present reliability problems (e.g. local rather than national data, data not representative of the retail level, uncertainty on the method to calculate averages).

Other national data

The Reitox national focal points were contacted in order to provide names of experts who might be in a position to answer the specific questionnaire developed

for the purpose of this study. For the United Kingdom and the Netherlands, information was obtained by interviewing a number of experts in both countries. Replies to the questionnaire were received from eleven countries: Austria (two sources), Belgium (two sources), Czech Republic (two sources), Estonia, Finland, Germany, Ireland, Luxembourg, Portugal, Slovenia and Spain, but only six countries in total were able to provide potency trend data. The data collected by these means (in 13 countries) are presented below.

Austria

Figure 4 shows the THC content of resin and herbal cannabis in Austria as provided by the Federal Ministry of the Interior. Measurements were made on seizures above 200 g. No distinction was made between imported and domestically produced cannabis, although it was stated that production of the latter was negligible. There is no clear time trend for either product.

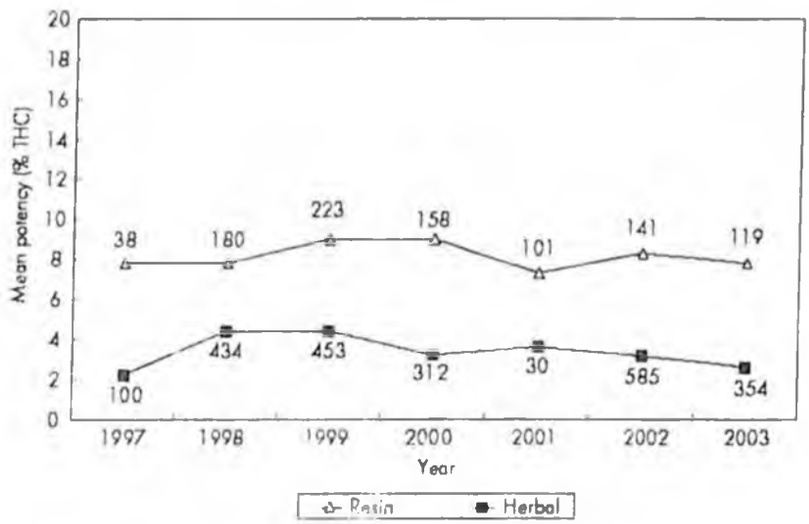


Figure 4: Mean potency (% THC) of cannabis products (1997-2003) in Austria. Values against each point represent the number of measurements.

Czech Republic

Figure 5 shows the THC content of resin and herbal cannabis in the Czech Republic as measured on police seizures and reported by the Institute of Criminalistics. In both cases, there is some evidence that the potency has increased in the period 1997-2003. However, no information was available on the sampling strategy or sample sizes and no distinction was made between imported and domestically produced cannabis.

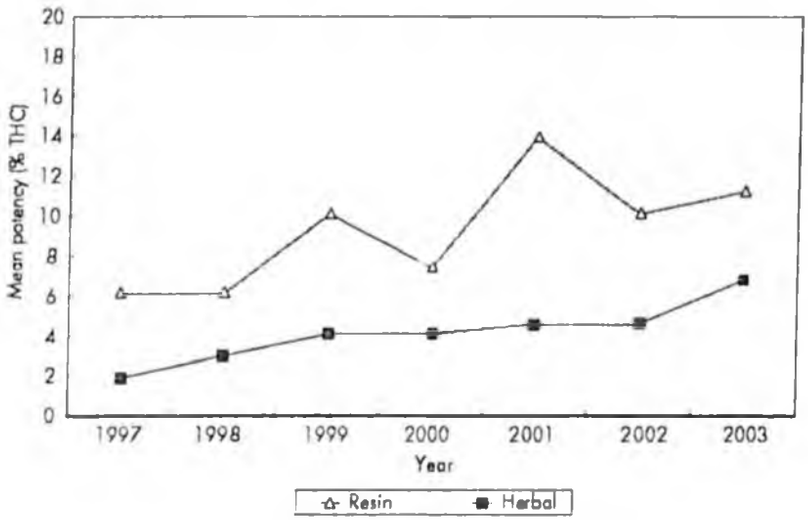


Figure 5: Mean potency (% THC) of cannabis products (1997-2003) in the Czech Republic

Germany

Figure 6 shows the THC content of resin and herbal cannabis in Germany. The potency of herbal cannabis showed an upward trend in the period 1997–2002, but no long-term trend was obvious for cannabis resin. No distinction was made between imported and domestically produced products. The samples derived from seizures by law enforcement agencies. Each year, the THC content of around 6 000 samples above a weight threshold of 7.5 g were determined by the Bundeskriminalamt, laboratories in the 16 Laender and by five customs laboratories.

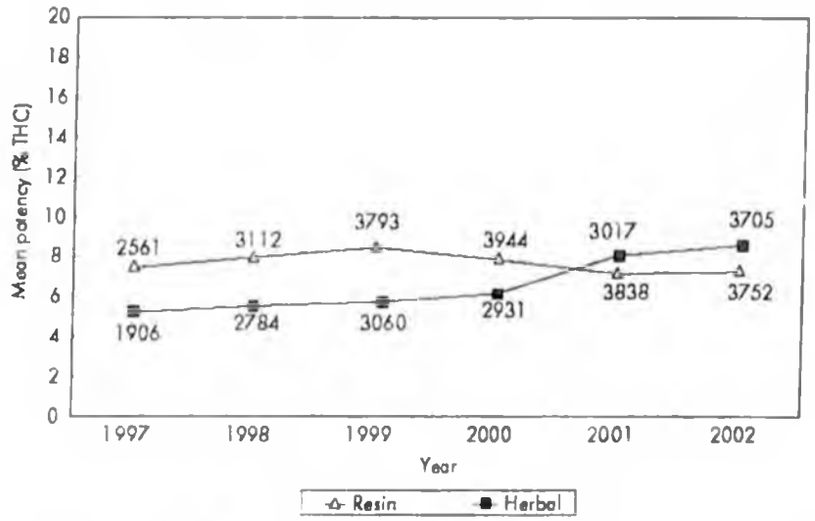


Figure 6: Mean potency (% THC) of cannabis products (1997–2002) in Germany. Values against each point represent the number of measurements.

Netherlands

The THC content of various cannabis products in the Netherlands (Niesink, 2000; Niesink et al., 2002) is shown in Figure 7. Dutch resin (nederhasj) is a locally produced material (see Glossary). Samples were obtained from 'coffee shops'. There are around 800 of these establishments where small-scale supply of cannabis products is tolerated by Dutch law. The total number of samples in the three periods was: sinsemilla = 376; imported herbal = 147; imported resin = 291; Dutch resin = 60. Apart from imported herbal cannabis, the year-on-year increases in THC level were statistically significant ($P < 0.001$).

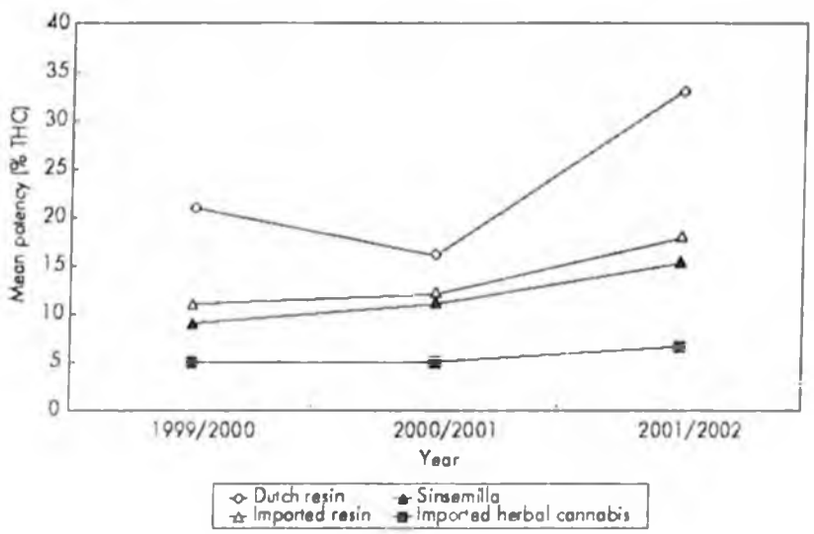


Figure 7: Mean potency (% THC) of cannabis products (1999–2002) in the Netherlands (Note that scale on the y-axis is twice that for the mean potency in other countries.)

Portugal

Figure 8 shows the THC content of resin and herbal cannabis in Portugal from 1997 to 2003. These were derived from all large seizures (>10 kg) and a random sample of smaller seizures. Although it appears that the potency of cannabis resin has increased, the trend in THC content of herbal cannabis is not clear, particularly because of the small sample size. The value for herbal cannabis in 1999 was not available.

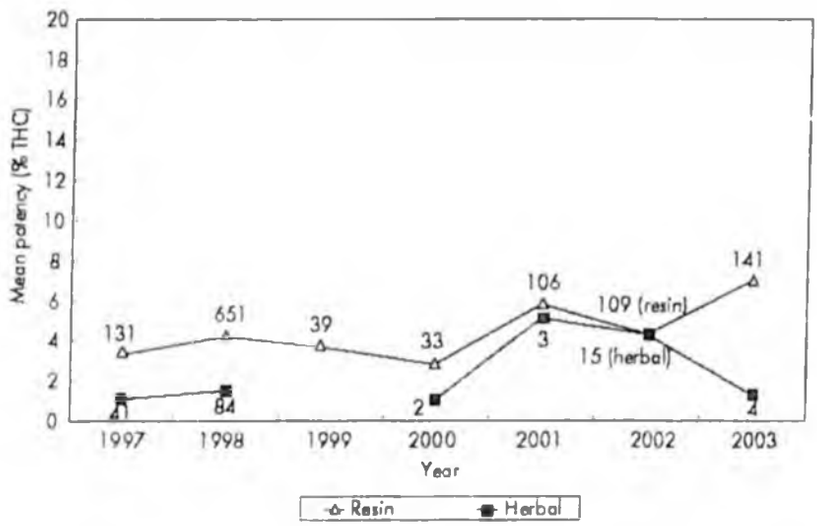


Figure 8: Mean potency (% THC) of cannabis products (1997–2003) in Portugal. Values against each point represent the number of measurements.

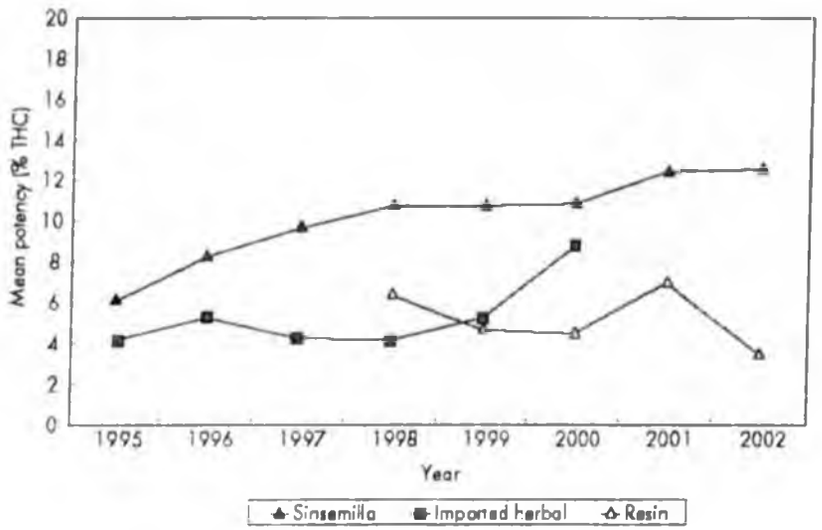


Figure 9: Mean potency (% THC) of cannabis products examined in the UK (Forensic Science Service, 1995–2002).

United Kingdom

The THC content of various cannabis products examined in the United Kingdom by the Forensic Science Service from 1995 to 2002 (Forensic Science Service, 2003) is shown in Figure 9. The samples derived mostly from police seizures and are judged to be reasonably representative of the material seized for each cannabis product. The total sample size was: sinsemilla = 938; imported herbal = 117; resin = 97. There were no data for resin before 1998 and insufficient data for imported herbal cannabis in 2001 and 2002. There has been a clear trend for an increase in the potency of sinsemilla, but little evidence that the potency of resin or imported herbal cannabis has changed.

For a number of years, the Laboratory of the Government Chemist (LGC) produced data on annual trends in cannabis potency and the variation in THC content of imported material derived from customs seizures (Baker et al., 1980, 1981, 1982; Gough, 1991). Figure 10 shows the THC content of all seized cannabis products in the period 1975–1989 as reported in the most recent publication of the series

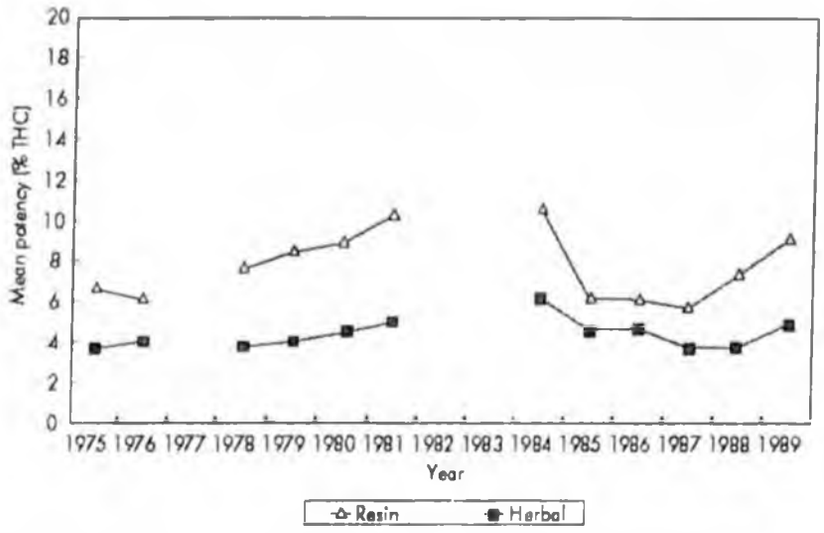


Figure 10: Mean potency (% THC) of cannabis products examined in the UK (Laboratory of the Government Chemist, 1975–1989)

(Pitts et al., 1990). There are major changes on a year-to-year basis, particularly with resin, but no clear overall trend can be discerned for either product. The mean THC content of herbal cannabis and resin was close to 4% and 8% respectively over this period. No data were published after 1989, but information provided by the LGC for 2003 showed that this situation has changed little: the mean THC content of herbal cannabis (type unspecified) was 7.0% (N = 23) and for resin was 5.1% (N = 6).

Miscellaneous data

Two replies to the questionnaire were obtained from **Belgium**: from the Institute of Public Health and from the Drugs and Toxicology Unit of the National Institute of Criminology and Criminalistics (NICC). Data for 2003 (January to October) only were provided by the Institute of Public Health on the questionnaire. These showed that the mean THC content of resin was 15.2% and herbal 14.2%. No summary of the THC data was provided by the NICC, but it stated that there had been no clear trend in the potency of herbal cannabis or cannabis resin in the period 1995–2002; that during this period both herbal cannabis and cannabis resin had

a mean THC content of around 12%, and in 2003 the mean THC content of herbal cannabis was 13.3% and that of cannabis resin 11.5%.

Although the **Estonian** Police Forensic Science Laboratory occasionally measures the THC content of cannabis products, insufficient data were available to determine trends in potency (source: reply to the questionnaire).

In **Finland**, the THC content of herbal cannabis is determined on request but no data were provided (source: reply to the questionnaire).

In **Ireland**, analysis of cannabis products for THC is carried out on an occasional basis; the limited data show that the potency of resin has increased from 2.3% in 1981 to 4.2% in 2000. For herbal cannabis, the increase in this period was from 1.4% to 6.2% (source: reply to the questionnaire).

In **Greece**, Stefanidou et al. (1998) reported that the THC content of illicit herbal cannabis seized by customs and police in two areas of Greece ranged from <1% to >4%.

Hungary did not report mean THC levels before 2002 in Standard table 14, or respond to the questionnaire, but the annual national report to the EMCDDA for 2003 notes that the highest THC level found in herbal cannabis has steadily increased since 1996, although even by 2001 this was still a modest 6%.

Analysis of cannabis products for THC is only carried out occasionally in **Luxembourg**; recent samples (type unspecified) contained up to 14% THC (source: reply to the questionnaire).

In **Spain**, the THC content of cannabis products is measured on all seizures above 4 g, but no data were provided in the questionnaire except for the comment that the mean potency of resin had increased from 5.5% in 1994 to 12% in 2002.

Older data on THC levels in European countries can be found in isolated reports, but they provide little useful information on trends. Thus Fairbairn and Liebmann (1974) planted seeds from imported cannabis and allowed them to grow outdoors in southern England. THC levels in the flowering tops ranged from <1% to >7%. The authors concluded that a warm climate with abundant sunshine was not essential to produce substantial amounts of THC. Cannabis plants growing in Jutland (Denmark) in 1988 were found to have mean total THC levels of <1%

(grown outdoors) and 1.35% (grown under glass). In the flowering tops of those grown under glass, the mean THC content was 2.13% (Kaa, 1989). Earlier, Felby and Nielsen (1985) had found mean total levels of 1.55% (range 0.1-4.2%) for plants growing on Bornholm (Denmark). The authors commented that these findings were broadly similar to THC levels of imported herbal cannabis.

Cannabis resin: variations in potency across Europe

To a large extent, and excluding the special situation of locally produced Dutch nederhasj, the cannabis resin consumed in Europe in recent years has originated mostly from North Africa, with smaller amounts coming from south-west Asia. Since resin is rarely adulterated, it could be argued that, in any given year, all laboratories have been measuring broadly similar material. As noted in the section *Natural variation of THC content in cannabis products* (Chapter 2), there is considerable natural variation in the potency of cannabis products even in a single time period. However, if laboratories made sufficient measurements, then the mean potency of cannabis resin in any year should be found to be similar for all countries. In Figure 11, the respective year-on-year trends for cannabis resin potency, already depicted by country in the section *Other national data*, are brought together. Not only is there no overall time trend, but also there is considerable variation in the reported THC levels, both against time in any one country and between countries at any one time. It is not obvious why there should be consistently less THC in cannabis resin in Portugal compared with cannabis resin in, for example, Austria or the Czech Republic. This finding raises questions about the accuracy of measurement of THC in different laboratories/countries. In other words, if all analysts had used the same THC reference standard for instrumental calibration, then these differences might not have occurred.

In the Netherlands, there has been a marked rise in the potency of cannabis resin caused by the domestic production of nederhasj. Figure 12 shows the unweighted mean potency of cannabis resin for the other countries (i.e. excluding the Netherlands). As with the data derived from Standard table 14 (Table 1), there is no clear trend. This diagram (Figure 12) only covers 1998-2002: the years for which all five countries provided data. It is not possible to derive a similar comparison for herbal cannabis in different countries since, in some cases, no distinction is made between two distinct products, i.e. imported and home-grown cannabis.

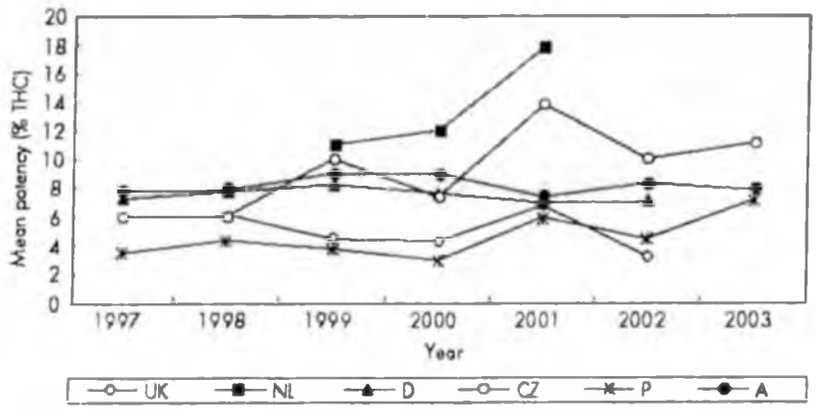


Figure 11: Mean potencies (% THC) of imported cannabis resin in Europe (1997–2003) showing the variation between different laboratories/countries. (UK = United Kingdom, NL = Netherlands, D = Germany, CZ = Czech Republic, P = Portugal, A = Austria)

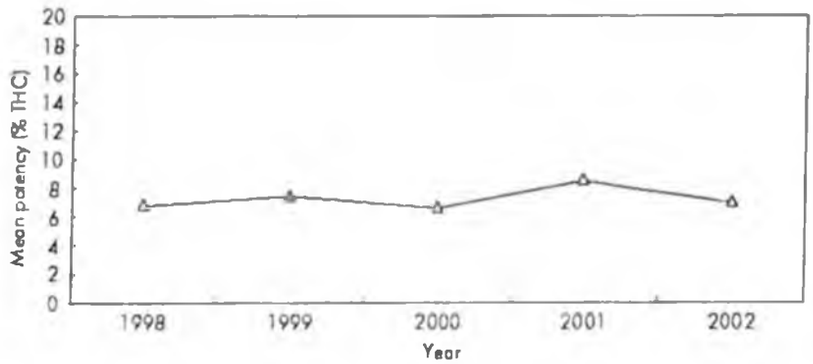
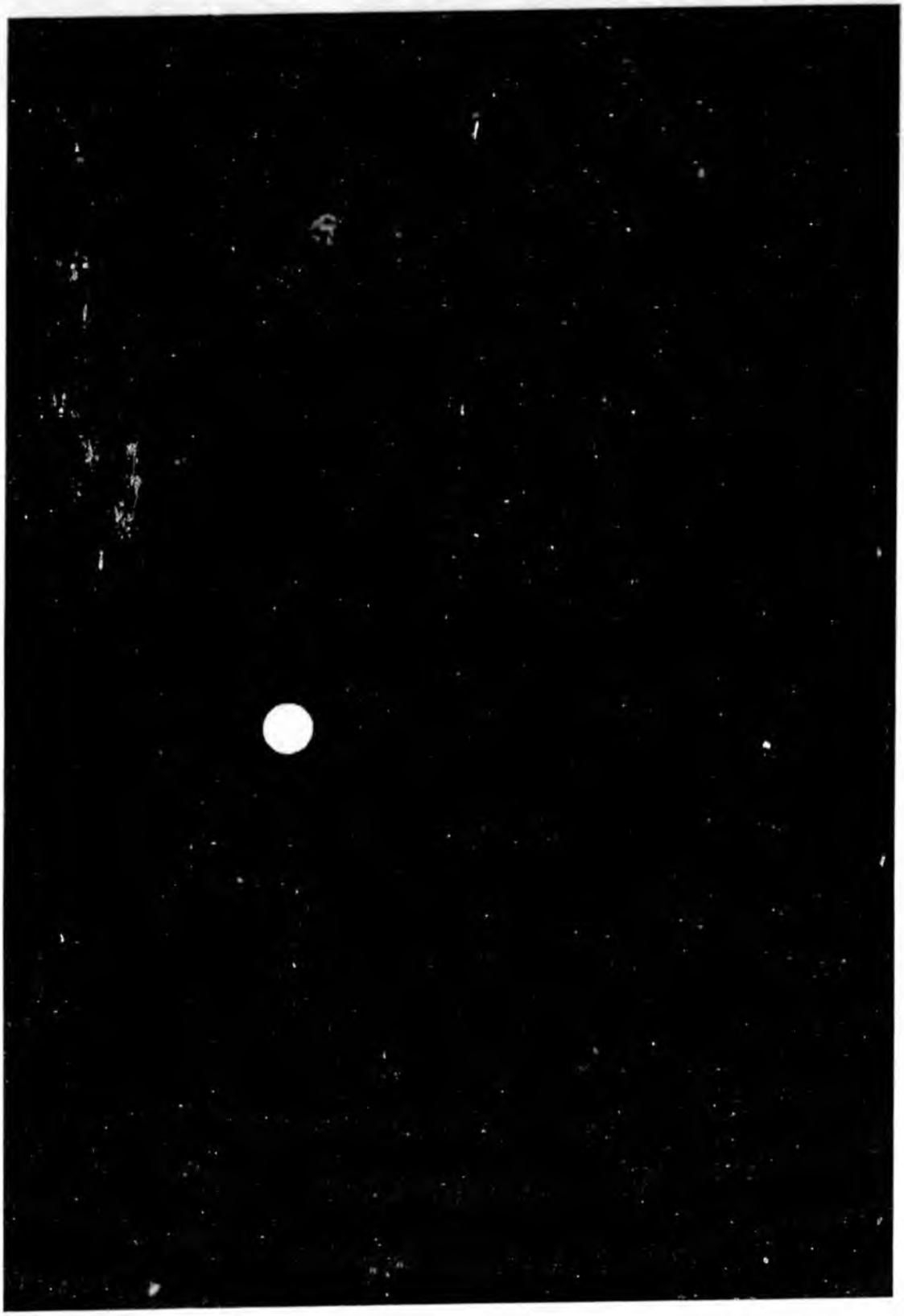


Figure 12: The overall mean potency (% THC) of cannabis resin in Europe (1998–2002) based on data supplied in the questionnaire by the countries shown in Figure 11, but excluding the Netherlands



Chapter 4: The cannabis market in Europe: potency considerations

Chapter 4: The cannabis market in Europe: potency considerations

The relative consumption of different cannabis products in Europe

The increases that have occurred with time in the potency of some types of cannabis must be put into the context of the relative consumption and production of the various products in different countries. Table 3 sets out estimates of the relative proportion of each cannabis product on the domestic market in recent years in those countries for which data were available in the published literature or were supplied directly in response to the questionnaire or were derived indirectly from the relative number of samples examined. Cannabis oil is uncommon in all countries and is not included in Table 3.

Table 3: Relative consumption (%) of cannabis products in European countries since 1999

Country	Imported herbal cannabis	Cannabis resin	Sinsemilla	Domestic resin
Austria	70 (*)	30 (**)	–	–
Belgium	80 (*)	20 (**)	–	–
Czech Republic	90 (*)	10 (**)	–	–
Estonia	85 (*)	15 (**)	–	–
Germany	40 (*)	60 (**)	–	–
Ireland	5	90	5	0
Netherlands	3	29	67	1
Portugal	10 (*)	90 (**)	–	–
United Kingdom	15	70	15	0

(*) All herbal, imported or not.
(**) All resin, imported or not.

National statistics from law enforcement agencies show a situation where the proportion of resin seized in Europe decreases from west to east. Thus, for the period 1996–2001, resin accounted for 79% of the total weight of resin and herbal cannabis seized in Western Europe, but in Eastern Europe this proportion was 13% (UNODC, 2003). This is easily understood when it is recognised that Morocco is the world's largest producer of resin, much of which is destined for Europe. Indeed, the greatest weight of resin is seized in Spain, the first country of transit for this North African material.

However, in relation to the market shares of different cannabis products, seizures may not necessarily parallel availability and consumption, particularly if a country has a large number of small-scale cultivation set-ups that may go undetected by police. Thus, in terms of consumption, the countries of Europe still fall into two clear groups according to whether (a) herbal cannabis or (b) cannabis resin are the most commonly consumed products, but in this division of the countries the east–west split is no longer obvious. The first group (a) includes Belgium, the Netherlands, Austria, Czech Republic and Estonia. In the second group (b) are the United Kingdom, Ireland, Germany and Portugal. The higher relative consumption of herbal cannabis in the Netherlands can be partly explained by the flourishing domestic production of sinsemilla (nederwiet) and the large number of tolerated retail outlets for this product in coffee shops. In the United Kingdom, it is estimated that herbal material comprises only one-third of all cannabis consumed (Atha, 2003) and that around half of this is imported (Hough et al., 2003). The dominance of resin in Ireland is suggested by the fact that over 90% of reefer cigarettes examined in a survey contained resin (Buchanan and O'Connell, 1988). Maguire (2001) in Ireland also noted that over 90% of the samples submitted to him by the Garda Drug Unit were resin. The predominant use of herbal cannabis in Eastern Europe is consistent with the pattern of drug seizures (UNODC, 2003), and may reflect the greater separation of these markets from the production sites in North Africa and the local cultivation of cannabis having a greater importance compared to that in Western Europe.

The effective THC level in Europe

The data in the section *Other national data* (Chapter 3) and Table 3 can be combined to give the overall trend in THC levels as perceived by the average user.

This will be termed the effective potency and is derived by weighting the potency of each product by its fractional share of the market and then summing the individual values. For example, if in a given year the THC contents of different products are *a*%, *b*% and c% and the respective share of the market is *x*, *y* and *z* (where $x + y + z = 1$), then the effective THC level in that year is given by $(ax + by + cz)$. It is assumed that the market share data in Table 3 were typical for the entire period. Figure 13 shows the effective potency in several European countries. It will be seen that, apart from the Netherlands, there has been no marked increase in the effective THC level in the five other countries. Since the THC contents of imported herbal cannabis and cannabis resin have shown no real change over the years, then, other patterns of behaviour being constant, the typical consumer in countries where most cannabis products are imported (e.g. United Kingdom) will have been partly shielded from the increased potency of sinsemilla. Although not developed graphically here, the United Kingdom data for the earlier period 1975–1989 (Figure 10) suggest that the effective potency in the United Kingdom has been around 6 % for the past thirty years. In Ireland, where resin is also the main product, the effective potency in 2000 was closer to 4 %.

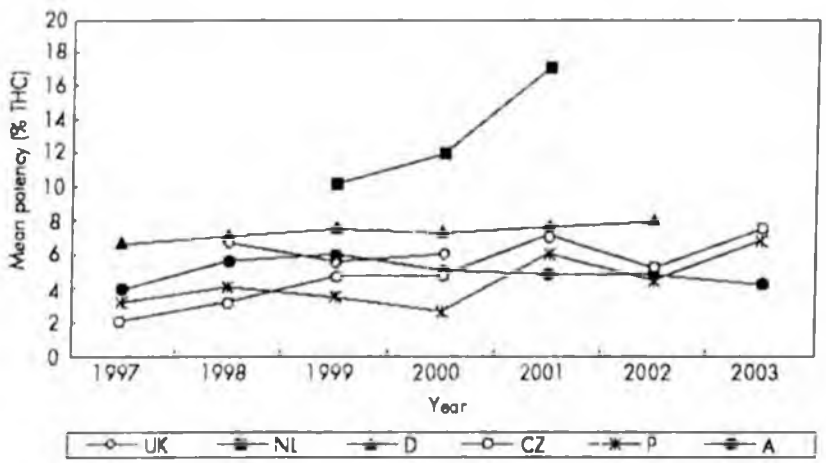


Figure 13: Effective potency (% THC) of cannabis products in several European countries (UK = United Kingdom, NL = Netherlands, D = Germany, CZ = Czech Republic, P = Portugal, A = Austria).

There are two important limitations that must be borne in mind in drawing conclusions from this analysis. First, data are only available from six countries for this analysis. Second, whilst it is reported that home-grown herbal cannabis does not currently hold a major share of the market in countries other than the Netherlands, systematic data to support this contention are limited. This suggests an urgent need to improve our understanding of the relative market share of different cannabis products and track changes in the illicit cannabis market over time.

Extent of cannabis cultivation in Europe

Since cannabis can be cultivated by indoor methods using artificial lighting, it may be grown in all countries. However, the highest level of production in Europe occurs in the Netherlands and to a lesser extent in the surrounding countries. The Institute of Forensic Medicine in Innsbruck claimed that the domestic production of cannabis in Austria is negligible. In the United Kingdom, each year police raid several hundred indoor cannabis cultivation scenes, ranging from rooms in homes to large-scale factories. Although the interception rate is unknown, there are likely to be many thousands of illicit cultivation sites in operation at any one time. Although nearly half of all herbal cannabis consumed in the United Kingdom is of the sinsemilla type, some has clearly been imported and the significance of domestic production is difficult to estimate. In some countries, seeds and specific equipment for indoor cannabis cultivation (e.g. lights, rock wool, nutrient media and irrigation systems) can be bought from retail shops, but the recent trend has been for on-line sales through the Internet.

Although fibre-phenotype cannabis is easily cultivated, even in northern latitudes, the climate in most European countries is not suitable for the economic outdoor production of drug-phenotype cannabis. Domestic production of cannabis resin in Europe is almost entirely located in the Netherlands, where it is produced from herbal cannabis grown indoors. But even here it is a minor contributor to the overall cannabis economy.

Cannabis content of cigarettes

On a weight basis, the content of cannabis cigarettes examined in the United Kingdom and Ireland over the past twenty years has been remarkably constant (Figure 14). Thus, the typical reefer cigarette contains about 200 mg of herbal

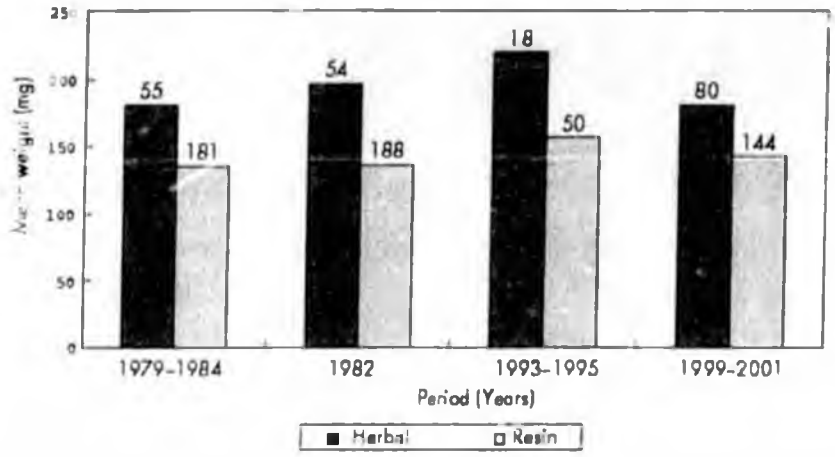


Figure 14: Mean herbal cannabis and cannabis resin content of reefer cigarettes examined in the Forensic Science Service (UK) over a twenty-year period. The sample size in each case is shown above the bar

cannabis or 150 mg of cannabis resin, equivalent to around 10 mg of THC (Humphreys and Joyce, 1982; Bal and Griffin, 2001). Similar findings were reported in Ireland by Buchanan and O'Connell (1998), where the mean herbal cannabis content of cigarettes was 260 mg (N = 179) and the mean resin content was 102 mg (N = 2 025). The absence of any decline in the amount of herbal cannabis or resin used may suggest that there has been no long-term increase in the THC content of the average cigarette. In other words, users have not felt a need to consume less herbal cannabis or resin in their cigarettes. The assertion by Ashton (House of Lords, 1998) that "... a typical 'joint' today may contain 60–150 milligrams or more of THC", suggests a potency of over 50%: a value far in excess of even the most extreme samples.

Street prices

In the absence of THC measurements, street prices of cannabis could provide indirect information on changes in the quality of cannabis, particularly if there is a price differential between different forms.

In the Netherlands (Trimbos, 2002) there has been a close correlation between the mean THC content of different products and the price (Figure 15). A correlation also occurs within samples of sinsemilla although factors other than the amount of active constituent, such as variety, may also be involved (Niesink et al., 2002).

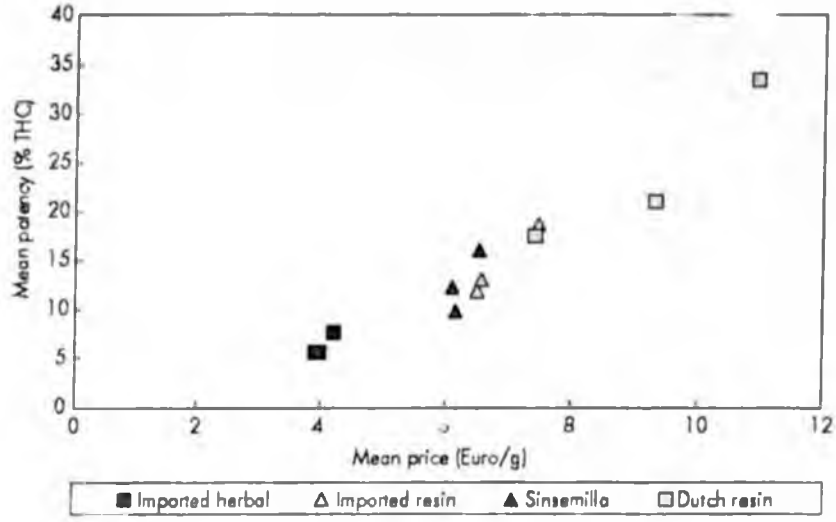
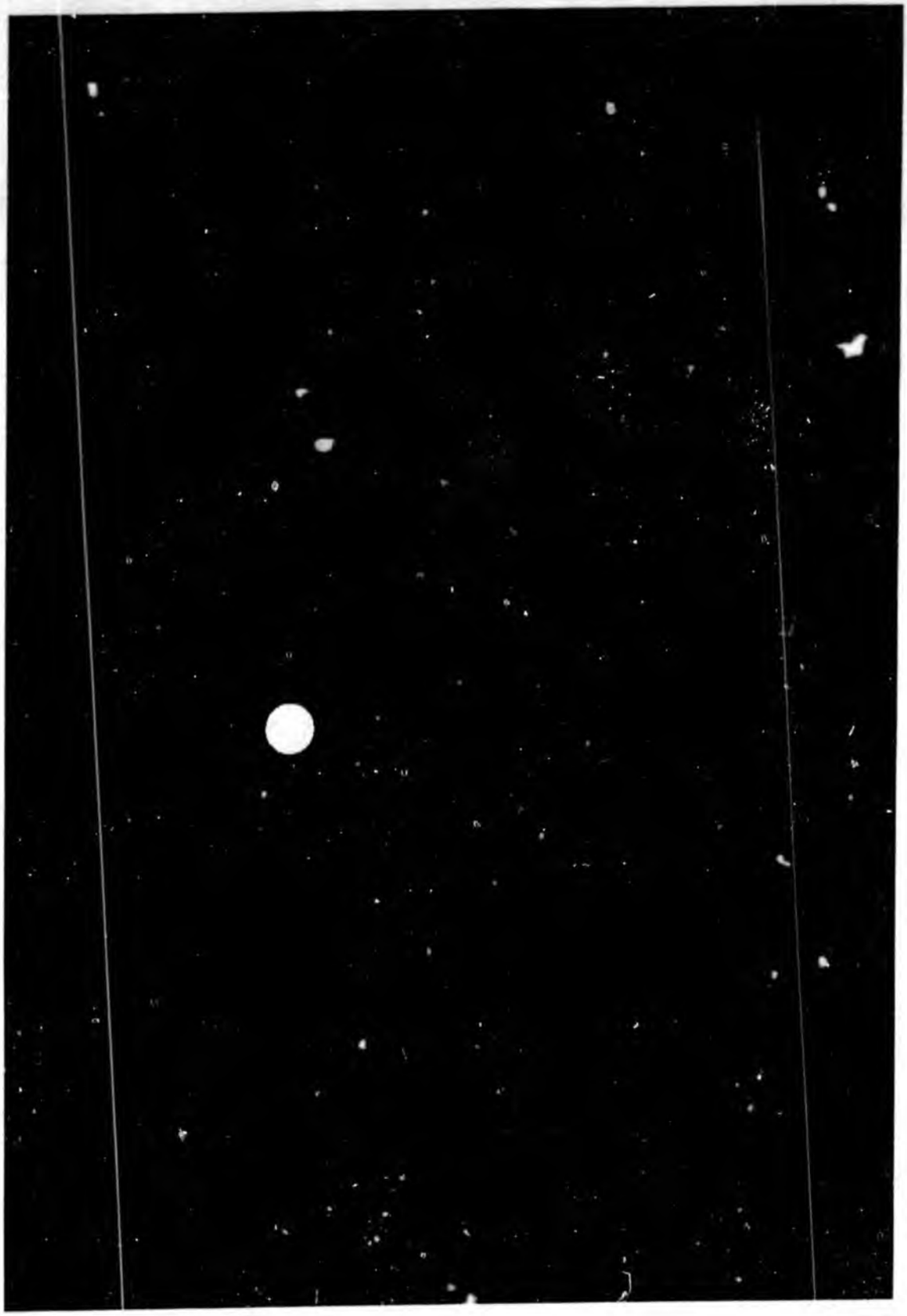


Figure 15: Correlation between price (EUR/g) and the mean THC content of various products in the Netherlands. Three sets of prices/THC levels are shown for each of the four products: they relate to measurements in winter 1999, 2001 and 2002 respectively.

In the United Kingdom, good quality sinsemilla sells for an average EUR 6-7/g, whereas imported cannabis and cannabis resin are mostly priced at an average of EUR 4-5/g (Atha, 2003). This differential (i.e. a factor of approximately 1.5) is consistent with the relative THC concentrations in recent years as shown in Figure 9. In Germany, resin is sold for EUR 4-9/g and herbal cannabis for EUR 5-11/g. In the Czech Republic, sinsemilla costs EUR 3 or more per gram, but other herbal cannabis is EUR 0.6-1/g. By contrast, in Portugal, resin sells for an average EUR 2.49/g whereas herbal cannabis, a lower potency product, sells for EUR 4/g. In Luxembourg, both herbal cannabis and cannabis resin sell for around EUR 8/g.

There was some inconsistency in the estimates of the price of cannabis products at street level between data collected specifically for the purposes of this study (questionnaire) and those provided by Reitox national focal points as part of the EMCDDA ongoing monitoring activities. This discrepancy is perhaps not surprising given the complexities of producing reliable price information on the illicit drug market. Nonetheless, it does suggest the need for more consideration of how methods can be improved to provide a better picture of this important facet of illicit drug use.



Chapter 5: Trends in cannabis potency in other countries

Chapter 5: Trends in cannabis potency in other countries

USA

Data on the THC content of cannabis products in the USA have been collected by ElSohly et al. (1984, 2000) for many years as part of the University of Mississippi Potency Monitoring Project. Samples were submitted by law enforcement agencies and it has to be assumed that they were representative of the market. Mean THC values are shown in Figure 16 for normal herbal cannabis, sinsemilla and resin. The anomalously high value for resin in 1997 (19.24%) has been excluded; it was based on only five values and is over nine standard deviations above the mean potency for the period 1980–1996. Although there has been an increase in the potency of herbal cannabis over the twenty-five-year period, cannabis resin (and hash oil) showed no long-term trends since 1980 when data were first collected. Although the potency of sinsemilla showed a clear upward trend in the final three years of the study, no such trend was obvious when the longer period of 1980–1995 is examined, particularly in view of the wide variations in potency that occurred from year to year (ElSohly et al., 2000). The THC content of herbal cannabis increased from around 1% before 1980 to around 4% in 1997. This increase, when seen in the European context, is deceptive. Before 1980, all mean herbal cannabis THC levels in the ElSohly study were less than 2.4%. By contrast, and as shown in Figure 10, comparable levels at that time in the United Kingdom were twice as great. In other words, it must be assumed that the quality of herbal cannabis consumed in the USA more than twenty years ago was unusually poor, but that in recent years it has risen to levels typical of Europe. So even the modest increase found by ElSohly et al. (2000) may be less significant than it seems. A recent analysis of cannabis seized in Florida in 2002 (Newell, 2003) showed amounts of THC found in samples ranging from 1.41% to 12.62%; the average THC content was 6.20%, which is almost identical to the 2002 value reported by the University of Mississippi Potency Monitoring Project.

However, there are major differences in the market between the USA and Europe. In most European countries, cannabis resin, originating almost entirely from North Africa, is more commonly used than herbal cannabis. Herbal cannabis imported into Europe originates from the Caribbean, Africa and the Far East. In the USA, normal forms of herbal cannabis are either grown domestically or imported from Mexico, with Canada a major supplier of sinsemilla (DEA, 2002). By contrast, cannabis resin is uncommon in the USA. Thus in the latter years of the studies by ElSohly et al. (2000), cannabis resin comprised less than 1% of samples.

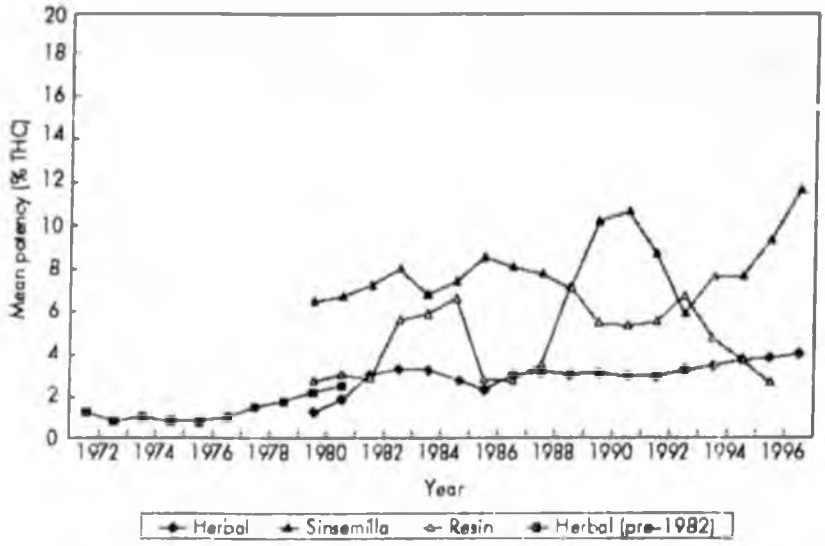


Figure 16: Mean potency (% THC) of cannabis products examined at the University of Mississippi, USA (1972–1997).

The effective THC level in the USA

The effective potency of cannabis products was defined in the section *The effective THC level in Europe* (Chapter 4). In the USA for the period 1980–1997, the approximate mean respective shares of the material examined were: herbal cannabis, 85%; sinsemilla, 5%; resin, 3%; other, 7%, where 'other' includes minor products such as 'ditchweed' (poor quality, locally grown cannabis), hash oil and Thai sticks. Figure 17 shows the effective potency experienced by users in the USA using data published by ElSohly et al. (2000) for the mean THC content of all samples examined. Although there is a slight upward trend over the period 1980–1997, the effective potency of the aggregated cannabis products has been low by European standards, largely as a result of the low proportion of sinsemilla consumed.

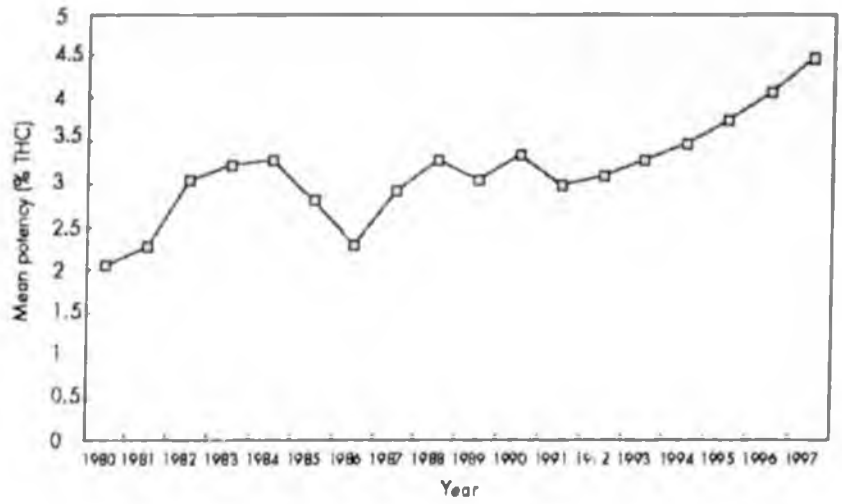


Figure 17: Effective potency (% THC) of cannabis products in the USA.

New Zealand and Australia

Poulsen and Sutherland (2000) reported the potency of cannabis products from 1976 to 1996 in New Zealand. In the earlier years of this study, the material examined was mainly imported cannabis oil and resin, and both local and imported cannabis plant material seized by the police. In later years, little imported material was seized: cannabis plants were grown locally, cannabis oil was manufactured locally and cannabis resin was rarely seized. Cannabis leaf contained on average 1 % THC and the female flowering heads contained on average 3.5% THC. The average potency of cannabis oil fell from a peak of 34 % THC in 1985 to 13% THC in 1995. Over the twenty-year period, the average potency of the cannabis products available to the user did not increase. In Australia, Hall and Swift (2000) found only a modest increase in the THC content of cannabis in recent years and suggested that the increase in cannabis-related problems among young Australians was more likely to be due to earlier and heavier use. The absence of any clear time trend in cannabis potency in New Zealand and Australia is similar to the situation reported above for most European countries, but despite the focus on domestic production in New Zealand in recent years, the THC levels are low by European standards.

Chapter 6: Identification of information gaps, priorities for future research and recommendations

Chapter 6: Identification of information gaps, priorities for future research and recommendations

There are a number of areas that require attention at national level if information on cannabis potency is to be collected, analysed and made available in a systematic way including: nomenclature, relative consumption of cannabis products, extent of domestic indoor cultivation, street prices, laboratory analysis, data collection and finally data presentation at the European level.

Nomenclature of cannabis products

At present, a variety of different names are used to describe similar materials. It is suggested that *herbal cannabis* (i.e. not 'marijuana', 'leaf', 'weed', 'grass', 'flowering tops', 'buds', 'drug-phenotype', etc.) should be used to refer to the fresh or (more commonly) dried leaves and flowering tops, but excluding stalk, roots and seeds of *Cannabis sativa*. The term *hemp* should be reserved, if necessary, for cannabis of the fibre-phenotype. When a distinction is required between imported and domestically grown herbal cannabis, then the former should be described as *imported herbal cannabis* and not 'seeded cannabis'. Since cannabis cultivated by intensive indoor methods invariably derives from unfertilised female plants, then this material should be called *sinsemilla* rather than 'unseeded', 'nederwiet', 'skunk', etc. *Cannabis resin* or just *resin* (i.e. imported products) should be used in preference to 'hashish' or 'hash', but when locally produced resin is involved, for example in the case of the Netherlands, *'Dutch' resin* may be more acceptable than 'nederhasj'. *Hash oil*, the term in most common use, and *cannabis oil* are both acceptable for solvent extracts of herbal cannabis or cannabis resin. Given that it is necessary to build a consensus of concerned authorities for the adoption of a common nomenclature, it may be desirable for the EMCDDA to work towards this objective within its work to harmonise definitions and produce standardised data on the European drug situation.

Relative consumption of cannabis products

In most countries, estimates of the relative consumption of different cannabis products are based largely on seizure data. Such data have limits and may not directly reflect drug availability as experienced by drug users or the relative

market share of different cannabis products. Given the importance of this information in estimating the potency of the cannabis being consumed in Europe there is an urgent need to improve data quality in this area. One possible way forward is to complement statistics from drug seizures with data from user surveys carried out at the retail level. Such information is necessary if it is required to track the health impact of cannabis potency, since this is more a function of product type (particularly sinsemilla versus cannabis resin) than other factors. Currently, such activities are limited, but methodologically feasible, and could be accomplished for relatively modest resource investment. Both focused surveys of cannabis users and general population survey approaches could prove useful.

Extent of domestic indoor cultivation

Following on from the previous recommendation, it is important to understand better the extent of domestic cannabis production, the different types of production methods used, as well as the use of domestically produced cannabis products compared to imported products and how this varies within Europe and over time. Experience in the Netherlands suggests that the availability of cannabis produced locally, with more sophisticated techniques and higher yielding varieties, has a major impact on potency, even within a single cannabis product. Even when herbal production is considered, it is important to note the relative potency of the products being produced, changes in overall potency over time and the proportion of the product that is of exceedingly high potency. In wider Europe, it is important to remember that home-produced cannabis may not always benefit from hydroponics or other sophisticated growing techniques. These factors all need to be considered in any comprehensive analysis of the cannabis market in Europe.

Content of cannabis cigarettes

Few countries have published data on the herbal cannabis or cannabis resin content of cigarettes. This information would be useful as a proxy measure for potency as well as a means of tracking methods of consumption (i.e. use with or without tobacco).

Pharmacology

Most pharmacological studies on the effects of cannabis potency have been carried out in North America. Because of major differences in overall potency levels and methods of consumption (i.e. use with or without tobacco) between North America and Europe, it would be useful to conduct similar studies in Europe, reflecting European consumption norms. As well as covering the relationship between smoking behaviour and potency, such studies should also include the relationship between potency and blood THC/metabolite levels. Monitoring over time the methods and practices used by cannabis consumers may also be important. For example, some anecdotal reports exist of a move towards the use of water pipes in some countries, and new smoking technologies have been advertised in the media aimed at cannabis smokers.

Street prices

In Europe, information is collected routinely by the EMCDDA on drug prices at retail level. However, as discussed earlier, the quality and comparability of this information needs to be reviewed and standard methods for collection and reporting developed. Important here is developing classification and reporting standards that distinguish between different cannabis products. Data from the Netherlands suggest a close relationship between potency and price.
It is necessary to explore this issue in other countries and in the context of consumer preferences and other drug supply side information.

Laboratory analysis

The data examined in this survey strongly suggest that there could be problems in the accurate analysis of THC. In the first instance, this suggests it is necessary to organise quality assurance trials to determine both precision and accuracy of laboratory measurements in all member states. From this, recommendations on best practice could be developed. Possible partners in this endeavour would be the European Network of Forensic Science Institutes (ENFSI) and the United Nations Office of Drugs and Crime (UNODC).

Statistical aspects of data collectio

When compiling data, many laboratories calculate simple mean values (often called averages: the sum of all values divided by the number of values). In a few cases, weighted means may be calculated (see, for example, ElSohly et al., 1984). The weighted mean takes account of the fact that not all samples may be of equal size. When considering seized material for example, the weighted mean is effectively the mean that would be found if all seizures were to be pooled and thoroughly mixed. Furthermore, few authors consider whether the distribution of potency is normally distributed or if other measures of central tendency such as the median or mode would be better. It is recommended that data submitted to the EMCDDA should always indicate details about the sampling strategy, sample size, the mean, and where possible more detailed descriptive statistical information (e.g. mode and median values, standard deviation, treatment of outliers).

Other policy issues

Statements in the popular media that the potency of cannabis has increased by ten times or more in recent decades are not supported by the data from either the USA or Europe. As discussed in the body of this report, systematic data are not available in Europe on long-term trends and analytical and methodological issues complicate the interpretation of the information that is available. Data are stronger for medium and short-term trends where no major differences are apparent in Europe, although some modest increases are found in some countries. The greatest long-term changes in potency appear to have occurred in the USA. It should be noted here that before 1980 herbal cannabis potency in the USA was, according to the available data, very low by European standards. A caveat here is that there is some question to how far the historical data provide a true representation of the situation. More recently, potency data suggest a convergence with the European situation. For the reasons discussed earlier in this report, caution should be made in drawing direct comparisons between Europe and the USA on this issue.

It should be noted that the modest changes that have occurred in THC levels in Europe appear largely confined to the relatively recent appearance on the market of intensively cultivated cannabis. Herbal cannabis is less commonly consumed than cannabis resin in most European countries, although this may be beginning to change. It should also be made clear that the THC content of cannabis products

is extremely variable and there have always been some samples that have had a high potency. Nonetheless, some hydroponically grown cannabis appears to be consistently of high potency. This product appears to have at present only a relatively small market share in most countries. A note of caution is required because the available data makes it difficult to judge with confidence the actual market share of high potency cannabis or to monitor trends. The issues raised by an increase or potential increase in the availability of high-potency cannabis may make it prudent to consider whether specific targeted demand or supply side activities are needed.

In considering individual dose exposure to cannabis and the relationship to health and other problems, it must be noted that cannabis potency is only one factor and possibly of limited importance. Hall et al. (2001) note that individual exposure to cannabis may have risen but this is more likely to be influenced by earlier initiation and more frequent and intensive patterns of use rather than the potency of the cannabis used in any one exposure. An evaluation carried out by the 'Co-ordination Centre Assessment and Monitoring New Drugs' (CAM) in the Netherlands concluded that higher-potency cannabis products did not pose any additional risk than those present for cannabis products as a whole, either to the individual, to society, to public order or criminality (W. Best, personal communication, 2004). In this respect, it is noted that cannabis with a potency of 18 % is available as a prescription medicine in the Netherlands. Even if some potency increases in illicit cannabis have occurred, the absence of direct evidence of any clear additional health risk should be noted. However, overall, the evidence base in this area is weak. If acute cannabis problems are considered, such as panic attacks, a short-term dose-related impact is plausible. The relationship of cannabis consumption to the development of psychiatric disorders is also poorly understood, and again it would be prudent to consider if high-potency cannabis might be an issue here. In summary, the extent to which high-potency cannabis increases the short and long-term dose to which individuals are exposed remains unclear, as does the evidence of any clear and direct additional health risks. This remains, therefore, a critically important area for future research studies as this information is a pre-requisite to understanding the potential public health impact of high-potency cannabis.

Glossary (1)

BC-bud: *Sinsemilla* produced in Canada (BC = British Columbia)

Bracts: Structures situated at the base of the flowers of *Cannabis sativa*, which may partly surround a developing seed and which are rich in *glandular trichomes*

Buds: Flowering tops of female *Cannabis sativa*

Cannabidiol: One of several *cannabinoids* in *Cannabis sativa*

Cannabinoid: One of a group of compounds found only in *Cannabis sativa* including *cannabidiol, cannabinol and tetrahydrocannabinol*

Cannabinol: One of several *cannabinoids* in *Cannabis sativa*

Cannabis oil: See *hash oil*

Cannabis resin: Material produced by mechanically separating the resinous parts of the *flowering tops* of *Cannabis sativa* from other vegetable matter

***Cannabis sativa* L:** Generally regarded as the only species in the genus *Cannabis* and sole source of *cannabinoids*. Classified by Linneaus in the eighteenth century

Ditchweed: Low quality *herbal cannabis* growing wild in North America

Dronabinol: Synthetic preparation of *tetrahydrocannabinol* with medicinal uses

Drug-phenotype: Variety of *Cannabis sativa* where the ratio [(% *tetrahydrocannabinol* + % *cannabinol*)/% *cannabidiol*] is greater than 1.0

Dutch resin: Light green or brown *Cannabis resin* produced mostly in the Netherlands from locally grown *herbal cannabis* using sieves or other separation methods

Fibre-phenotype: Variety of *Cannabis sativa* where the ratio [(% *tetrahydrocannabinol* + % *cannabinol*)/% *cannabidiol*] is less than 1.0

Flowering tops: *Herbal cannabis* excluding leaf. May be used to mean *sinsemilla* or seeded material

(1) Italicised words and terms are themselves defined.

Glandular trichomes: Microscopic features used to identify *herbal cannabis* or *cannabis resin*. They produce an exudate containing *cannabinoids* and are located mostly around the *flowering tops* of female plants of *Cannabis sativa*

Grass: *Herbal cannabis*

Hash oil: A dark green or black tar-like material made by solvent extraction of either *cannabis resin* or *herbal cannabis*. May contain 30-50% *tetrahydrocannabinol*

Hashish: *Cannabis resin* (North America and elsewhere)

Hemp: *Herbal cannabis* with low *potency* used for fibre production

Herbal cannabis: Normally restricted to the fresh or (more commonly) dried leaves and *flowering tops*, but excluding stalk, roots and seeds of *Cannabis sativa*

Imported herb: *Herbal cannabis* from non-European, often tropical, sources and generally found as a mixture of *leaf, flowering tops* and seeds in compressed blocks

Isolator (also ice-o-lator): Device consisting of a mesh bag used to separate resinous particles from *herbal cannabis* in the production of *nederhasj*

Joint: A cannabis cigarette (also spliff, reefer etc.)

Leaf: *Herbal cannabis* that may or may not contain *flowering tops*

Marijuana: *Herbal cannabis* (North America)

Nederhasj: See *Dutch resin*

Nederwiet: *Sinsemilla* produced in the Netherlands

Potency: The *tetrahydrocannabinol* content. Used in preference to *purity*

Purity: The proportion of active constituent in a product, but less suitable for cannabis products where *potency* is preferred

Sinsemilla: 'Without seed' (Spanish). The highest *potency herbal cannabis* comprising the *flowering tops* of unfertilised female plants of *Cannabis sativa* produced in open cultivation or, nowadays, by indoor methods

Skuff: Alternative term for *nederhasj*

Skunk: *Herbal cannabis* with a characteristic odour that has been typically grown by indoor intensive cultivation and may have a high *potency*

Spacecake: Cake made using *herbal cannabis* most commonly found in the Netherlands

Tetrahydrocannabinol (THC): The principal *cannabinoid* with sought-after psychopharmacological effects

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"Psychological and social sequelae of cannabis and other illicit drug use by young people: a systematic review of longitudinal, general population studies"

John Macleod, et al.
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Psychological and social sequelae of cannabis and other illicit drug use by young people: a systematic review of longitudinal, general population studies

John Macleod, Rachel Oakes, Alex Copello, Ilana Crome, Matthias Egger, Mathew Hickman, Thomas Oppenkowski, Helen Stokes-Lampard, George Davey Smith

Summary

Background Use of illicit drugs, particularly cannabis, by young people is widespread and is associated with several types of psychological and social harm. These relations might not be causal. Causal relations would suggest that recreational drug use is a substantial public health problem. Non-causal relations would suggest that harm-reduction policy based on prevention of drug use is unlikely to produce improvements in public health. Cross-sectional evidence cannot clarify questions of causality; longitudinal or interventional evidence is needed. Past reviews have generally been non-systematic, have often included cross-sectional data, and have underappreciated the extent of methodological problems associated with interpretation.

Methods We did a systematic review of general population longitudinal studies reporting associations between illicit drug use by young people and psychosocial harm.

Findings We identified 48 relevant studies, of which 16 were of higher quality and provided the most robust evidence. Fairly consistent associations were noted between cannabis use and both lower educational attainment and increased reported use of other illicit drugs. Less consistent associations were noted between cannabis use and both psychological health problems and problematic behaviour. All these associations seemed to be explicable in terms of non-causal mechanisms.

Interpretation Available evidence does not strongly support an important causal relation between cannabis use by young people and psychosocial harm, but cannot exclude the possibility that such a relation exists. The lack of evidence of robust causal relations prevents the attribution of public health detriments to illicit drug use. In view of the extent of illicit drug use, better evidence is needed.

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See Commentary page 1568

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Introduction

The use of illicit drugs amongst young people seems to be widespread and may be increasing.[1] Cannabis is the most widely used illicit substance, although use of psychostimulants also appears quite common; use of opiates seems less common. Most of these drug users do not access drug treatment services and the consequences of their drug use are unclear. Physical health problems aside, there are concerns that illicit drug use, particularly cannabis use, could cause psychological and social problems.[2] Cannabis use has been shown to be associated with psychological health problems, use of other illegal drugs, reduced educational attainment, and antisocial behaviour.[3] The causal basis of these associations has not been established. If associations are non-causal, harm-reduction policies based on the prevention of drug use are likely to be ineffective. Conversely, a causal association could mean that "recreational" illicit drug use, in view of its apparent extent, represents an important, and substantially hidden, public health problem.

Causal explanations for associations between drug use and psychosocial harm compete with three alternative explanations: reverse causation, where drug use is a consequence, rather than a cause, of psychosocial problems; bias, where the association is an artifact of study methodology; and confounding, when drug use is associated with other factors that predispose to psychosocial problems.

A causal relation between drug use and psychosocial harm could plausibly be mediated by two principal mechanisms: directly, through neurophysiological pathways, or indirectly, through involvement in the criminal culture and commerce associated with use of an illegal substance.[1,4] Past reviews of the relevant evidence have often been non-systematic and have used restricted search strategies. Much evidence is cross-sectional and derives from highly selected samples. Such evidence is limited as a basis for inferring true causal relations and their possible relevance to public health. We therefore undertook a systematic review of general population, longitudinal studies relating illicit drug use by young people to subsequent psychological and social harm.

Methods

Search strategy and selection criteria

We searched the general electronic databases MEDLINE, EMBASE, CINAHL, PsycLIT, and Web of Science, and the specialist databases of the Lindesmith Center, DrugScope, US National Institute on Drug Abuse and Substance Abuse and Mental Health Services Administration, and Addiction Abstracts, with an agreed battery of search terms (available from the authors) in July, 2000. This search was updated in July, 2001, and again in June, 2003. Addiction Abstracts was hand-searched for the period not covered by the electronic database. Key individuals in the specialty of addictions

	Participants and setting*	Drug exposure measures†	Other measures‡	Main findings§
National Longitudinal Study on Adolescent Health[9,10]	National representative sample of 7–12th grade students sampled from 80 high schools and their "feeder" schools in the USA. Recruited in 1995. 79% of schools selected agreed to participate. 75% of eligible students in these schools (n=90118) completed a self completion questionnaire. Random sub sample of these selected for follow up home interview in 1996. 79·5% of these (12118) contacted	Self-reported frequency of cannabis and other drug use via standard instrument. Categorical scale derived from these data	Cigarette smoking, alcohol use, sex, family structure, parent education, age, ethnic origin	Cannabis use associated with violent behaviour (tobacco and alcohol use show similar associations)
The Boston Schools Project[8,9]	1925 students from three public schools in Boston, USA, recruited aged 14–15 years in 1969 and studied yearly until 1973. Surveyed again in 1981. 79% (1521) had complete follow up	Self-reported frequency of cannabis and other drug use via standard instrument. Categorical scale derived from these data	Socialisation, grade point average, self-reported physical and psychological health problems	Adolescent cannabis use associated with adult drug use. Little apparent association between use and psychological health or work related factors
The Children in the Community Project[6,11,12]	Population-based sample of families in New York State, USA. 976 participants aged 5–10 years at recruitment in 1975. 709 followed up until age 27 years	Self-reported frequency of cannabis and other drug use via standard instrument. Categorical scale derived from these data	Personality factors, family factors, parental drug use, sibling factors, peer factors, licit drug use; all self-reported via standard instruments	Little apparent association between cannabis use and either depression or anxiety. Association between cannabis use and antisocial personality although lower reported delinquency. Lower frequency of cannabis use associated with better parenting, higher frequency with unemployment and lone parenthood
The Central Harlem Study[6,13]	Population based sample of black adolescents recruited in 1968–69 from Central Harlem, New York City, USA. Initial sample of 688 aged 12–17 years. 392 (59%) followed up till 1990	Cumulative use index based on self report of lifetime use (more than once) of nine classes of substance (marijuana, LSD, cocaine, heroin, methadone, "uppers", "downers", inhalants, alcohol)	Lifestyle and health behaviours, social ties and networks, adult social attainment	Cannabis and cocaine use associated with greater reported psychological problems. Associations with opiate use inconsistent
The Christchurch Health and Development Study[6,14]	Birth cohort of 1265 children born in Christchurch, New Zealand, during mid 1977. Reassessed regularly until age 21 years. 80% had complete follow-up	Self-reported frequency of cannabis use via standard instrument. Categorical scale derived from these data	Licit drug use, family background and parental factors, childhood behaviour, early problem behaviour, early psychological problems, educational history, cognitive ability, peer affiliations, antisocial behaviour, social environment, history of sexual abuse; generally self-reported, some use of official records	Cannabis use associated with lower educational attainment, greater use of other illicit drugs, poorer psychological health, and greater involvement in antisocial behaviour
Dunedin Multidisciplinary Health and Development Study[6,15]	Birth cohort of all children born in Dunedin, New Zealand between April 1, 1972, and March 31, 1973, who were still resident locally when the study began in 1975. 1649 children born during study recruitment period, 1139 of these still resident locally at age 3 years, 1037 of these successfully recruited to study (91%). Reassessed regularly until age 26 years. 96% of survivors had complete follow up	Self-reported frequency of cannabis use via standard instrument. Categorical scale derived from these data	Perinatal assessment, early physical health and development, physical and psychological health in childhood, emotional and educational development, social and family environment, cognitive abilities, adolescent physical and psychological health, licit drug use, antisocial behaviour; generally self-reported, some use of official records	Cannabis use associated with greater reported psychological problems. Similar associations with tobacco and alcohol use
East Harlem Study[16]	1332 African American and Puerto Rican adolescents (mean age 14 years at recruitment) from 11 schools in East Harlem, New York City in 1990. 66% followed up 5 years later	Self-reported frequency of cannabis and other drug use via standard instrument. Categorical scale derived from these data	Adolescent personality attributes, family relationship characteristics, peer factors, residential area, acculturation measures	Cannabis use associated with later licit and illicit drug problems and with problem behaviours in participant, siblings and peers
The LA Schools Study[6,17]	1634 students in grades 7, 8, and 9 recruited from 11 schools in Los Angeles, USA in 1976. Assessed regularly over the subsequent 21 years. 477 (30%) had complete follow-up	Self-reported frequency of cannabis and other drug use via standard instrument. Categorical scale derived from these data	Social conformity, family formation, deviant behaviour, sexual behaviour, educational pursuits, livelihood pursuits, mental health including depression, social integration and conformity, relationship quality, divorce,	Drug use (generally judged as a latent variable dominated by cannabis use) associated with lower educational commitment. Little apparent association with psychological problems other than increased reported symptoms with cocaine use.

(continues next page)

	Participants and setting*	Drug exposure measures†	Other measures‡	Main findings§
			sensation seeking, parental support, academic aspiration, parental drug problems, psychological distress	Drug use associated with greater involvement in drug crime, lower involvement in violent crime, and higher income in young adulthood
New York Schools Study[20,29]	1636 adolescents enrolled in New York State public secondary schools in 1971. Aged 15 years at recruitment. Interviewed again in 1980, 1984, and 1990. 1160 (71%) had complete follow up	Self-reported frequency of cannabis and other drug use via standard instrument. Categorical scale derived from these data	Income, marital status, education level, ethnic origin, peer activity, employment history, self-assessed health	Initiation of drug use usually follows an orderly sequence from tobacco and alcohol, through cannabis to other drugs. Drug use associated with higher income in early adulthood, lower income in later adulthood
National Collaborative Perinatal Project (NCPP)[30]	Sub-sample of NCPP cohort (birth cohort followed till age 7 years); African-American participants in Philadelphia contacted again at age 24 years and again at 26 years. About 70% (380) of target sub-sample had complete follow-up	Self-reported frequency of cannabis and other drug use via standard instrument. Categorical scale derived from these data	Perinatal and early life environmental factors, early health and development, academic performance, school behaviour and adjustment (from school records), personality, social integration, reported illness symptoms, reported antisocial behaviour and sexual behaviour	Cannabis use associated with antisocial personality and reports of criminal offences
National Longitudinal Survey of Youth[31,32]	National representative sample of 12686 young people (aged 14–21 years) from the non-institutionalised civilian segment of the US population, recruited in 1979. Ongoing regular assessment with about 90% retention	Self-reported frequency of cannabis and other drug use via standard instrument. Categorical scale derived from these data (questions about drug use were added in 1984)	Alcohol use, educational attainment, ethnic origin, family background, parental factors, cognitive function, religion, employment history, social position	Cannabis and cocaine use associated with problematic interpersonal relationships. No apparent association with income
Pittsburgh Youth Study[33]	School based sample of 850 boys from public schools in Pittsburgh. Mean age 13.25 years at recruitment, followed up until mean age 18·5 years.	Self-reported frequency of cannabis and other drug use via standard instrument. Categorical scale derived from these data. Parent/teacher reports used to corroborate reports in some instances	Antisocial behaviour and conduct disorders, psychological symptoms, relations with parents, neighbourhood factors, sexual behaviour, educational attainment	Cannabis use associated with violent behaviour
Project Alert[34,35]	4500 adolescents from 30 junior high and middle schools in California and Oregon participating in evaluation of a preventive intervention. Mean age of participants at baseline 13 years, followed up for 4 years	Self-reported frequency of cannabis and other drug use via standard instrument. Categorical scale derived from these data. Salivary cotinine used to validate reported tobacco use (suggested to participants that sample could also be tested for cannabis—it was not, but this suggestion may have influenced validity of reported cannabis use)	Family and parental factors, social position and environment, employment history, educational history, anti-social behaviour, peer factors, religiosity	Cannabis use associated with lower educational attainment. No association with violent behaviour
South Eastern Public schools study[36]	Four longitudinal surveys within the US SE public schools. Participants recruited in grades 6–8 in 1985–87 and followed up till 1993–94. 1392 subjects (55·1%) had complete follow up	Indicator variable derived from self reported age of initiation of use of cannabis and other illicit drugs	Ethnicity, parental factors, educational attainment from combination of self-report and official records	Cannabis use associated with lower educational attainment. Similar but weaker association with tobacco use, no association with alcohol use
Swedish Military Conscripts study[37–39]	Different subgroups of 50 465 Swedish men age 18–20 years conscripted for national military service in 1969–70. Follow up in official records to 1986, recently extended to 1996	Self-reported frequency of cannabis and other drug use via standard instrument. Categorical scale derived from these data (90% of sample provided usable data)	Social position, licit drug use, parental and family factors, behavioural factors, psychological factors	Cannabis use associated with later injection drug use (association between use of other illicit drugs and injection much stronger). Cannabis use associated with incidence of clinical schizophrenia. Cannabis use not associated with increased mortality by middle adulthood after adjustment—specific mortality from suicide not reported
Woodlawn study[40,41]	1242 African American 1st grade students starting school in 1966–76 in a disadvantaged inner-city neighbourhood of Chicago. Follow up assessments in 1976–77 and 1992–94. (84% of original cohort located, 96% of those interviewed)	Self-reported frequency of cannabis and other drug use via standard instrument. Categorical scale derived from these data	Licit drug use, family factors, parental factors, behavioural development, psychological problems, social integration, sexual behaviour, anti-social behaviour, educational history, employment history religiosity	Cannabis use not associated with reported suicidal thoughts or attempts

*In some instances data on completeness of follow-up not reported. †"Standard instrument" means some details of validation given. ‡Main groups of other measures as reported, for complete list see individual publications. §Main findings related to psychosocial outcomes reported as of June 2003, only prospective associations noted (ie, those where exposure assessment preceded outcome assessment).

Table 1: **Description of studies reviewed in detail**

(details available on request) were asked to identify evidence unlikely to be found through the other sources. Both published and unpublished evidence, along with that not published in English (which was translated), was judged.

We included all prospective studies based in the general population that measured use of any illicit drug by individuals aged 25 years or younger at the time of use and related these data to any measure of psychological or social harm assessed subsequently.

Quality assessment

Quality assessment was undertaken after initial searches in July, 2000. Two reviewers assessed methodological quality of studies independently against set criteria (sample size and representativeness, age at recruitment, duration and completeness of follow-up, apparent validity and reliability of exposure and outcome measures, and degree of adjustment for potential confounding factors). Formal quantitative quality scoring was not used, since it can be misleading and give a false sense of objectivity.[9]

Reviewers made an independent overall assessment of study quality based on the above criteria, and assigned studies to categories of higher quality, uncertain quality, or lower quality. Studies were judged to be of higher quality if the probability of selection bias seemed low, exposure to drugs was assessed with a validated instrument, follow-up was over several years, and analyses were adjusted for important confounding factors. Validity and relevance of psychosocial outcome measurement was also considered. Initial agreement between reviewers was high (weighted κ>0·9). Reviewers then discussed, and agreed, which studies of higher or uncertain quality warranted more detailed consideration. Corresponding authors on papers deriving from these studies were contacted and asked to supply any relevant unpublished data.

We assessed the potential for quantitative synthesis of study results against criteria for combinability. Results were also summarised descriptively.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data synthesis, data interpretation, or writing of the report

Results

We located more than 200 publications deriving from 48 longitudinal studies reporting associations between drug use by young people and psychological or social outcomes. Five studies were not published in English. All studies were observational. All had published results in peer-reviewed journals; however, some additional publications in books and unpublished papers were identified through personal contact. Many studies used composite measures of illicit drug use, making it impossible to infer effects of specific drugs. Most drug-specific results related to use of cannabis. Many studies reported substantial losses to follow-up and made either no, or little, attempt to adjust estimates for possible confounding factors. 16 studies were classified as of higher methodological quality (table 1). The remaining 32 studies are summarised, in terms of their ostensible findings and with a brief methodological critique, in table 2. All studies were judged, but appraisal was focused on evidence from the 16 in table 1.

Recruitment strategies, and thus the precise relation of the study population to the general population, varied substantially (tables 1 and 2). In all studies, exposure to illicit drugs was measured through uncorroborated self-report. Although some measures were similar across studies, no two studies measured either illicit drug exposure or psychosocial outcome in the same way. Additionally, potential confounding factors were inconsistently assessed across studies. Because of these considerations, we felt that quantitative synthesis (meta-analysis) was likely to be misleading and did not attempt to do this.[10]

We report our principal findings on relations between cannabis use and educational attainment, use of other drugs, psychological health, antisocial behaviour, and other social problems. Illustrative crude and adjusted effect estimates in relation to these outcomes are described in table 3. Findings on relations between use of other illicit drugs and psychosocial problems are also summarised. Key publications are cited; a full list of publications is available on request.

Cannabis use was consistently associated with reduced educational attainment. Most relevant studies indexed this outcome through objective and apparently valid measures. The strength and magnitude of the association varied. Adjustment of estimates for potential confounding factors generally led to their attenuation, which was often substantial.

Cannabis use was consistently associated with use of other drugs. In all but one relevant study, other drug use was indexed by uncorroborated self-report (in one study, use of injected drugs was corroborated by inspection of injection sites).[11] The strength and magnitude of these associations varied, although in one study, both were substantial.[11] In this study, as with most studies, the outcome reported was other drug use, rather than drug problems. Adjustment of estimates for potential confounding factors generally led to their attenuation.

Cannabis use was inconsistently associated with psychological problems. Some studies found no association, although others reported associations between increased use and increased problems. Within these latter studies, patterns of association with specific psychological problems were inconsistent. In most studies, psychological problems were indexed through self-report of symptoms, some assessed according to standard diagnostic criteria. The outcome was clinical mental illness (schizophrenia) in only one study.[16] This report also mentioned a crude association between cannabis use and mortality from suicide, but did not report actual estimates.[16] A crude association with all-cause mortality disappeared on adjustment for confounding factors. Adjustment of other estimates of increased psychological problems for potential confounding factors generally led to their attenuation, which was often substantial.

Cannabis use was inconsistently associated with antisocial or otherwise problematic behaviour. In most studies these outcomes were indexed through uncorroborated self-report. In some studies corroboration was sought from other sources. In studies that did report associations between greater use and behavioural problems, adjustment of estimates for potential confounding factors generally led to their attenuation, often substantially so.

Evidence of effect modification according to sex and ethnic origin (where these were reported separately) was inconsistent across studies. Cannabis use at a younger age was consistently associated with greater subsequent problems.

Two studies reported associations between use of cocaine and opiates and subsequent psychological

	Participants and setting	Main relevant findings*	Comments*
Studies reporting outcomes related to general drug exposure			
Sadava 1973, Canada[42]	College "freshmen"	Low expectations of goal attainment and more "pro-drug" attitudes associated with drug problems	Probable selection bias, limited adjustment for confounding, significance of outcome measures unclear
Annis 1975, Canada[43]	High school students	Use of both licit and illicit drugs positively associated with school dropout from official records	No adjustment for confounding
Benson 1984 and 1985, Sweden[44,45]	Male military conscripts	Drug use associated with higher rates of criminality, health problems and mortality as ascertained from official records	Crude exposure measurement and no adjustment for confounding
Friedman 1987, USA[46]	Volunteer high school students reporting drug use	Drug use and self-reported psychological distress higher amongst this sample than in a reference cohort	Probable selection bias, little adjustment for confounding, arguably a case control study
Choquet 1988, France[47]	High school students	Drug use associated with higher self-reported health problems and use of health services	No adjustment for confounding in analyses reported
Farrell 1993, USA[48]	High school students	Drug use associated with lower self-reported emotional restraint in a reciprocal manner	Probable selection bias, limited adjustment for confounding, significance of outcome measure unclear
Hutzinga 1994, USA[49]	"High risk" youths	Positive association between drug use and self-reported antisocial behaviour	This association is alluded to in text though actual analyses are not presented. Impossible to critically appraise
Sanford 1994, Canada[50]	Population based sample of adolescents	Heavy drug use associated with a greater risk of reporting work-force involvement (as opposed to continued schooling)	Potential selection bias due to large loss to follow up
Schulenberg 1994, USA[51]	High school students	Drug use and lower grade point average positively associated with later self-reported drug use	Focus of the surveys is on patterns and antecedents, rather than consequences, of drug use
Anthony 1995, USA[52]	Population based sample of adolescents reporting drug use	Earlier drug use associated with greater risk of developing later self-reported drug problems	Possible selection bias and limited adjustment for confounding. Focus of the epidemiological catchment area programme (of which this was a sub-study) is on the descriptive epidemiology of mental illness in the community rather than the consequences of drug use.
Farrington 1995, UK[53]	"Working-class" male school children	Positive association between drug use and measures of anti-social behaviour derived from self-report, school reports and official records	Specific relation between drug exposure and subsequent behavioural outcomes not reported. Focus of the study is on antecedents of "delinquency". Drug use is reported as part of the delinquency spectrum
Krohn 1997, USA[54]	"High risk" school children.	Drug use positively associated with earlier school leaving, earlier independent living and earlier parenthood—particularly among women	Possible selection bias. Limited adjustment for confounding
Luthar 1997, USA[55]	High school students	Drug use associated with increased risk of self-reported depression, maladjustment and internalising of problems	Small study, short follow-up limited adjustment for confounding
Stanton 1997, USA[56]	Black adolescents recruited from an HIV risk reduction project	Drug use weakly associated with self-reported risky sex, fighting, and weapon carrying	Possible selection bias, limited adjustment for confounding
Rao 2000, USA[57]	Female high school students	Substance use disorder positively associated with self-reported depression	Possible selection bias, small sample, limited adjustment for confounding
Weiser 2002, Israel[4]	Male military conscripts	Drug abuse associated with doubling of risk of schizophrenia	Drug abuse only assessed in high risk sub-sample, limited adjustment for confounding†
Studies reporting outcomes related to specific drug exposure			
Epstein 1984, Israel[58]	High school students	Alcohol and tobacco use associated with earlier sexual intercourse and earlier leaving of education. Cannabis use also reported to be associated with the latter (analyses not shown)	Small study, no adjustment for confounding. Since latter analyses not reported impossible to critically appraise in this regard
Kaplan 1986, USA[59]	High school students	Early cannabis use along with use associated with self-reported psychological distress, associated with greater reported escalation of use and later psychological distress	Potential selection bias. Focus of the study is not on consequences of drug use
Tubman 1990, USA[60]	Children of "middle class" families	Alcohol, tobacco and cannabis use all positively associated with self-reported symptoms of psychological distress.	Small study, possible selection bias, focus on antecedents rather than consequences of drug use
Scheier 1991, USA[61]	High school students in drug prevention programme	Cannabis use positively associated with risk of use of other illicit drugs and with socially negative attitudes	Probable selection bias, limited adjustment for confounding
Hammer 1992, Norway[62]	"High risk" adolescents	Cannabis use positively associated with self-reported symptoms of psychological distress	Possible selection bias, limited adjustment for confounding
Degonda 1993, Switzerland[63]	Population based sample of young adults	Cannabis use positively associated with self-reported symptoms of agoraphobia and social phobia	Possible selection bias, limited adjustment for confounding
Romero 1995, Spain[64]	High school students	Cannabis use inconsistently associated with different dimensions of self-reported self-esteem	Loss to follow-up not reported, limited adjustment for confounding, relevance of outcome unclear
Andrews 1997, USA[65]	Adolescents responding to an advertisement	Tobacco and cannabis use associated with lower academic motivation in a reciprocal manner.	Self-selected sample with high loss to follow up Limited control of confounding
Patton 1997, Australia[17]	High school students	Frequent cannabis use strongly positively associated with reported risk of self-harm in females. Weak, negative association in males.	Short follow up, limited adjustment for confounding
Hansell 1991 and White 1998, USA[66,67]	Telephone survey of adolescents	Cannabis and cocaine use associated with higher self-reported aggression and psychological distress	Possible selection bias, limited adjustment for confounding, relevance of outcome measures unclear

(continues next page)

	Participants and setting	Main relevant findings*	Comments*
Costello 1999, USA[46]	"High risk" adolescents	Alcohol, tobacco, cannabis, and other drug use positively associated with self-reported psychological distress and behavioural problems	Probable selection bias, limited adjustment for confounding
Duncan 1999, USA[11]	"High-risk" adolescents	Alcohol, tobacco, and cannabis use all positively associated with risky sexual behaviour. Association strongest for tobacco	Small sample, possible selection bias, limited adjustment for confounding
Perkonigg 1999, Germany[12]	Population based sample of adolescents	Cannabis use and dependence were generally sustained over the follow-up period	Focus of publications to date from this study has not been consequences of drug use
Huertas 1999, Spain[13]	High school students	Cannabis, alcohol, and tobacco use positively associated with poorer school performance	No adjustment for confounding
Braun 2000, USA[14]	Population based sample of adolescents	Cannabis and tobacco use weakly associated with lower income and less prestigious employment. Association stronger with tobacco and amongst white participants	Possible selection bias, limited adjustment for relevant confounders (focus of the study is on development of cardiovascular risk)
Brook 2002, Colombia[15]	Population based sample of adolescents	Cannabis use associated with risky sexual behaviours	Limited adjustment for confounding†

*Summaries and comments are based on evidence available following initial searches and quality assessment in 2000, except †study identified through subsequent searches or contact with experts.

Table 2: **Summary of other studies identified in review listed in chronological order of relevant publications**

symptoms; results were mixed.[13,14,16] Amphetamines and ecstasy (3,4-methylenedioxymethamphetamine, MDMA) seem to be widely used illicit drugs.[1] We identified no studies meeting our selection criteria that reported effects of either amphetamine or ecstasy use.

Discussion

In this review, we found little evidence from longitudinal studies in the general population about the outcomes of exposure to any illicit drugs other than cannabis. We confirmed the existence of evidence of associations between cannabis use and psychosocial harm; however, the extent and strength of this evidence seemed less than is perhaps sometimes assumed. Furthermore, the causal nature of these associations is far from clear. Some seem to fulfil at least some of the traditional criteria for establishing causality.[18] They are fairly consistent; cause seems to precede effect, and a plausible mechanism can be advanced. The criterion of specificity of association was less consistently fulfilled. In several studies (tables 1 and 2) tobacco and alcohol showed similar associations as cannabis with psychosocial outcomes. This finding does not suggest a causal mechanism mediated through drug-specific neurophysiological effects or involvement in criminalised commerce, since tobacco and alcohol have distinct neurophysiological effects, and they are not illegal. Existence of a dose-response relation, in which magnitude of the outcome varies with magnitude of the exposure is another criterion often invoked. In many studies, existence of such a relation was impossible to assess since only binary exposure categories were examined. Where effects of more than two exposure categories were reported, a graded association with outcome from higher to lower exposure was sometimes noted. Interpretation of these gradients was complicated by the fact that in almost all studies, frequency of drug use, rather than dose, was assessed. Quantity used was probably closely related to frequency, and frequency measures allowed inference of extent of drug involvement, which is of relevance to social mechanisms of causation.

However, empirical evidence has shown that associations can fulfil these criteria, and still be unlikely to

	Measure of cannabis use and measure of outcome	Crude estimate	Adjusted estimate
Outcome/study			
Educational attainment			
Christchurch[16]	Any use before age 15 years and odds ratio for school dropout	8·1 (4·3–15·0)	3·1 (1·2–7·9)
Project Alert[46]	One point increase on frequency of use scale and odds ratio for school dropout	1·68 (p<0·001)	1·13 ("not significant")
Australian schools*[17]	Weekly use at ages 15, 16, and 17 years and odds ratio for early school leaving	6·8 (2·8–1·6)	5·6 (2·0–1·5)
		3·2 (1·4–7·3)	2·2 (0·91–6·0)
		1·8 (0·69–4·6)	1·1 (0·40–2·9)
Use of other drugs			
Swedish conscripts[11]	Report that cannabis "most used illicit drug" and odds ratio for later injection drug use	6·8 (4·9–9·4)	3·3 (1·9–5·9)
Christchurch[16]	Weekly use and odds ratio for use of any other drug	142·8 (92·3–222·9)	59·2 (36·0–97·5)
Psychological health			
Christchurch[14,16]	Any use before age 15 years and odds ratio for reported anxiety, depression or suicidal thoughts	2·7(1·3–4·1)	1·2 (0·5–2·8)
		2·9(1·6–5·1)	1·4 (0·7–2·7)
		3·6(2·1–6·1)	1·4 (0·7–2·8)
	Cannabis dependence at age 18 years and rate ratio for reported psychotic symptoms	2·3 (1·7–3·2)	1·8 (1·2–2·6)
Dunedin[11]	Any use at age 15 years and odds ratio for any mental disorder (sexes combined)	2·69†	0·97 (0·59–1·60)
	Any use at age 18 years and odds ratio for any mental disorder in males and in females	3·59†	2·00 (1·29–3·09)
		1·54†	0·75 (0·47–1·17)
Swedish conscripts[48]	Use on more than 50 occasions and odds ratio for clinical diagnosis of schizophrenia	6·7 (4·5–10·0)	3·1 (1·7–5·5)
Australian schools*[18]	Daily use at age 15 years and odds ratio for reported depression in males and in females	1·9 (0·93–3·8)	1·1 (0·55–2·6)
		8·6 (4·2–18·0)	5·6 (2·6–12·0)
Antisocial behaviour			
Christchurch[16]	Any use before age 15 years and odds ratios for conduct disorder, reported offending and police contact	7·0 (4·3–11·4)	1·0 (0·5–2·1)
		5·7 (3·3–10·0)	0·8 (0·6–2·7)
		4·8 (2·5–9·3)	2·1 (0·9–4·8)

*Study summarised in table 2, relevant results published subsequent to initial quality assessment. †95% CIs were not reported. Adjustment factors for individual estimates are not given. Measures available are described in table 1, but adjustments did not necessarily include the full range of available measures.

Table 3: **Crude and adjusted estimates of effects of cannabis use on selected psychosocial outcomes**

be causal.[66,67] Alternative explanations of reverse causation, bias, and confounding are discussed.

Psychosocial problems might be more a cause than a consequence of cannabis use, especially with regard to associations between use and mental illness. Some studies adjusted for psychological symptoms reported at baseline or excluded incident problems occurring during early follow-up. Nevertheless, unreported or subclinical psychological problems might have preceded and precipitated cannabis use. Individuals with a pre-existing tendency to experience psychological difficulties might have a greater inclination to develop problematic patterns of drug use (for example, depressed individuals are more likely to start smoking tobacco and less likely to stop than those who are not depressed).[82] Cannabis use might also exacerbate existing predispositions to psychological problems.

Exposure to cannabis use and experience of psychosocial problems might have been associated with both study recruitment and retention leading to selection bias that could affect the apparent association between cannabis use and harm. Measurement bias is another possibility. Some empirical evidence suggests reasonable validity of self-reported drug use, although other evidence shows that in some situations, especially general population studies in which the drug-use status of participants has not been previously recorded, this method can be unreliable.[83,84] Random misclassification of drug-use status will simply lead to dilution of apparent effects, but systematic misclassification, especially when it affects both exposure and outcome measurement, can generate spurious effects. For example, an individual may have a general tendency to value either conformist or non-conformist, behaviour, and this tendency may influence their reporting. In this situation one would expect artefactual associations between greater reported use of cannabis and greater reported use of other drugs or other non-conformist behaviours. Since most associations of cannabis use with use of other drugs, and with antisocial behaviour, are based exclusively on self-reported measures, the effect of this type of bias must be considered. In other contexts, reporting bias has been shown to be capable of generating strong and substantial associations between measures that, individually, seem to have high validity.[85]

Discounting confounding is probably the most serious interpretational challenge in observational epidemiology.[65] Both cannabis use and adverse psychosocial outcomes seem to share common antecedents related to various forms of childhood adversity, and factors relating to peer-group and family.[66,67] The relation between cannabis use and harm might simply reflect these associations; cannabis use could be a marker, rather than a cause, of a life trajectory more likely to involve adverse outcomes.

There are no completely reliable means to identify confounded associations within observational data, and instances where apparently robust observational evidence has later been shown to be seriously misleading are common.[65] The importance of this issue to the epidemiology of drug use might have been underestimated. In particular, the extent to which confounding can be overcome through statistical adjustment seems to have been overestimated. Adjustment is useful, but its power to abolish the confounded component of an association depends on the completeness and precision of measurement of the confounders.[68] Only three studies[18–20,30] included in our analysis had any prospectively measured indices of the early life factors that may covary with both cannabis use and harm. It seems unlikely that even these measures were complete or precise.

Unmeasured, as well as measured, potential confounders can be taken into account through techniques such as fixed effects regression and latent variable modelling.[17,69] These approaches allow more sophisticated adjustment. The main value of adjustment is to allow the comparison of adjusted with unadjusted estimates, but few studies provided both of these estimates. The most informative examples of those that did are summarised in table 3. Attenuation of estimates towards the null value, on adjustment, suggests confounding by the adjustment factor. In this situation, residual confounding can be assumed to be present. Unchanged or strengthened estimates suggest that confounding by the factor adjusted for is unlikely—confounding by another factor is still possible. In table 3, almost all adjusted estimates are substantially attenuated towards the null value. With attenuation of this relative magnitude even small degrees of measurement imprecision in the confounders could account for the residual effects.

Sensitivity analyses are another means to explore the possibility of confounding. A recent application of this principle to North American data showed that confounding by a factor termed "propensity for drug use" could explain associations between cannabis use and use of other drugs.[69] Both environmental and genetic factors could underlie such a propensity.[81]

Further evidence against a simple causal explanation for associations between cannabis use and psychosocial harm relates to population patterns of the outcomes in question. For example, incidence of schizophrenia seems to be strongly associated with cannabis exposure over a fairly short period (four-fold to five-fold relative risks over follow-up of 10–30 years). Cannabis use appears to have increased substantially amongst young people over the past 30 years, from around 10% reporting ever use in 1969–70, to around 50% reporting ever use in 2001, in Britain and Sweden.[70] If the relation between use and schizophrenia were truly causal and if the relative risk was around five-fold then the incidence of schizophrenia should have more than doubled since 1970. However population trends in schizophrenia incidence suggest that incidence has either been stable or slightly decreased over the relevant time period.[71,72]

The above considerations suggest that a non-causal explanation is possible for most associations between cannabis exposure and both psychological and social harm. It is important to clarify these questions, and evidence meeting this requirement could come from several sources. Birth cohorts provide the ideal prospective design within which to investigate the role of early life factors.[54] They are expensive and time consuming, and ensuring complete follow-up is challenging. However two of the studies we identified successfully adopted this design.[15,20] Other ongoing birth cohorts whose participants are now entering adolescence exist.[73] These studies could provide valuable information, especially if they incorporated approaches to measurement other than those completely reliant on uncorroborated self-report.

The principle of "Mendelian randomisation" is proving useful in cardiovascular and cancer epidemiology.[74] If level of exposure to a putative environmental cause is substantially affected by a particular genetic polymorphism, then analysis of effect by genotype is unlikely to be confounded by environmental factors. Study of polymorphisms affecting neuroreceptor affinity for the psychoactive components of cannabis may have potential in this regard.[75] The statistical power is generally

low in such studies, however, and sample sizes need to be large.[98,99] Finally, experimental studies are the traditional approach to overcoming problems of selection bias and confounding. If experimental reduction in cannabis exposure were associated with reductions in psychosocial harm, this would be stronger evidence for a true causal relation. Currently, this approach is limited by the absence of interventions that substantially or reliably reduce exposure to cannabis.[100] Concerns have been expressed about the public health effects of ecstasy use;[101] the same principles should guide research to provide evidence relating to this drug. Evidence on public health effects of opiate use seems likely to be most feasibly obtained through follow-up of population-based cohorts of opiate users.[102]

In this review we did not consider physical health outcomes. Clearly, some types of illicit drug use lead to serious physical harm, but the extent of this problem outside known treatment populations is unclear. It is probable that cannabis use is associated with some physical harm, since most users apparently smoke the drug with tobacco. Intermittent use confined to adolescence or early adulthood might have small effects, but data confirming that this pattern of use predominates, or measuring the prevalence of other usage patterns, are limited. Little reassurance is available from the evidence we identified. Only one study reported mortality up to middle adulthood and found no increase with cannabis use, however the same study showed no mortality increase associated with tobacco use.[39]

Drug policy is sometimes justified on the basis of a causal relation between drug use and psychosocial harm. We have shown that evidence for this relation is not strong. However it would be naive to assume that scientific evidence is generally an important determinant of policy, especially in this area.[103,104]

No search strategy can ensure identification of all relevant evidence. Our search was the most comprehensive of any we are aware of in this field and was recently updated. However, it is probable that we missed some potentially relevant evidence. Given the general issues of interpretation we have discussed, it seems unlikely that such omissions would have substantially altered our conclusions. Our quality assessment was inevitably subjective; however, we undertook it as a guide to readers and to make the task of the review more manageable. We contacted only authors of higher-quality studies to identify further evidence, although again it seems unlikely that this procedure introduced substantial bias.

Despite widespread concern, we have found no strong evidence that use of cannabis in itself has important consequences for psychological or social health. This finding is not equivalent to the conclusion that use of cannabis is harmless in psychosocial terms; problems with the available evidence render it equally unable to support this proposition. Better evidence is needed in relation to cannabis, which is widely used, and in relation to other drugs that, although less widely used, might have important effects.

Contributors

J Macleod, A Copello, I Crome, M Egger, M Hickman, and G Davey Smith devised the search strategy. Electronic searches, expert contact, and retrieval of references were undertaken by R Oakes and T Oppenkowski. Hand searches were undertaken by J Macleod and I Crome. Quality assessment was undertaken by J Macleod, M Egger, and H Stokes-Lampard. Data synthesis and interpretation was discussed by J Macleod, A Copello, I Crome, M Egger, M Hickman, H Stokes-Lampard, and G Davey Smith. J Macleod wrote the first draft of this report, all authors contributed to the final draft.

Conflict of interest statement

None declared.

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