



THE CANNABIS EXPERIMENT

As marijuana use becomes more acceptable, researchers are scrambling to answer key questions about the drug.

BY DANIEL CRESSEY

In 2013, Beau Kilmer took on a pretty audacious head count. Citizens in the state of Washington had just voted to legalize marijuana for recreational use, and the state's liquor control board, which would regulate the nascent industry, was anxious to understand how many people were using the drug — and importantly, how much they were consuming.

The task was never going to be straightforward. Users of an illicit substance, particularly heavy users, often under-report the amounts they take. So Kilmer, co-director of the RAND Drug Policy Research Center in Santa Monica, California, led a team to develop a web-based survey that would ask people how often they had used cannabis in the past month and year. To help them gauge the amounts, the surveys included scaled pictures showing different quantities of weed. The survey, along with other data the team had collected, revealed a rift between



Retailers in Colorado can now sell cannabis to the public.

have gone further, legalizing the drug for recreational consumption. A handful of other states including California and Massachusetts are expected to vote on similar recreational-use measures by the end of 2016.

But the rapid shift has caught researchers on the back foot. “Broadly speaking, there’s about 100 times as many studies on tobacco or alcohol as there are on illegal substances,” says Christian Hopfer, a psychiatry researcher at the University of Colorado School of Medicine in Aurora. “I don’t think it’s the priority it should be.”

Despite claims that range from its being a treatment for seizures to a cause of schizophrenia, the evidence for marijuana’s effects on health and behaviour is limited and at times conflicting. Researchers struggle to answer even the most basic questions about cannabis use, its risks, its benefits and the effect that legalization will have.

The quick shifts in policies should provide a plethora of natural experiments, but the window will not be open for long. “There’s an opportunity here. Some of the most informative research we can do is right at the moment the market changes,” says Robert MacCoun, a social psychologist and public-policy researcher at Stanford Law School in California who worked with Kilmer on the research done in Washington.

WHAT ARE THE NEGATIVE EFFECTS?

For years, the debate over the drug’s safety has been polarized. Those seeking legalization claim that it is basically harmless. Yet governments around the world have placed cannabis among the most-dangerous illegal drugs, running hard-hitting campaigns warning of the threats that it poses to mental health and social well-being.

Scientists are fairly sure about some things, particularly when it comes to the short-term effects. They know, for instance, that it impairs memory and coordination, and can cause paranoia and psychosis². These are some of the classic symptoms of being ‘high’ and can have major health effects in and of themselves. Studies have found, for example, that drivers are between twice and seven times as likely to crash if they have recently smoked the drug^{3,4}.

In the longer term, effects are less clear, but there are a few that most scientists agree on. Contrary to many popular arguments, there is evidence that cannabis is addictive. Around 9% of users become dependent on the drug, showing signs of addiction such as developing tolerance or experiencing withdrawal symptoms when they stop using. Beyond that, however, long-term effects have been difficult to pin down.

Cannabis is often smoked, and this can raise the risk of respiratory problems and

possibly lung cancer. A 2008 study in New Zealand found that smoking pot increased the risk of lung cancer by 8% for each ‘joint-year’ (the equivalent of smoking a joint per day for one year), even after taking tobacco use into account⁵. But other studies have found little to no correlation with lung cancer, even for heavy users⁶.

Other health outcomes are even more difficult to disentangle from confounding factors. Some researchers have found links to poor educational performance, low social attainment — such as job status — and altered brain development. For example, the Christchurch Health and Development Study — which followed almost 1,300 children born in New Zealand in 1977 — found that people who used cannabis daily are around 50% more likely to have psychotic symptoms⁷ than are non-users and are at greater risk of not finishing school⁸.

And another study from New Zealand, which followed 1,000 people in Dunedin from birth to age 38, shows that persistent cannabis use, especially if started young, correlates with steeper declines in IQ in later

“Marijuana research is like tobacco research in the ’60s. Any study about harms is challenged.”

life and with problems with memory and reasoning compared with people who have never used the drug⁹.

Hall says that the association with negative social and mental-health outcomes has been consistently observed, but the debate “is how we explain that association”, which he says will probably involve a combination of factors.

The difficulty, says Valerie Curran, a psychopharmacologist at University College London, lies in teasing apart correlation and causation, because “there are so many confounders”. For example, adolescents who use cannabis are probably also drinking excessive amounts of alcohol and engaging in other risky activities. Attributing the effects to one particular substance or behaviour is therefore very difficult.

Similar problems abound in the hotly contested link between cannabis and schizophrenia. Multiple studies have shown an increased risk of this mental-health disorder

perception and reality. Based on prior data, state officials had estimated use at about 85 tonnes per year; Kilmer’s research suggested that it was actually double that, about 175 tonnes¹. The take-home message, says Kilmer, was “we’re going to have to start collecting more data”.

Scientists around the world would echo that statement. Laws designed to legalize cannabis or lessen the penalties associated with it are taking effect around the world. They are sweeping the sale of the drug out of stairwells and shady alleys and into modern shopfronts under full view of the authorities. In 2013, Uruguay became the first nation to legalize marijuana trade. And several countries in Europe — Spain and Italy among them — have moved away from tough penalties for use and possession. Thirty-nine US states plus Washington DC have at least some provisions for medicinal use of the drug. Washington, Colorado, Alaska and Oregon

in people who use cannabis versus people who do not. A study of 50,000 Swedish men aged 18–20 found that heavy users were around three times more likely to develop schizophrenia than those who had never used the drug¹⁰. Although the increase in risk was significant, the overall risk is still low — just 1.4% of men who reported using cannabis developed the disorder, compared with 0.6% of those who said they had never tried the drug. Some cannabis advocates suggest that the link may be down to people with such problems ‘self-medicating’, but this is difficult to prove.

Many of the negative health outcomes seem to be exacerbated if the drug is used in adolescence, leading to suggestions that cannabis is adversely affecting developing brains. And effects may also be linked to the drug’s potency, which in itself is hard to pin down.

As cannabis use becomes legal, the data may become easier to collect. But the drug’s use is still low compared with alcohol and tobacco, says Wayne Hall, an addiction researcher at the University of Queensland in Brisbane, Australia, so it is hard to draw firm conclusions. Marijuana may be the most popular illegal drug, he says — about 44% of US adults have used it at some point in their lives according to one source — but only about one in ten have used it in the past year. By contrast, around 70% drank alcohol in that time. “The number of people who use it with any regularity for a long time is pretty small. The longer-term consequences are really understudied,” says Hall.

HOW STRONG IS IT?

A major question for researchers — and a complication in interpreting the evidence — is dosing. There are more than 85 cannabinoid chemicals in pot. The one of most interest to researchers — and users — is tetrahydrocannabinol (THC). Growers have been able to breed high concentrations of the chemical into strains of the plant meant for recreational and medicinal use. A potency-monitoring programme run by the University of Mississippi for the US National Institute on Drug Abuse (NIDA) found that THC levels have steadily increased in the United States¹¹, from 2–3% in 1985–95 to 4.9% in 2010. The increase is even starker for imported cannabis seized by law-enforcement officials. For these drugs, potency has gone from less than 4% in the late 1980s and early 1990s to more than 12% in 2013.

But it is hard to determine the amounts of THC being consumed by the average customer. It is unclear, for example, whether users ‘titrate’ their doses, adjusting their intake according to the potency. Nicotine users are known to do this with cigarettes, but nicotine does not impair judgement in the same way that cannabis does. And the

Reefer madness

After more than a century of fairly lenient laws surrounding cannabis, public attitudes in the United States and elsewhere shifted against the drug in the early 1900s.

Anti-marijuana propaganda escalated in the 1930s, with films depicting the horrors that befell users (see right).

1976

The Netherlands decriminalizes possession, use and sale of small quantities of marijuana.

1996

California becomes the first state to legalize medical cannabis, through Proposition 215.

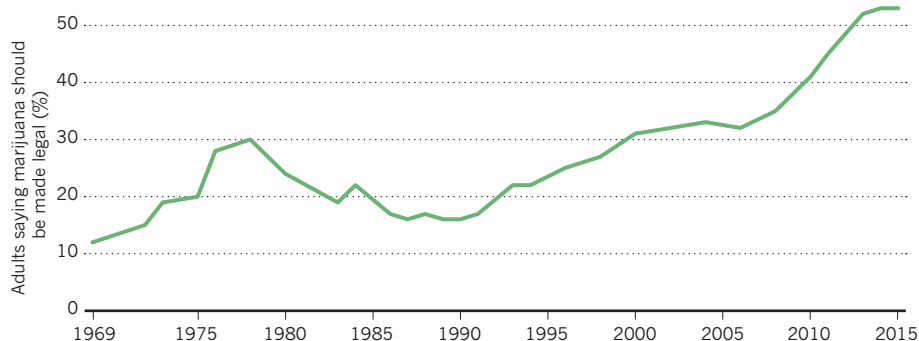
2012

Washington and Colorado vote to legalize recreational marijuana for adults aged 21 or older, although the drug does not become available for sale until 2015.



IMAGE: MOVIE POSTER IMAGE ART/GETTY; DATA SOURCE: PEW RESEARCH CENTER

Survey data have revealed a dramatic shift in attitudes towards marijuana in the United States.



effects of THC are less immediate, especially for edible forms.

The escalating potency raises questions about previous research because users in older studies may have been consuming lower-potency cannabis, and the effects may be different (see ‘Research gaps’). A study published earlier this year, for example, linked high-potency cannabis to a threefold-increased risk of psychosis versus non-use but found no association with lower-potency forms¹². And many researchers have complained that the pot approved for study in experiments funded by NIDA is a poor match for what is used recreationally or medicinally.

In tandem with changing laws, the Colorado Department of Public Health and Environment (CDPHE) is establishing reference labs to check the potency of what is sold. And the US government is expanding the varieties of marijuana that researchers with federal funding can obtain.

In places where the drug is legal, existing labelling standards may also be inadequate. A survey done between August and October last year found that only 17% of edible cannabis products in San Francisco, Los Angeles and

Seattle had accurate labels. More than half had less THC than claimed, and some contained significantly more¹³. “A lot of people get a rude surprise,” says MacCoun.

ARE THERE MEDICAL BENEFITS?

Although states are starting to ease restrictions on recreational use of marijuana, what got the ball rolling in changing public perceptions and the legal landscape for pot were the arguments for its medical use.

Colorado introduced its rules allowing medical marijuana more than a decade before it allowed recreational use. The amendment to the state’s constitution listed eight conditions for which marijuana was approved: cancer, glaucoma, HIV/AIDS, cachexia (a progressive wasting syndrome), persistent muscle spasms, seizures, severe nausea and severe pain. But, says Larry Wolk, executive director and chief medical officer of the CDPHE, “those are dictated by the constitution and not necessarily by medical research”.

Although there is a huge amount of anecdotal evidence — and well-organized advocacy groups that campaign for easier access to medical marijuana — there is little conclusive scientific evidence for many of the

claimed medical benefits. One of the reasons for this dearth of evidence is that money generally has been obtainable only for research on the negative effects of cannabis. That is beginning to change.

When Colorado first legalized the drug, its public-health department began collecting fees from patients who applied to purchase pot at medical dispensaries. By 2014, the state had amassed more than US\$9 million, most of which was ploughed back into a medical marijuana research programme selected by the CDPHE. Among the projects funded by the Colorado millions, there are two investigating whether cannabinoids can help to mitigate seizures in childhood epilepsy. Similar research is being pursued in the United Kingdom and elsewhere in the United States.

Another, more-established use is for people with multiple sclerosis. A cannabis-based spray has been approved in 27 countries for treatment of muscle problems associated with the disease, such as spasms.

Other claimed benefits of marijuana, such as boosting appetite in people with AIDS, are supported by more-limited evidence. If positive effects can be clearly demonstrated, it would be a huge vindication for marijuana advocates. It might also go some way towards justifying medical-marijuana legislation.

In the meantime, however, scientists are watching the emerging cannabis frontier with wary eyes. "I think it's an experiment," says Robert Booth, a psychiatry researcher at the University of Colorado. "When this study is all said and done, we'll know a whole lot about the effects of marijuana."

WHAT HAPPENS WHEN YOU MAKE IT LEGAL?

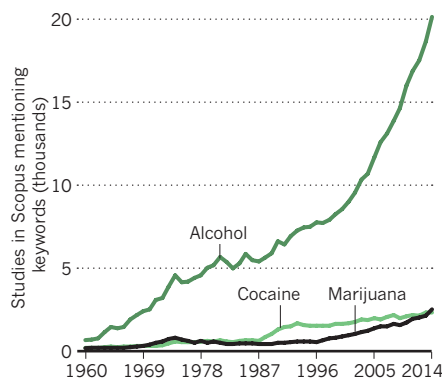
One of the biggest questions is how legalization will change usage patterns. One place in which researchers are looking for answers is Europe, where cannabis regulation tends to be much lighter than it is in the United States (see 'Reefer madness'). In the United Kingdom, some police forces overlook cannabis use and small-scale growing operations. Spain allows private consumption, but still has restrictions on sales.

The most extreme and long-standing example is the Netherlands, which decriminalized the possession and sale of small quantities of cannabis in 1976. But although some streets of Amsterdam have been transformed into pungent tourism hotspots, the country as a whole has not changed its habits much.

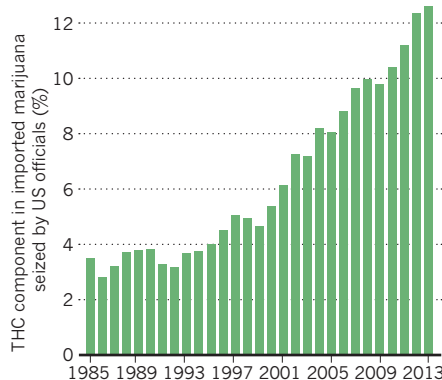
Although hard data on cannabis use in Europe is patchy, the Netherlands does not have hugely more users than other nations. Data aggregated by the United Nations Office on Drugs and Crime put use in the Netherlands at about 7%. That is more than in Germany (5%) and Norway (5%), about the same as in the United Kingdom and less than in the United States (15%). Nor has the Netherlands

Research gaps

Published research on marijuana lags behind that of other drugs, such as alcohol and cocaine, according to a search of the bibliographic database Scopus.



The amount of tetrahydrocannabinol (THC) in cannabis has risen sharply in the past three decades, raising concerns about the relevance of older research and studies using less-potent varieties of the drug.



seen a huge spike in use of harder drugs, dampening fears that marijuana serves as a gateway to more-dangerous substances such as heroin and cocaine. The message from the Netherlands, says Franz Trautmann, a drugs-policy researcher at the Trimbos Institute in Utrecht, the Netherlands, is that "a very liberal policy doesn't lead to a skyrocketing prevalence". Rather, cannabis is endemic, he says. "We can't control this through prohibition. This is something which more and more is recognized."

But the lesson from the Netherlands may be limited because the drug is still illegal, and growing and selling large quantities is still punishable by law. Colorado has gone further by legalizing not merely the drug's use, but the whole production chain, and that could have fundamentally different effects on the economics of pot. "Legalized production really raises the prospect of a dramatic drop in price," says MacCoun. "It's conceivable marijuana prices could drop 75–80% in a fully legalized model." (Although Uruguay legalized the drug in 2013, it reportedly has struggled to regulate production and to set up working dispensaries.)

The effects of a sharp drop in cost are

unknown. Taxation may also have unintended consequences. If states tax by weight, users might look to higher-potency strains to save money. And once cannabis is a business, it gains a business lobby. Cannabis researchers already talk of being bombarded with e-mails from pro-cannabis groups if they make negative comments about the drug. "Marijuana research is like tobacco research in the '60s," says Hopper. "Any study about harms is challenged. It's really something." Many fear that the big money now to be found in cannabis will drive attempts to obfuscate the risks. "If the commercial interests are too big, then the profit interest is prevailing above the health interest. This is what I'm afraid of," says Trautmann.

Legalization provides an opportunity to answer some important questions. In a few years, Colorado, Washington and others will know (if only roughly) how legalization affects usage patterns, the number of car crashes and the number of people seeking help for drug dependency. The CDPHE-funded programmes will have added to the knowledge of beneficial effects. And continuing long-term studies of large groups of users will provide more evidence for statisticians who are attempting to disentangle correlation and causation on the negative impacts.

"When a jurisdiction changes its marijuana laws, that provides an opportunity for greater leverage on the questions of cause and effect," says MacCoun. But, he adds, the signals will only really be clear if the laws result in a dramatic increase in use — something that is neither a given, nor necessarily desirable. "Obviously, we don't want marijuana use to rise just to allow us to answer our questions, but if it does, we'll be poring over all the data." ■

Daniel Cressey writes for Nature from London.

1. Kilmer, B. et al. *Before the Grand Opening: Measuring Washington State's Marijuana Market in the Last Year Before Legalized Commercial Sales* (RAND Corp., 2013); available at go.nature.com/ibu8vl
2. Volkow, N. D., Baler, R. D., Compton, W. M. & Weiss, S. R. B. *N. Engl. J. Med.* **370**, 2219–2227 (2014).
3. Hall, W. *Addiction* **110**, 19–35 (2014).
4. Ramaekers, J. G., Berghaus, G., van Laar, M. & Drummer, O. H. *Drug Alcohol Depend.* **73**, 109–119 (2004).
5. Aldington, S. et al. *Eur. Respir. J.* **31**, 280–286 (2008).
6. Hashibe, M. et al. *Cancer Epidemiol. Biomarkers Prev.* **15**, 1829–1834 (2006).
7. Fergusson, D. M., Horwood, L. J. & Ridder, E. M. *Addiction* **100**, 354–366 (2005).
8. Fergusson, D. M., Horwood, L. J. & Beutrais, A. L. *Addiction* **98**, 1681–1692 (2003).
9. Meier, M. H. et al. *Proc. Natl Acad. Sci. USA* **109**, E2657–E2664 (2012).
10. Zammit, S., Allebeck, P., Andreasson, S., Lundberg, I. & Lewis, G. *Br. Med. J.* **325**, 1199 (2002).
11. Office of National Drug Control Policy *National Drug Control Strategy: Data Supplement 2014* (White House, 2014); available at go.nature.com/mm8qyk
12. Di Forti, M. et al. *Lancet Psychiatry* **2**, 233–238 (2015).
13. Vandrey, R. et al. *J. Am. Med. Assoc.* **313**, 2491–2493 (2015).