



The modern interior of a cannabis dispensary in Louisville, Colorado.

SAFETY

Balancing act

As interest builds in the potential health benefits of cannabis, accumulating evidence confirms that taking the drug also carries risks.

BY EMILY SOHN

Last October, Canada became the second country, after Uruguay, to allow the use of cannabis not only for medical reasons, but also for recreational purposes. In the lead-up to its full legalization, the Canadian government commissioned a study of the drug's potential harmful effects so that it could make responsible decisions about how the drug should be sold, packaged and taxed, says Fiona Clement, a health-policy researcher at the University of Calgary's Cummings School of Medicine.

Clement and her colleagues analysed the findings of 68 reviews of cannabis research¹. Of the reviews, 62 showed associations between the drug and various adverse outcomes, including impaired driving, increased risk of stroke and testicular cancer, brain changes that could affect learning and memory, and a particularly consistent link between cannabis use and mental illnesses involving psychosis. Risks

were highest for teenagers, pregnant women and people already at risk of mental illness.

Evidence of the drug's acute and chronic risks is building, but many questions still remain about how much cannabis is too much and how compounds in the plant interact to buffer or exacerbate the harmful effects. As claims of health benefits become increasingly common, these are important questions to answer. Users and lawmakers need be aware of the risks to be able to make informed choices, say researchers.

"I believe strongly that there are benefits to cannabinoids for medical purposes. And I believe that many thousands of people use cannabis safely," says Andrew Monte, an emergency physician and medical toxicologist at the University of Colorado Anschutz Medical Campus in Aurora. But, as with any drug on the market, he says, users need to know about the potential side effects.

"Cannabis is not the root of all evil, nor is it the cure for all diseases," Monte says. "You've

got to understand what the good is and what the bad is, and then make a balanced decision."

IMMEDIATE HARMS

Along with countries including Canada and Uruguay, 33 US states have legalized cannabis for medical use. Eleven also allow recreational use. And evidence is accumulating to support the use of specific cannabis compounds, especially cannabidiol (CBD), for a variety of health conditions, including seizures and inflammation².

But a look at what happens when the use of cannabis becomes more widespread suggests that the drug can also have downsides, including acute injuries and illnesses. In 2000, Colorado legalized medical marijuana. Further policy changes in 2009 made the substance easier to get hold of, and between 2008 and 2014, licences for medical marijuana in the state increased from less than 5,000 to more than 100,000. In 2012, the state also legalized recreational use, and

CYRUS MCCORMICK/THE DENVER POST/GETTY

shops began selling cannabis products in 2014.

As cannabis has lost its stigma in Colorado, Monte's research shows that the need for health care for cannabis-related reasons has risen³. Between 2012 and 2014, cannabis-related visits to emergency departments at a group of Colorado hospitals increased by around 40%, from 824 per 100,000 visits to 1,146 per 100,000. Many of those visits were related to mental illnesses, which were diagnosed five times more frequently in people who had used cannabis than in those who hadn't.

Colorado hospitals have also seen a growing number of cases of marijuana use leading to cyclic vomiting syndrome, a condition characterized by vomiting and severe abdominal pain. Occurrences of this condition doubled at two Denver hospitals after the liberalization of medical cannabis². Burns are another risk. In a 2015 analysis⁴, Monte's group found that the University of Colorado burns centre admitted 29 people for marijuana-related burns between 2009 and 2014, compared with no burns cases before the policy changed. Most were incurred during the process of extracting the plant's main psychoactive ingredient, tetrahydrocannabinol (THC), for making butane hash oil.

Cannabis is also causing more of other types of accident than it used to. From 2009 to 2015, Children's Hospital of Colorado in Aurora saw 81 children under 10 years of age who had been accidentally poisoned by cannabis, and the state's poison-control centre dealt with 163 cases of children in the same age group, with a mean age of about 2. The rate of marijuana-related visits to the children's hospital nearly doubled from 1.2 per 100,000 people two years before legalization to 2.3 per 100,000 two years after legalization⁵. The number of cases at the poison-control centre increased by 34% per year during the study period, far outpacing a 19% annual increase in the rest of the country.

Studies with driving simulators suggest that cannabis also raises the risk of car accidents⁶, although those data are harder to quantify because cannabis lingers in the bloodstream, and drivers in collisions might have more than one drug in their system.

Adverse outcomes do not seem to be abating in the state, even after years of legalization. Between 2012 and 2016 (the latest data available), there were nearly 10,000 cannabis-related visits to the University of Colorado Health Emergency Department⁷. Reasons included psychiatric, cardiovascular and gastrointestinal symptoms. Edible products accounted for about 10% of visits, even though, in 2016, they made up just 0.3% of THC sales in the state.

"There are risks, absolutely," Monte says. "And we need to be open and transparent about what those risks are with patients."

THIS IS YOUR BRAIN

Some of the negative health effects of cannabis could be long-lasting, particularly for heavy users and young people. Increasing evidence points specifically to the risks of THC. When

cannabis is ingested or inhaled, THC binds to cannabinoid receptors in the brain, leading to changes in mood, memory, appetite and perception of pain, among other effects.

In heavy users, those effects might linger even after the intoxication has ended. Studies vary in the definition of 'heavy' use, but the term generally refers to people who use cannabis at least three times a week, often every day and usually for years. That kind of regular use has been associated with lower scores on tests of memory, attention, planning and decision-making, says Nadia Solowij, a brain researcher at the University of Wollongong in Australia and co-director of the Australian Centre for Cannabinoid Clinical and Research Excellence in Callaghan. In a 2016 review⁸ of 105 studies, Solowij and colleagues found that, after 12 to 24 hours of abstinence, heavy users performed worse than non-users and less-frequent users on tasks that assessed verbal learning and memory.

And although several weeks of abstinence can lead to some recovery of cognitive function, imaging studies suggest⁹ that extensive use is associated with longer-lasting changes to the function and structure of the brain. For example, studies have measured reduced volume of the hippocampus, which is involved in memory, in long-term cannabis users.

Psychosis is another major area of concern. Studies show that cannabis can raise the risk of early-onset of psychotic symptoms in those predisposed to the illness, especially with daily use

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of cannabis that is high in THC. In her review for the Canadian government¹, Clement and her colleagues found that people who used cannabis frequently or heavily had a higher risk of developing schizophrenia and psychotic symptoms than did people who never used it. "It should give us pause," Clement says. "We may not understand exactly the relationship between cannabis and these psychosis-related mental illnesses, but there's definitely something there."

It might be that people who have or are predisposed to psychotic mental illnesses are more likely to use cannabis. But growing evidence supports the idea that cannabis might, in some cases, have a causal role¹⁰, although longitudinal studies are still needed. In the largest study¹⁰ yet to assess the connection, scientists analysed data from about 900 people who visited 11 psychiatric-service sites across Europe and Brazil for treatment for their first episode of psychosis. With data from many people over multiple sites — where the availability of high-potency strains varied — the study showed a strong association between daily cannabis use and the likelihood of developing a psychotic disorder. For those who used particularly potent, high-THC strains, the risk was fivefold greater. Assuming a causal connection, the researchers estimated that eliminating the availability of

highly potent cannabis would prevent 12% of cases of first-episode psychosis.

The brain's reward system seems to be a prime target of long-term effects, says Francesca Filbey, a cognitive neuroscientist at the University of Texas at Dallas. She and her colleagues used functional magnetic resonance imaging to look at brain activity in 53 people who had used cannabis every day for the past 60 days, and more than 5,000 times in total¹¹. When viewing images of cannabis paraphernalia, the chronic users had a much stronger reward-system response than they did to images of fruit. Those patterns differed from what the researchers observed in non-users, who reacted more strongly to the fruit.

Although the study could not show that cannabis use is what caused those changes in the brain, Filbey says, her study, and others — including imaging studies that show down-regulation of cannabinoid receptors in heavy users — suggest that chronic use might make people become less motivated to seek out other typically rewarding and often important experiences, such as social interactions. They might also need more cannabis as time progresses to achieve their desired high. Increasingly, it seems that certain genetic factors might make some people more susceptible to these changes, which can lead to addiction, also known as cannabis-use disorder.

As many as 30% of people who use cannabis develop symptoms consistent with addiction. They develop cravings, damage relationships and give up other activities they once enjoyed, says Alan Budney, a clinical-research psychologist at the Dartmouth Geisel School of Medicine in Hanover, New Hampshire. They struggle to stop using the drug, and many experience withdrawal symptoms. Studies are mixed on how prevalent cannabis-use disorder is and whether it is becoming more common. But as cannabis becomes more readily available, one concern is that more people at risk of developing an addiction will try it. "It is important to make sure people realize that cannabis has some risk potential for addiction," he says. "It can develop into a severe problem. It's not easy to recover from."

The developing brains of teenagers seem to be especially vulnerable to cannabis's long-term effects. People who start using cannabis regularly and heavily before the age of 16 might end up using it more frequently and consuming more of it as adults¹². Compared with non-users and people who start after age 16, those who use cannabis before that age make more errors on tests that assess executive function, a set of skills involved in planning and decision-making. And early use seems to affect the organization of white matter in the brain, which facilitates communication between brain regions and neural connections. These changes are related to higher levels of impulsivity, but only in users who start early.

Starting young might accelerate memory loss, adds Solowij. Her data suggest that adolescents



Campaigners smoke cannabis at a rally in Boston, Massachusetts, to refute public-health criticisms.

who use cannabis a few times a week for two to three years develop memory impairments similar to those reported in adult users who started in young adulthood and have been consuming the drug regularly for at least 20 years¹³.

SEEKING BALANCE

For people seeking guidance on which strains have lower levels of THC, or how much cannabis might be useful therapeutically, there remain major gaps in knowledge — and no scientific evidence to back up the recommendations made by cannabis sellers. Definitive studies that follow many people for years are still missing. “Nobody has even got close to researching dosing,” Budney says.

Adding to the complexity, various compounds in cannabis seem to interact, changing the effects of cannabis depending on their relative concentrations. In a randomized controlled trial with 36 people published this year¹⁴, Solowij and her colleagues found that low doses of CBD enhanced the intoxicating — and potentially psychosis-inducing — effects of THC, especially in infrequent users. Cannabis with high levels of THC and small amounts of CBD also exacerbated cognitive impairment relative to THC alone or THC alongside a larger amount of CBD, according to still unpublished data. This is important because cannabis strains have become increasingly rich in THC since the 1960s. In Colorado, Monte says, a large joint might contain 100 milligrams of THC — 10 to 20 times the dose used in studies of pain control.

Solowij also found, however, that high doses of CBD reduced the psychoactive effects of THC — suggesting, as has other evidence, that CBD might have a protective effect on the brains of cannabis users¹⁴. In another study, Solowij and colleagues administered 200 milligrams of CBD daily to 20 regular cannabis users, who continued to use the drug¹⁵. After about 10 weeks, the researchers saw improvements in cognition,

depression and psychotic symptoms, as well as growth in part of the hippocampus. “We saw improvement in brain structure, which is quite astounding,” Solowij says.

But evidence of the potential benefits of cannabis remain murky, says Budney. He is unconvinced that data support the use of cannabis for any medical conditions except some forms of childhood epilepsy (see page S2) and muscle spasticity disorders. Sales pitches commonly heard at cannabis dispensaries promising that the drug will reduce stress, aid sleep and relieve pain are “complete mumbo jumbo,” he says.

Claims of cannabis’s benefits, particularly for people who are already healthy, are often overblown, adds Monte. But cannabis might not be as harmful as some critics suspect either. Despite the alleged risks, no evidence has been found of links between, for example, cannabis and inflammation of the arteries or cancers of the lung, head and neck. Other concerns haven’t been explored well enough to know whether there’s a link. According to Clement’s analysis for the Canadian government¹, there is not enough evidence to say whether cannabis contributes to bone loss or a variety of cancers, among other conditions.

For many adults, researchers say, moderate use is probably fine. “I compare it to alcohol,” says Earl Miller, a cognitive neuroscientist at the Massachusetts Institute of Technology’s Picower Institute for Learning and Memory in Cambridge. “Too much or the wrong situation can be bad, but in other situations it can be beneficial. I think we’re going to find the same thing with cannabis.”

The cost–benefit balance varies from person to person, Solowij says. If cannabis helps a child’s seizures, for example, the risk of having a slightly poorer memory for names probably doesn’t matter that much. Still, researchers such as Solowij who study the harmful effects of cannabis often find themselves pigeonholed

as crusaders against cannabis. “I’m not anti-cannabis,” she says. “I’m a scientist, and I am genuinely interested in what happens in the brain in cannabis users.”

It remains difficult to study cannabis in the United States, where federal regulations mean that researchers are required to jump through many administrative hoops to conduct studies, Budney says. Even when they get permission to do studies, researchers don’t have access to all the cannabis products that consumers can purchase from dispensaries — they must obtain their supply from the sole government-approved source, the University of Mississippi in Oxford. But the wave of legalization is helping scientists accumulate more data, partly because it is easier for doctors and patients to talk about cannabis. In Colorado, physicians ask about cannabis use straight away, Monte says. “It becomes less of a hidden behaviour,” he adds.

As long as most governments take a less liberal stance on cannabis than Canada, public funding for cannabis research is likely to remain thin on the ground. In these places, the onus to fund research might fall on private individuals — and some are already stepping up. In April, an alumnus of the Massachusetts Institute of Technology and Harvard University gave US\$9 million to support cannabis research at the institutions, including studies of how cannabis influences brain development and schizophrenia. Miller, who will receive some funding from the gift, plans to study patterns of brain activation in response to cannabis, with the goal of understanding how the drug affects cognition.

“Once we understand on the brain level what effect it is having on cognition, then we can see how it can be applied for all sorts of purposes, but first we need to know exactly what it’s doing,” Miller says. “If it’s going to be introduced to society in a big way, we need to know what the potential harms and benefits are.” ■

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