



Is Marijuana as Safe as We Think?

Permitting pot is one thing; promoting its use is another.

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A few years ago, the National Academy of Medicine convened a panel of sixteen leading medical experts to analyze the scientific literature on cannabis. The report they prepared, which came out in January of 2017, runs to four hundred and sixty-eight pages. It contains no bombshells or surprises, which perhaps explains why it went largely unnoticed. It simply stated, over and over again, that a drug North Americans have become enthusiastic about remains a mystery.

For example, smoking pot is widely supposed to diminish the nausea associated with chemotherapy. But, the panel pointed out, “there are no good-quality randomized trials investigating this option.” We have evidence for marijuana as a treatment for pain, but “very little is known about the efficacy, dose, routes of administration, or side effects of commonly used and commercially available cannabis products in the United States.” The caveats continue. Is it good for epilepsy? “Insufficient evidence.” Tourette’s syndrome? Limited evidence. A.L.S., Huntington’s, and Parkinson’s? Insufficient evidence. Irritable-bowel syndrome? Insufficient evidence. Dementia and glaucoma? Probably not. Anxiety? Maybe. Depression? Probably not.

Then come Chapters 5 through 13, the heart of the report, which concern marijuana’s potential risks. The haze of uncertainty continues. Does the use of cannabis increase the likelihood of fatal car accidents? Yes. By how much? Unclear. Does it affect motivation and cognition? Hard to say, but probably. Does it affect employment prospects? Probably. Will it impair academic achievement? Limited evidence. This goes on for pages.

We need proper studies, the panel concluded, on the health effects of cannabis on children and teen-agers and pregnant women and breast-feeding mothers and “older populations” and “heavy cannabis users”; in other words, on everyone except the college student who smokes a joint once a month. The panel also called for investigation into “the pharmacokinetic and pharmacodynamic properties of cannabis, modes of delivery, different concentrations, in various populations, including the dose-response relationships of cannabis and THC or other cannabinoids.”

Figuring out the “dose-response relationship” of a new compound is something a pharmaceutical company does from the start of trials in human subjects, as it prepares a new drug application for the F.D.A. Too little of a powerful drug means that it won’t work. Too much means that it might do more harm than good. The amount of active ingredient in a pill and the metabolic path that the ingredient takes after it enters your body—these are things that drugmakers will have painstakingly mapped out before the product comes on the market, with a tractor-trailer full of supporting documentation.

With marijuana, apparently, we’re still waiting for this information. It’s hard to study a substance that until very recently has been almost universally illegal. And the few studies we do have were done mostly in the nineteen-eighties and nineties, when cannabis was not nearly as potent as it is now. Because of recent developments in plant breeding and growing techniques, the typical concentration of THC, the psychoactive ingredient in marijuana, has gone from the low single digits to more than twenty per cent—from a swig of near-beer to a tequila shot.

Are users smoking less, to compensate for the drug’s new potency? Or simply getting more stoned, more quickly? Is high-potency cannabis more of a problem for younger users or for older ones? For some drugs, the dose-response curve is linear: twice the dose creates twice the effect. For other drugs, it’s nonlinear: twice the dose can increase the effect tenfold, or hardly at all. Which is true for cannabis? It also matters, of course, how cannabis is consumed. It can be smoked, vaped, eaten, or applied to the skin. How are absorption patterns affected?

Last May, not long before Canada legalized the recreational use of marijuana, Beau Kilmer, a drug-policy expert with the RAND Corporation, testified before the Canadian Parliament. He warned that the fastest-growing segment of the legal market in Washington State was extracts for inhalation, and that the mean THC concentration for those products was more than sixty-five per cent. “We know little about the health consequences—risks and benefits—of many of the cannabis products likely to be sold in nonmedical markets,” he said. Nor did we know how higher-potency products would affect THC consumption.

When it comes to cannabis, the best-case scenario is that we will muddle through, learning more about its true effects as we go along and adapting as needed—the way, say, the once extraordinarily lethal innovation of the automobile has been gradually tamed in the course of its history. For those curious about the worst-case scenario, Alex Berenson has written a short manifesto, **“Tell Your Children: The Truth About Marijuana, Mental Illness, and Violence.”**

Berenson begins his book with an account of a conversation he had with his wife, a psychiatrist who specializes in treating mentally ill criminals. They were discussing one of the many grim cases that cross her desk—“the usual horror story, somebody who’d cut up his grandmother or set fire to his apartment.” Then his wife said something like “Of course, he was high, been smoking pot his whole life.”

Of course? I said.

Yeah, they all smoke.

Well . . . other things too, right?

Sometimes. But they all smoke.

Berenson used to be an investigative reporter for the *Times*, where he covered, among other things, health care and the pharmaceutical industry. Then he left the paper to write a popular series of thrillers. At the time of his conversation with his wife, he had the typical layman’s view of cannabis, which is that it is largely benign. His wife’s remark alarmed him, and he set out to educate himself. Berenson is constrained by the same problem the National Academy of Medicine faced—that, when it comes to marijuana, we really don’t know very much. But he has a reporter’s tenacity, a novelist’s imagination, and an outsider’s knack for asking intemperate questions. The result is disturbing.

The first of Berenson’s questions concerns what has long been the most worrisome point about cannabis: its association with mental illness. Many people with serious psychiatric illness smoke lots of pot. The marijuana lobby typically responds to this fact by saying that pot-smoking is a *response* to mental illness, not the cause of it—that people with psychiatric issues use marijuana to self-medicate. That is only partly true. In some cases, heavy cannabis use does seem to cause mental illness. As the National Academy panel declared, in one of its few unequivocal conclusions, “Cannabis use is likely to increase the risk of developing schizophrenia and other psychoses; the higher the use, the greater the risk.”

Berenson thinks that we are far too sanguine about this link. He wonders how large the risk is, and what might be behind it. In one of the most fascinating sections of “Tell Your Children,” he sits down with Erik Messamore, a psychiatrist who specializes in neuropharmacology and in the treatment of schizophrenia. Messamore reports that, following the recent rise in marijuana use in the U.S. (it has almost doubled in the past two decades, not necessarily as the result of legal reforms), he has begun to see a new kind of patient: older, and not from the marginalized communities that his patients usually come from. These are otherwise stable middle-class professionals. Berenson writes, “A surprising number of them seemed to have used only cannabis and no other drugs before their breaks. The disease they’d developed looked like schizophrenia, but it had developed later—and their prognosis seemed to be worse. Their delusions and paranoia hardly responded to antipsychotics.”

Messamore theorizes that THC may interfere with the brain’s anti-inflammatory mechanisms, resulting in damage to nerve cells and blood vessels. Is this the reason, Berenson wonders, for the rising incidence of schizophrenia in the developed world, where cannabis use has also increased? In the northern parts of Finland, incidence of the disease has nearly doubled since 1993. In Denmark, cases have risen twenty-five per cent since 2000. In the United States, hospital emergency rooms have seen a fifty-per-cent increase in schizophrenia admissions since 2006. If you include cases where schizophrenia was a secondary diagnosis, annual admissions in the past decade have increased from 1.26 million to 2.1 million.

Berenson’s second question derives from the first. The delusions and paranoia that often accompany psychoses can sometimes trigger violent behavior. If cannabis is implicated in a rise in psychoses, should we expect the increased use of

marijuana to be accompanied by a rise in violent crime, as Berenson's wife suggested? Once again, there is no definitive answer, so Berenson has collected bits and pieces of evidence. For example, in a 2013 paper in the *Journal of Interpersonal Violence*, researchers looked at the results of a survey of more than twelve thousand American high-school students. The authors assumed that alcohol use among students would be a predictor of violent behavior, and that marijuana use would predict the opposite. In fact, those who used only marijuana were three times more likely to be physically aggressive than abstainers were; those who used only alcohol were 2.7 times more likely to be aggressive. Observational studies like these don't establish causation. But they invite the sort of research that could.

Berenson looks, too, at the early results from the state of Washington, which, in 2014, became the first U.S. jurisdiction to legalize recreational marijuana. Between 2013 and 2017, the state's murder and aggravated-assault rates rose forty per cent—twice the national homicide increase and four times the national aggravated-assault increase. We don't know that an increase in cannabis use was responsible for that surge in violence. Berenson, though, finds it strange that, at a time when Washington may have exposed its population to higher levels of what is widely assumed to be a calming substance, its citizens began turning on one another with increased aggression.

His third question is whether cannabis serves as a gateway drug. There are two possibilities. The first is that marijuana activates certain behavioral and neurological pathways that ease the onset of more serious addictions. The second possibility is that marijuana offers a safer alternative to other drugs: that if you start smoking pot to deal with chronic pain you never graduate to opioids.

Which is it? This is a very hard question to answer. We're only a decade or so into the widespread recreational use of high-potency marijuana. Maybe cannabis opens the door to other drugs, but only after prolonged use. Or maybe the low-potency marijuana of years past wasn't a gateway, but today's high-potency marijuana is. Methodologically, Berenson points out, the issue is complicated by the fact that the first wave of marijuana legalization took place on the West Coast, while the first serious wave of opioid addiction took place in the middle of the country. So, if all you do is eyeball the numbers, it looks as if opioid overdoses are lowest in cannabis states and highest in non-cannabis states.

Not surprisingly, the data we have are messy. Berenson, in his role as devil's advocate, emphasizes the research that sees cannabis as opening the door to opioid use. For example, two studies of identical twins—in the Netherlands and in Australia—show that, in cases where one twin used cannabis before the age of seventeen and the other didn't, the cannabis user was several times more likely to develop an addiction to opioids. Berenson also enlists a statistician at N.Y.U. to help him sort through state-level overdose data, and what he finds is not encouraging: "States where more people used cannabis tended to have more overdoses."

The National Academy panel is more judicious. Its conclusion is that we simply don't know enough, because there haven't been any "systematic" studies. But the panel's uncertainty is scarcely more reassuring than Berenson's alarmism. Seventy-two thousand Americans died in 2017 of drug overdoses. Should you embark on a pro-cannabis crusade without knowing whether it will add to or subtract from that number?

Drug policy is always clearest at the fringes. Illegal opioids are at one end. They are dangerous. Manufacturers and distributors belong in prison, and users belong in drug-treatment programs. The cannabis industry would have us believe that its product, like coffee, belongs at the other end of the continuum. "Flow Kana partners with independent multi-generational farmers who cultivate under full sun, sustainably, and in small batches," the promotional literature for one California cannabis brand reads. "Using only organic methods, these stewards of the land have spent their lives balancing a unique and harmonious relationship between the farm, the genetics and the terroir." But cannabis is not coffee. It's somewhere in the middle. The experience of most users is relatively benign and predictable; the experience of a few, at the margins, is not. Products or behaviors that have that kind of muddled risk profile are confusing, because it is very difficult for those in the benign middle to appreciate the experiences of those at the statistical tails. Low-frequency risks also take longer and are far harder to quantify, and the lesson of "Tell Your Children" and the National Academy report is that we aren't yet in a position to do so. For the moment, cannabis probably belongs in the category of substances that society permits but simultaneously discourages. Cigarettes are heavily taxed, and smoking is prohibited in most workplaces and public spaces. Alcohol can't be sold without a license and is kept out of the hands of children. Prescription drugs have rules about dosages, labels that describe their risks, and policies that govern their availability. The advice that seasoned potheads sometimes give new users—"start low and go slow"—is probably good advice for society as a whole, at least until we better

understand what we are dealing with.

Late last year, the commissioner of the Food and Drug Administration, Scott Gottlieb, announced a federal crackdown on e-cigarettes. He had seen the data on soaring use among teen-agers, and, he said, “it shocked my conscience.” He announced that the F.D.A. would ban many kinds of flavored e-cigarettes, which are especially popular with teens, and would restrict the retail outlets where e-cigarettes were available.

In the dozen years since e-cigarettes were introduced into the marketplace, they have attracted an enormous amount of attention. There are scores of studies and papers on the subject in the medical and legal literature, grappling with the questions raised by the new technology. Vaping is clearly popular among kids. Is it a gateway to traditional tobacco use? Some public-health experts worry that we’re grooming a younger generation for a lifetime of dangerous addiction. Yet other people see e-cigarettes as a much safer alternative for adult smokers looking to satisfy their nicotine addiction. That’s the British perspective. Last year, a Parliamentary committee recommended cutting taxes on e-cigarettes and allowing vaping in areas where it had previously been banned. Since e-cigarettes are as much as ninety-five per cent less harmful than regular cigarettes, the committee argued, why not promote them? Gottlieb said that he was splitting the difference between the two positions—giving adults “opportunities to transition to non-combustible products,” while upholding the F.D.A.’s “solemn mandate to make nicotine products less accessible and less appealing to children.” He was immediately criticized.

“Somehow, we have completely lost all sense of public-health perspective,” Michael Siegel, a public-health researcher at Boston University, wrote after the F.D.A. announcement:

Every argument that the F.D.A. is making in justifying a ban on the sale of electronic cigarettes in convenience stores and gas stations applies even more strongly for real tobacco cigarettes: you know, the ones that kill hundreds of thousands of Americans each year. Something is terribly wrong with our sense of perspective when we take the e-cigarettes off the shelf but allow the old-fashioned ones to remain.

Among members of the public-health community, it is impossible to spend five minutes on the e-cigarette question without getting into an argument. And this is *nicotine* they are arguing about, a drug that has been exhaustively studied by generations of scientists. We don’t worry that e-cigarettes increase the number of fatal car accidents, diminish motivation and cognition, or impair academic achievement. The drugs through the gateway that we worry about with e-cigarettes are Marlboros, not opioids. There are no enormous scientific question marks over nicotine’s dosing and bio-availability. Yet we still proceed cautiously and carefully with nicotine, because it is a powerful drug, and when powerful drugs are consumed by lots of people in new and untested ways we have an obligation to try to figure out what will happen.

A week after Gottlieb announced his crackdown on e-cigarettes, on the ground that they are too enticing to children, Siegel visited the first recreational-marijuana facility in Massachusetts. Here is what he found on the menu, each offering laced with large amounts of a drug, THC, that no one knows much about:

- Strawberry-flavored chewy bites
- Large, citrus gummy bears
- Delectable Belgian dark chocolate bars
- Assorted fruit-flavored chews
- Assorted fruit-flavored cubes
- Raspberry flavored confection
- Raspberry flavored lozenges
- Chewy, cocoa caramel bite-sized treats
- Raspberry & watermelon flavored lozenges
- Chocolate-chip brownies.

He concludes, “This is public health in 2018?” ☹

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