



## The Effects of Marijuana

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### Introduction

The first reports of using marijuana medically date from 2737 B.C. when it was mentioned in ancient medical texts in China.<sup>1</sup> Ancient texts from India, Africa, Greece and elsewhere refer to its medicinal use.<sup>2</sup> Modern western medicine first became aware of medical marijuana when an Irish doctor, William O'Shaughnessy, wrote about it after returning from India in 1842.<sup>3</sup> The United States Pharmacopeia (USP) is the official register of legitimate medicinal products for the US; marijuana was added in 1851. It was recommended in those days for pain relief, muscle relaxation, appetite stimulation, and sedation. Concerns about its recreational hallucinogenic use led to it being criminalized in the US in 1937 and removed from the USP in 1942. In 1970 it was listed as a Schedule 1 drug, meaning it has no accepted medical use and many dangers.<sup>4</sup>

In spite of this legal classification, marijuana remained in use within some alternative medicine circles, as well as becoming the most widely used illegal drug in the US.<sup>5</sup> Such recreational use continues to increase among adolescents and young adults. Controversy over its legal status came to greater public attention when California passed Proposition 215 in 1996.<sup>6</sup> Now 20 states and the District of Columbia have voted to legalize marijuana for medicinal purposes.<sup>7</sup> Such an approach raises concerns about whether any medical therapy should be approved by popular vote rather than expert review as normally carried out by the Food & Drug Administration (FDA). Two states have legalized its use for recreational purposes, and a recent poll found that three-quarters believe marijuana use will be legal nationwide soon.<sup>8</sup>

Before examining the details of this controversy, clarification is needed on a number of different terms used in this debate, particularly "medical marijuana." This paper is concerned primarily with the use of plant material from *Cannabis sativa* either to get high or to treat various conditions, particularly chronic pain, weight loss, and glaucoma. The plant is most usually smoked, although it is also consumed in other ways, being mixed into various foods like brownies and cookies. The term "medical marijuana" will be used here for this specific use. Marijuana is used in the same ways (primarily smoked) for recreational purposes to get high, relax, and trigger other perceptual changes. Together, these are called marijuana's psychoactive effects and are viewed as its benefits by recreational users but (usually) its adverse effects by medicinal users. Whenever marijuana is used without being prefaced by 'medical,' its recreational use will be intended.

### Marijuana's Many Components

The evidence regarding the effectiveness and safety of medical marijuana is further complicated by two related research areas that have received considerable attention in recent decades. One of these is the path followed in the development of pharmaceutical drugs from many traditional remedies. It has been estimated that about half of the prescription drugs available today originally were identified in natural sources such as plants and marine organisms. The

development of aspirin is typical of what happens here: the bark of the willow tree had been used for centuries as a natural remedy for the treatment of headaches and joint inflammation.<sup>9</sup>

As pharmaceutical sciences developed in the nineteenth century, scientists became concerned about the large number of different compounds in natural remedies and the wide variability of their amounts from one batch to another. They started to purify the active ingredients and put standard doses into products, aiming to produce more effective and safer medications. At the German company, Bayer, a substance called “salicylic acid” was purified from willow bark and found to have pain relieving effects. However, it was also very irritating to the stomach. They found that by chemically modifying it slightly, producing acetylsalicylic acid, they could reduce this adverse effect yet retain its effectiveness. They had made aspirin, which is now manufactured completely from chemical starting materials without using willow bark.

The same general approach has been taken with the cannabis plant. In 1964, THC (short-hand for delta-9-tetrahydrocannabinol) was identified as the primary psychoactive ingredient in marijuana. Another very important chemical in marijuana is cannabidiol (CBD). When THC and CBD occur together, such as in marijuana, CBD appears to modify some of THC’s effects, such as reducing its ability to cause anxiety or impair memory.<sup>10</sup> However, natural remedies often contain many other ingredients, some of which also affect the human body. Cannabis is an extreme example of this. It contains about 60 “cannabinoids,” chemicals related to THC and CBD, and also more than 400 other chemicals from at least 18 different chemical families. For this reason, the plant material has been called “a complex chemical slush.”<sup>11</sup> When the plant is smoked, it has been estimated that the smoke contains over 2,000 chemical compounds. Given so many different chemicals, smoking marijuana leads to numerous different effects in different parts of the body and is one of the reasons why it can have many different adverse effects.

On top of the large mixture of compounds in marijuana, the amount of any one active ingredient varies considerably. The amount of active ingredient in a particular species of plant is as variable as the weather (and partly because of the weather). When farmers and cultivators get involved, they may try to influence how much of a particular compound their plants contain. The relative quantity of THC and CBD in plant material has been changing as growers seek to provide marijuana with maximal psychoactive effect. Due to cannabis cultivation, the average THC content in marijuana has increased from 2 percent in 1980 to 4.5 percent in 1997 to 8.55 percent in 2006.<sup>12</sup> A 2010 study conducted in Japan found that this average had increased to 11.2 percent, with one batch containing 22.6 percent THC.<sup>13</sup> Overall, THC content is believed to range from 3 to 25 percent.<sup>14</sup> Thus, not only can marijuana lead to a large number of effects, these can vary from batch to batch because of differing concentrations of the active ingredients.

### **Pharmaceutical Developments**

Because of limitations like those above, pharmacy has moved away from using plant materials to using formulations with precisely known doses, i.e. tablets, capsules, metered aerosol sprays, etc. If a plant chemical causes an effect in the body, the safest way to use it is when known quantities are delivered giving reproducible effects. As with aspirin, scientists looked for ways to make synthetic forms of THC. In 1985, chemically manufactured THC was approved as the drug dronabinol (Marinol). Another closely related drug, nabilone (Cesamet), was released the same year. These were approved for treating chemotherapy-related nausea and vomiting and AIDS-related loss of appetite. Another pharmaceutical called nabiximols (Sativex) has been

available in Canada since 2005 to treat pain from cancer or multiple sclerosis, and is now approved in 10 countries.<sup>15</sup> This is a liquid mixture of THC and CBD that patients spray into their mouths in an attempt to mimic the way smoking marijuana delivers its active ingredients. The information leaflet for nabiximols has a long list of serious adverse effects. Finally, rimonabant (a synthetic cannabinoid) has been available in Europe since 2006 to treat nicotine dependence and reduce appetite in obese people.<sup>16</sup> It has not been approved in the US because of concerns that it causes depression and suicidal behavior.

Advocates of medical marijuana claim the plant material is preferable to purified drugs because the different components will naturally interact with one another to minimize negative effects and promote good effects. However, there is no guarantee of this, and the large number of ingredients may exacerbate the side effects. Regardless, even though some of these purified drugs are effective, none of them have become widely used, in large part because of their serious adverse effects. At the same time, researchers claim that “future advances will result from developing highly selective, pure pharmaceuticals taken orally to bypass the health consequences of smoke exposure.”<sup>17</sup> Marijuana may lead to health benefits, but in the same indirect way that willow bark led to aspirin.

While currently available pharmaceuticals from marijuana have limitations, much research is underway to develop other purified pharmaceuticals. Researchers are also seeking to understand how marijuana affects humans and have identified a naturally occurring biological system. Marijuana stimulates this system, so it has been called the endogenous cannabinoid system, or endocannabinoid system. A whole set of compounds and networks on which they work have been found throughout the human body, but especially in the brain.<sup>18</sup> Much like the more familiar systems involving adrenaline or steroid hormones, these help us understand how the body normally works and why external agents (like drugs) have their effects. The key compound in this system is called anandamide (from the Sanskrit word meaning pleasure or delight). It was identified in 1992, so research is in its early stages with this whole system. This information helps researchers understand how marijuana works, and also explains why its effects are experienced throughout the body and also explains why marijuana can have a wide variety of adverse effects.

### **Effectiveness**

After California voters legalized medical marijuana in 1996, the White House Office of National Drug Control Policy asked the Institute of Medicine (IOM) to review the scientific evidence on marijuana. IOM is a private, nonprofit organization that advises the federal government on controversial medical matters. Its report was issued in 1999 and concluded that, “Until a nonsmoked rapid-onset cannabinoid drug delivery system becomes available, we acknowledge that there is no clear alternative for people suffering from *chronic* conditions that might be relieved by smoking marijuana, such as pain or AIDS wasting.”<sup>19</sup> They highlighted that studies on smoked marijuana itself were lacking and called for further research into this area specifically.

In 2005, the British Royal College of Physicians found almost no evidence to support medical marijuana, primarily because very little research had involved participants smoking marijuana.<sup>20</sup> The focus of studies had primarily been on pharmaceutical cannabinoids, especially dronabinol. However, in 2007 the first randomized controlled trial of smoking

marijuana was published and since then a few more have been reported.<sup>21</sup> A 2013 review of this research identified six trials involving smoked marijuana.<sup>22</sup> Overall, these found that smoking marijuana showed statistically significant improvements in pain, particularly chronic pain. However, the reviewers also concluded that the research is sparse and has important limitations. Most of the studies were very small (fewer than 50 patients), used cigarettes with varying amounts of THC, and individual patient responses varied considerably. While serious adverse effects were rare, mild-to-moderate adverse effects were common, especially drowsiness, headache, dry mouth, dizziness, dry eyes, and difficulty with concentration or memory. The reviewers concluded, as most recent authorities have, that “medical cannabis should be considered only when treatment failure with standard therapy has occurred or when adjunctive therapy is appropriate.”<sup>23</sup> These conclusions highlight an important reality: even when evidence supports medical marijuana, its adverse effects can be a significant problem.

The other common use of medical marijuana is for muscle spasms in patients with multiple sclerosis. Here, almost all the research has been conducted with the pharmaceutical cannabinoid, nabiximols, and involved patients who were not getting relief from conventional medications. A very small number of trials have been conducted, finding nabiximols to effectively relieve muscle spasms in multiple sclerosis patients. Few serious adverse effects with nabiximols were reported, and mild-to-moderate adverse events resolved quickly. Based on this evidence, the reviewers concluded that nabiximols or medical marijuana should be reserved for multiple sclerosis patients for whom standard therapies do not relieve their muscle spasms.<sup>24</sup>

### **Adverse Effects of Marijuana**

Marijuana is used recreationally for its psychoactive effects. Many claim these are positive, but a growing list of negative psychiatric effects have been documented. These are supported by new forms of brain scanning studies that show serious problems. Even casual use of marijuana by young adults has been shown to reduce the size of specific regions of the brain important for emotion and motivation. While these changes have not been found in all studies, this may be due to differences in the study methods. An April 2014 study involved several different ways of measuring this effect and found that the effect on brain structure was clear and dose-dependent.<sup>25</sup> One of the principal investigators concluded, “This study raises a strong challenge to the idea that casual marijuana use isn’t associated with bad consequences.”<sup>26</sup> Based on this and other published studies, the researcher went on to state, “I’ve developed a severe worry about whether we should be allowing anybody under age 30 to use pot unless they have a terminal illness and need it for pain.”<sup>27</sup>

Debate over marijuana often centers on its adverse effects. Those in favor of its use point out that it is the most commonly used illegal drug in the world and yet has not led to anything like a pandemic of adverse effects.<sup>28</sup> Although adolescents who use marijuana heavily tend to also abuse it and other drugs as adults, a direct causal link that would support it being a “gateway drug” has not been established.<sup>29</sup> It is also pointed out that no one has reported a lethal overdose from marijuana.<sup>30</sup> Recent research now shows that the body’s natural endocannabinoid system does not influence the brainstem which controls vital organ functions and thus direct lethal effects are not to be expected.<sup>31</sup>

While people are highly unlikely to poison themselves with marijuana, this does not mean it is safe. Claims that smoking cannabis is an innocent recreational pastime that has been the victim

of ideological and political persecution are far from the truth. Evaluating this area is challenging because of the way claims are made. Many people claim they have used marijuana safely. However, they may have had negative effects that they attributed to other things, like other substances they consumed at the time or preexisting conditions they had. To account for those, researchers carry out controlled studies. However, these are very difficult with something like marijuana. Researchers face legal and ethical problems doing any research on an illegal drug. Even when possible, getting people to accurately report on an illegal activity can be challenging. Also, marijuana is often used in combination with other drugs (either for treating medical conditions or when used recreationally), making it difficult to separate out marijuana's effects. In addition, since the amount of active ingredients varies greatly in marijuana, as does how it is consumed, even further variation in the effects occurs.

Marijuana smoke contains thousands of chemicals, some of which are toxic and found in similar or higher amounts in tobacco smoke.<sup>32</sup> For this reason, the risk of cancer among marijuana smokers has been studied extensively. A study published in 1999 reported that the risk of head and neck cancer in adults who had smoked marijuana at any time was 2.6 times higher than for those who never used marijuana.<sup>33</sup> However, later studies did not find this increased risk and likewise, studies into the risk of lung cancer have been inconsistent. At this point, the impact of smoking marijuana on someone's risk of cancer is unclear, although cancer-causing chemicals are found in its smoke.

It is ironic, though, that at the same time as the dangers of tobacco smoking are leading to increased restrictions, restrictions on another smoking habit are being relaxed. Marijuana smokers typically breathe in the smoke more deeply, raising concerns about its damaging effects on the lungs.<sup>34</sup> Persistent cough, bronchitis, emphysema and other respiratory diseases can develop from chronic marijuana smoking, especially among those who also smoke tobacco.

The impact of smoking marijuana on the heart is better established. Studies have found that marijuana increases heart rate (by an average of 19 beats/minute) but decreases variability in heart rate.<sup>35</sup> This is particularly problematic in patients with heart disease, especially if they are taking other cardiac medications. Marijuana has complex and varying cardiovascular effects, some of which may even be positive. Because of the uncertainty in this area, one review concluded: "Patients at high risk for coronary heart disease should be advised to avoid using cannabis."<sup>36</sup> The patient information leaflet which comes with nabiximols warns against its use in patients with various cardiovascular diseases.<sup>37</sup> Many other physical effects of smoking marijuana are being investigated, but we will now turn to the psychiatric adverse effects.

Evidence of physical changes in the brain adds weight to other studies that link marijuana use with cognitive and psychiatric problems. The endocannabinoid system plays a crucial role in brain development during adolescence. Adolescents who start smoking marijuana have higher rates of poor academic performance, behavioral problems, memory problems, reduced attention, depression and anxiety.<sup>38</sup> However, not everyone experiences these effects, which is part of the challenge here. "Although cannabis is an enjoyable diversion for most, it is linked to self-medication, addiction, or mental illness in a few, particularly those who start young."<sup>39</sup> The social policy challenge is how much we should place some people at risk of harm just so that others can enjoy themselves.

One area of particular concern is an association between marijuana use and psychosis. The relationship between the two is complicated, and considerable debate has occurred over whether marijuana causes psychosis or triggers it in people who are already predisposed to it. A 2013 review concluded: "It is now known beyond doubt that cannabis acts as a component cause of psychosis, that is, it increases the risk of psychosis in people with certain genetic or environmental vulnerabilities, though by itself, it is neither a sufficient nor a necessary cause of psychosis."<sup>40</sup> Apart from genetic factors, smoking marijuana at younger ages and using forms with higher amounts of THC increase this risk. The risk is real; what is unclear is which young people will develop psychosis, or schizophrenia, because they used marijuana.

In addition to specific psychiatric illnesses, about 7-10 percent of regular recreational users of marijuana become dependent, where they need more to get the same effect.<sup>41</sup> Another 10 percent become addicted, with "its relaxing properties transforming into a constant need that interferes with interpersonal and occupational advancement."<sup>42</sup> Chronic users who stop marijuana can trigger withdrawal symptoms, with effects like irritability, anxiety, aggression, restlessness, insomnia, nausea, and cramping.<sup>43</sup> Compared to other abused drugs, these can be mild and short-lived for some, but for others they can be long-lasting. A formal cannabis withdrawal syndrome was added to the 2013 version of the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders (DSM-V)*.<sup>44</sup>

Many of the psychiatric side effects have indirect social consequences. Just one will be highlighted here. Like alcohol, marijuana negatively effects how well people drive or carry out complex motor activities. In spite of this, driving under the influence of marijuana is widespread. In parts of California, 20 percent of nighttime weekend drivers have tested positive for THC.<sup>45</sup> A systematic review examined studies involving actual car crashes where drivers were tested for recent use of marijuana.<sup>46</sup> This found that the risk of drivers being in a serious or fatal crash was almost doubled if they had smoked marijuana recently compared to those who had not.

A 2014 review examined controlled research studies into the impact of smoking marijuana on driving in simulators.<sup>47</sup> Numerous studies demonstrated driver impairment after participants were allowed to smoke as much marijuana as they wished. Driving impairment was highest in the two hours after smoking, but was still seen six hours after smoking. Some, but not all, studies have shown impairment the day after smoking marijuana. When alcohol and drugs that impair psychomotor skills are used with marijuana, the impairment is even worse. The reviewers concluded that patients using medical marijuana (who typically smoke less than recreational users) should be warned against driving after smoking medical marijuana.

## **Conclusion**

All of these data, and a lot more that could have been included, point to marijuana being a drug with serious adverse effects. While many people may not experience any of them, their range and extent point to the legalization of marijuana being a very risky enterprise. Recent discoveries about the endocannabinoid system, and its main component, anandamide, help explain why marijuana impacts the brain so significantly, and the whole body in general. While our brains and bodies make and use cannabinoids, this in no way justifies using marijuana. It is a crude and poor replacement for the way our bodies have been carefully created. "Exogenous plant-derived THC is a sledgehammer compared with anandamide's delicate chisel, the former

causing marked disruption of neuronal signaling and circuit dynamics in the finely tuned endogenous system and inducing addiction in the susceptible.”<sup>48</sup> Nowhere would we allow bulldozers to run amok through a beautifully designed garden, even if some found pleasure in that freedom.

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<sup>3</sup> J. Michael Bostwick, “Blurred Boundaries: The Therapeutics and Politics of Medical Marijuana,” *Mayo Clinic Proceedings* 87.2 (2012): 172-86.

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<sup>17</sup> Bostwick, “Blurred Boundaries,” p. 179.

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