

# Medical Marijuana: Weeding Out The Truth

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### Abstract

The advent of medical marijuana as a therapeutic tool remains a work in progress. The Canadian courts enacted the Marihuana for Medical Purposes Regulations (MMPR) on April 1, 2014, but the government of Canada has not endorsed the use of dried cannabis as a medicine. Despite the popular conception that dried marijuana is not addictive, there is clinical evidence of a cannabis use disorder as defined by the Diagnostic and Statistical Manual of Mental Disorders V and the World Health Organization. Indeed, the status of dried cannabis as a therapeutic agent is complicated and controversial. Cannabinoids, the primary psychoactive compound in cannabis, appear to possess a variety of beneficial medicinal effects, particularly as adjuvant analgesics, but also demonstrate an adverse side effect profile, including potential psychopathologies and toxicities. The merit of dried cannabis as a pharmacologic agent has been further compromised by questions of route of administration, dosing and efficacy. These observations highlight a double bind: the discrepancy between the law that sanctions the use of dried cannabis as a medicine, and the responsibility of physicians to adhere to evidence-based practice. The advent of regulated legal access to marijuana expected by July of 2018 mandates a robust understanding of this dilemma.

Cannabis sativa, acquired from hemp plants, has been used recreationally and therapeutically since 2800 BC, but the regulatory status of this substance currently remains in limbo.<sup>1,2</sup> The Canadian courts enacted the Marihuana for Medical Purposes Regulations (MMPR) on April 1, 2014 in order to expedite the dispensation of dried marijuana

for specified medical purposes.<sup>3</sup> However, the Government of Canada neither endorses nor approves dried cannabis as a medicine.<sup>4</sup>

Although dried cannabis is generally perceived by the public as a non-addictive substance, there is clinical evidence of a distinct cannabis use disorder as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM) V and the World Health Organization.<sup>5-7</sup> This cannabis use disorder can be complicated by potential psychopathologies, including the precipitation of psychosis, as well as toxicities impacting upon major organ systems.<sup>1</sup>

On the other hand, there is no question that cannabinoids appear to possess a range of beneficial therapeutic effects, particularly as adjuvant analgesics, allowing for a reduced dosage of pain medication. It has been demonstrated that cannabinoids produce their pain relieving qualities by interfacing with the opioid system and by preventing the development of tolerance to narcotics.<sup>1,8,9</sup> Concurrently, animal experimentation has shown that the endogenous cannabinoid system, called the endocannabinoid system, can also act independently in the suppression of chronic pain and may be superior to the opioid system in terms of pain relief.<sup>1,10</sup>

A complex homeostatic balance including cannabinoid receptors type one (CB1) and two (CB2), physiologic receptor activators or agonists, known as endocannabinoids, exogenous agonists, including  $\Delta^9$ -tetrahydrocannabinol (THC), and antagonists or receptor blockers have been defined.<sup>1</sup> From a functional perspective, endocannabinoids are released post-synaptically as a “retrograde messenger” to inhibit presynaptic calcium channels leading to decreased neurotransmitter release.<sup>1</sup> The net effect of the endocannabinoid system is to function as a “rheostatic” mechanism modulating neuronal excitability.<sup>1,11</sup>

Smoking dried marijuana can flood the endocannabinoid system with THC, mimicking the brain’s own natural cannabinoids and thus relieving pain.<sup>1,12</sup> It also directly stimulates the brain’s final common pathway for addiction in the mesolimbic reward system. Since all drugs that lead to addiction raise hedonic tone and increase dopamine in this brain area, the end result of these neuroadaptations is a more rapid high than can be produced by the body’s natural processes.<sup>12</sup> These brain changes are more likely to affect those individuals who are either genetically or environmentally vulnerable to addiction, with the latter category including persons afflicted with mental illness.<sup>1</sup>

The administration of cannabis by the inhalation route further complicates the issue of addictive liability because smoking is not a safe vehicle for pharmaceutical adminis-

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tration.<sup>1,13,14</sup> Marijuana smoke not only contains hundreds of chemicals that are potentially toxic to the respiratory system and other organs, but it is also a medium allowing for a rapid rate of diffusion of THC through the lungs into the nervous system, causing intoxication. As a consequence, an increased risk of motor vehicle crashes, poor school or work performance, and cognitive impairments have been more prevalent in active users.<sup>14</sup> Indeed, a long-term retrospective cohort study has reported that smoking cannabis is associated with an increased risk of lung cancer (hazard ratio: 2.12; 95% CI (1.08-4.14)).<sup>15</sup> Acute coronary events in young adults have also been linked to smoking marijuana (hazard ratio: 1.9; 95% CI (0.6-6.3)).<sup>16</sup> Furthermore, dried cannabis has also been contraindicated in individuals under the age of 25, those who have a history of psychosis, addictive disease, cardiovascular disease, respiratory disease, or those who are pregnant, planning to become pregnant or breastfeeding.<sup>14</sup>

The duration of analgesic action of smoked cannabis has been estimated at about three to four hours.<sup>17,18</sup> One controlled trial found that 25 milligrams, or one inhalation of 9 percent THC, relieved neuropathic pain with minimal intoxication. It has been suggested that four times daily dosing at this level be implemented to treat chronic neuropathic pain.<sup>17,18</sup> Indeed, a single inhalation of cannabis has been reported to produce a serum level of 45 micrograms per liter of THC, whereas levels associated with euphoria are in the range of 50-100 micrograms per liter.<sup>14</sup> Health Canada has endorsed prescriptions of up to 5 grams, or 5000 milligrams, per day, and licensed producers have been marketing potent strains containing 30 percent THC, thus raising issues of safety.<sup>14,17</sup>

Even a fixed dose of THC in a cannabis cigarette contains more than 480 compounds, including at least 66 cannabinoids, of indeterminate utility and harm.<sup>19</sup> The method and depth of inhalation, the length of time the breath is held, individual vital capacity, escaped smoke, and other factors further complicates precise dosing.<sup>14</sup>

There have been only five randomized controlled trials of smoked cannabis.<sup>18,20-23</sup> They range in duration from one to fifteen days, with a combined total of 182 participants comparing smoked cannabis with placebo rather than an alternative treatment.<sup>17,18,20-23</sup> Given this caution, researchers have suggested that cannabis proved more efficacious than placebo in managing neuropathic pain secondary to HIV infection and trauma, and in managing the spasticity associated with multiple sclerosis. It has been postulated that cannabis be considered for palliative care or reserved for patients whose pain is refractory to other pharmaceutical therapies.<sup>17</sup> However, it has also been emphasized that there is limited evidence of benefit from smoked cannabis in common conditions such as fibromyalgia or back pain, particularly when these maladies are associated with mental illness or substance use disorders.<sup>17,24</sup>

The College of Family Physicians of Canada, The Canadian Medical Association and The Federation of Medical Regulatory Authorities of Canada have universally opposed the use of smoked cannabis as a medicine.<sup>17</sup> However, these objections do not extend to the medical benefit of cannabis products in general. The pharmaceutical cannabinoid nabilone (Cesa-

met), a synthetic structural analogue of THC, has been used therapeutically as an appetite stimulant, adjunct analgesic for neuropathic pain, and anti-emetic.<sup>1</sup> Nabiximols (Sativex), a 1:1 mixture of THC and cannabidiol, has been approved by Health Canada as an antispasmodic for the treatment of multiple sclerosis.<sup>1</sup> Additionally, synthetic THC (dronabinol, Marinol) has been marketed as a Schedule III preparation, defined as drugs with a moderate to low potential for physical and psychological dependence, for similar indications in the United States.<sup>1</sup> These organizations have also continued to support additional research by Health Canada with a view to developing preparations with limited addictive liability, analgesic and anxiolytic efficacy, and other possible indications.<sup>25</sup> Non-psychoactive cannabinoids such as cannabidiol remain the subject of intense investigative interest, as does the function of the endocannabinoid system in the tonic regulation of food intake, cardiovascular tone, learning, as well as analgesia.<sup>1</sup> These inquiries recognize the phylogenetic persistence of the cannabinoid system and argue against abandoning cannabis as a useful medical substrate.

Moving forward, the regulated legal access to marijuana expected by July of 2018 does not relieve medical practitioners of their role as “gatekeepers” of the health-care system.<sup>25</sup> It has been suggested that timely access to dried cannabis for medical purposes can be achieved through a single, non-medical system and that patient requests for information might be satisfied by those involved in such retail distribution. However, there has been equal concern that the lack of physician supervision might blur the line between therapy and recreation, and open the door to misuse and possible dependency.<sup>25</sup> These considerations, combined with the stigma associated with having to purchase cannabis for medical purposes from a non-medical retail dispensary create a conundrum that has yet to be resolved. Whether distributed by a sales person or medical professional, the removal of prohibitions on dried marijuana involves risks to health, both known and unknown.<sup>1,25</sup> The evidence for the use of dried cannabis for therapeutic purposes has not yet met the standard set by the Food and Drug Regulations for pharmaceuticals in the Canadian marketplace, and there is a great incentive for further research that examines the drug as a bonafide pharmaceutical.

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