

MAYO CLINIC  
PROCEEDINGSCannabis—A Valuable Drug That Deserves  
Better Treatment

About 150 years ago, a French psychiatrist, J. J. Moreau, conducted a novel clinical experiment in which he administered hashish to humans. His volunteers, including Moreau himself, experienced “occurrences of delirium or of actual madness. . . .” He concluded that “There is not a single, elementary manifestation of mental illness that cannot be found in the mental changes caused by hashish. . . .”<sup>1</sup> In contrast, most marijuana users today will presumably state that their senses appear enhanced, concomitant with an increase in relaxation and euphoria; while forgetfulness is enhanced, their focus on their surroundings is augmented.<sup>2</sup> These surprisingly contrasting experiences are due to the ingestion or smoking of products of the same plant, and neither is inaccurate if one considers the difference in doses presumably taken, the presence in cannabis (a term that includes both marijuana and hashish preparations) of at least 2 compounds with opposite effects— $\delta$ -9-tetrahydrocannabinol (THC), the psychoactive component, and cannabidiol (CBD), a nonpsychoactive constituent—and the different users’ susceptibilities to the effects of the drug. It is also well known that the activity of THC is biphasic in many assays—low and high doses may cause opposite effects.<sup>3</sup> Presumably the Moreau volunteers consumed (orally) huge amounts of North African hashish, which has a very high concentration of THC. However, North Americans and Europeans today generally smoke cannabis and can titrate (ie, finely adjust) the level of the psychotropic effects and thus do not typically reach the high psychotic state.

Cannabidiol modifies the effects of THC. Thus, CBD blocks anxiety provoked by THC<sup>4</sup>; cannabis with high CBD content is associated with fewer psychotic experiences than cannabis with low CBD content,<sup>5</sup> and CBD attenuates the memory-impairing effects produced by THC.<sup>6</sup> Cannabidiol is also a potent anti-inflammatory compound and has an anti-autoimmune diabetes effect (in a mouse model).<sup>7</sup> However, most users are not aware of the amounts of THC and CBD in the cannabis they use. Most of the marijuana sold illegally today in the United

States actually contains no CBD, or very low amounts of it, and the THC levels in marijuana may vary from about 3% to 25%. These large variations of THC levels are due mainly to the different sources of the drug, but even samples from the same source may vary, depending on the portion of the plant and the plant’s age. Hence, much of the statistics based on “street users” is quite useless.

Modern medical practice is based on the administration of defined levels of drugs. Most physicians are not comfortable prescribing a plant product with varying concentrations of active pharmacological compounds, and certainly no other prescribed drug is administered by smoking. However, from a medical point of view, marijuana is a valuable drug. It lowers certain types of pain; has antianxiety, anti-inflammatory, and antispastic effects; and enhances appetite.<sup>3</sup> Its adverse effects are also well known. It can precipitate anxiety attacks or even schizophrenia in susceptible individuals, although, surprisingly, the extent of schizophrenia in the general population does not seem to have increased in parallel with the very wide use of marijuana for recreational purposes. The United Nations Office on Drugs and Crime has estimated that in 2006 cannabis was used (presumably mostly for recreation) by 166 million adults.<sup>8</sup> Dependence to cannabis has been noted in about 9% of heavy users.<sup>8</sup>

Recent research has shown that many of the therapeutic effects of cannabinoids are not due solely to the cannabinoid CB1 receptors, whose stimulation causes the cannabis psychoactivity, but also to CB2 receptor activation, which causes no psychoactivity but attenuates inflammation, decreases injury, and accelerates regeneration in many disease states.<sup>9</sup> However, essentially all the published research on specific CB2 stimulation has been done in animals.

The current issue of *Mayo Clinic Proceedings* has 2 articles on cannabis. One of them, by Simonetto et al, deals with the rather uncommon severe vomiting seen in some “street marijuana” users.<sup>10</sup> The other, by Bostwick, is a general review on the therapeutic

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effects of cannabis and the politics of medical use of marijuana.<sup>11</sup>

Hyperemesis is not an acute effect of cannabis smoking. In the case series reported by Simonetto et al,<sup>10</sup> hyperemesis appeared in most patients after more than 2 years of smoking at least once a week. Surprisingly, most patients (83%) had lost weight (median loss, 12 kg), and 23% had diarrhea. These are not effects expected in cannabis users. On the contrary, THC is known to block vomiting,<sup>12</sup> enhance appetite,<sup>13</sup> and cause constipation.<sup>14</sup> The authors do not discuss these observations, but it is tempting to speculate that an endogenous CB1 receptor antagonist-like compound is produced as a result of prolonged THC use, perhaps involving some form of a novel "cannabinoid immune-type reaction." If this speculation is correct, such an endogenous CB1 receptor antagonist would be expected to block some physiologic processes affected by THC. Indeed, synthetic CB1 receptor blockers are known to cause weight loss,<sup>15,16</sup> induce nausea,<sup>15</sup> and increase defecation.<sup>17</sup> Other mechanisms of the hyperemesis are also conceivable. Simonetto et al suggest that "the central effects of long-term cannabis use on the hypothalamic-pituitary-adrenal axis might play a major role in the development of [cannabinoid hyperemesis]." While these suggestions have a certain intellectual appeal, we should not forget that the quality of the material used by these patients is unknown and that we know nothing about the presence (or levels) of additional cannabis constituents or foreign substances (most commonly pesticides) with unknown pharmacological effects that may have been included in the street marijuana consumed. Hence, although the direct connection between hyperemesis and cannabis seems reasonable, full proof is lacking. Nevertheless, the authors' viewpoint is of clinical importance: "Given the prevalence of cannabis use worldwide, the very recent recognition of [cannabinoid hyperemesis], and the paucity of [cannabinoid hyperemesis] literature, it is likely that this disease is under-recognized and underdiagnosed."

The article by Bostwick deals with the therapeutics and politics of medical use of marijuana. He has critically and very well presented both aspects. In most countries, including the United States, marijuana is a Schedule I controlled substance (high potential for abuse; no currently accepted medical use). Like individuals, countries can also be hypocritical. In contrast to marijuana, THC, also called dronabinol, is a Schedule III drug (has potential for abuse less than that of substances in Schedules I or II). Dronabinol is an approved drug in the United States and numerous other countries for several medical conditions, mostly as an antiemetic during cancer chemotherapy and to improve appetite in

patients with human immunodeficiency virus. Nabilone, marketed as Cesamet, a synthetic analogue of THC, is actually a Schedule II drug (high potential for abuse) and is prescribed for similar indications. It parallels the effects of THC, although it is more potent and its activity persists longer than that of THC. A 50:50 THC:CBD mixture of cannabis plant origin (named Sativex) is in medical use as an oral spray in many European countries, as well as in Canada. There is also a plethora of articles on the therapeutic effects of marijuana. For example, Abrams et al<sup>18</sup> recently showed that "vaporized cannabis augments analgesia in individuals with chronic pain on a treatment regimen of stable doses of sustained-release morphine or oxycodone, and that the mechanism of augmentation is not explained by elevation of plasma opioid concentrations or inhibition of opioid metabolism." Aren't all the aforementioned evidence of "currently accepted medical use"?

In his article, Bostwick points out that "[a]s the mysteries of the endocannabinoid system were unraveled . . . , a rationale for both its recreational and sweeping medical effects has emerged," and he therefore recommends that marijuana should be rescheduled as something other than Schedule I. This rescheduling, Bostwick argues, would facilitate future research on marijuana. Whether intended by him or not, it also would make marijuana available by prescription. The presence of 2 active compounds in cannabis may open the possibility of individualized treatment. By modifying the ratio of THC:CBD, it should be possible to establish a personal dose for specific patients, depending on the diagnosis and the individual susceptibility. However, to make such treatment possible, we should demand that medical marijuana be supplied with an analysis of at least its 2 major constituents and that a variety of mixtures should be available. Various types of marijuana preparations for oral administration should also be attainable.

Research on specific CB2 receptor agonists promises to lead to novel drugs, which may, in part at least, diminish the need for medical marijuana. Nevertheless, I believe that medical marijuana as a therapeutic entity is here to stay. It is being used in numerous medical conditions, at times with considerable success. Are we entitled to neglect a valuable drug?

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