

# Chapter I.

## Cannabis and cannabinoids for medical, scientific and “recreational” use: risks and benefits

1. The Governments of several States have passed legislation allowing patients suffering from certain health conditions (such as terminal cancer, epilepsy and neurological illnesses) to use cannabinoids and cannabis to treat the symptoms of their illnesses (see box 1 for definitions of key terms). Some medical cannabis programmes have had an adverse impact on public health because they have not been effectively regulated in line with the international

drug control treaties, resulting in the diversion of cannabis to non-medical use. In several countries, poorly regulated medical cannabis programmes and the associated lower perception of risk may have contributed to the legalization of non-medical cannabis use, contrary to the international drug control treaties (see para. 5 and sections H–K below).

### Box 1.

#### Some key terms

1. “Cannabis and its derivatives” describes all products derived from the cannabis plant. Cannabis plant products include the flowering tops (marijuana), compressed cannabis resin (hashish), cannabis oils, concentrated cannabis extracts (waxes) and edible preparations (e.g., infusions, cookies and chocolates).
2. Cannabinoids are substances found only in the cannabis plant. There are estimated to be 104 unique, naturally occurring cannabinoids but the 2 that have been most extensively studied are THC and CBD:
  - THC produces the psychoactive effects, such as euphoria, relaxation and heightened sensory experiences, sought by “recreational” users
  - CBD has few psychoactive effects. It may moderate the psychoactive effects of THC and has antioxidant, anti-inflammatory and neuroprotective effects
3. Synthetic cannabinoids are substances produced in the laboratory that have similar effects to THC or other cannabinoids (e.g., nabilone).
4. Approved pharmaceutical cannabinoids include dronabinol, nabilone, nabiximols and CBD. Research is being conducted on the potential uses of other cannabinoids.

*Sources:* National Academies of Sciences, Engineering, and Medicine, *The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research* (Washington, D.C., National Academies Press, 2017); WHO, *The Health and Social Effects of Nonmedical Cannabis Use* (Geneva, 2016); and Leslie L. Iversen, *The Science of Marijuana*, 2nd ed. (Oxford, Oxford University Press, 2008).

2. Cannabis is included under Schedules I and IV of the Single Convention on Narcotic Drugs of 1961 as amended by the 1972 Protocol<sup>1</sup> because it produces dependence and has adverse public health consequences (see section E below).<sup>2</sup> Those consequences include injuries in motor vehicle crashes, mental illnesses such as psychoses, impaired cognitive and educational performance, disrupted adolescent development and adverse effects on fetal development. Cannabis use that begins during adolescence can damage the developing brain at a time of increased vulnerability.

3. The main cannabinoids with psychoactive properties, namely, THC and its isomers and their stereochemical variants, are included in Schedule I of the Convention on Psychotropic Substances of 1971<sup>3</sup> because they have the capacity to produce a state of dependence and constitute a public and social problem.

4. In its annual report for 2017,<sup>4</sup> INCB re-examined the terminology surrounding the medical use of cannabinoids. Accordingly, in the present chapter, the term “medicinal cannabinoids” refers only to cannabinoids that have been extracted from the plant or synthesized, have had their safety and effectiveness evaluated in controlled clinical trials and have been licensed for use as medicines.

5. Poorly controlled programmes for the medicinal use of cannabinoids can potentially have adverse effects on public health. They may increase non-medical cannabis use among adults and contribute to the legalization of non-medical cannabis use by weakening public perceptions of the risks of using cannabis and reducing public concern about legalizing non-medical (so-called “recreational”) cannabis use, which is contrary to the international drug control treaties.

6. In the present chapter, the conditions under which the international treaties allow the medical use of cannabinoids are specified. The chapter also contains a brief summary of the evidence on the safety and effectiveness

of cannabinoids for various types of medical use. The strengths and limitations of different regulatory approaches to permitting the medical use of cannabinoids, including the risks of diversion of cannabis to non-medical use, are also described. The chapter contains a discussion on how weak regulation of medical cannabis programmes may facilitate moves to legalize the non-medical use of cannabis and concludes with recommendations on how States should implement programmes for medicinal cannabinoids that comply with the requirements of the international drug control treaties.

## A. Cannabis, its derivatives and the international drug control conventions

7. Article 4, paragraph (c), of the 1961 Convention as amended limits the use of drugs scheduled under the Convention, including cannabis and its derivatives, to medical and scientific purposes. Under the Convention, cannabinoids may be evaluated in controlled clinical trials to assess the benefits and harms of their use in medicine.

8. The treaties set out requirements on States parties as to how they may allow the use of cannabis and its derivatives for medical purposes. For example, articles 23 and 28 of the 1961 Convention as amended require that Governments establish a national cannabis agency to control the production and regulate the supply of cannabinoids for medical use. The national agency is required to license producers, purchase and take possession of stocks and maintain a monopoly on wholesale trading and stocks. The agency must provide annually to INCB estimates of the quantities of the drug that will be used for medical purposes and must also provide estimates of the number of patients who will be treated with the drug.

9. In order to prevent abuse of and trafficking in cannabis, States parties must take measures to prevent the unauthorized cultivation of cannabis plants and must seize and destroy illicitly cultivated cannabis crops. All programmes for the medical use of cannabinoids must be developed and implemented under the full authority of the State concerned.

10. The treaties require that effective legislative frameworks are put in place to ensure the medically supervised use of cannabis and its derivatives and to prevent the diversion of cannabis and its derivatives to non-medical

<sup>1</sup>United Nations, *Treaty Series*, vol. 976, No. 14152.

<sup>2</sup>At the time of finalizing the present report, the WHO Expert Committee on Drug Dependence was due to hold its forty-first meeting (12–16 November 2018), during which it was to conduct a critical review of, inter alia, cannabis and cannabis-related substances, namely cannabis and cannabis resin, extracts and tinctures of cannabis, delta-9-THC and isomers of THC, to advise the Director General of WHO on any recommendation or assessment to be transmitted by WHO to the Commission on Narcotic Drugs for its consideration pursuant to articles 3, paragraphs 3 (iii), 4, 5 and 6 of the 1961 Convention as amended, and article 2, paragraph 4, of the Convention on Psychotropic Substances of 1971.

<sup>3</sup>United Nations, *Treaty Series*, vol. 1019, No. 14956.

<sup>4</sup>E/INCB/2017/1.

use. Governments allowing the medical use of cannabis must ensure that cannabis is prescribed by competent medical practitioners according to sound medical practice and based on sound scientific evidence.

11. Cannabinoids should be approved for medical use on the basis of scientific evidence on their quality, safety and efficacy for medical use from controlled clinical trials. Approved medicinal cannabinoids should be prescribed by a physician and dispensed by a pharmacist. Governments should monitor prescribers, dispensers and patients to ensure that those cannabinoids are not diverted to non-medical use or abuse.

12. The Board has repeatedly stated that personal cultivation of cannabis for medical purposes is inconsistent with the 1961 Convention as amended because, inter alia, it heightens the risk of diversion.<sup>5</sup> Personal cultivation of cannabis to be used for medical purposes does not allow Governments to exercise the supervision required by the 1961 Convention over the production, manufacture, export, import and distribution of, trade in and use and possession of cannabis, the establishment of estimates of medical usage, the furnishing of related statistical returns or the implementation of the provisions of article 28 of that Convention. In addition to the risks of diversion, allowing private individuals to cultivate cannabis for personal medical consumption may present additional health risks, in that the dosages and levels of THC consumed may be different from those medically prescribed. The production of very high THC concentrates and extracts for “medical use” heightens the Board’s concerns about the risks of diversion for non-medical use.

## B. Pharmaceutical registration and prescription regimes

13. Smoking cannabis is not a medically acceptable way to obtain standardized doses of cannabinoids for two reasons: first, cannabis plants vary in their composition, which makes it difficult to prescribe specific doses;<sup>6</sup> second, there are health risks to patients from inhaling the carcinogens and toxins in cannabis smoke.<sup>7</sup>

<sup>5</sup>Ibid., para. 177.

<sup>6</sup>EMCDDA, *Cannabis Legislation in Europe: An Overview* (Luxembourg, Publications Office of the European Union, 2018), p. 7.

<sup>7</sup>United States of America, National Academies of Sciences, Engineering, and Medicine, *The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research* (Washington, D.C., National Academies Press, 2017).

14. Attempts to market and promote the medical use of cannabis products as “herbal medicines” are inconsistent with the classification of cannabis and its derivatives under the 1961 and 1971 conventions.

15. Pharmaceutical-quality cannabinoids should be approved for clearly defined medical uses by the country’s pharmaceutical regulatory system. The pharmacological specificity of cannabinoids to treat defined medical conditions should be demonstrated in order to avoid their being used to treat medical conditions for which there is limited evidence of benefit. Cannabinoids approved in these ways can best deliver high-quality, standardized doses of known substances for medical use.<sup>8</sup>

16. Medical regulatory authorities license the medical use of a drug when there is evidence that the drug has been manufactured to a required level of quality and safety. Those authorities also require evidence from randomized controlled clinical trials that show that the drug is safe and effective, i.e., that the drug is more effective than a placebo, or equally as effective as an active treatment, when used to treat patients with a specified medical disorder.<sup>9</sup>

17. While assessing the potential for a controlled substance to be used for medical purposes, States should make sure that the therapeutic advantages it provides cannot be afforded by some other non-controlled drug with no or few addiction-producing properties.<sup>10</sup>

18. Once drugs have been approved for medical use, medical colleges and clinical societies often develop clinical practice guidelines for their use. Such guidelines are designed to assist prescribers with regard to how best to incorporate the use of new drugs into clinical practice, for example, the disorders for which they may be used, whether they will be used as first-line or later-line treatments, and if they will be used as adjuncts or monotherapies.

<sup>8</sup>Jennifer H. Martin, Yvonne Bonomo and Adrian D. B. Reynolds, “Compassion and evidence in prescribing cannabinoids: a perspective from the Royal Australasian College of Physicians”, *Medical Journal of Australia*, vol. 208, No. 3 (February 2018).

<sup>9</sup>Odilia Osakwe, “Pharmaceutical regulation: the role of Government in the business of drug discovery”, in *Social Aspects of Drug Discovery, Development and Commercialization*, Odilia Osakwe and Syed A. A. Rizvi, eds. (London, Elsevier, 2016); and Lembit Rågo and Budiono Santoso, “Drug regulation: history, present and future”, in *Drug Benefits and Risks: An International Textbook of Clinical Pharmacology*, revised 2nd ed., Chris J. van Boxtel, Budiono Santoso and I. Ralph Edwards, eds. (Uppsala, Sweden, Uppsala Monitoring Centre, 2008).

<sup>10</sup>Martin, Bonomo and Reynolds, “Compassion and evidence in prescribing cannabinoids”.

19. After a drug is licensed for medical use, the health authorities may monitor adverse effects among patients who use it. Post-market surveillance is needed to detect rare but serious adverse effects that may not be detected in the clinical trials used to obtain a licence for the drug's medical use. Clinical trials are usually short term and conducted in highly selected patient populations. Rarer adverse effects of medical use may only come to light when a drug has been used to treat a large number of unselected patients.

20. A company that markets a drug can promote its use to medical practitioners for the approved medical uses. Physicians may use approved drugs off-label, that is, to treat medical conditions other than those for which the drugs have been approved. The regulatory system, however, does not allow companies to promote the use of a drug beyond its approved indications, for example, by expanding the indications for its use, encouraging doctors to prescribe it off-label, or overstating its benefits or understating any adverse effects.

21. Many national pharmaceutical regulatory systems have established special-access schemes that enable patients with serious illnesses (such as cancer) to access unapproved medicines. This requires evidence that the patient has failed to respond to conventional treatment and patients must give informed consent for the use of an unapproved medicine. Medicines obtained in this way may have been approved for medical use in other countries but are not available in the country where a patient lives, or the medicine may still be undergoing clinical trial.<sup>11</sup> They usually require a prescription from a licensed medical practitioner and approval by the pharmaceutical regulator to import and use the drug.

## C. Medical uses of cannabinoids

22. A large variety of preparations containing cannabinoids are used in various regions of the world to provide different dosage forms and concentrations of active and psychoactive ingredients by different routes of administration. They are used in the belief that they will alleviate a wide range of symptoms, often in the absence of high-quality evidence that they are safe and effective. In many cases, it is unclear what cannabinoids these

products contain (active principles and dosage), what the best route of administration is or what their adverse side effects may be. When used in these ways, patients may confuse the acute euphoric effects of cannabinoids for longer-term medicinal effectiveness.<sup>12</sup>

23. The results of some controlled clinical trials suggest that some cannabinoids may relieve the symptoms of some illnesses, but not modify the underlying diseases.<sup>13</sup> Such cannabinoids are primarily used in combination with other drugs and typically only after a patient has failed to respond to other approved treatments for his or her condition. Cannabinoids are not first-line treatments for any of these conditions. The following summary of the evidence on the effectiveness of cannabinoids for medical uses is drawn from systematic reviews of the literature.<sup>14</sup>

### (a) Neuropathic pain and spasticity in multiple sclerosis

24. Randomized clinical trials have compared the efficacy of nabiximols (which contain equal amounts of THC and CBD) with a placebo in treating muscle spasm and neuropathic pain in patients with multiple sclerosis. Patients given nabiximols reported less muscle spasticity than patients given a placebo, but the differences in muscle spasticity identified by physicians were marginal.<sup>15</sup>

25. Systematic reviews of trials have found that nabiximols reduce neuropathic pain more than a placebo in patients with multiple sclerosis. However, the cannabinoids were only marginally more effective than a placebo: a 50 per cent reduction in pain was reported by 21 per cent of patients who received the cannabinoid and

<sup>11</sup>J. Martinalbo and others, "Early market access of cancer drugs in the EU", *Annals of Oncology*, vol. 27, No. 1 (January 2016), pp. 96–105.

<sup>12</sup>Martin, Bonomo and Reynolds, "Compassion and evidence in prescribing cannabinoids".

<sup>13</sup>Vincenzo Di Marzo and Luciano De Petrocellis, "Plant, synthetic, and endogenous cannabinoids in medicine", *Annual Review of Medicine*, vol. 57 (2006), pp. 553–574; Institute of Medicine, *Marijuana and Medicine: Assessing the Science Base* (Washington, D.C., National Academies Press, 1999); *The Health Effects of Cannabis and Cannabinoids*.

<sup>14</sup>Including *The Health Effects of Cannabis and Cannabinoids*; and Penny F. Whiting and others, "Cannabinoids for medical use: a systematic review and meta-analysis", *Journal of the American Medical Association*, vol. 313, No. 24 (June 2015), pp. 2456–2473.

<sup>15</sup>*The Health Effects of Cannabis and Cannabinoids*; Whiting and others, "Cannabinoids for medical use"; and John Zajicek and others, "Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised placebo-controlled trial", *Lancet*, vol. 362, No. 9395 (November 2003), pp. 1517–1526.

by 17 per cent of those who received a placebo.<sup>16</sup> There have not been any trials comparing the analgesic effects of cannabinoids with other analgesics such as non-steroidal anti-inflammatory drugs.

### (b) Intractable childhood epilepsy

26. Randomized controlled trials have compared the frequency of epileptic seizures in children with Dravet and Lennox-Gastaut syndromes (rare genetic forms of epilepsy) who were given CBD or a placebo in addition to other anti-epileptic drugs. CBD produced a larger reduction in the frequency of seizures than the placebo, but more clinical trials are needed to identify the doses of CBD that reduce seizures with a minimum of adverse effects.<sup>17</sup> Clinical trials are also needed to assess the efficacy of CBD in treating other types of epilepsy in children and adults.

### (c) Cannabinoids as anti-emetics

27. Randomized clinical trials have been held to assess whether THC (taken orally) is more effective in reducing nausea and vomiting than a placebo or another anti-emetic drug in cancer patients whose nausea and vomiting are caused by chemotherapy. Systematic reviews have drawn different conclusions on their efficacy, ranging from a Cochrane review that concluded that the evidence was of low quality<sup>18</sup> to a study in which “conclusive evidence” was found that THC (or a cannabinoid with similar effects) was more effective in reducing nausea and vomiting than a placebo or the anti-emetic drug with which it was compared.<sup>19</sup>

28. A major limitation of these trials is that THC was compared with a drug that is no longer used and that is much less effective in controlling nausea and vomiting than newer drugs.<sup>20</sup> There have been very few clinical

trials in which the effects of THC were compared with drugs such as ondansetron.<sup>21</sup>

### (d) Appetite stimulation

29. In 1992, THC was approved in the United States of America for use as an appetite stimulant in the treatment of AIDS-related wasting. Systematic reviews have concluded that the clinical trials provide weak evidence for the use of THC as an appetite stimulant because of a substantial risk of bias in those trials.<sup>22</sup> There is also little clinical need to stimulate the appetite of AIDS patients because few persons infected with HIV develop AIDS-related wasting if treated with highly active antiretroviral drugs. There are other medical disorders in which appetite may need to be stimulated (e.g., cancer and anorexia nervosa), but the evidence for the medical use of cannabinoids in those disorders is weak.<sup>23</sup>

## D. Adverse effects of short-term medicinal cannabinoid use

30. Evaluations of the adverse effects of medicinal cannabinoids have only been short term. Randomized, controlled clinical trials of cannabinoids to treat nausea and vomiting have assessed adverse effects over 1–6 days and trials for appetite, pain and spasticity in multiple sclerosis have lasted for 8–15 weeks.

31. An analysis of adverse events in 79 randomized clinical trials of cannabinoids in treating the conditions indicated above found that patients receiving a cannabinoid were approximately three times more likely than patients receiving a placebo to have an adverse event, nearly three times more likely to cease treatment because of adverse events and 40 per cent more likely to report a serious adverse event. The adverse events most often reported by patients receiving medicinal cannabinoids were dizziness, dry mouth, disorientation, euphoria, confusion and drowsiness.<sup>24</sup>

<sup>16</sup>Martin Mücke and others, “Cannabis-based medicines for chronic neuropathic pain in adults”, *Cochrane Database of Systematic Reviews*, No. 3 (2018).

<sup>17</sup>Emily Stockings and others, “Evidence for cannabis and cannabinoids for epilepsy: a systematic review of controlled and observational evidence”, *Journal of Neurology, Neurosurgery and Psychiatry*, vol. 89, No. 7 (July 2018).

<sup>18</sup>Whiting and others, “Cannabinoids for medical use”.

<sup>19</sup>*The Health Effects of Cannabis and Cannabinoids*.

<sup>20</sup>*Marijuana and Medicine*; and Rudolph M. Navari, “Pharmacological management of chemotherapy-induced nausea and vomiting: focus on recent developments”, *Drugs*, vol. 69, No. 5 (March 2009), pp. 515–533.

<sup>21</sup>*The Health Effects of Cannabis and Cannabinoids*; and Navari, “Pharmacological management of chemotherapy-induced nausea and vomiting”.

<sup>22</sup>*The Health Effects of Cannabis and Cannabinoids*; and Whiting and others, “Cannabinoids for medical use”.

<sup>23</sup>*The Health Effects of Cannabis and Cannabinoids*.

<sup>24</sup>Whiting and others, “Cannabinoids for medical use”.

## E. Adverse effects of long-term use of cannabis and its derivatives

32. The adverse health effects of short- and long-term use of cannabis for non-medical reasons are summarized in box 2 below. By contrast, there is very limited information on the adverse effects of using cannabinoids regularly (e.g., daily) for medical purposes over periods of months and years.<sup>25</sup> Cannabis dependence is a probable consequence of long-term medical cannabinoid use.<sup>26</sup> It is reasonable to assume, in the light of experience with other drugs, that the risk of dependence would be higher for patients with chronic pain using cannabinoids daily for months than the risk for patients using THC to treat chemotherapy-induced nausea for a week or less. There are no data on those risks, however.

33. Long-term cannabis smoking is associated with an increased risk of chronic bronchitis, but the evidence is mixed as to whether daily cannabis smoking increases the risk of chronic obstructive pulmonary disease.<sup>27</sup> The respiratory risks of non-medical cannabis use<sup>28</sup> arise because it is smoked, in many cases with tobacco and by tobacco smokers.<sup>29</sup> A patient taking medicinal cannabinoids orally would avoid those respiratory harms.

34. Long-term, daily, non-medical use of cannabis has been associated with poorer memory, attention, decision-making and planning in adolescents and young adults. Those effects may be of concern in patients with neurological disorders for whom regular use of cannabinoids could worsen any cognitive impairments caused by their disorders.<sup>30</sup>

<sup>25</sup>Tongtong Wang and others, “Adverse effects of medical cannabinoids: a systematic review”, *Canadian Medical Association Journal*, vol. 178, No. 13 (June 2008), pp. 1669–1678.

<sup>26</sup>Wayne Hall, Louisa Degenhardt and Michael Lynskey, *The Health and Psychological Effects of Cannabis Use*, Monograph Series, No. 44, 2nd ed. (Canberra, Commonwealth Department of Health and Ageing, 2001).

<sup>27</sup>WHO, *The Health and Social Effects of Nonmedical Cannabis Use* (Geneva, 2016); and *The Health Effects of Cannabis and Cannabinoids*.

<sup>28</sup>Jeanette M. Tetrault and others, “Effects of marijuana smoking on pulmonary function and respiratory complications: a systematic review”, *Archives of Internal Medicine*, vol. 167, No. 3 (February 2007), pp. 221–228.

<sup>29</sup>Wan C. Tan and others, “Marijuana and chronic obstructive lung disease: a population-based study”, *Canadian Medical Association Journal*, vol. 180, No. 8 (April 2009), pp. 814–820.

<sup>30</sup>Rebecca D. Crean, Natania A. Crane and Barbara J. Mason, “An evidence-based review of acute and long-term effects of cannabis use on executive cognitive functions”, *Journal of Addiction Medicine*, vol. 5, No. 1 (March 2011), pp. 1–8; and Nadia Solowij and others, “Cognitive functioning of long-term heavy cannabis users seeking treatment”, *Journal of the American Medical Association*, vol. 287, No. 9 (2002), pp. 1123–1131.

35. Daily use of cannabis may precipitate psychotic symptoms and disorders in young persons, especially in those with a personal or family history of such disorders. There are no data on the risk of psychosis in older patients using cannabinoids. Persons with a personal or family history of psychosis would be wise to avoid using cannabinoids.<sup>31, 32</sup> The non-psychoactive cannabinoid, CBD, may have anti-psychotic effects that require further investigation.

36. The cardiovascular risks of long-term cannabis and cannabinoid use may be a concern in older patients who have a higher risk of cardiovascular disease.<sup>33</sup> Epidemiological investigations into cardiovascular outcomes in patients using cannabinoids for medical purposes are needed.

## F. Medical use of approved cannabinoids

37. A number of countries, mostly in Europe and North America, permit the medical use of cannabinoids (see table 1). The United States Food and Drug Administration, for example, has approved several cannabinoids for medical use. In 1985, it approved a synthetic THC, dronabinol (Marinol), for use as an anti-emetic drug in cancer patients undergoing chemotherapy. Nabilone (Cesamet), a synthetic cannabinoid (with similar effects to THC), was approved in 1992 in capsule form as an appetite stimulant in patients with AIDS-related wasting.<sup>34</sup> In June 2018, the Food and Drug Administration approved the use of a CBD product (Epidiolex) to treat patients aged 2 years and older with Lennox-Gastaut and Dravet syndromes.

<sup>31</sup>Louisa Degenhardt and Wayne Hall, “Is cannabis use a contributory cause of psychosis?”, *Canadian Journal of Psychiatry*, vol. 51, No. 9 (August 2006), pp. 555–565; *The Health and Social Effects of Nonmedical Cannabis Use*; and *The Health Effects of Cannabis and Cannabinoids*.

<sup>32</sup>Philip McGuire and others, “Cannabidiol (CBD) as an adjunctive therapy in schizophrenia: a multicenter randomized controlled trial”, *American Journal of Psychiatry*, vol. 175, No. 3 (2018), pp. 225–231.

<sup>33</sup>Wayne Hall and Rosalie Liccardo Pacula, *Cannabis Use and Dependence: Public Health and Public Policy*, reissued ed. (Cambridge, Cambridge University Press, 2010).

<sup>34</sup>*Marijuana and Medicine*; and Douglas C. Throckmorton, Deputy Director for Regulatory Programs, Center for Drug Evaluation and Research, Food and Drug Administration, Department of Health and Human Services, “Researching the potential medical benefits and risks of marijuana”, statement to the Subcommittee on Crime and Terrorism, Committee on the Judiciary, United States Senate, 13 July 2016.

**Box 2.****Adverse effects of cannabis use on health**

The short-term adverse effects of cannabis use include:

- Intoxication, with disturbed consciousness, cognition, perception, affect or behaviour, and psychophysiological functions
- Panic attacks, hallucinations and vomiting (in a minority of first-time users)
- Impairment of driving and an increased risk of road traffic injuries (1.3–2.0-fold)
- Possible triggering of coronary events in younger cannabis smokers
- Adverse effects on the fetus if a mother smokes cannabis during pregnancy

The long-term psychosocial effects of regular cannabis use include:

- Dependence (the risk is 1 in 10 among those who have ever used it, 1 in 6 for adolescent users and 1 in 3 for daily users)
- More severe and persistent negative outcomes among adolescents than among adults
- A dose-response relationship between cannabis use in adolescence and the risk of developing psychotic symptoms or schizophrenia in young adulthood
- Increased risk of early school leaving, cognitive impairment, illicit use of other drugs, depressive symptoms and suicidal ideation and behaviour (when cannabis is used daily in adolescence and young adulthood)

The other longer-term physiological risks of regular cannabis use may include:

- Chronic and acute bronchitis and injury to bronchial lining cells
- Myocardial infarctions and strokes in young cannabis users
- An increased risk of cancer and other respiratory diseases if used with tobacco
- Testicular cancer (the link requires further investigation)

Source: WHO, *The Health and Social Effects of Nonmedical Cannabis Use* (Geneva, 2016).

**Table 1.**

**Pharmaceutical cannabinoids that have been approved for medicinal use**

Cannabinoid	Composition	Trade name	Route	Indication
Dronabinol	Synthetic <i>delta-9</i> -THC	Marinol	Oral capsule	Nausea and vomiting <sup>a</sup>
Nabilone	Synthetic cannabinoid that mimics the effects of THC	Cesamet	Oral capsule	Nausea and vomiting; appetite stimulation <sup>b</sup>
Nabiximols	Cannabis extract with equal doses of THC and CBD	Sativex	Oral mucosal spray	Muscle spasticity and pain in multiple sclerosis <sup>c</sup>
CBD	CBD extracted from cannabis plants	Epidiolex	Oil for oral use	Epilepsy in Lennox-Gastaut and Dravet <sup>d</sup> syndromes for patients aged 2 years and older

<sup>a</sup> National Academies of Sciences, Engineering, and Medicine, *The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research* (Washington, D.C., National Academies Press, 2017).

<sup>b</sup> Ibid.

<sup>c</sup> United Kingdom, electronic Medicines Compendium (eMC), “Sativex Oromucosal Spray”. Available at [www.medicines.org/uk](http://www.medicines.org/uk).

<sup>d</sup> United States Food and Drug Administration.

38. Dronabinol and nabilone have not been widely used in the United States because patients find it difficult to achieve therapeutic effects without adverse side effects.<sup>35</sup> When THC is taken orally, its effects have a delayed onset; often, patients either do not receive enough THC to achieve a therapeutic effect or they receive too much and experience adverse side effects.<sup>36</sup>

39. In several countries, including the United Kingdom of Great Britain and Northern Ireland, nabiximols (Sativex) have been approved to treat muscle spasms in multiple sclerosis patients,<sup>37</sup> but have not been widely used, in part because of the absence of public subsidies, which increases the cost borne by patients.

## G. Special-access schemes for medicinal cannabinoids

40. Several countries around the world have established special-access schemes for cannabinoids. The paragraphs below contain examples of schemes that have been described in the literature. It is not a complete account, because schemes in many countries have been in operation for shorter periods of time and information on how they operate is not yet readily available.

41. Since 2001, Israel has allowed the medical use of cannabis, with the approval and oversight of the Medical Cannabis Unit in the Ministry of Health. The Unit issues permits for patients to use herbal cannabis and nabiximols for medical purposes on the recommendation of physicians. It also authorizes growers to produce cannabis and supply it to patients.

42. Israel supplies herbal cannabis as an oil or as dried flower for smoking or vaporization. The physician specifies the THC and CBD content. Nabiximols are licensed to treat moderate to severe spasticity in multiple sclerosis patients and to treat cancer pain.<sup>38</sup>

<sup>35</sup> Franjo Grotenhermen, “Cannabinoids for therapeutic use: designing systems to increase efficacy and reliability”, *American Journal of Drug Delivery*, vol. 2, No. 4 (2004), pp. 229–240; and *Marijuana and Medicine*.

<sup>36</sup> Grotenhermen, “Cannabinoids for therapeutic use”; and Leslie L. Iversen, *The Science of Marijuana*, 2nd ed. (Oxford, Oxford University Press, 2007).

<sup>37</sup> Iversen, *The Science of Marijuana*; and Ethan Russo and Geoffrey W. Guy, “A tale of two cannabinoids: the therapeutic rationale for combining tetrahydrocannabinol and cannabidiol”, *Medical Hypotheses*, vol. 66, No. 2 (2006), pp. 234–246.

<sup>38</sup> Jacob Ablin and others, “Medical use of cannabis products: lessons to be learned from Israel and Canada”, *Der Schmerz*, vol. 30, No. 1 (January 2016).

43. Since July 2014, the medical use of cannabinoids in Israel has only been permitted if the physician has utilized and the patient has failed to respond to recognized treatments. Approved uses include cancer treatment; inflammatory bowel disease; neuropathic pain after more than a year of treatment in a pain clinic; AIDS-related wasting; neurological diseases such as multiple sclerosis, Parkinson’s disease and Tourette’s syndrome; post-traumatic stress disorder; and terminal illnesses.<sup>39</sup>

44. In 2003, legislation was passed in the Netherlands to allow physicians to prescribe cannabis for a range of medical indications. Cannabis is produced under government licence by a private company and dispensed by pharmacists to patients in a standardized form for oral consumption, on a doctor’s prescription.

45. In 2011, legislation was passed in Switzerland to allow the medical use of cannabis to treat chronic pain and spasticity, under exceptional circumstances with the approval of the Swiss Federal Office of Public Health. Doctors can request a licence for each patient to use a commercially available synthetic THC (dronabinol) or a tincture of *cannabis sativa* containing 5 per cent THC, prepared by a pharmacist.

## H. Poorly regulated medical cannabis programmes in North America

46. Under medical cannabis programmes in Canada and some states in the United States, patients have been allowed to purchase cannabis from commercial outlets for use for a variety of medical conditions, under minimal medical supervision. Weak regulation of medical usage has allowed the diversion of cannabis to non-medical use and, according to some, has facilitated the legalization of non-medical cannabis use in some states in the United States.<sup>40</sup> The key features of these programmes are summarized in box 3 and elaborated upon in the following paragraphs.

47. In some states in the United States, the medical use of cannabis was legalized through citizen-initiated referendums. For example, in 1996 in California, voters voted

<sup>39</sup> Ibid.

<sup>40</sup> Beau Kilmer and Robert J. MacCoun, “How medical marijuana smoothed the transition to marijuana legalization in the United States”, *Annual Review of Law and Social Science*, vol. 13 (2017), pp. 181–202.

**Box 3.****Features of poorly regulated medical cannabis programmes**

Poorly regulated medical cannabis programmes:<sup>a</sup>

- (a) Allow the smoking of cannabis for “medical” purposes;
- (b) Allow “medical cannabis use” for a wide variety of medical conditions in the absence of evidence of safety and effectiveness from controlled clinical trials for such use;
- (c) Allow the provision of non-standardized cannabis products under minimal medical supervision, often authorized for a fee by physicians with no specialist expertise or history of treating the patient;
- (d) Allow patients to either grow their own cannabis or purchase cannabis products from commercial outlets that produce cannabis illicitly.

<sup>a</sup>Beau Kilmer and Robert J. MacCoun, “How medical marijuana smoothed the transition to marijuana legalization in the United States”, *Annual Review of Law and Social Science*, vol. 13 (2017), pp. 181–202.

in favour of proposition 215, on allowing cannabis to be used to treat nausea, weight loss, pain and muscle spasm, and any other illness for which it may provide relief.

48. In the United States, the medical use of cannabis is now allowed in more than 30 states and the Federal District of Columbia. Those states differ in how they regulate their medical cannabis programmes. In some states, “medical use” is defined very broadly and cannabis may be sold by commercial dispensaries to persons with a medical recommendation. In other states, the use of cannabis is restricted to limited medical conditions and the sale of cannabis by commercial dispensaries is not permitted.<sup>41</sup>

49. The profiles of patients in medical cannabis programmes in California suggest that “medical use” is very loosely defined in that state. During the period 2001–2007, of 4,117 patients in the San Francisco Bay Area, 77 per cent were males. Most (88 per cent) started using cannabis before the age of 19 and 90 per cent were daily smokers.<sup>42</sup> In a representative survey of Californian adults, 7 per cent reported “medical cannabis use”. The highest rate was among those aged 18–24 (10 per cent) and the lowest rate (1.5 per cent) was among persons aged over 65.<sup>43</sup> Those characteristics do not correspond to the

cases highlighted in advocacy for medical uses of cannabis, namely, older adults with terminal illnesses, persons with neurological diseases and children with epilepsy.

50. Most medical cannabis programmes in the United States do not comply with the requirements of the international drug control treaties or United States national law. The cannabis sold in dispensaries may be illicitly produced and sold. There may be substantial diversion of cannabis products intended for medical use to non-medical use. There is often little or no scientific evidence to support the effectiveness of many of the purported medical uses of cannabis and there is very little medical supervision of these “medical” uses of cannabis.

51. In April 2001, the Government of Canada passed legislation allowing patients to access cannabis for medical purposes.<sup>44</sup> They could do so if they had a terminal illness and a life expectancy of less than 12 months; multiple sclerosis, a spinal cord injury or disease, cancer pain, AIDS, arthritis or epilepsy; or another serious medical condition that had not been relieved by conventional treatments.<sup>45</sup>

<sup>41</sup>Rosalie Liccardo Pacula and Rosanna Smart, “Medical marijuana and marijuana legalization”, *Annual Review of Clinical Psychology*, vol. 13 (2017), pp. 397–419.

<sup>42</sup>Thomas J. O’Connell and Ché B. Bou-Matar, “Long term marijuana users seeking medical cannabis in California (2001–2007): demographics, social characteristics, patterns of cannabis and other drug use of 4117 applicants”, *Harm Reduction Journal*, vol. 4, No. 16 (2007).

<sup>43</sup>Suzanne Ryan-Ibarra, Marta Induni and Danielle Ewing, “Prevalence of medical marijuana use in California, 2012”, *Drug and Alcohol Review*, vol. 34, No. 2 (March 2015), pp. 141–146.

<sup>44</sup>Tony Bogdanoski, “Accommodating the medical use of marijuana: surveying the differing legal approaches in Australia, the United States and Canada”, *Journal of Law and Medicine*, vol. 17, No. 4 (February 2010), pp. 508–531; and Philippe G. Lucas, “Regulating compassion: an overview of Canada’s federal medical cannabis policy and practice”, *Harm Reduction Journal*, vol. 5, No. 5 (2008).

<sup>45</sup>Philippe G. Lucas, “It can’t hurt to ask; a patient-centered quality of service assessment of Health Canada’s medical cannabis policy and program”, *Harm Reduction Journal*, vol. 9, No. 2 (2012); and Anthony C. Moffat, “The legalisation of cannabis for medical use”, *Science and Justice*, vol. 42, No. 1 (January 2002), pp. 55–57.

52. In response to a succession of decisions made by courts in Canada, the Government was obliged to extend access to cannabis and its derivatives for therapeutic purposes. This broadened the definition of “medical use” and established a cannabis cultivation industry in which licensed producers can provide cannabis directly to patients with medical documents authorizing the medical use of cannabis. The expanded list of indications allowed any doctor to prescribe cannabis to a patient whom the doctor thought might benefit.<sup>46</sup> Persons authorized to use cannabis for medical purposes can also cultivate their own supply or designate another person to do so on their behalf, a practice that is inconsistent with the provisions of the Conventions (see para. 12 above). The application of successive court decisions based on constitutional arguments therefore led to an outcome where the medical cannabis programme does not comply with the international drug control treaties in important aspects.

## I. Adverse public health effects of medical cannabis programmes

53. Researchers and policymakers have raised concerns that poorly regulated medical cannabis programmes in states of the United States may have increased the non-medical use of cannabis among young people. Researchers have evaluated those concerns by comparing survey data on cannabis use in adolescents in states in the United States that have and have not legalized the medical use of cannabis.

54. The largest study using national survey data<sup>47</sup> found that there was no change in adolescent cannabis use before and after the passage of laws permitting the medical use of cannabis. Analyses of cannabis use in young people aged 12 to 20 in the United States National Household Survey of Drug Use also failed to find increases in such use.<sup>48</sup>

<sup>46</sup>Benedikt Fischer, Sharan Kuganesan and Robin Room, “Medical marijuana programs: implications for cannabis control policy – observations from Canada”, *International Journal of Drug Policy*, vol. 26, No. 1 (January 2015), pp. 15–19.

<sup>47</sup>Deborah S. Hasin and others, “Medical marijuana laws and adolescent marijuana use in the USA from 1991 to 2014: results from annual, repeated cross-sectional surveys”, *Lancet Psychiatry*, vol. 2, No. 7 (July 2015), pp. 601–608.

<sup>48</sup>Hefei Wen, Jason M. Hockenberry and Janet R. Cummings, “The effect of medical marijuana laws on adolescent and adult use of marijuana, alcohol, and other substances”, *Journal of Health Economics*, vol. 42 (July 2015), pp. 64–80.

55. However, cannabis use has increased among adults over the age of 21 in states that have adopted legislation permitting the medical use of cannabis.<sup>49</sup> Adults in states with legislation permitting medical use of cannabis have higher rates of daily cannabis use and cannabis abuse and dependence than adults who live in states that have not passed such legislation. The number of adult males seeking treatment for cannabis use disorders has also increased more in states with medical cannabis laws;<sup>50</sup> that increase has occurred among persons who were not referred by the criminal justice system.

56. The evidence is mixed on the effects of medical cannabis legislation on motor vehicle fatalities. Some studies<sup>51</sup> have found an increase in the number of drivers involved in fatal crashes with cannabis in their bloodstream in states that have passed medical cannabis legislation while others<sup>52</sup> have found a decrease in that number. A study comparing trends in fatal motor vehicle crashes in Colorado and 34 states without medical cannabis legislation between 1994 and 2011 found a larger increase in cannabis-related fatalities in Colorado after 2009. There was no change in the number of alcohol-related fatalities in Colorado or the 34 states without medical cannabis laws.<sup>53</sup>

## J. Legalization of non-medical cannabis use

57. “Medical cannabis” programmes in some states in the United States have been used by advocates of cannabis legalization to promote the legalization of non-medical cannabis use in those states. States that were the first to legalize non-medical cannabis use (Colorado, Oregon and Washington) had poorly regulated “medical cannabis” programmes, with dispensaries being used to create a de facto legal cannabis market for non-medical users. In

<sup>49</sup>Ibid.

<sup>50</sup>Yu-Wei Luke Chu, “The effects of medical marijuana laws on illegal marijuana use”, *Journal of Health Economics*, vol. 38 (December 2014), pp. 43–61.

<sup>51</sup>Scott V. Masten and Gloriam Vanine Guenzburger, “Changes in driver cannabinoid prevalence in 12 U.S. States after implementing medical marijuana laws”, *Journal of Safety Research*, vol. 50 (September 2014), pp. 35–52.

<sup>52</sup>D. Mark Anderson, Benjamin Hansen and Daniel I. Rees, “Medical marijuana laws, traffic fatalities, and alcohol consumption”, *Journal of Law and Economics*, vol. 56, No. 2 (May 2013), pp. 333–369.

<sup>53</sup>Stacy Salomonsen-Sautel and others, “Trends in fatal motor vehicle crashes before and after marijuana commercialization in Colorado”, *Drug and Alcohol Dependence*, vol. 140 (July 2014), pp. 137–144.

those states, cannabis was provided through dispensaries to any person who satisfied the broad criteria used to define “medical use”.<sup>54</sup>

58. The legal tolerance of cannabis dispensaries allowed a quasi-legal commercial cannabis industry to develop in those states. In Colorado, the medical cannabis retail industry helped to design the regulatory system for non-medical cannabis use, and its members were given early entry to the market.<sup>55</sup>

59. The expansion of poorly regulated “medical cannabis” programmes has been accompanied by increased public support for the legalization of non-medical cannabis use in the United States.<sup>56</sup>

60. The decrease in the perceived risks of cannabis use and active social marketing of cannabis by the cannabis industry presents major challenges in preventing cannabis use among young people. Unsubstantiated claims about the medical benefits of cannabis have been accompanied by reductions in the perceived risks of using cannabis among young people in the United States.<sup>57</sup> Cannabis use by adults in the states of the United States in which non-medical cannabis has been legalized may encourage adolescents to use the drug at a time when their brains are especially vulnerable to its adverse effects.

## K. Implications for international drug control

61. The legalization of non-medical use of cannabis contravenes the international drug control treaties. Universal and full implementation of the treaties is put at serious risk because States parties, such as Canada and Uruguay (as well as states in the United States), have legalized cannabis for non-medical use. The actions of those countries and state jurisdictions undermine the treaties. They may also encourage other States parties to follow their example and use it as a justification for doing so.

<sup>54</sup>Kilmer and MacCoun, “How medical marijuana smoothed the transition to marijuana legalization in the United States”.

<sup>55</sup>Wayne Hall and Michael Lynskey, “Evaluating the public health impacts of legalizing recreational cannabis use in the United States”, *Addiction*, vol. 111, No. 10 (October 2016), pp. 1764–1773.

<sup>56</sup>Kilmer and MacCoun, “How medical marijuana smoothed the transition to marijuana legalization in the United States”.

<sup>57</sup>Hannah Carliner and others, “Cannabis use, attitudes, and legal status in the U.S.: a review”, *Preventive Medicine*, vol. 104 (November 2017), pp. 13–23.

62. In 2013, Uruguay legalized the non-medical use of cannabis, permitted the sale of cannabis through pharmacies and allowed the establishment of cannabis growers’ clubs and home production by users. In 2018, Canada legalized commercial cannabis production and sale for non-medical use by adults; the policy was implemented in October 2018.

63. Experience with alcohol and tobacco suggests that legalization will reduce the perceived risks of using cannabis and social disapproval of adult cannabis use, and increase the diversion of cannabis to persons who are under the minimum legal age to purchase and use it.<sup>58</sup> The legalization of non-medical cannabis use is also likely to increase cannabis use among adult users by making cannabis more widely available, including at a lower price and in more potent forms, such as concentrates. Over the next few decades, such legalization is also likely to increase the number of new users among adolescents and young adults.

64. One argument used by advocates of legalizing cannabis for non-medical use is that it will restrict minors’ access to cannabis. Experience in the State of Washington raises serious doubts about this claim. Authorities have reported substantial numbers of licensed cannabis businesses selling cannabis to minors, an offence punishable only by small fines.

65. Any increases in non-medical cannabis use will increase the adverse effects of cannabis on public health. The most likely effects are increased rates of motor vehicle injuries, cannabis dependence and abuse, psychoses and other mental disorders, and poor psychosocial outcomes in adolescents.

66. The legalization of non-medical cannabis use in some States will make it more difficult to enforce international drug control treaty provisions in neighbouring States that do comply with those provisions. It will be more difficult, for example, to prevent cross-border trafficking in cannabis products from States that have legalized non-medical cannabis use to neighbouring countries that have not done so.

<sup>58</sup>Rosalie Liccardo Pacula and others, “Developing public health regulations for marijuana: lessons from alcohol and tobacco”, *American Journal of Public Health*, vol. 104, No. 6 (June 2014), pp. 1021–1028.

## L. Conclusions and recommendations

67. The medical use of cannabinoids is allowed under the international drug control treaties only if States comply with the treaty requirements that are designed to prevent diversion to non-medical use. The treaties require that States license and control cannabis production for medical use, provide estimates of the national requirements for cannabis for medical purposes and ensure that medicinal cannabinoids are used in accordance with evidence on their safety and effectiveness and under medical supervision. Taking those measures should also contribute to maintaining the integrity of the pharmaceutical regulatory system.

68. Recent reviews of the evidence from clinical trials indicate that: (a) there is weak evidence that dronabinol may be useful in treating nausea and vomiting in cancer patients; (b) there is moderate evidence that nabiximols may be useful in treating neuropathic pain and muscle spasticity in patients with multiple sclerosis; and (c) there is moderate evidence that CBD may reduce seizure frequency in some genetic intractable childhood epilepsy syndromes. Cannabinoids are not a first-line treatment for any of those conditions.

69. The evidence that cannabinoids can relieve symptoms of some medical illnesses does not justify the “medical use” of cannabis by smoking. Smoking a crude plant product is not a safe or reliable way to obtain standardized doses of cannabinoids.

70. Poorly controlled programmes for the medicinal use of cannabinoids can potentially have adverse effects on public health. They may increase non-medical cannabis use among adults and contribute to the legalization of non-medical cannabis use by weakening public perceptions of the risks of using cannabis and reducing public concern about legalizing non-medical (so-called “recreational”) cannabis use, which is contrary to the international drug control treaties.

71. Governments that have created special-access schemes to allow the medical use of cannabis should ensure that those programmes are not used to de facto legalize cannabis for non-medical use. Governments should limit the indications for medical use to those for which there is evidence of efficacy, restrict use to medicinal cannabinoids, and monitor the prescription and use of cannabinoids to minimize their diversion and abuse.

72. Under medical cannabis programmes implemented in Canada and possibly in some other States, and in some states in the United States, the medical use of cannabinoids is poorly regulated. Those programmes are inconsistent with the international drug control treaties in failing to control cannabis production and supply. They fail to ensure that good-quality medicines are provided under medical supervision and they enable cannabis and its derivatives to be diverted to non-medical use.

73. “Medical cannabis” programmes may also have been used by advocates of the legalization of cannabis use to facilitate the legalization of non-medical cannabis use, which is contrary to the international drug control treaties. Such programmes have used very broad definitions of “medical use” and allowed commercial businesses to supply illicitly produced cannabis. In the United States, those programmes also appear to have reduced public perceptions of the risks of using cannabis and have weakened public concern about cannabis legalization.

74. Governments that allow the medicinal use of cannabinoids should monitor and evaluate the effects of the programmes. Such monitoring should include collecting data on the number of patients who use cannabinoids, the medical conditions for which they use them, patient and clinician assessments of their benefits, and rates of adverse events. Governments should also monitor the extent of diversion of cannabinoids to non-medical use, and in particular their diversion for use by minors.