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The Medicalization of Cannabis as an Ethical Challenge in the 21st Century

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Abstract

With a 12.000-year history, cannabis is one of the most widely used plants for traditional healings. Perhaps no topic is more controversial than the use of cannabis-based medicines in clinical practice, having in mind significant negative effects of smoking marijuana on physical and mental health. After a long period of prohibition for the use of this drug, due to the emphasized potential of the cannabis extract in helping with different diseases, nowadays cannabis is the subject of global reaffirmation. However, although cannabis is one of the most explored plants in science history, many ethical challenges regarding its medicalization are still very much present.

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THE MEDICALIZATION OF CANNABIS AS AN ETHICAL CHALLENGE IN THE 21st CENTURY

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INTRODUCTION

Cannabis is not a medicine. It is poisonous and addictive. This is what we've learned, and we also have our own prejudices, and it's hard, hard to get it out of my head... I prescribe other medications much more freely than I would have prescribed cannabis. That's it. That's a fact. But I am willing to be persuaded that I'm wrong. Especially after I heard Professor Raphi Mechoulam. I heard him several times, two or three times. I was very impressed.

Family physician (physician 19)⁴

Cannabis or hemp plant is an annual flowering plant that grows in tropical and temperate climates, and belongs to the *Cannabis* genus of the

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⁴ Yuval Zolotov, Simon Vulfsons, Dana Zarhin, and Sharon Sznitman, "Medical cannabis: An oxymoron? Physicians' perceptions of medical cannabis," *International Journal of Drug Policy* 57 (2018): 4-10.

family *Cannabaceae*.⁵ With its history dating twelve thousand years back, cannabis is one of the most widely used plant for different traditional healings.² However, perhaps no topic is more controversial than the use of compounds and extracts from cannabis in clinical practice, having in mind significant negative effects of smoking marijuana on physical and mental health, as well as social and occupational functioning.⁶ Namely, marijuana has a range of adverse health effects, particularly relating to young people, because of higher risk for psychosis, traffic accidents and cognitive impairment.⁷ The Centers for Disease Control and Prevention (CDC) refers to marijuana as an illegal drug, and The Drug Enforcement Agency (DEA) classifies marijuana as Schedule I along with heroin and lysergic acid diethylamide.⁸

The psychoactive- and medicinal uses of *Cannabis sativa* (marijuana) have been well known for millennia.⁹ The first documentation of

⁵ Elizabeth Black, Brian Hocum, and Kevin Black, *Ethics and science, cannabinoids and healthcare* (Chicago: Relias Media, 2018). Ran Abuhasira, Liat Shbירו, and Yuval Landschaft, “Medical use of cannabis and cannabinoids containing products - Regulations in Europe and North America,” *European Journal of Internal Medicine* 49 (2018): 2-6. Andrea Mastinu, Marika Premoli, Giulia Ferrari-Toninelli, Simone Tambaro, Giuseppina Maccarinelli, Maurizio Memo, and Sara Anna Bonini, “Cannabinoids in health and disease: pharmacological potential in metabolic syndrome and neuroinflammation,” *Hormone Molecular Biology and Clinical Investigation* 36 (2018): doi: 10.1515/hmbci-2018-0013. Hemant Goyal, Rubayat Rahman, Abhilash Periseti, Nihar Shah, and Rajiv Chhabra, “Cannabis in liver disorders: a friend or a foe?,” *The European Journal of Gastroenterology & Hepatology* 30 (2018): 1283-1290. Shira Hirsch and Joseph Tam, “Cannabis: From a plant that modulates feeding behaviors toward developing selective inhibitors of the peripheral endocannabinoid system for the treatment of obesity and metabolic syndrome,” *Toxins* 11 (2019): doi: 10.3390/toxins 11050275.

⁶ Elizabeth Black, et al., *Ethics and science, cannabinoids and healthcare*.

⁷ Elizabeth Black, et al., *Ethics and science, cannabinoids and healthcare*. Judith Booth and Jörg Bohlmann, “Terpenes in *Cannabis sativa* – from plant genome to humans,” *Plant Science* 284 (2019): 67-72. Sabrina Jarvis, Sean Rassmussen, and Blaine Winters, “Role of the endocannabinoid system and medical cannabis,” *The Journal for Nurse Practitioners* 13 (2017): 525-531. Maria Steenkamp, Esther Blessing, Isaac Galatzer-Levy, Laura Hollahan, and William Anderson, “Marijuana and other cannabinoids as a treatment for posttraumatic stress disorder: a literature review,” *Journal of Depression and Anxiety* 34 (2017): 207-216. Robert Torrence, Don Rojas, and Lucy Troup, “Residual effects of cannabis use on attentional bias towards fearful faces,” *Neuropsychologia* 119 (2018): 482-488.

⁸ Elizabeth Black, et al., *Ethics and science, cannabinoids and healthcare*.

⁹ Joseph Tam, Liad Hinden, Adi Drori, Shiran Udi, Shahar Azar, and Saja Baraghithy, “The therapeutic potential of targeting the peripheral endocannabinoid/CB1 receptor system,” *European Journal of Internal Medicine* 49 (2018): 23-29.

cannabis as a medicine appeared in China 5000 years ago when it was recommended for malaria, constipation, rheumatic pains and, mixed with wine, as a surgical analgesic.¹⁰ In India, even before 1000 years BC, this plant was used for various functions, such as hypnotic medicine and a tranquiliser useful in the treatment of anxiety, mania and hysteria.¹¹ Also, the Assyrians inhaled cannabis to relieve symptoms of depression.¹² Pedacius Dioscorides, a Greek physician, between 50 and 70 AD classified different plants, including *Cannabis sativa*, and described the benefits derived from its use in “*De Materia Medica*.”¹³ Roman historian Pliny the Younger, in his pioneering encyclopedia on the natural world, mentions the use of cannabis, too.¹⁴

Although medicinal preparations containing cannabis were widely used in many societies for centuries, Dr. William O’Shaughnessy introduced it as a modern medicine in Europe in 1839 after the publication of his book “*On the preparations of the Indian hemp, or gunjah*.”¹⁵ Thus, in 1842, he emphasized the efficacy of “Indian hemp,” or

¹⁰ Andrea Mastinu et al., “Cannabinoids in health and disease: pharmacological potential in metabolic syndrome and neuroinflammation.”

¹¹ Raphael Mechoulam, Shimon Ben-Shabat, Lumir Hanus, Moshel Ligumsky, Norbert Kaminski, Antony Schatz, Asher Gopher, Shlomo Almog, Billy Martin, David Compton, Roger Pertwee, Graeme Griffin, Michael Bayewitch, Jacob Barg, and Zvi Vogel, “Identification of an endogenous 2-monoglyceride, present in canine gut, that binds to cannabinoid receptors,” *Biochemical Pharmacology* 50 (1995): 83-90.

¹² Ethan Russo and Geoffrey Guy, “A tale of two cannabinoids: the therapeutic rationale for combining tetrahydrocannabinol and cannabidiol,” *Medical Hypotheses* 66 (2006): 234-246.

¹³ Andrea Mastinu et al., “Cannabinoids in health and disease: pharmacological potential in metabolic syndrome and neuroinflammation.”

¹⁴ Elizabeth Black et al., *Ethics and science, cannabinoids and healthcare*.

¹⁵ Elizabeth Black et al., *Ethics and science, cannabinoids and healthcare*. Andrea Mastinu et al. “Cannabinoids in health and disease: pharmacological potential in metabolic syndrome and neuroinflammation.” Subodh Kumar, Phulen Sarma, Harish Kumar, Ajay Prakash, and Bikash Medhi, “Modulation of endocannabinoid system: Success lies in the failures,” *Indian Journal of Pharmacology* 50 (2018): 155-158. William Brooke O’Shaughnessy, “On the preparations of the Indian hemp, or gunjah (*Cannabis indica*): Their effects on the animal system in health, and their utility in the treatment of tetanus and other convulsive diseases,” *Transactions of the Medical and Physical Society of Bengal* (1838-1840): 421-461. William Brooke O’Shaughnessy, “On the preparations of the Indian hemp, or gunjah (*Cannabis indica*),” *Provincial Medical Journal and Retrospect of the Medical Sciences* 123 (1843): 363-369. Craig Reinerman, Helen Nunberg, Fran Lanthier, and Tom Heddleston, “Who are medical marijuana patients? Population characteristics from nine California assessment clinics,” *Journal of Psychoactive Drugs* 43 (2011): 128-135.

psychoactive cannabis, as a painkiller, a muscle relaxant, and “an anticonvulsive remedy of the greatest value.”¹⁶ In Paris, Moreau used cannabis for psychiatric patients and summarized in his published book “*Du Hachisch et de l’Alienation Mentale: Etudes Psychologiques*” describing acute effects of cannabis.¹⁷ Medical interest in cannabis remained in the limelight worldwide for several years due to its psychoactive effects, as well as possible therapeutic use in other domains, such as cholera, rabies and tetanus.¹⁸

At the beginning of the 20th century, cannabis extracts were used for the treatment of mental disorders, especially as sedatives and hypnotics.¹⁹ Cannabis-based therapeutic agents were prescribed in medical practice in the United States of America (USA) for more than 90 years.²⁰ Namely, cannabis was listed in the USA pharmacopeia from 1851 to 1944, when it was removed due to fears related to its psychoactive effects.²¹ In addition, by the 1930s, cannabis had become subject to federal regulations in the USA, which eventually prohibited its use by the Marijuana Tax Act of 1937.²² The prohibition was accompanied by moral demonization of cannabis, as it was presented to the public as a harmful drug associated with crime and insanity, so its use decreased rapidly.²³ However, after the identification of the main components of cannabis and the discovery of the endocannabinoid (EC) system as a key part of human physiology, in recent decades cannabis is subject of global

¹⁶ Elizabeth Black et al., *Ethics and science, cannabinoids and healthcare*.

¹⁷ Jacques Joseph Moreau, *Du Hachisch et de l’Alienation Mentale: Etudes Psychologiques*, Paris, *Librarie de Fortin Mason, 1845 (English edition, New York: Raven Press, 1972)*.

¹⁸ *Ibidem*.

¹⁹ Ethan Russo and Geoffrey Guy, “A tale of two cannabinoids: the therapeutic rationale for combining tetrahydrocannabinol and cannabidiol,” 234-246.

²⁰ Hemant Goyal et al., “Cannabis in liver disorders: a friend or a foe?,” 1283-1290.

²¹ Elizabeth Black et al, *Ethics and science, cannabinoids and healthcare*. Ethan Russo and Geoffrey Guy, “A tale of two cannabinoids: the therapeutic rationale for combining tetrahydrocannabinol and cannabidiol,” 234-246. Hemant Goyal et al., “Cannabis in liver disorders: a friend or a foe?,” 1283-1290.

²² Yuval Zolotov et al., “Medical cannabis: An oxymoron? Physicians’ perceptions of medical cannabis,” 4-10. Daniel Kruger and Jessica Kruger, “Medical cannabis users’ comparisons between medical cannabis and mainstream medicine,” *Journal of Psychoactive Drugs* 51 (2019): 31-36.

²³ Yuval Zolotov et al., “Medical cannabis: An oxymoron? Physicians’ perceptions of medical cannabis,” 4-10. Ran Abuhasira et al., “Medical use of cannabis and cannabinoids containing products,” 2-6.

reaffirmation, supported with large number of clinical studies for its medical potential.²⁴

Modern era for cannabis started during the 1960s by Mechoulam's group, who isolated and reported the correct structure and stereochemistry of cannabidiol (CBD), Δ^9 -tetrahydrocannabinol (Δ^9 -THC, the main psychoactive component of marijuana),²⁵ Δ^8 -tetrahydrocannabinol (Δ^8 -THC),²⁶ cannabigerol,²⁷ cannabichromene (CBC),²⁸ and cannabicyclol (CBL).²⁹ Currently, 545 natural compounds have been identified from cannabis.³⁰ On these, 144 have been isolated and identified as cannabinoids (phytocannabinoids).³¹ The first attempt to successfully identify a cannabinoid was made in 1899 by Wood and his colleagues,³² who isolated cannabinol (CBN).³³

In the early 1990s, with the isolation of endogenous cannabinoids (endocannabinoids) termed as anandamide (arachidonoyl ethanolamide/

²⁴ Pál Pacher, Sándor Batkai, and George Kunos, "The endocannabinoid system as an emerging target of pharmacotherapy," *Pharmacological Reviews* 58 (2006): 389-462. Ran Abuhassira et al., "Medical use of cannabis and cannabinoids containing products - Regulations in Europe and North America," 2-6. Andrea Mastinu et al., "Cannabinoids in health and disease." Shira Hirsch and Joseph Tam, "*Cannabis*." Subodh Kumar et al., "Modulation of endocannabinoid system," 155-158.

²⁵ Raphael Mechoulam and Youval Shvo, "Hashish. I. The structure of cannabidiol," *Tetrahedron* 19 (1963): 2073-2078. Yehiel Gaoni and Raphael Mechoulam, "Isolation, structure, partial synthesis of an active constituent of hashish," *Journal of American Chemical Society* 86 (1964): 1646-1647. Raphael Mechoulam and Yehiel Gaoni, "The absolute configuration of delta-1-tetrahydrocannabinol, the major active constituent of hashish," *Tetrahedron Letters* 12 (1967): 1109-1111.

²⁶ Richard Hively, William Mosher, and Fukun Hoffmann, "Isolation of trans-delta-tetrahydrocannabinol from marijuana," *Journal of the American Chemical Society* 88 (1966): 1832-1833.

²⁷ Yehiel Gaoni and Raphael Mechoulam, "The structure and synthesis of cannabigerol, a new hashish constituent," *Proceedings of the Chemical Society* 86 (1964): 1646-1647.

²⁸ Yehiel Gaoni and Raphael Mechoulam, "Cannabichromene, a new active principle in hashish," *Chemical Communications* 1 (1966): 20-21.

²⁹ Leslie Crombie, Roger Ponsford, Arnon Shani, Boris Yagnitinsky, and Raphael Mechoulam, "Hashish components. Photochemical production of cannabicyclol from cannabichromene," *Tetrahedron Letters* 55 (1968): 5771-5772.

³⁰ Shira Hirsch and Joseph Tam, "*Cannabis*."

³¹ Shira Hirsch and Joseph Tam, "*Cannabis*." Subodh Kumar et al., "Modulation of endocannabinoid system: Success lies in the failures," 155-158.

³² Thomas Barlow Wood, Newton Spivey, and Thomas Hill Easterfield, "Cannabinol. Part I," *Journal of the Chemical Society* 75 (1899): 20-36.

³³ Shira Hirsch and Joseph Tam, "*Cannabis*."

AEA)³⁴ and 2-arachidonoyl glycerol (2-AG),³⁵ as well as successful cloning and characterization of cannabinoid-specific receptors (CB1 and CB2) in the brain and peripheral organs,³⁶ the interest of the scientist community again shifted toward marijuana.³⁷ The EC system, acting both centrally and peripherally, is ubiquitously present in humans and animals.³⁸ It has been suggested that its homeostatic roles are “relax, eat, drink, rest, sleep, save, store, forget and protect.”³⁹ However, its role in physiological and pathological conditions are still incompletely known.

³⁴ William Devane, Lumir Hanus, Aviva Breuer, Roger Pertwee, Lesley Stevenson, Graeme Griffin, Dan Gibson, Asher Mandelbaum, Alexander Ettinger, and Raphael Mechoulam, “Isolation and structure of a brain constituent that binds to the cannabinoid receptor,” *Science* 258 (1992): 1946-1949.

³⁵ Takayuki Sugiura et al, “2-arachidonoyl glycerol: A possible endogenous cannabinoid receptor ligand in brain,” *Biochemical and Biophysical Research Communications* 215 (1995): 89-97.

³⁶ William Devane, Francis 3rd Dysarz, Ross Johnson, Lawrence Melvin, and Allyn Howlett, “Determination and characterization of a cannabinoid receptor in rat brain,” *Molecular Pharmacology* 34 (1988): 605-613. Lisa Matsuda, Stephen Lolait, Michael Brownstein, Alice Young, and Tom Bonner, “Structure of a cannabinoid receptor and functional expression of the cloned cDNA,” *Nature* 346 (1990): 561-564. Sean Munro, Kerrie Thomas, and Muna Abu-Shaar, “Molecular characterization of a peripheral receptor for cannabinoids,” *Nature* 365 (1993): 61-65. Tian Hua, Kiran Vemuri, Mengchen Pu, Lu Qu, Gye Won Han, Yiran Wu, Suwen Zhao, Wenqing Shui, Shanshan Li, Anisha Korde, Robert Laprairie, Edward Stahl, Jo-Hao Ho, Nikolai Zvonok, Han Zhou, Irina Kufareva, Beili Wu, Qiang Zhao, Michael Hanson, Laura Bohn, Alexandros Makriyannis, Raymond Stevens, and Zhi-Jie Liu, “Crystal structure of the human cannabinoid receptor CB1,” *Cell* 167 (2016): 750-762. Zhenhua Shao, Jie Yin, Karen Chapman, Magdalena Grzemska, Lindsay Clark, Junmei Wang, and Daniel Rosenbaum, “High-resolution crystal structure of the human CB1 cannabinoid receptor,” *Nature* 540 (2016): 602-606. Tian Hua, Kiran Vemuri, Spyros Nikas, Robert Laprairie, Yiran Wu, Lu Qu, Mengchen Pu, Anisha Korde, Shan Jiang, Jo-Hao Ho, Gye Won Han, Kang Ding, Xuanxuan Li, Haiguang Liu, Michael Hanson, Suwen Zhao, Laura Bohn, Alexandros Makriyannis, Raymond Stevens, and Zhi-Jie Liu, “Crystal structures of agonist-bound human cannabinoid receptor CB1,” *Nature* 547 (2017): 468-471. Xiaoting Li, Tian Hua, Kiran Vemuri, Jo-Hao Ho, Yiran Wu, Lijie Wu, Petr Popov, Othman Benchama, Nikolai Zvonok, Kara Locke, Lu Qu, Gye Won Han, Malliga Iyer, Resat Cinar, Nathan Coffey, Jingjing Wang, Meng Wu, Vsevolod Katritch, Suwen Zhao, George Kunos, Laura Bohn, Alexandros Makriyannis, Raymond Stevens, and Zhi-Jie Liu, “Crystal structure of the human cannabinoid receptor CB2,” *Cell* 176 (2019): 459-467.

³⁷ Shira Hirsch and Joseph Tam, “*Cannabis*.” Subodh Kumar et al., “Modulation of endocannabinoid system,” 155-158.

³⁸ Subodh Kumar et al., “Modulation of endocannabinoid system,” 155-158.

³⁹ Vincenzo Di Marzo, “Endocannabinoids and other fatty acid derivatives with cannabimimetic properties: Biochemistry and possible physiopathological relevance,” *Biochimica et Biophysica Acta* 1392 (1998): 153-175.

In 1999, Health Canada and Canadian Institutes of Health Research jointly started a dedicated Cannabis research initiative named as “Medical Marijuana Research Program.”⁴⁰ To date, numerous clinical trials are going on evaluating the therapeutic applications of cannabis and its derivatives.⁴¹

CANNABIS IS A MEDICINE, OR NOT. IS THAT A QUESTION?

Medical cannabis includes raw herbal (botanical) cannabis, cannabis extract and cannabinoids.⁴² The taxonomy of cannabis is debated because some people espouse cannabis as a single species with *Cannabis indica*, *Cannabis sativa* and *Cannabis ruderalis* as three different subspecies.⁴³ On the other hand, some have recommended three distinct species.⁴⁴ The term “herbal cannabis” may refer to anyone of these species.⁴⁵ Authorization of raw herbal cannabis is still generally unaccepted.⁴⁶ Thus, only four countries (Canada, Germany, Israel and the Netherlands), together with more than 50% of the states in the USA have fully authorized its medical use.⁴⁷

Cannabis extract is any extract, usually by organic solvents to produce oil, which is extracted from the plant, and any preparation consisting

⁴⁰ Subodh Kumar et al., “Modulation of endocannabinoid system,” 155-158.

⁴¹ Subodh Kumar et al., “Modulation of endocannabinoid system,” 155-158. Elizabeth Black, et al., *Ethics and science, cannabinoids and healthcare*. Andrea Mastinu et al., “Cannabinoids in health and disease.”

⁴² Ran Abuhāsira et al., “Medical use of cannabis and cannabinoids containing products,” 2-6.

⁴³ Elizabeth Black, Brian Hocum, and Kevin Black, *Ethics and science, cannabinoids and healthcare*. Ran Abuhāsira, Liat Shbiro, and Yuval Landschaft, “Medical use of cannabis and cannabinoids containing products,” 2-6. Shira Hirsch and Joseph Tam, “*Cannabis*.” Elizabeth Black, Brian Hocum, and Kevin Black, *Ethics and science, cannabinoids and healthcare*. Ran Abuhāsira, Liat Shbiro, and Yuval Landschaft, “Medical use of cannabis and cannabinoids containing products,” 2-6.

⁴⁴ Ran Abuhāsira, Liat Shbiro, and Yuval Landschaft, “Medical use of cannabis and cannabinoids containing products,” 2-6. Shira Hirsch and Joseph Tam, “*Cannabis*.” Judith Booth and Jörg Bohlmann, “Terpenes in *Cannabis sativa*,” 67-72.

⁴⁵ Ran Abuhāsira, Liat Shbiro, and Yuval Landschaft, “Medical use of cannabis and cannabinoids containing products,” 2-6. Shira Hirsch and Joseph Tam, “*Cannabis*.”

⁴⁶ Ibidem.

⁴⁷ Ran Abuhāsira, Liat Shbiro, and Yuval Landschaft, “Medical use of cannabis and cannabinoids containing products,” 2-6.

mainly of it.⁴⁸ Currently, there are only three cannabinoid-based medicines, available for marketing in different countries⁴⁹ (Table 1). These preparations have a statute of borderline products or medicines depending on the concentration of THC in the final product.⁵⁰ The good side of cannabinoids is the ability to combine them as an “add-on” therapy with existing conventional therapy.⁵¹

Table 1. Cannabinoid-based medicine

Medicine and administration route	Content	The main indications and authorization
<i>Nabiximols</i> (Sativex [®]) oromucosal spray	cannabinoids THC and CBD	multiple sclerosis associated spasticity EMA* and FDA# not authorized
<i>Nabilone</i> (Cesamet [®]) (Canemes [®]) oral capsules	Synthetic cannabinoid similar to THC	nausea and vomiting due to chemotherapy treatments FDA approved Cesamet in USA
<i>Dronabinol</i> (Marinol [®]) (Syndros [®]) oral capsules or an oral solution	synthetic Δ^9 - THC	anorexia associated with weight loss in AIDS and nausea and vomiting due to cancer chemotherapy FDA approved Dronabinol in USA

* EMA - the European Medicines Agency

FDA - the United States Food and Drug Administration

⁴⁸ Ibidem.

⁴⁹ Kiran Vemuri and Alexandros Makriyannis, “Medicinal chemistry of cannabinoids,” *Clinical Pharmacology & Therapeutics* 97 (2015): 553-558. Elizabeth Black, Brian Hocum, and Kevin Black, *Ethics and science, cannabinoids and healthcare*. Ran Abuhasira, Liat Shbiro, and Yuval Landschaft, “Medical use of cannabis and cannabinoids containing products,” 2-6.

⁵⁰ Elizabeth Black, et al., *Ethics and science, cannabinoids and healthcare*. Orrin Devinsky, et al., “Trial of cannabidol for drug-resistant seizures in the Dravet syndrome,” 2011-2020.

⁵¹ Andrea Mastinu, et al., “Cannabinoids in health and disease: pharmacological potential in metabolic syndrome and neuroinflammation.” Daniel Kruger and Jessica Kruger, “Medical cannabis users’ comparisons between medical cannabis and mainstream medicine,” 31-36.

Many European countries authorized use of *Nabiximols* and *Nabilone* by the noncentralized route through the competent national authorities.⁵² Canada also approved these cannabinoid-based medicines.⁵³ However, in February 2012, *Dronabinol* was withdrawn from the Canadian market by the manufacturer (not for safety reasons).⁵⁴ Besides, there have been considerable arguments in favor of the existence of beneficial cannabinoids, such as CBD.⁵⁵ In relation to, EMA has approved CBD for treatment of Dravet syndrome, perinatal asphyxia, graft-versus-host disease, Lennox-Gastaut syndrome, West syndrome and tuberous sclerosis.⁵⁶ Additionally, EMA has approved a combination of THC and CBD from extracts of the cannabis sativa for the treatment of glioma.⁵⁷ Recently, FDA approved *Epidiolex* (CBD) for the treatment of Lennox-Gastaut syndrome and Dravet syndrome of children.⁵⁸ *Epidiolex* is the first FDA-approved drug that contains a purified drug derived from marijuana.⁵⁹

Cannabis use among individuals older than 12 years old has increased from 6.2% in 2002 to 8.3% in 2015,⁶⁰ making it one of the most

⁵² Ran Abuhassira, et al., “Medical use of cannabis and cannabinoids containing products,” 2-6.

⁵³ Orrin Devinsky, Helen Cross, Linda Laux, Eric Marsh, Iin Miller, Rima Nababout, Ingrid Scheffer, Elizabeth Thiele, Stephen Wright, and Cannabidiol in Dravet Syndrome Study Group, “Trial of cannabidiol for drug-resistant seizures in the Dravet syndrome,” *The New England Journal of Medicine* 376 (2017): 2011-2020. István Ujváry and Lumir Hanus, “Human metabolites of cannabidiol: a review on their formation, biological activity and relevance in therapy,” *Cannabis and Cannabinoid Research* 1 (2016): 90-101. Ran Abuhassira, et al., “Medical use of cannabis and cannabinoids containing products,” 2-6. Elizabeth Black, et al., *Ethics and science, cannabinoids and healthcare*.

⁵⁴ Ran Abuhassira, et al., “Medical use of cannabis and cannabinoids containing products,” 2-6. United Nations Office on Drugs and Crime (UNODC), *World Drug Report 2013* (New York: UNODC, 2013). James Anthony, et al., “Cannabis epidemiology,” 6340-6352.

⁵⁵ István Ujváry and Lumir Hanus, “Human metabolites of cannabidiol,” 90-101.

⁵⁶ István Ujváry and Lumir Hanus, “Human metabolites of cannabidiol,” 90-101. Elizabeth Black, et al., *Ethics and science, cannabinoids and healthcare*.

⁵⁷ Elizabeth Black, et al., *Ethics and science, cannabinoids and healthcare*. Subodh Kumar, et al., “Modulation of endocannabinoid system: Success lies in the failures,” 155-158.

⁵⁸ Elizabeth Black, et al., *Ethics and science, cannabinoids and healthcare*.

⁵⁹ Elizabeth Black, et al., *Ethics and science, cannabinoids and healthcare*. Subodh Kumar, et al., “Modulation of endocannabinoid system: Success lies in the failures,” 155-158.

⁶⁰ Robert Torrence, et al., “Residual effects of cannabis use on attentional bias towards fearful faces,” 482-488.

commonly abused substances in the world after alcohol and tobacco.⁶¹ Nowadays, despite associated health risks with the use of cannabis, its recreational use is permitted in Uruguay and Canada.⁶² Simultaneously, medical cannabis is legal in 34 states of the USA.⁶³ California was beginning a trend toward relaxing legal prohibitions against cannabis production and use.⁶⁴ Over the course of several years, other states have passed legislation allowing marijuana purchase, possession and usage to some degree.⁶⁵ Today, medical cannabis is also legal in 31 countries (Argentina, Australia, Canada, Chile, Colombia, Croatia, Cyprus /for cancer treatment only/, Czech Republic, Denmark, Finland, Germany, Great Britain, Greece, Israel, Italy, Jamaica, Luxembourg, Malta, Mexico, Netherlands, North Macedonia, Norway, Peru, Poland, Portugal, Republic of Korea, San Marino, Sri Lanka, Switzerland, Uruguay and Zimbabwe).⁶⁶ It should be noted that in many countries, there is a considerable gap between the official authorizations, which may be quite permissive, to the actual access of patients to medical cannabis.⁶⁷

Despite the frequent use of the phrase “medicalization of cannabis,” it is not clear what it means to different stakeholders (physicians, nurses, patients, employers, insurance companies, pharmaceutical firms, government and regulating bodies, as well as cannabis cultivators and cannabis medicine dispensaries) involved in medical cannabis policy

⁶¹ United Nations Office on Drugs and Crime (UNODC), *World Drug Report 2013* (New York: UNODC, 2013). Hemant Goyal, et al., “Cannabis in liver disorders,” 1283-1290.

⁶² William Tilburg, et al., “Emerging public health law and policy issues concerning state medical cannabis programs,” 108-111.

⁶³ James Anthony, Catalina Lopez-Quintero, and Omayma Alshaarawy, “Cannabis epidemiology: a selective review,” *Current Pharmaceutical Design* 22 (2017): 6340-6352. William Tilburg, James Hodge Jr., and Camille Gourdet, “Emerging public health law and policy issues concerning state medical cannabis programs,” *The Journal of Law, Medicine & Ethics* 47S2 (2019): 108-111. United Nations Office on Drugs and Crime (UNODC), *World Drug Report 2013* (New York: UNODC, 2013).

⁶⁴ Elizabeth Black, et al., *Ethics and science, cannabinoids and healthcare*. Craig Reinerman, et al., “Who are medical marijuana patients?,” 128-135.

⁶⁵ United Nations Office on Drugs and Crime (UNODC), *World Drug Report 2013* (New York: UNODC, 2013).

⁶⁶ William Tilburg, et al., “Emerging public health law and policy issues concerning state medical cannabis programs,” 108-111.

⁶⁷ Ran Abuhaira, et al., “Medical use of cannabis and cannabinoids containing products,” 2-6.

development.⁶⁸ Across all different regulatory systems worldwide, physicians hold a vital role in the integration of medical cannabis into clinical practice. As a sociological and theoretical concept, medicalization „describes a process by which nonmedical problems become defined and treated as medical problems, usually in terms of illnesses or disorders.”⁶⁹ The medicalization or incorporation of cannabis into medicine is complicated, keeping in mind that the knowledge of its properties and effects is still limited.⁷⁰ Additionally, cannabis is a plant rather than a pharmaceutical product, which law in many countries following the UN drug convention still defines as an illicit substance with no medicinal value.⁷¹ As the interest in cannabis medical research accelerates (over 10000 scientific papers have been published and its number is rapidly increasing) and the involvement of pharmaceutical companies in developing cannabis-based treatments grows, it is necessary for physicians to be knowledgeable and capable of informing patients on matters related to medicinal or recreational cannabis use.⁷²

Biomedical ethics typically recognizes four fundamental principles that have to be weighed against each other in consideration of medical issues from an ethical standpoint.⁷³ These principles are *beneficence* (the ethical mandate for physicians to help their patients), *respect for autonomy* (the ethical right of every patient to direct his or her own health choices), *non-maleficence* (the ethical mandate for physicians to avoid harm to their

⁶⁸ Yuval Zolotov, et al., “Medical cannabis: An oxymoron?,” 4-10. Subodh Kumar, et al., “Modulation of endocannabinoid system: Success lies in the failures,” 155-158. Daniel Kruger and Jessica Kruger, “Medical cannabis users’ comparisons between medical cannabis and mainstream medicine,” 31-36. Peter Conrad, “Medicalization and social control,” 209-232. UN, *Single convention on narcotic drugs*, www.unodc.org/pdf/convention_1961_en.pdf. (accessed February 13, 2021).

⁶⁹ Peter Conrad, “Medicalization and social control,” *The Annual Review of Sociology* 18 (1992): 209-232. Craig Reinerman, et al., “Who are medical marijuana patients?,” 128-135.

⁷⁰ UN, *Single convention on narcotic drugs*, www.unodc.org/pdf/convention_1961_en.pdf. (accessed February 13, 2021).

⁷¹ UN, *Single convention on narcotic drugs*, www.unodc.org/pdf/convention_1961_en.pdf. (accessed February 13, 2021). Peter Conrad, “Medicalization and social control,” 209-232.

⁷² Elizabeth Black, et al., *Ethics and science, cannabinoids and healthcare*. Daniel Kruger and Jessica Kruger, “Medical cannabis users’ comparisons between medical cannabis and mainstream medicine,” 31-36.

⁷³ Sylvie Fainzang, “The other side of medicalization: self-medicalization and self medication,” *Culture, Medicine and Psychiatry* 37 (2013): 488-504.

patients, or to maximize benefit relative to harm where some degree of harm is unavoidable), and *justice* (the ethical consideration of distribution of health resources in light of relative scarcity, fairness and equality).⁷⁴ Although CBD has a positive profile of efficiency and safety, and gives encouraging results in the treatment of patients with inflammations, diabetes mellitus, cancer, affective disorders, neurodegenerative diseases and epilepsy,⁷⁵ it is increasingly unethical to continue supporting the traditionally accepted position that there are no legitimate medical applications for cannabis.⁷⁶ Studies are continuing to emerge showing compelling benefits in many common pathological and pathophysiological conditions, as well as various functional disorders and organic diseases.⁷⁷ In relation to, medical application of cannabis is considered an effective measure in the treatment of pain,⁷⁸ anxiety,⁷⁹ seizure disorders⁸⁰ and multiple sclerosis spasticity.⁸¹ In addition, recently published data indicated the potential usefulness of CB1 blockade in the treatment of high-fat diet (HFD)-induced nonalcoholic fatty liver disease (NAFLD).⁸²

⁷⁴ Elizabeth Black, et al., *Ethics and science, cannabinoids and healthcare*.

⁷⁵ Thomas Strouse, "Cannabinoids in medical practice," *Cannabis and Cannabinoid Research* 1 (2016): 38-43.

⁷⁶ Elizabeth Black, et al., *Ethics and science, cannabinoids and healthcare*.

⁷⁷ Thomas Strouse, "Cannabinoids in medical practice," 38-43.

⁷⁸ Thomas Strouse, "Cannabinoids in medical practice," 38-43. Iftach Sagy, et al., "Ethical issues in medical cannabis use," 20-22.

⁷⁹ Maria Steenkamp, et al., "Marijuana and other cannabinoids as a treatment for posttraumatic stress disorder: a literature review," 207-216. Robert Torrence, et al., "Residual effects of cannabis use on attentional bias towards fearful faces," 482-488. Ethan Russo and Geoffrey Guy, "A tale of two cannabinoids," 234-246.

⁸⁰ Iftach Sagy, Tal Peleg-Sagy, Leonid Barski, Lior Zeller, and Alan Jotkowitz, "Ethical issues in medical cannabis use," *European Journal of Internal Medicine* 49 (2018): 20-22.

⁸¹ Katarina Vesic, Slavica Djukic-Dejanovic, Milica Borovcanin, Janko Samardzic, and Gordana Toncev, "Cannabis as a possible treatment for spasticity in multiple sclerosis," *Serbian Journal of Experimental and Clinical Research* 17 (2016): 61-66. István Ujváry and Lumir Hanus, "Human metabolites of cannabidiol," 90-101. Thomas Strouse, "Cannabinoids in medical practice," 38-43.

⁸² Bojan Jorgačević, Dušan Mladenović, Milica Ninković, Milena Vesković, Vesna Dragutinović, Aleksandar Vatazević, Danijela Vučević, Rada Ješić Vukičević, and Tatjana Radosavljević, "Rimonabant improves oxidative/nitrosative stress in mice with nonalcoholic fatty liver disease," *Oxidative Medicine and Cellular Longevity* (2015): doi:10.1155/2015/842108. Bojan Jorgačević, Danijela Vučević, Ivana Đuričić, Slađana Šobajić, Dušan Mladenović, Milena Vesković, Rada Ješić Vukičević, and Tatjana Radosavljević, "The effect of cannabinoid receptor 1 blockade on hepatic free fatty acid

Generally speaking, physicians in their practice are expected to prescribe unstandardized agents with no EMA and FDA approval with potentially unexpected effects and adverse reactions.⁸³ Physicians are also required to discuss with their patients' potential risks and benefits before prescribing any treatment or medication.⁸⁴ Since medical cannabis dosing and potency is not regulated, there is an unavoidable knowledge gap.⁸⁵ Lack of sufficient knowledge regarding the exact content and purity of medical cannabis derivatives, and interaction with other drugs impair the patients' ability to reach a fully informed decision. Besides, there is a lack of data on the long term effects of cannabis use, which impacts physician and patient decision making.⁸⁶ Moreover, the relationship of some psychiatric conditions with cannabis utilization, such as anxiety, depression, posttraumatic stress disorder, acute psychosis disorders and schizophrenia among users with preexisting genetic vulnerability remained unclear and can put the physician who prescribed them in a constant conflict.⁸⁷

Cannabis has been proposed as an alternative treatment for chronic pain and may help curb the opioid epidemic by serving as a substitute, or as a dose reducer when used in combination with opioids.⁸⁸ Therefore allowing cannabis use as a therapeutic approach earlier in the course of the disease may be a more ethical approach for some patients, especially where the risks might be considered low.⁸⁹ However, since there is no

profile in mice with nonalcoholic fatty liver disease," *Chemistry and Physics of Lipids* 204 (2017): 85-93. Bojan Jorgačević, Danijela Vučević, Milena Vesković, Dušan Mladenović, Dušan Vukičević, Rada Ješić Vukičević, Vera Todorović, and Tatjana Radosavljević, "The effect of cannabinoid receptor 1 blockade on adipokine and proinflammatory cytokine concentration in adipose and hepatic tissue in mice with nonalcoholic fatty liver disease," *Canadian Journal of Physiology and Pharmacology* 97 (2019): 120-129. Tatjana Radosavljević, "The role of neuroendocrine-inflammatory axis in pathogenesis of nonalcoholic fatty liver disease (in Serbian)," *Medical Investigations (Medicinska Istraživanja)* 51 (2017): 17-18. Danijela Vučević, "The influence of endocannabinoid system on development of metabolic syndrome (in Serbian)" *Medical Investigations (Medicinska Istraživanja)* 52 (2018): 27-28.

⁸³ Iftach Sagy, et al., "Ethical issues in medical cannabis use," 20-22.

⁸⁴ Ibidem.

⁸⁵ Ibidem.

⁸⁶ Ibidem.

⁸⁷ Ibidem.

⁸⁸ Ibidem. Elizabeth Black, et al., *Ethics and science, cannabinoids and healthcare*. Ran Abuhasira, et al., "Medical use of cannabis and cannabinoids containing products," 2-6.

⁸⁹ Elizabeth Black, et al., *Ethics and science, cannabinoids and healthcare*.

clear guidelines of when to prescribe medical cannabis, the vague indications and relatively high availability of medical cannabis may lead to over-use, misuse, and eventually to illegal trading with third party similar to the broad use of opioids.⁹⁰

Smoking medical cannabis is the most popular administrating method, which may be associated not only with cough, phlegm, bronchitis and other adverse effects on the respiratory tracts of the users, but also with second hand smoke effects on the environment, such as minor impairment on psychomotor abilities and working memory, as well as increase emergency visits and lower cognitive functioning among exposed children.⁹¹ These findings imply that smoked medical cannabis contradicts the harm principle, in which an individual is free to abuse illicit agent unless it does not harm others.⁹² On the other hand, according to the principle of respect of autonomy, many patients prefer administrating medical cannabis via smoking methods as the best route of its administrating (shorter half-life, but higher bioavailability compared to oral medical cannabis regimens). Thus, these two contradicting ethical considerations need to be balanced.⁹³

CONCLUSION

Due to the lack of knowledge on how legalized medical and recreational use of cannabis might affect public health and patients medical choices, more research is needed on this topic. It is increasingly important to educate all stakeholders about its use and side effects, and investigate its potential to be substituted for prescription drugs. Accordingly, physician focus should be on established safety and efficacy data from credible trials and chemically defined compounds, risk vs. benefit concepts, relevant pharmacologic data, and contemporary use trends. Besides, physicians should elicit cannabis use in standard medical histories and consider the pharmacologic implications of cannabis alongside other medications as part of overall medication management. To accomplish this, the use of cannabis should be addressed in a manner that avoids

⁹⁰ Iftach Sagy, et al., “Ethical issues in medical cannabis use,” 20-22.

⁹¹ Elizabeth Black, et al., *Ethics and science, cannabinoids and healthcare*. Iftach Sagy, et al., “Ethical issues in medical cannabis use,” 20-22.

⁹² Iftach Sagy, et al., “Ethical issues in medical cannabis use,” 20-22.

⁹³ *Ibidem*.

bias, presumption, or implicit judgment. Finally, although cannabis is one of the most explored plants in science history, an ethical approach to its medicalization indicates that “conscience without knowledge is not useful, and knowledge without conscience is immorality and danger.”

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