Medical Cannabis: Toward a New Policy and Health Model for an Ancient Medicine

Davide Fortin 1, Fabienne Marcellin 2, Patrizia Carrieri 2*, Julien Mancini 2 and Tangui Barré 2

1 University Paris 1 Sorbonne, Paris, France, 2 Aix Marseille Univ, INSERM, IRD, SESSTIM, Sciences Economiques & Sociales de la Santé & Traitement de l’Information Médicale, ISSPAM, Marseille, France

Keywords: cannabis, drug policy, cannabis flowers, marijuana, real-word evidence, France, patient-reported outcomes (PROs)

INTRODUCTION

Cannabis has been grown and exploited by mankind for its therapeutic properties since ancient times (1). Although a growing number of countries have approved cannabis-based products for medical use, high-quality evidence for cannabis itself (understood in this article as the unprocessed flowering tops of the plant) in this context is lacking, and only a few jurisdictions to date have approved the medical use of cannabis, mostly as magistral preparations (2). The reason for this lies in the large variation in cannabis material as a plant (3, 4). Real-word data on the medical use of cannabis could be of benefit to patients worldwide, healthcare professionals, policymakers, and researchers (3, 5, 6). In this article, we discuss these points and propose that the collection of patient-reported outcomes (PROs) could be a cornerstone of a medical cannabis policy.

CANNABIS, A SQUARE PEG IN THE ROUND HOLE OF EVIDENCE-BASED MEDICINE THAT RELIES EXCLUSIVELY ON RANDOMIZED CONTROLLED TRIALS

The recent discoveries of cannabinoids (compounds interacting with cannabinoid receptors) and of the endocannabinoid system (ECS) have boosted the expansion of cannabis-related research (7). The ECS is a signaling network composed of cannabinoid receptors (CB1 and CB2), their ligands (endocannabinoids), and ligand synthesizing and degrading enzymes. It is a complex system, expressed through most organs, and is involved in many physiological pathways. Phytocannabinoids (cannabinoids from plants, generally from cannabis) interact with the ECS and may bring consequent health effects (8).

The two most abundant and studied phytocannabinoids are Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD). Evidence-based medicine (EBM) focusing on these purified “major” cannabinoids has led to the development of several drugs including dronabinol (THC), nabilone (synthetic analog of THC), Epidiolex (CBD), and nabiximols (a balanced mixture of THC and CBD). These drugs have been approved for a very limited number of conditions such as resistant epilepsy.

The therapeutic potential of cannabis is not limited to the effects of THC and CBD, or to their interactions with CB1 and CB2 (8). Numerous “minor” phytocannabinoids, such as Δ9-tetrahydrocannabinvarin, cannabichromene, cannabigerol, and cannabinoil, act on the ECS in ways which likely engender health effects (8, 9). However, far fewer studies have investigated their potential benefits. Phytocannabinoids may also interact with receptors other than cannabinoid receptors (8), and between-phytocannabinoid interactions have also been highlighted (10, 11).
In addition to phytocannabinoids, the Cannabis genus also produces non-cannabinoid compounds, including terpenoids (12), which may also be medically useful (13–15). The pharmacological contributions of minor cannabinoids and non-cannabinoid compounds have been highlighted and popularized under the term “entourage effect” (16, 17). Through synergistic mechanisms between different cannabis chemical components (over 500 have been identified to date (18, 19)), “full-spectrum” cannabis extracts may have different and potentially superior effects to those observed with purified major cannabinoids (16, 17).

Unlike purified cannabinoids, cannabis constitutes a mixture of multi-target active compounds that interact with each other. There is great genetic variability between cannabis plants (20). Each chemical variety of cannabis (chemovar or chemotype) has a specific profile of various cannabinoid and non-cannabinoid compounds depending on its genetic make-up (16, 21). This profile can change depending on pre- and post-harvest environmental factors (22–25). Accordingly, each of these various “cocktails” is likely to have a different impact (including adverse effects) on different people, according to the individual's genetic factors (26–28). This diversity in effects may match the diversity of individual needs, may help reduce treatment gaps, and may lessen the burden of therapeutic deadlocks.

Indications for treatment by cannabinoids, supported by low to moderate certainty of evidence, include chronic pain, some treatment resistant epilepsies, and nausea and vomiting caused by chemotherapy (29, 30). However, evidence is lacking for cannabis, for several reasons. First, in order to follow EBM principles, randomized-controlled trials (RCT) are needed. Very few RCT have been conducted with cannabis (31). RCT necessitates a stable, standardized, and characterized product to test against another product in a characterized sample of patients. However, standardization/characterization is a problem when dealing with plant material (32). Second, given the variability of cannabis materials, the external validity of RCT results would be highly questionable. Moreover, cannabis material available to researchers may be different to what is available to users (33). Third, RCT are expensive, and the lack of patentability for findings means little economic incentive to conduct such research (4). Fourth, there would be difficulties in interpreting the evidence because of the variety of compounds involved. Consequently, cannabis as a “regular” medicinal product (i.e., a drug delivered through prescription for a given condition and with a given posology) is unlikely to be approved in the foreseeable future.

REAL-WORLD IS THE NEW EVIDENCE

Despite the lack of RCT-based evidence, many patient reports and large scale observational studies have attested to the medical effectiveness of cannabis (3, 34). We believe that in the context of medical cannabis, the current approach to EBM which sees RCT as the exclusive means for valid evidence of treatment effectiveness, needs to be reconsidered. More specifically, in the context of medical cannabis, we agree with the view that RCT are “intensive, expensive interventions delivered in leading medical centers by world-class experts and requiring very skilled intervention delivery and high fidelity, administered to uncomplicated, highly motivated patients, [which] cannot be expected to work equally well in the messy, real-world, under-resourced public health settings around the world dealing with complex comorbid patients living in stressful, non-supportive environments” (35).

Real-world evidence, including PROs [i.e., where health status is reported directly by the patient, without interpretation by a clinician or anyone else (36)], is now building up to a pattern of evidence, emphasizing the effectiveness of using medical cannabis to treat pain syndromes as well as various psychiatric conditions (3). Real-world evidence can be used to complement RCT or to serve as a precursor to them in order to increase the speed at which evidence is generated, and to reduce costs (5). For instance, emulating randomized trials from large observational databases and statistical methods to account for bias (37) hold great promise for assessing cannabis’ effectiveness (38, 39).

CURRENT MODELS OF REGULATORY FRAMEWORKS FOR MEDICAL CANNABIS

Currently, two main types of regulatory frameworks exist for medical cannabis: the accommodative North American framework, and the restrictive European one. In the U.S., citizen-initiated referenda have led to the legalization of medical cannabis, whereby therapy is dispensed according to state-level regulation (4). Initially permitted for a small number of health conditions, the list has progressively grown to the point where almost all adults can now access it where it is legal (40). Home cultivation, sometimes subject to quantity restriction and/or registration, is also permitted in some U.S. states. Currently, over 50% of U.S. states have fully authorized the medical use of cannabis (2). In Canada, the medical cannabis market was designed by policymakers, but similarly to the U.S., it allows patients to buy cannabis from a licensed producer. Medical practitioners and registered nurses are responsible for providing a document that allows access. The major differences with the U.S. are the need for a bona fide doctor-patient relationship, and the lack of retail distribution, which can only be home delivered (41). Patients in Canada can also register to produce a limited amount of cannabis for their own medical purposes, or designate someone to produce it on their behalf.

On the contrary, in European countries where medical cannabis (or cannabis-based products) is legal, there are significant restrictions both on eligible medical conditions and on the types of products available (40). Medical cannabis-based products are mostly made available through special access schemes and as a last intention treatment, meaning that the patient must have previously tried other commonly used treatment options. The most common authorized medical cannabis-based products are standardized drugs containing cannabinoids. Only six European countries (Czech Republic, Denmark, Italy, Netherlands, Portugal, and Germany) have established programs allowing patients to access cannabis.
(i.e., herbal preparations) (42). Italy and Netherlands only permit access to cannabis decontaminated through gamma-irradiation [and therefore undergoing a few changes in the terpene profile (43)] (4). Pharmaceutical products containing cannabinoids are usually reimbursed from the health system under specific conditions (44). Costs for cannabis can be reimbursed if conventional treatments have failed and under specific conditions (e.g., upon prior approval in Germany). In all the above-cited North American and European jurisdictions, most regulators allow physicians to decide which indications they will prescribe cannabis for (2).

TOWARD RECIPROCITY: WHERE PRACTICE FUELS KNOWLEDGE AND VICE-VERSA

Given the huge numbers of patients looking for symptom relief from different health conditions, the limitations of the European (access too restrictive) and North American [high risk of cannabis use disorder (45)] medical cannabis policies, need to be tackled (4). To ensure optimal use of medical cannabis and to best meet the needs of patients (e.g., symptom alleviation), healthcare professionals (e.g., providing a clear picture of cannabis’ effects and indications for medical use), and society (e.g., potentially decreasing health-care reimbursement costs), it is essential to implement high-quality, structured and systematic collection of real-world evidence, especially PROs. Indeed, as PROs come directly from the patient, their evolution is likely to reflect users’ satisfaction derived from a treatment, and its impact on quality of life. Health-related quality of life measures can then be analyzed and translated in terms of cost-effectiveness (or cost-utility), and contribute in guiding decision-makers (46–48). PROs measure outcomes important to patients than cannot be captured through clinical measures, and offer opportunities to ensure that the patients’ voice is at the heart of the health-care model. Symptom (e.g., pain) alleviation is a common motive for cannabis use (rather than disease curation), and PROs are particularly fitted to assess severity of symptoms and/or associated distress (49–51). PROs can be collected through user-friendly self-administered questionnaires, including electronic ones (49, 50), and at home (52, 53). Therefore, collection of PROs may need virtually no training for patients and health professionals.

Efforts should be made to ensure collaboration between stakeholders, to establish a standard set of tools, measures and methods, to formulate a clear governance process for generating real-world evidence based on PROs, to minimize workload and technical complexity, to provide guidance on how to interpret and use data, and to ensure that patients and clinicians gain value from assessment through real-time access to PROs data so that treatment can be individually tailored (6). Collecting data on the cannabis chemovar used, and patients’ patterns of use (i.e., route and frequency of administration) is also indispensable.

Proposing a complete model for medical cannabis (or full-spectrum extracts) care is out of the scope of the present article. Nevertheless, we suggest a few points to consider when creating or adapting medical cannabis policy. Given its use since antiquity, the safety profile of cannabis is well-known. However, while THC-related harms (54, 55) and the very real risk of dependence (45, 56) have been described in detail, drug-drug interactions remain under-documented (57). Accordingly, the individual benefit/risk ratio should precede any prescription through an assessment of potential contraindications or limitations. Minimization of combustion-based routes of administration should be emphasized (58, 59) and supported by providing appropriate material such as vaporizers (60).

We also suggest that incentives be implemented to combine the collection of PROs with the dispensing of medical cannabis, through a post-marketing type assessment. By doing so, an accessible, standardized, high-quality corpus of real-world evidence on the medical use of cannabis would be generated and grow with time and experience. By systematically collecting and documenting cases that were previously anecdotal, as well as by characterizing optimal patterns of use for conditions concerning large number of cases, such systematic data would inform and benefit both patients and physicians. We can therefore expect a high level of social acceptability of combining collection of PROs with the dispensing of medical cannabis, more or less in line with acceptability of participatory and/or community research frameworks.

FINAL CONSIDERATIONS

In this opinion article, we discussed the difficult marrying the highly variable, multiple-component, and multiple-target drug that is cannabis to EBM which is currently exclusively based on RCT. In our opinion, the traditional empirical use of cannabis needs to be reconciled with an EBM which does not solely rely on RCT. We hypothesize that incorporating the collection of PROs into medical cannabis policy would benefit patients, healthcare professionals, and society.

AUTHOR CONTRIBUTIONS

DF, FM, PC, and JM designed the article and reviewed it. TB designed the article, wrote the manuscript draft, and reviewed it. All authors contributed to the article and approved the submitted version.

ACKNOWLEDGMENTS

Our thanks to Jude Sweeney (Milan, Italy) for the English revision and copyediting of the manuscript.
REFERENCES
1. Pisanti S, Bifulco M. Medical cannabis: a plurimillennial history of an evergreen. J Cell Physiol. (2019) 234:8342–51. doi: 10.1002/jcp.27725
2. Abubasira R, Shibro L, Landschaft Y. Medical use of cannabis and cannabinoids containing products – regulations in Europe and North America. Eur J Intern Med. (2018) 49:2–6. doi: 10.1016/j.ejim.2018.01.001
3. Schlag AK, O’Sullivan SE, Zafar RR, Nitt DJ. Current controversies in medical cannabis: recent developments in human clinical applications and potential therapeutics. Neuropharmacology. (2021) 191:108586. doi: 10.1016/j.neuropharm.2021.108586
4. Fortin D, Massin S. Medical cannabis: thinking out of the box of the healthcare system. J Econ Sante. (2020) 2:110–8. doi: 10.9119/jes.2020.0110
5. Banerjee R, Erridge S, Salazar O, Mangal N, Couch D, Pacchetti B, et al. Real world evidence in medical cannabis research. Ther Innov Regul Sci. (2022) 56:8–14. doi: 10.1007/s40441-021-00346-0
6. Calvert MJ, O’Connor DJ, Basch EM. Harnessing the patient voice in real-world evidence: the essential role of patient-reported outcomes. Nat Rev Drug Discov. (2019) 18:731–2. doi: 10.1038/s41573-019-00088-7
7. Matiolo CBD, Sarzi DS, Justolbin B, Lemos RPM, Camargo FAO, Stefenson VM. A bibliometric analysis of cannabis publications: six decades of research and a gap on studies with the plant. Publications. (2018) 6:40. doi: 10.3936/publications.2018.0400040
8. Piscitelli F, Di Marzo V. Cannabinoids: a class of unique natural products using molecular approaches. In: Chandra S, Lata H, ElSohly MA, editors. Cannabis sativa L–Botany and Biotechnology. Cham: Springer International Publishing, (2017) p. 395–418. doi: 10.1007/978-3-319-54564-6_19
9. Rosenthaler S, Pöhn B, Kolmanz C, Huu CN, Krewenka C, Huber A, et al. Cannabis and its secondary metabolites: their use as therapeut ic drugs, toxicological aspects, and analytical determination. Medicines. (2019) 6:31. doi: 10.3390/medicines6010031
10. Milay L, Berman P, Shapira A, Guberman O, Meiri D. Metabolic profiling of cannabis based products and cannabinoids. RMJ. (2019) 365:11141. doi: 10.1186/s12920-017-11141-5
11. Legare CA, Raup-Konsavage WM, Vrana KE. Therapeutic potential of cannabis, cannabidiol, and cannabinoid-based pharmaceuticals. Pharmacology. (2022) 107:131–49. doi: 10.1159/000521683
12. Kluetz PG, O’Connor DJ, Soltsy K. Incorporating the patient experience into medical cannabis research. Ther Innov Regul Sci. (2021) 55:1223–7. doi: 10.1080/10826084.2020.1731547
13. Kluetz PG, O’Connor DJ, Soltsy K. Emulating a novel clinical trial using existing observational data. Am J Prev Med. (2019) 57:471–82. doi: 10.1016/j.amepre.2019.02.015
14. Blanton HL, Barnes RC, McMann MC, Bilbrey JA, Wilkerson JL, Guindon J. Sex differences and the endocannabinoid system in pain. Pharmacol Biochem Behav. (2021) 202:173107. doi: 10.1016/j.pbb.2021.173107
15. Caccavo TR, Hindocha C, Green SF, Bloomfield MAP. Medicinal use of cannabis products and cannabinoids. BMJ. (2019) 365:l1141. doi: 10.1136/bmj.l1141
16. Ablin J, Ste-Marie PA, Schäfer M, Häusser W, Fitzcharles MA. Medical use of cannabis products: lessons to be learned from Israel and Canada. Schmerz Berlin. (2016) 30:3–13. doi: 10.1007/s00482-015-0083-4
42. Belackova V, Shanahan M, Ritter A. Mapping regulatory models for medicinal cannabis: a matrix of options. Aust Health Rev. (2018) 42:403–11. doi: 10.1071/AH16257
43. Hazekamp A. Evaluating the effects of gamma-irradiation for decontamination of medicinal cannabis. Front Pharmacol. (2016) 7:108. doi: 10.3389/fphar.2016.00108
44. Krcevski-Skvarc N, Wells C, Häuser W. Availability and approval of cannabis-based medicines for chronic pain management and palliative/supportive care in Europe: a survey of the status in the chapters of the European pain federation. Eur J Pain Lond Engl. (2018) 22:440–54. doi: 10.1002/ejp.1147
45. Gilman JM, Schuster RM, Potter KW, Schmitt W, Wheeler G, Pachas GN, et al. Effect of medical marijuana card ownership on pain, insomnia, and affective disorder symptoms in adults: a randomized clinical trial. JAMA Netw Open. (2022) 5:e222106. doi: 10.1001/jamanetworkopen.2022.2106
46. Hutubessy RC, Baltussen RM, Torres-Edejer TT, Evans DB. Generalised cost-effectiveness analysis: an aid to decision making in health. Appl Health Econ Policy. (2002) 1:89–95.
47. Kim DD, Basu A. How does cost-effectiveness analysis inform health care decisions? AMA J Ethics. (2021) 23:E639–47. doi: 10.1010/amajethics.2021.639
48. Lau VI, Xie F, Basmaji J, Cook DJ, Fowler R, Kiflen M, et al. Health-Related quality-of-life and cost utility analyses in critical care: a systematic review. Crit Care Med. (2021) 49:575–88. doi: 10.1097/CCM.0000000000004851
49. Goldberg SL, Paramathan D, Khoury R, Patel S, Jagun D, Arunajadai S, et al. A patient-reported outcome instrument to assess symptom burden and predict survival in patients with advanced cancer: flipping the paradigm to improve timing of palliative and end-of-life discussions and reduce unwanted health care costs. Oncologist. (2019) 24:76–85. doi: 10.1634/theoncologist.2018-0238
50. Clapham S, Daveson BA, Allingham SF, Morris D, Blackburn P, Johnson CE, et al. Patient-reported outcome measurement of symptom distress is feasible in most clinical scenarios in palliative care: an observational study involving routinely collected data. Int J Qual Health Care. (2021) 33:mzab075. doi: 10.1093/intqhc/mzab075
51. Kall M, Marcellin F, Harding R, Lazarus JV, Carrieri P. Patient-reported outcomes to enhance person-centred HIV care. Lancet HIV. (2020) 7:e59–68. doi: 10.1016/S2352-3018(19)30345-5
52. Wittmer LM, Giesinger JM, Zabernigg A, Rumpold G, Szatkay M, Oberguggenberger AS, et al. Evaluation of patient-reported outcome assessment with cancer patients in the hospital and at home. BMC Med Inform Decis Mak. (2015) 15:110. doi: 10.1186/s12911-015-0230-y
53. Cowan RA, Suidan RS, Andikyan V, Rezk YA, Einstein MH, Chang K, et al. Electronic patient-reported outcomes from home in patients recovering from major gynecologic cancer surgery: a prospective study measuring symptoms and health-related quality of life. Gynecol Oncol. (2016) 145:362–6. doi: 10.1016/j.ygyno.2016.08.335
54. Volkow ND, Baler RD, Compton WM, Weiss SRB. Adverse health effects of marijuana use. N Engl J Med. (2014) 370:2219–27. doi: 10.1056/NEJMra1402309
55. Volkow ND, Swanson JM, Evins AE, DeLisi LE, Meier MH, Gonzalez R, et al. Effects of cannabis use on human behavior, including cognition, motivation, and psychosis: a review. JAMA Psychiatry. (2016) 73:292–7. doi: 10.1001/jamapsychiatry.2015.3278
56. Leung J, Chan GCK, Hides L, Hall WD. What is the prevalence and risk of cannabis use disorders among people who use cannabis? A systematic review and meta-analysis. Addict Behav. (2020) 109:106479. doi: 10.1016/j.addbeh.2020.106479
57. Cox EJ, Maharaao N, Patilea-Vrana G, Unadkat JD, Rettie AE, McCune JS, et al. A marijuana-drug interaction primer: precipitants, pharmacology, and pharmacokinetics. Pharmaco1 Ther. (2019) 201:25–38. doi: 10.1016/j.pharmthera.2019.05.001
58. Tashkin DP, Roth MD. Pulmonary effects of inhaled cannabis smoke. Am J Drug Alcohol Abuse. (2019) 45:596–609. doi: 10.1080/00952990.2019.1627366
59. Kaplan AG. Cannabis and lung health: does the bad outweigh the good? Palm Ther. (2021) 7:395–408. doi: 10.1007/s41030-021-00171-8
60. Lanz C, Mattson J, Soydaner U, Breneisen R. Medicinal cannabis: in vitro validation of vaporizers for the smoke-free inhalation of cannabis. PLoS ONE. (2016) 11:e0147286. doi: 10.1371/journal.pone.0147286

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher’s Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Fortin, Marcellin, Carrieri, Mancini and Barré. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.