https://doi.org/10.1590/1806-9282.2023D693

Cannabis products: medical use

César Eduardo Fernandes[1], José Eduardo Lutaif Dolci[1], Leonardo Sobral Navarro[2], Marcelo Allevato[3], Clóvis Francisco Constantino[4], Rodrigo Pastor Alves Pereira[5], Carlos Roberto de Mello Rieder[6], Flávia Torino[2], Wanderley Marques Bernardo[1*] Antônio Geraldo da Silva[3]

The Guidelines Project, an initiative of the Brazilian Medical Association, aims to combine information from the medical field to standardize how to conduct, and to assist in the reasoning and decision-making of doctors. The information provided by this project must be critically evaluated by the physician responsible for the conduct that will be adopted, depending on the conditions and the clinical condition of each patient.
Guideline conclusion: 5 January 2023. Submission: 6 January 2023.

INTRODUCTION

The Board of the Brazilian Medical Association triggered the formation of a commission with the purpose of contributing to current scientific knowledge on the use of cannabis-derived products in patient health care.

This scientific committee met weekly and virtually for about 2 months, during which analyses and documents were discussed and developed on the therapeutic indications of products derived from cannabis, focusing on indications based on efficacy and safety, as well as compassionate use, in addition to aspects of a regulatory nature.

We know that there are limits of scientific knowledge in the timeline on all aspects involved in the health care of our patients, which have been overcome since the dawn of medicine through ethical aspect for the needs of patients combined with the constant generation of scientific evidence that guarantees the lowest level of uncertainty regarding the benefit and safety of all clinical situations faced on a daily basis by physicians.

This is not different with regard to products derived from cannabis, and therefore current scientific knowledge allows us to make inferences at the moment, which can be modified as new consistent evidence emerges, allowing this scientific document to be lively and permanently updated, incorporating this evidence.

This responsible and modern behavior protects the needs of patients by disseminating and implementing evidence-based recommendations with the health system, which guarantees medical decision-making with low uncertainty, high benefit, and safety, especially in compassionate indications that, despite the lack of efficacy, are applicable consistently and are conditioned to the use of informed consent signed between doctor and patient.

This document is made up of four different and complementary parts, expressed in a summary way that allows a quick understanding of its content and conclusions: (1) regulatory aspects of the use of products of cannabis; (2) cannabis use in pediatric patients with autism spectrum disorder (ASD); (3) medical use of cannabis-derived products: efficacy and safety; and (4) compassionate medical use of cannabis-derived products.

REGULATORY ASPECTS OF THE USE OF CANNABIS PRODUCTS[1,2]

Analysis carried out based on the rules published by ANVISA demonstrates the regulatory evolution of cannabis products in Brazil.

Collegiate Board Resolution No. 3 of January 26, 2015, as a framework, including a brief analysis of Technical Note No.

[1]Associação Médica Brasileira – São Paulo (SP), Brazil.
[2]Ordem dos Advogados do Brasil – São Paulo (SP), Brazil.
[3]Associação Brasileira de Psiquiatria – São Paulo (SP), Brazil.
[4]Sociedade Brasileira de Pediatria – São Paulo (SP), Brazil.
[5]Sociedade Brasileira de Medicina de Família e Comunidade – São Paulo (SP), Brazil.
[6]Academia Brasileira de Neurologia – São Paulo (SP), Brazil.
*Corresponding author: wmbernardo@usp.br
Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on January 06, 2023. Accepted on January 10, 2023.

01/2017/GMESP/GGMED/ANVISA – 01/09/2017, enabled the registration of Mevatyl (Nabiximols), which to date is the only cannabis-derived drug registered in Brazil.

The current regulatory context, composed of "RDC's" No. 327, 659, and 660 – all from ANVISA, was analyzed and demonstrated the regulatory challenges that are being faced by the agency, especially due to the characteristics of "cannabis products" (innumerable dilutions and regulation in the countries of origin).

RDC No. 327/2019 also disciplines the possibility that the final phase of the process of elaboration of the cannabis product is carried out in Brazil, provides the form of prescription (prescription A or B) based on the percentage of THC present in the product (up to 0.2% mg/mL), and describes the processes for dispensing, tracking, storage, and import.

The alternatives that the physician can use to prescribe cannabis products for their patient were also analyzed (products available at the pharmacy/RDC 327 and prescription of imported product for direct purchase by the patient with prior authorization from ANVISA/RDC 660), as well as the importance of formalizing the informed consent form (proposed treatment, desired effects, possible adverse reactions, chosen product, and effective consent of the patient or his/her legal representative).

We understand the need to analyze the concepts of "compassionate use" and "expanded access" in view of the expression used by ANVISA in the aforementioned resolutions that are in force: "other therapeutic options available in the Brazilian market have been exhausted."

This expression brings us to the concepts of "compassionate use" and "expanded access," which are subject to regulation by RDC 38/2013 of the same agency. This analysis is relevant and deserves special attention because, depending on the interpretation of these concepts, we will have a direct impact on the daily lives of physicians who consider this therapeutic possibility viable.

PEDIATRIC USE OF CANNABIS IN ASD[3]

The considerations and recommendations woven below, in relation to pediatric use in ASD, are derived from the position of the Brazilian Society of Pediatrics carried out through a document published and released recently[3].

Cannabidiol (CBD) is not without its adverse effects, the most commonly reported being drowsiness, increased appetite, and irritability. They published a case of a patient with a severe psychotic crisis that required interruption of treatment. In addition, in all published studies, however, the administration of CBD was performed concomitantly with other medications already used by patients; therefore, it is not possible to relate adverse effects to a specific drug, and it is also important to emphasize that it is not possible to evaluate the long-term safety of CBD, since the studies do not bring patient follow-up data for a period longer than 6 months.

To date, the literature that associates cannabinoids with the treatment of ASD symptoms is based on case reports or open, uncontrolled clinical trials with a limited number of participants. To date, only one randomized, double-blind clinical trial has been performed.

It is also important to note that the subjective reports of parents and caregivers of people with autism were used as a basis for determining the effectiveness of CBD in several of these studies. Based on this fact, it is possible that expectations regarding a new treatment may have influenced the responses provided.

The lack of methodologically adequate studies has contributed to the emergence of several anecdotal reports of exceptional, sometimes miraculous, improvements in autism, attributed to the use of CBD. Coupled with the frustration of many family members with the lack of a readily effective treatment, many have advocated the unrestricted use of CBD as a treatment for ASD.

In view of the quality scientific evidence currently available, the safe prescription of cannabinoids for the treatment of ASD symptoms should not be widely indicated. Well-designed studies are in progress and may pave the way to clarifying the potential role of these drugs in neurobehavioral diseases. So far, common sense and caution are recommended, which can be summarized as follows:

1. Every doctor who treats people with ASD must be informed and trained about CBD, as well as about the different treatments considered alternatives for autism. It is known that around 60% of family members of people within the autism spectrum have already tried one or more treatments that have yet to be proven to be effective, and it is up to physicians to know them and guide them in this regard.
2. It is necessary to create a doctor-patient relationship of mutual trust, without judgment by the clinician. Once the link is generated, evidence of efficacy and safety of the different treatments can be more easily discussed.
3. Evidence of safety and efficacy must be constantly reviewed, as new studies are frequently published.
4. Many physicians receive requests directly from family members to prescribe CBD, but the shared decision is obtained only through proper understanding of autism (about the clinical characteristics, available treatments, expected benefits, and potential risks).

5. Finally, the use of CBD in autism is still based on a small number of studies, individual medical experience, and the expectations of patients' relatives.

MEDICINAL USE OF CANNABIS-DERIVATIVE PRODUCTS: EFFECTIVENESS AND SAFETY[4-59]

As defined previously in the methodology, analyses were selected if they meet two requirements: significant differences between cannabis and placebo, and a quality of evidence assessed as moderate or high. Under these conditions, the only analysis and results that met these requirements are those related to the treatment with cannabis (CBD) in drug-resistant seizures such as the failure of ≥2 appropriate and tolerated antiepileptic drugs (either as monotherapy or in combination) to achieve sustained freedom from crises. Six RCTs were included to support this assessment, which evaluated the use of CBD plus usual therapy in the treatment of patients with Drave syndrome, Lennox-Gastaut syndrome, and Tuberous sclerosis complex, compared to placebo plus usual therapy. The CBD versus placebo comparison was evaluated for the outcome's reduction in the frequency of seizures and total seizures (all types), the number of patients with a response equal to or greater than 50%, and the impression of clinical improvement by the patient or caregiver, adverse events, and tolerability to treatment.

As the analyses showed homogeneous results (low heterogeneity), the results of the three clinical situations were kept together for common outcomes. The quality of the evidence will be expressed using GRADE terminology. The use of CBD was compared to placebo in patients with Dravet syndrome, Lennox-Gastaut syndrome, and Tuberous sclerosis complex in a follow-up period of 12–16 weeks.

Benefit

- Shows an absolute reduction in seizure frequency of 33%; being necessary to treat three patients for a benefit (number need to treat [NNT]=3). Moderate quality of evidence.
  - Increases the number of patients with a ≥50% reduction in the frequency of seizures by 20% (NNT=5). High quality of evidence.
  - Increases the number of patients with no seizures by 3% (NNT=33). Moderate quality of evidence.
  - Improvement in caregiver – or patient – rated clinical impression by 21% (NNT=5). High quality of evidence.

Damage

- Increases serious adverse events by 16% (number need to harm [NNH]=6). Moderate quality of evidence.
  - Increases the risk of abandoning treatment by 12% (NNH=8). High quality of evidence.

Benefit/harm ratio

For patients who maintain adherence to treatment with CBD, a relevant reduction in the number of monthly seizures is estimated, assuming the risk of adverse events is severe, with a negative NNT/NNH ratio of 0.83 (NNT/NNH: 5/6), favorable to the adoption of the treatment.

Recommendation

This evaluation, with meta-analysis, supports the use of CBD in the treatment of patients with convulsive crises, originating in the Dravet syndrome, Lennox-Gastaut syndrome, and Tuberous sclerosis complex, who are resistant to the usual drugs, presenting satisfactory benefits in the reduction of convulsive crises and tolerable toxicity.

COMPASSIONATE MEDICINAL USE OF CANNABIS DERIVATIVES[4-59]

In patient health care, we are faced with limits in the results of our actions in many clinical situations, despite all the therapeutic arsenal that we have today. These limits can occur in acute events with unfavorable outcomes, but they can also be present in diseases or symptoms of a chronic, recurrent, or even terminal nature. In these situations of intractability, refractoriness, or nonresponsiveness to available conventional treatments, the individuality of patients plays a fundamental role in medical decision-making, and the term "compassionate treatment" has been used for the personalized care of these patients, through therapeutic alternatives not included among the conventional or usual treatments.

However, despite the individual and exceptional character of compassionate use, these therapeutic forms must have been studied, whether or not associated with conventional treatments, through the same parameters used for evaluating the efficacy and safety of treatments already in use today.

These parameters (see guideline for the efficacy and safety of the medicinal use of cannabis derivatives) minimally involve parallel randomized controlled clinical trials, comparing cannabis derivatives with conventional treatments or with placebo, demonstrating superiority or absence of difference in relevant and present outcomes in more than one study (aggregated data) as a manifestation of refractoriness.

This evaluation and consequently the synthesis of evidence will not express the result and analysis already expressed in the evaluation of the efficacy and safety of the medicinal use of cannabis products, in which the clinical situations directly benefited are those associated with seizures, resistant to drugs such as failure of more than 2 appropriate and tolerated antiepileptic drugs (either as monotherapy or in combination) to achieve sustained freedom from seizures, namely: in Drave syndrome, Lennox-Gastaut syndrome, and Tuberous sclerosis complex.

Unlike the review and meta-analysis of the efficacy and safety of medicinal use of cannabis-derived products, the synthesis of evidence in this evaluation of compassionate medicinal use of these products is not necessarily based on significant differences between cannabis and placebo, nor on the quality of minimally moderate or high evidence.

However, regardless of the superiority result or the quality of the evidence, but dependent on a result not inferior to placebo, this synthesis is based on quantified direct evidence (derived from parallel randomized clinical trials) or qualified indirect evidence (extrapolated from direct evidence, considering potential refractory outcomes that were correlated or also associated with other diseases, which were studied through crossover randomized clinical trials).

It is also necessary to remember that the clinical situations included here for compassionate use are those in which all conventional and currently available therapeutic resources have already been exhausted, and despite this, nonresponsive patients remain with refractory symptoms (outcomes) that are related to their clinical situation or underlying disease.

The clinical situations with their respective analyzed outcomes (benefit and harm) that are likely to be treated compassionately with cannabis-derived products are as follows:

1. Cancer patients (direct evidence): Low to very low quality of evidence.
    - Pain: No difference in the number of responders comparing THC: CBD (up to 16 oral sprays/day, at follow-up ranging from 2 to 5 weeks) to placebo.
    - Opioid use: No difference in opioid consumption with THC+CBD oral spray compared to placebo.
    - Nutrition: Increase in nutrition measured by intake in kcal/day favorable to oral THC treatment (at doses ranging from 0.5 to 5.0 mg/day) when compared to placebo.
    - Adverse events: 11% increased risk of adverse events (95% confidence interval [CI]+6% to+16%) with the use of THC (27 mg/ml)+CBD (25 mg/mL) (up to 16 oral sprays/day in follow-up ranging from 2 weeks to 35 days) when compared to placebo.
2. Patients with neuropathic pain – nononcological (direct evidence): Low to very low quality of evidence.
    - Reduction in intensity (>30%): Response increase by 13% (95%CI 1–25%) with the use of THC associated with CBD (2.7 and 2.5 mg, respectively, oral spray) or THC (9 at 24 mg/day orally), in a follow-up ranging from 15 to 52 weeks, when compared to placebo.
    - Pain (VAS): There is no difference in the visual analog scale (VAS) score with the use of THC: CBD or THC when compared to placebo.
    - Adverse events (total): 14% increased risk of total adverse events (95%CI +6% to +22%) with the use of THC associated with CBD (2.7 and 2.5 mg, respectively, oral spray), in follow-up ranging from 15 to 52 weeks, when compared to placebo.
    - Adverse events (treatment-related): Increased risk of treatment-related adverse events by 26% (95%CI +15% to +38%) with the use of THC associated with CBD [(2.7 and 2.5 mg, respectively, of oral spray) or THC (1–4 mg/day VO)], in a follow-up ranging from 5 to 15 weeks, when compared to placebo.
3. Patients with chronic pain – nononcological (direct evidence): Low to very low quality of evidence.
    - Pain (VAS): There is no difference in pain intensity with the use of THC when compared to placebo.
    - Adverse Events: There is no difference in the risk of serious adverse events with the use of (THC: CBD or THC) when compared to placebo.
4. Patients with multiple sclerosis (direct evidence) and spinal cord injury (indirect evidence): Low to very low quality of evidence.
    - Spasticity: In patients with multiple sclerosis, response is found to be increased by 13% (95%CI 9–17%) with the use of THC: CBD [(2.7 and 2.5 mg, respectively, oral spray) or (THC 10.0–25.0 mg and CBD 5.0–25.0 mg/day VO)], in a follow-up ranging from 6 to 48 weeks, when compared to placebo. In patients with spinal cord injury, there is a reduction in spasticity (nonquantified effect and indirect evidence) with the use of THC, when compared to placebo.
    - Pain (response): Response (responders) increased by 8% (95%CI 3–14%) with the use of THC associated with CBD [(2.7 and 2.5 mg, respectively, oral spray) or (10–25 mg and 5–25 mg/day VO, respectively)] or THC (10 mg/day), in a follow-up ranging from 6 to 48 weeks, when compared to placebo.

- Adverse events (total): 12% increased risk of total adverse events (95%CI +7% to +17%) with the use of THC associated with CBD [(2.7 and 2.5 mg, respectively, oral spray) or (10.0–25.0 mg and 5.0–25.0 mg/day orally, respectively)] or THC (7–15 mg/day), in a follow-up ranging from 3 weeks to 36 months, when compared to placebo.
- Serious adverse events: There is no risk difference in serious adverse events with the use of THC: CBD or THC when compared to placebo.

5. Patients undergoing chemotherapy (direct evidence): Low to very low quality of evidence.
   - Nausea and/or vomiting (response): Response increased by 42% (95%CI 18–67%) with the use of THC associated with CBD (2.7 and 2.5 mg, respectively, oral spray) or THC (2.5–20 mg/day VO), in a follow-up ranging from immediate to 5 days, when compared to placebo.
   - Nausea and/or vomiting (absence): There is no difference in the absence of nausea and/or vomiting with the use of THC when compared to placebo.
   - Adverse events: Increased risk of adverse events by 28% (95%CI 3–53%) with the use of THC associated with CBD (2.7 and 2.5 mg, respectively, oral spray) or THC (2.5–20 mg/day orally), in a follow-up ranging from immediate to 5 days, when compared to placebo.

Recommendation

Compassionate use of cannabis-derived products can be used in the following patients with their respective refractory symptoms: cancer (pain, opioid use, and nutrition); neuropathic and chronic (noncancer) pain; multiple sclerosis (spasticity and pain); spinal cord injury (spasticity); and chemotherapy (nausea and/or vomiting). In all these clinical situations, there is an increased risk of adverse events (total or serious) with the use of cannabis-derived products. The quality of evidence is low or very low.

AUTHORS' CONTRIBUTIONS

WMB: Data curation, Formal Analysis, Methodology, Writing – original draft, Writing – review & editing. **CEF:** Project administration, Supervision, Writing – review & editing. **JELD:** Writing – review & editing. **CEF, JELD, LSN, MA, CFC, RPAP, CRMR, FT, WMB:** Conceptualization, Investigation, Validation.

REFERENCES

1. Ministry of Health. Resolution of the Collegiate Board - RDC No. 03 of January 26, 2015. Ministry of Health (MS) National Health Surveillance Agency (ANVISA). Available from: https://bvsms.saude.gov.br/bvs/saudelegis/anvisa/2015/rdc0003_26_01_2015.pdf
2. National Health Surveillance Agency. Technical Note Technical Note No. 01/2017/GMESP/GGMED/ANVISA – 01/09/2017. National Health Surveillance Agency (ANVISA). Available from: https://static.poder360.com.br/2017/01/mevatyl.pdf.
3. Brazilian Society of Pediatrics. Indications for cannabis use in pediatric patients with neurodevelopmental disorders and/or epilepsy: an evidence-based review. Orientation Manual. Scientific Departments of Neurology and Pediatrics of Development and Behavior (2022-2024 term). Brazilian Society of Pediatrics. No. 32, December 13, 2022. Available from: https://www.sbp.com.br/imprensa/detalhe/nid/indicacoes-para-o-uso-da-cannabis-em-pacientes-pediatricos-com- neurodevelopmental-disorders-and/or-epilepsy-an-evidence-based-review/
4. Todaro B. Cannabinoids in the treatment of chemotherapy-induced nausea and vomiting. J Natl Compr Canc Netw. 2012;10(4):487-92. https://doi.org/10.6004/jnccn.2012.0048
5. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. https://doi.org/10.1136/bmj.n71
6. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898. https://doi.org/10.1136/bmj.l4898
7. Grade Working Group. [cited on June 2022]. Available from: https://www.gradeworkinggroup.org
8. McMaster University. GRADEpro GDT: GRADEpro Guideline Development Tool [Software]. McMaster University, 2020 (developed by Evidence Prime, Inc.). Available from: gradepro.org.
9. Wiesmann UN, DiDonato S, Herschkowitz NN. Effect of chloroquine on cultured fibroblasts: release of lysosomal hydrolases and inhibition of their uptake. Biochem Biophys Res Commun. 1975;66(4):1338-43. https://doi.org/10.1016/0006-291x(75)90506-9
10. Johnson JR, Burnell-Nugent M, Lossignol D, Ganae-Motan ED, Potts R, Fallon MT. Multicenter, double-blind, randomized, placebo-controlled, parallel-group study of the efficacy, safety, and tolerability of THC:CBD extract and THC extract in patients with intractable cancer-related pain. J Pain Symptom Manage. 2010;39(2):167-79. https://doi.org/10.1016/j.jpainsymman.2009.06.008
11. Portenoy RK, Ganae-Motan ED, Allende S, Yanagihara R, Shaiova L, Weinstein S, et al. Nabiximols for opioid-treated cancer patients with poorly-controlled chronic pain: a randomized, placebo-controlled, graded-dose trial. J Pain. 2012;13(5):438-49. https://doi.org/10.1016/j.jpain.2012.01.003
12. Fallon MT, Albert Lux E, McQuade R, Rossetti S, Sanchez R, Sun W, et al. Sativex oromucosal spray as adjunctive therapy in advanced cancer patients with chronic pain unalleviated by optimized opioid therapy: two double-blind, randomized, placebo-controlled phase 3 studies. Br J Pain. 2017;11(3):119-33. https://doi.org/10.1177/2049463717710042
13. Lichtman AH, Lux EA, McQuade R, Rossetti S, Sanchez R, Sun W, et al. Results of a double-blind, randomized, placebo-controlled study of nabiximols oromucosal spray as an adjunctive therapy in advanced cancer patients with chronic uncontrolled pain. J Pain Symptom Manage. 2018;55(2):179-88.e1. https://doi.org/10.1016/j.jpainsymman.2017.09.001

14. Brisbois TD, Kock IH, Watanabe SM, Mirhosseini M, Lamoureux DC, Chasen M, et al. Delta-9-tetrahydrocannabinol may palliate altered chemosensory perception in cancer patients: results of a randomized, double-blind, placebo-controlled pilot trial. Ann Oncol. 2011;22(9):2086-93. https://doi.org/10.1093/annonc/mdq727
15. Turcott JG, Del Rocío Guillen Núñez M, Flores-Estrada D, Oñate-Ocaña LF, Zatarain-Barrón ZL, Barrón F, et al. The effect of nabilone on appetite, nutritional status, and quality of life in lung cancer patients: a randomized, double-blind clinical trial. Support Care Cancer. 2018;26(9):3029-38. https://doi.org/10.1007/s00520-018-4154-9
16. Dworkin RH, Turk DC, Farrar JT, Haythornthwaite JA, Jensen MP, Katz NP, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain. 2005;113(1-2):9-19. https://doi.org/10.1016/j.pain.2004.09.012
17. Farrar JT, Young JP, LaMoreaux L, Werth JL, Poole MR. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain. 2001;94(2):149-58. https://doi.org/10.1016/S0304-3959(01)00349-9
18. Devinsky O, Cross JH, Wright S. Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome. N Engl J Med. 2017;377(7):699-700. https://doi.org/10.1056/NEJMc1708349
19. Devinsky O, Patel AD, Thiele EA, Wong MH, Appleton R, Harden CL, et al. Randomized, dose-ranging safety trial of cannabidiol in Dravet syndrome. Neurology. 2018;90(14):e1204-11. https://doi.org/10.1212/WNL.0000000000005254
20. Miller I, Scheffer IE, Gunning B, Sanchez-Carpintero R, Gil-Nagel A, Perry MS, et al. Dose-ranging effect of adjunctive oral cannabidiol vs placebo on convulsive seizure frequency in Dravet syndrome: a randomized clinical trial. JAMA Neurol. 2020;77(5):613-21. https://doi.org/10.1001/jamaneurol.2020.0073
21. Devinsky O, Patel AD, Cross JH, Villanueva V, Wirrell EC, Privitera M, et al. Effect of cannabidiol on drop seizures in the Lennox-Gastaut syndrome. N Engl J Med. 2018;378(20):1888-97. https://doi.org/10.1056/NEJMoa1714631
22. Thiele EA, Marsh ED, French JA, Mazurkiewicz-Beldzinska M, Benbadis SR, Joshi C, et al. Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2018;391(10125):1085-96. https://doi.org/10.1016/S0140-6736(18)30136-3
23. Thiele EA, Bebin EM, Bhathal H, Jansen FE, Kotulska K, Lawson JA, et al. Add-on cannabidiol treatment for drug-resistant seizures in tuberous sclerosis complex: a placebo-controlled randomized clinical trial. JAMA Neurol. 2021;78(3):285-92. https://doi.org/10.1001/jamaneurol.2020.4607
24. Serpell M, Ratcliffe S, Hovorka J, Schofield M, Taylor L, Lauder H, et al. A double-blind, randomized, placebo-controlled, parallel group study of THC/CBD spray in peripheral neuropathic pain treatment. Eur J Pain. 2014;18(7):999-1012. https://doi.org/10.1002/j.1532-2149.2013.00445.x
25. Toth C, Mawani S, Brady S, Chan C, Liu C, Mehina E, et al. An enriched-enrolment, randomized withdrawal, flexible-dose, double-blind, placebo-controlled, parallel assignment efficacy study of nabilone as adjuvant in the treatment of diabetic peripheral neuropathic pain. Pain. 2012;153(10):2073-82. https://doi.org/10.1016/j.pain.2012.06.024
26. Selvarajah D, Gandhi R, Emery CJ, Tesfaye S. Randomized placebo-controlled double-blind clinical trial of cannabis-based medicinal product (Sativex) in painful diabetic neuropathy: depression is a major confounding factor. Diabetes Care. 2010;33(1):128-30. https://doi.org/10.2337/dc09-1029
27. Nurmikko TJ, Serpell MG, Hoggart B, Toomey PJ, Morlion BJ, Haines D. Sativex successfully treats neuropathic pain characterised by allodynia: a randomised, double-blind, placebo-controlled clinical trial. Pain. 2007;133(1-3):210-20. https://doi.org/10.1016/j.pain.2007.08.028
28. Vries M, Rijckevorsel DCM, Vissers KCP, Wilder-Smith OHG, Goor H, Pain and Nociception Neuroscience Research Group. Tetrahydrocannabinol does not reduce pain in patients with chronic abdominal pain in a phase 2 placebo-controlled study. Clin Gastroenterol Hepatol. 2017;15(7):1079-86.e4. https://doi.org/10.1016/j.cgh.2016.09.147
29. Blake DR, Robson P, Ho M, Jubb RW, McCabe CS. Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis. Rheumatology (Oxford). 2006;45(1):50-2. https://doi.org/10.1093/rheumatology/kei183
30. Chaves C, Bittencourt PCT, Pelegrini A. Ingestion of a THC-Rich cannabis oil in people with fibromyalgia: a randomized, double-blind, placebo-controlled clinical trial. Pain Med. 2020;21(10):2212-8. https://doi.org/10.1093/pm/pnaa303
31. Rizzo MA, Hadjimichael OC, Preiningerova J, Vollmer TL. Prevalence and treatment of spasticity reported by multiple sclerosis patients. Mult Scler. 2004;10(5):589-95. https://doi.org/10.1191/1352458504ms1085oa
32. Kister I, Bacon TE, Chamot E, Salter AR, Cutter GR, Kalina JT, et al. Natural history of multiple sclerosis symptoms. Int J MS Care. 2013;15(3):146-58. https://doi.org/10.7224/1537-2073.2012-053
33. Markovà J, Essner U, Akmaz B, Marinelli M, Trompke C, Lentschat A, et al. Sativex® as add-on therapy vs. further optimized first-line ANTispastics (SAVANT) in resistant multiple sclerosis spasticity: a double-blind, placebo-controlled randomised clinical trial. Int J Neurosci. 2019;129(2):119-28. https://doi.org/10.1080/00207454.2018.1481066
34. Schimrigk S, Marziniak M, Neubauer C, Kugler EM, Werner G, Abramov-Sommariva D. Dronabinol is a safe long-term treatment option for neuropathic pain patients. Eur Neurol. 2017;78(5-6):320-29. https://doi.org/10.1159/000481089
35. Ball S, Vickery J, Hobart J, Wright D, Green C, Shearer J, et al. The cannabinoid use in progressive inflammatory brain disease (CUPID) trial: a randomised double-blind placebo-controlled parallel-group multicentre trial and economic evaluation of cannabinoids to slow progression in multiple sclerosis. Health Technol Assess. 2015;19(12):vii-viii, xxv-xxxi, 1-187. https://doi.org/10.3310/hta19120
36. Vachová M, Novotná A, Mares J, Taláb R, Fiedler J, Lauder H, et al. A multicentre, double-blind, randomised, parallel-group, placebo-controlled study of effect of long-term Sativex® treatment on cognition and mood of patients with spasticity due to multiple sclerosis. J Mult Scler 2014; 1(2):22. https://doi.org/10.4172/2376-0389.1000122
37. Zajicek J, Ball S, Wright D, Vickery J, Nunn A, Miller D, et al. Effect of dronabinol on progression in progressive multiple sclerosis (CUPID): a randomised, placebo-controlled trial. Lancet Neurol. 2013;12(9):857-65. https://doi.org/10.1016/S1474-4422(13)70159-5
38. Langford RM, Mares J, Novotna A, Vachova M, Novakova I, Notcutt W, et al. A double-blind, randomized, placebo-controlled, parallel-group study of THC/CBD oromucosal spray in combination with the existing treatment regimen, in the relief of central neuropathic pain in patients with multiple sclerosis. J Neurol. 2013;260(4):984-97. https://doi.org/10.1007/s00415-012-6739-4
39. Zajicek JP, Hobart JC, Slade A, Barnes D, Mattison PG, MUSEC Research Group. Multiple sclerosis and extract of cannabis: results of the MUSEC trial. J Neurol Neurosurg Psychiatry. 2012;83(11):1125-32. https://doi.org/10.1136/jnnp-2012-302468

40. Notcutt W. A study to evaluate the effects of cannabis based medicine in patients with pain of neurological origin. Available from: ClinicalTrials.gov Identifier: NCT01606176; https://clinicaltrials.gov/ct2/show/NCT01606176

41. Novotna A, Mares J, Ratcliffe S, Novakova I, Vachova M, Zapletalova O, et al. A randomized, double-blind, placebo-controlled, parallel-group, enriched-design study of nabiximols* (Sativex(®)), as add-on therapy, in subjects with refractory spasticity caused by multiple sclerosis. Eur J Neurol. 2011;18(9):1122-31. https://doi.org/10.1111/j.1468-1331.2010.03328.x

42. Kavia RB, Ridder D, Constantinescu CS, Stott CG, Fowler CJ. Randomized controlled trial of Sativex to treat detrusor overactivity in multiple sclerosis. Mult Scler. 2010;16(11):1349-59. https://doi.org/10.1177/1352458510378020

43. Collin C, Ehler E, Waberzinek G, Alsindi Z, Davies P, Powell K, et al. A double-blind, randomized, placebo-controlled, parallel-group study of Sativex, in subjects with symptoms of spasticity due to multiple sclerosis. Neurol Res. 2010;32(5):451-9. https://doi.org/10.1179/016164109X12590518685660

44. Collin C, Davies P, Mutiboko IK, Ratcliffe S, Sativex Spasticity in MS Study Group. Randomized controlled trial of cannabis-based medicine in spasticity caused by multiple sclerosis. Eur J Neurol. 2007;14(3):290-6. https://doi.org/10.1111/j.1468-1331.2006.01639.x

45. Zajicek JP, Sanders HP, Wright DE, Vickery PJ, Ingram WM, Reilly SM, et al. Cannabinoids in multiple sclerosis (CAMS) study: safety and efficacy data for 12 months follow up. J Neurol Neurosurg Psychiatry. 2005;76(12):1664-9. https://doi.org/10.1136/jnnp.2005.070136

46. Rog DJ, Nurmikko TJ, Friede T, Young CA. Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. Neurology. 2005;65(6):812-9. https://doi.org/10.1212/01.wnl.0000176753.45410.8b

47. Svendsen KB, Jensen TS, Bach FW. Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomised double blind placebo controlled crossover trial. BMJ. 2004;329(7460):253. https://doi.org/10.1136/bmj.38149.566979.AE

48. Levin DN, Dulberg Z, Chan AW, Hare GM, Mazer CD, Hong A. A randomized-controlled trial of nabilone for the prevention of acute postoperative nausea and vomiting in elective surgery. Can J Anaesth. 2017;64(4):385-95. https://doi.org/10.1007/s12630-017-0814-3

49. Kleine-Brueggeney M, Greif R, Brenneisen R, Urwyler N, Stueber F, Theiler LG. Intravenous delta-9-tetrahydrocannabinol to prevent postoperative nausea and vomiting: a randomized controlled trial. Anesth Analg. 2015;121(5):1157-64. https://doi.org/10.1213/ANE.0000000000000877

50. Duran M, Pérez E, Abanades S, Vidal X, Saura C, Majem M, et al. Preliminary efficacy and safety of an oromucosal standardized cannabis extract in chemotherapy-induced nausea and vomiting. Br J Clin Pharmacol. 2010;70(5):656-63. https://doi.org/10.1111/j.1365-2125.2010.03743.x

51. Meiri E, Jhangiani H, Vredenburgh JJ, Barbato LM, Carter FJ, Yang HM, et al. Efficacy of dronabinol alone and in combination with ondansetron versus ondansetron alone for delayed chemotherapy-induced nausea and vomiting. Curr Med Res Opin. 2007;23(3):533-43. https://doi.org/10.1185/030079907x167525

52. Frytak S, Moertel CG, O'Fallon JR, Rubin J, Creagan ET, O'Connell MJ, et al. Delta-9-tetrahydrocannabinol as an antiemetic for patients receiving cancer chemotherapy. A comparison with prochlorperazine and a placebo. Ann Intern Med. 1979;91(6):825-30. https://doi.org/10.7326/0003-4819-91-6-825

53. Maas AI, Murray G, Henney H, Kassem N, Legrand V, Mangelus M, et al. Efficacy and safety of dexanabinol in severe traumatic brain injury: results of a phase III randomised, placebo-controlled, clinical trial. Lancet Neurol. 2006;5(1):38-45. https://doi.org/10.1016/S1474-4422(05)70253-2

54. Knoller N, Levi L, Shoshan I, Reichenthal E, Razon N, Rappaport ZH, et al. Dexanabinol (HU-211) in the treatment of severe closed head injury: a randomized, placebo-controlled, phase II clinical trial. Crit Care Med. 2002;30(3):548-54. https://doi.org/10.1097/00003246-200203000-00009

55. Boggs DL, Surti T, Gupta A, Gupta S, Niciu M, Pittman B, et al. The effects of cannabidiol (CBD) on cognition and symptoms in outpatients with chronic schizophrenia a randomized placebo controlled trial. Psychopharmacology (Berl). 2018;235(7):1923-32. https://doi.org/10.1007/s00213-018-4885-9

56. McGuire P, Robson P, Cubala WJ, Vasile D, Morrison PD, Barron R, et al. Cannabidiol (CBD) as an adjunctive therapy in schizophrenia: a multicenter randomized controlled trial. Am J Psychiatry. 2018;175(3):225-31. https://doi.org/10.1176/appi.ajp.2017.17030325

57. Naftali T, Bar-Lev Schleider L, Almog S, Meiri D, Konikoff FM. Oral CBD-rich cannabis induces clinical but not endoscopic response in patients with Crohn's disease, a randomised controlled trial. J Crohns Colitis. 2021;15(11):1799-806. https://doi.org/10.1093/ecco-jcc/jjab069

58. Naftali T, Mechulam R, Marii A, Gabay G, Stein A, Bronshtain M, et al. Low-dose cannabidiol is safe but not effective in the treatment for Crohn's disease, a randomized controlled trial. Dig Dis Sci. 2017;62(6):1615-20. https://doi.org/10.1007/s10620-017-4540-z

59. Naftali T, Bar-Lev Schleider L, Dotan I, Lansky EP, Sklerovsky Benjaminov F, Konikoff FM. Cannabis induces a clinical response in patients with Crohn's disease: a prospective placebo-controlled study. Clin Gastroenterol Hepatol. 2013;11(10):1276-80.e1. https://doi.org/10.1016/j.cgh.2013.04.034

https://doi.org/10.1590/1806-9282.2023D693ERRATUM

In the manuscript "Cannabis products: medical use", DOI: 10.1590/1806-9282.2023D693, published in the Rev Assoc Med Bras. 2023;69(3):358-364, on page 358:

Where it reads:

César Eduardo Fernandes[1], José Eduardo Lutaif Dolci[1], Leonardo Sobral Navarro[2], Marcelo Allevato[3], Clóvis Francisco Constantino[4], Rodrigo Pastor Alves Pereira[5], Carlos Roberto de Mello Rieder[6], Flávia Torino[2], Wanderley Marques Bernardo[1]*

It should read:

César Eduardo Fernandes[1], José Eduardo Lutaif Dolci[1], Leonardo Sobral Navarro[2], Marcelo Allevato[3], Clóvis Francisco Constantino[4], Rodrigo Pastor Alves Pereira[5], Carlos Roberto de Mello Rieder[6], Flávia Torino[2], Wanderley Marques Bernardo[1]*, Antônio Geraldo da Silva[3]