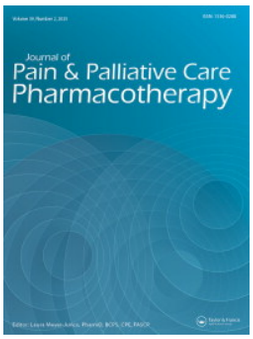

Taylor & Francis
Taylor & Francis Group

Journal of Pain & Palliative Care Pharmacotherapy

ISSN: 1536-0288 (Print) 1536-0539 (Online) Journal homepage: www.tandfonline.com/journals/ippc20

Effectiveness of Full Spectrum Cannabis Extracts in the Treatment of Chronic Pain: An Open Label Study

Aragon F., Lozada M., Bigatti G., González-José R., Kochen S. & McCarthy I.

To cite this article: Aragon F., Lozada M., Bigatti G., González-José R., Kochen S. & McCarthy I. (17 Jun 2025): Effectiveness of Full Spectrum Cannabis Extracts in the Treatment of Chronic Pain: An Open Label Study, Journal of Pain & Palliative Care Pharmacotherapy, DOI: 10.1080/15360288.2025.2517778

To link to this article: https://doi.org/10.1080/15360288.2025.2517778

View supplementary material

Published online: 17 Jun 2025.

Submit your article to this journal

View related articles

View Crossmark data

Full Terms & Conditions of access and use can be found at
https://www.tandfonline.com/action/journalInformation?journalCode=ippc20

JOURNAL OF PAIN & PALLIATIVE CARE PHARMACOTHERAPY
https://doi.org/10.1080/15360288.2025.2517778

Taylor & Francis
Taylor & Francis Group

ARTICLE

Check for updates

Effectiveness of Full Spectrum Cannabis Extracts in the Treatment of Chronic Pain: An Open Label Study

Aragon F., GP[a], Lozada M., PhD[b], Bigatti G., PhD[b,c], González-José R., PhD[b,d], Kochen S., MD[e] and McCarthy I., PharmD[a]

[a]Hospital Zonal Andrés Isola, Puerto Madryn, Argentina; [b]Programa Interdisciplinario de Cannabis, (CCT-CONICET-CENPAT), Puerto Madryn, Argentina; [c]Universidad Espíritu Santo, Guayaquil, Ecuador; [d]Instituto Patagónico de Ciencias Sociales y Humanas (IPCSH-CONICET), Puerto Madryn, Argentina; [e]Unidad Ejecutora en Neurociencias y Sistemas Complejos (ENyS), CONICET – Univ. Nacional A. Jauretche (UNAJ) – Hosp. El Cruce "N. Kirchner", F. Varela, Pcia Buenos Aires

ABSTRACT

The aim of this work was to assess the effectiveness of full-spectrum cannabis (THC and CBD) extracts as adjuvants in the treatment of chronic pain. This is a prospective, open label, longitudinal study. Major cannabinoids were analyzed in herbal preparations using high performance liquid chromatography (HPLC). Subjects were included when chronic pain diagnosis criteria was met according to physicians' diagnosis. A patient stratification protocol was developed using a visual analogue scale to measure pain, a numerical scale for life quality parameters and a self-administered health survey. Eighty-eight patients aged between 35 and 88 years were included. A significant decrease in both pain and other life quality parameters was observed between time zero and subsequent time intervals, excepting the "appetite" variable. Overall, 51 individuals reported a decrease in pain, 38 a decrease in anxiety and 48 in insomnia, with "decrease" defined as symptom reduction of 50% or more between the first and last consultation. In addition, 23 subjects reduced or discontinued other analgesics and/or anti-inflammatory drugs during the trial. Adverse effects were mild and reversible. These results are consistent with previous studies, supporting effectiveness and safety of cannabis extracts as adjuvants in the treatment of chronic pain.

ARTICLE HISTORY
Received 29 August 2024
Revised 23 May 2025
Accepted 31 May 2025

KEYWORDS
Herbal preparations; pain; full-spectrum cannabis

Introduction

Cannabis (*Cannabis sativa*, Linnaeus 1753) is a plant of Asian origin, which has been domesticated by humans and spread throughout the world for millennia. There are records of the use of cannabis in numerous cultures, from the 27th century BC onwards. Some varieties have been used for their fiber, others for their edible seeds, and others for their pharmacological properties (1). Between the 18th and 19th centuries, medicinal uses of tinctures, extracts, and oils were documented to treat various ailments, including pain, epilepsy, and spasms (2). However, restrictions imposed on cannabis in the twentieth century, together with the development of the pharmaceutical industry and synthetic drugs, paralyzed research and medicinal use of this plant until the end of the century. Since the 1960s, a renewed interest in this plant emerged and significant advances occurred in cannabis-related research (1). Around 1980 the first synthetic cannabinoids were approved for the treatment of anxiety, emesis, anorexia and pain. However, these compounds were not very successful, as they did not obtain the expected therapeutic effects (3,4). The first cannabinoid receptors (CB1 and CB2) were identified in the human body in the 1990s. This breakthrough was followed by the finding of their endogenous ligands, enabling the description of the endocannabinoid system, a clockwork of exquisite complexity encompassing the regulation mechanisms of these compounds at a molecular level (1,5).

Of the more than 400 active compounds described in the cannabis plant, tetrahydrocannabinol (THC) is perhaps the best known. It is a

CONTACT McCarthy I. mccarthy.irene@gmail.com Servicio de Farmacia, Hospital Zonal Andres Isola, Roberto Gomez 383, 9120, Puerto Madryn, Chubut, Argentina.
Supplemental data for this article can be accessed online at https://doi.org/10.1080/15360288.2025.2517778.
© 2025 Taylor & Francis Group, LLC

CB1 and CB2 receptor partial agonist and also acts on other molecular targets, exerting a powerful anti-inflammatory, antineoplastic, analgesic, muscle relaxant, anti-oxidative and antispasmodic effect. However, its psychotropic effects limit its use as an isolated compound. Cannabidiol (CBD), shares some of the properties of THC although it does not have a psychoactive effect. Its effects as an anxiolytic, anti-inflammatory, anticonvulsant, neuroprotector and immune system regulator have been widely reported (1,4,6). Furthermore, CBD behaves as a THC modulator, counteracting its psychoactive effect, therefore, preparations containing both cannabinoids are of high medicinal value, posing less risk of side effects at higher doses (4–8). Moreover, it has been observed that full-spectrum extracts (defined as preparations obtained from the whole plant as opposed to purification of one or some compounds from it) require a lower dose in comparison with their isolated counterparts to produce the same effect. This is proposed to be due to the so-called entourage effect, a synergic action of various cannabinoids and terpenes present in the herbal extract on the endocannabinoid system (9,10). Therefore, although isolated natural or synthetic cannabinoids still constitute the dominant model in the pharmaceutical industry, full-spectrum preparations are gaining momentum, rapidly growing as therapeutic alternatives (11–14).

One of the most widespread uses of cannabis extracts is to reduce pain. In a systematic review, evidence was found of the effectiveness of low doses of THC in the treatment of cancer-related pain, posing the need to change restrictive regulations in order to allow further research (15). In recent years, an ever-growing number of studies have analyzed the biological effectiveness of full-spectrum herbal preparations in the treatment of neuropathic pain and inflammation (16–18). A study of the effect of medicinal cannabis in patients with chronic pain, assessed not only pain reduction but quality of life improvement (19). Life quality indicators need to be included in surveys in order to take into account the multidimensional nature of pain, which is highly interconnected with other physiological (such as sleep or appetite) and emotional aspects of the individual.

The aim of this study was to evaluate the effectiveness of full-spectrum cannabis extracts as adjuvants in the treatment of chronic pain and to estimate their dose and posology. In addition, the study aimed to assess variations in other life quality-associated parameters and the appearance of adverse effects. In a preliminary observational study, a dose range of 1–5.4 mg/day of THC and 0–3.4 mg/day of CBD was observed to be related with a decrease in chronic pain and overall life quality indicators (20). We used this background data to calculate the final concentrations for full-spectrum cannabis herbal preparations for this study.

Materials and methods

Herbal preparations

Cannabis plants of defined varieties were grown as a part of this research. To obtain the herbal preparations, cannabis flowers were obtained from a mix of cultivars with chemotypes 1 (only expressing THC) and 2 (expressing both THC and CBD), which were extracted separately. Extracts were made in 50 g batches. Flowers were decarboxylated at 140 °C for 45 min in a circulation oven (BLUE M) and then immersed in 1 L of 96° ethanol for 30 min at room temperature with mechanical agitation. The ethanolic extract was filtered by gravity using a paper filter and evaporated in a rotary evaporator (BUCHI 461) until the resin was obtained. The resin was resuspended in 250 ml of extra virgin olive oil and stored in a refrigerator (2–8 °C) in amber bottles. Bean's test (which detects the presence of CBD) and thin layer chromatography (TLC) were performed to verify the correct chemotype of each individual batch. Once verified, all type-1 batches were mixed in a 5 L erlenmeyer flask and homogenized with manual mechanical shaking, giving a single pool. The same procedure was followed for type-2 batches. Samples were taken from each of the two pools and subjected to microbiological, heavy metal and cannabinoid composition quality controls. Major cannabinoids (THC, THCA, CBD, CBDA and CBN) concentrations were determined using high performance liquid chromatography (HPLC). Heavy metals and other elements were analyzed by Atomic Emission Spectrometry - Inductive Coupling Plasma (ICP-AES, Agilent 720). Microbiological analysis included the absence of fungi by visual inspection

under magnifying glass and of Escherichia coli with standard methods (Quanti Tray).

The concentrated extract pools were mixed accordingly, and diluted in extra virgin olive oil to the following final concentrations: 4 mg/mlTHC-2 mg/ml CBD, and 5 mg/ml THC- 2 mg/ml CBD.

Study design

This is a prospective, open label, single arm longitudinal study lasting six months, and was carried out at various ambulatory consulting rooms in a public hospital. As many other Latin American cities, our population is of mixed origin, with inhabitants of Native American, European, Asian, and South American descents (21). More recent admixture with people from Northern and Central Argentina were also registered (21).

Between 1 August 2022 and 1 February 2023 potential participants were selected among patients with chronic pain diagnosis, referred by General Practitioners (GP) involved in the study. As inclusion criteria, participants were required to be 18 years old or older, and be diagnosed with chronic pain, defined as pain suffered continuously for at least 3 months, and Visual Analogue Scale (VAS) equal to or more than 4. The VAS is an international scale for symptom monitoring and is validated in Spanish speaking individuals (23,24). After being informed about the particularities and potential benefits and risks involved in this study, participants were required to sign a written consent which had been previously revised and approved by the Hospital Bioethics Committee. This study is part of a three-step research program approved by the National Health Ministry. This program aimed to fuel the generation of scientific evidence on medicinal cannabis uses.

Exclusion criteria were: patients under 18 years old, active liver disease (bilirubin levels ≥10 mg/dl), active renal injury (creatinine levels ≥ 2 mg/dl), a history of addiction to psychoactive substances, history of psychosis, patients consuming cannabis-based preparations within the last month, as well as pregnant and breastfeeding people.

Chronic pain was subdivided into three categories based on its origin: musculoskeletal, neuropathic and oncological, using ICD-11 definitions (22). Patients were stratified per a pre-established protocol to one of two groups based on initial VAS score, one group with initial VAS between 4 and 7 and the other with initial VAS greater than 7. Other quality of life indicators were measured by an institution-specific numerical scale of life quality indicators (modeled after the scale by Vicente Herrero, et al. (23)) and the SF-12 self-administered health survey (25) (see further details in Supplementary Appendix 1 and 2, respectively). In addition, an in-house numerical scale of life quality indicators based on (23) and the SF-12 self-administered health survey was used at each consultation (25) (see further details in Supplementary Appendix 1 and 2, respectively).

The cannabis treatment was administered sublingually and added to the patients' usual medication scheme, and to their ongoing analgesic treatments. However, if participants reduced the dose or discontinued other analgesic or anti-inflammatory drugs during the trial, this was registered, following Haratounian et al (19). Patients were followed up every 30 days throughout the study period and were asked whether any adverse effects had occurred and any other observation made by participants was also registered. A titration scheme was followed starting with 0.6 mg THC/0.3 mg CBD or 0.75 mg THC/0.3 mg CBD depending on initial VAS score (Supplementary Appendix 1), and increased during treatment, until the desired effect was obtained. No maximum dose was pre-established.

Data analysis

The used protocol enabled the registering of variables such as pain, mood, appetite, fatigue, depression, anxiety and difficulty in sleeping. The subjective numerical scale had a range of 1–10, with 1 being the minimum desirable value (e.g. 1 no pain, 10 maximum pain, Supplementary Appendix 1). The results of the response variables were grouped into 3 time intervals: initial, up to 3 months, and from 3 to 6 months or more. In the case of 3 and 6 months, when more than one consultation throughout this period was present, the results were averaged. Their frequency distribution was qualitatively analyzed in the three intervals, to detect a possible shift toward the minimum values. In addition, a hypothesis test of paired samples (repeated measures over time,

Friedman test followed by Durbin-Conover contrasts) was carried out for each variable, to evaluate the hypothesis that there are no significant differences within subjects between times.

The doses of THC and CBD (in mg/day) that corresponded to an effective reduction in pain were estimated, considering as effective values of 3 or less in the subjective scale, or a 50% decrease with respect to initial score.

Results

Eighty-eight patients were included, of these, 69 were women. Age range was 35 to 88 years. Fifty-nine patients suffered from musculoskeletal pain, 17 from neuropathic pain and 5 from oncological pain (Table 1).

Of the 88 participants, 51 (65%) experienced pain reduction of greater than 50% between the first and last consultation. The frequency distribution of pain on the subjective scale shifted rapidly toward lower values. Results for pain are shown in Figure 1, and results concerning further variables are shown in Supplementary Appendix 3. Friedmann's test detected significant differences between time points for the subjects analyzed (χ^2=66.9, $p < .0000001$). Pairwise comparisons were significant for all groups (Durbin-Conover statistic = 8.9, 15.0 and 6.1 for initial vs. 3 months, initial vs. 6 months and 3 months vs. 6 months respectively, $p < .0000001$ for all three).

Similar results were obtained for the other variables, except for appetite (see histogram distributions in Supplementary Appendix 3). These trends were observed in the interval from initial consultation to 3 months of treatment, and further improved at 6 months.

In addition, 23 patients (26%) reduced or discontinued the use of other analgesics and/or anti-inflammatory drugs such as ibuprofen, diclofenac, tramadol and pregabalin. None of the participants increased doses or added concomitant analgesic drugs during the study.

Table 1. Descriptive statistics of patients taking part in the clinical study. m: musculoskeletal, n: neuropathic, o: oncological.

	Number of patients	Age (median [range])	Pain origin(m/n/o)
women	69	62[35–88]	55/11/3
Men	19	62[39–81]	11/6/2
Total	88	62[35–88]	66/17/5

The doses that were effective in controlling pain (defined as participants achieving a VAS of 3 or lower) were 3.9 ± 1.7 mg THC per day and 1.7 ± 0.7 mg CBD per day (average ± SD, n = 40). Of the 40 patients that reached a VAS 3 or less at time 6 months, 35 had started with a VAS of 7 or higher. The doses that were related with a 50% or more reduction in pain after 6 months were 4.1 ± 2.0 mg THC per day and 1.7 ± 0.8 mg CBD per day (n = 51).

Of the 88 participants, 12 (13.6%) reported adverse events that included nausea, headache, drowsiness, palpitations, insomnia and increased appetite. They were all considered mild using the World Health Organization (WHO) classification. All were dose-related and transient as they disappeared with a reduction in dose and/or if the following dose was not taken. Nine patients out of 88 (10%) did not return for the second visit and were considered drop-outs.

Discussion

There is ample evidence suggesting THC is effective in the management of chronic pain (14–19,26). Nevertheless, few of these studies were conducted with full-spectrum herbal preparations (16). Some authors have found that full-spectrum extracts may enhance the effect of THC, the primary active ingredient in pain reduction, and mitigate side effects due to a synergy with secondary active ingredients such as terpenes, flavonoids and other cannabinoids (11–13,16,17). In this study we assessed the effectiveness of full-spectrum cannabis extracts as adjuvants in the treatment of chronic pain, as well as changes in overall life quality parameters. We also estimated dose ranges and registered the appearance of adverse effects at these doses. We observed an important decrease in pain between the first and last consultation, at relatively low doses (~ 4 mg/day for THC and ~ 2 mg/day CBD). Similar trends were found for all life quality-associated parameters studied, except appetite, and side effects were mild, implying that significant pain reduction can be effectively and consistently obtained from herbal full-spectrum preparations.

Our choosing of an open label clinical trial allowed all potential beneficiaries access to this adjuvant treatment. The drawback of this type of design is the possibility of a significant placebo effect. In

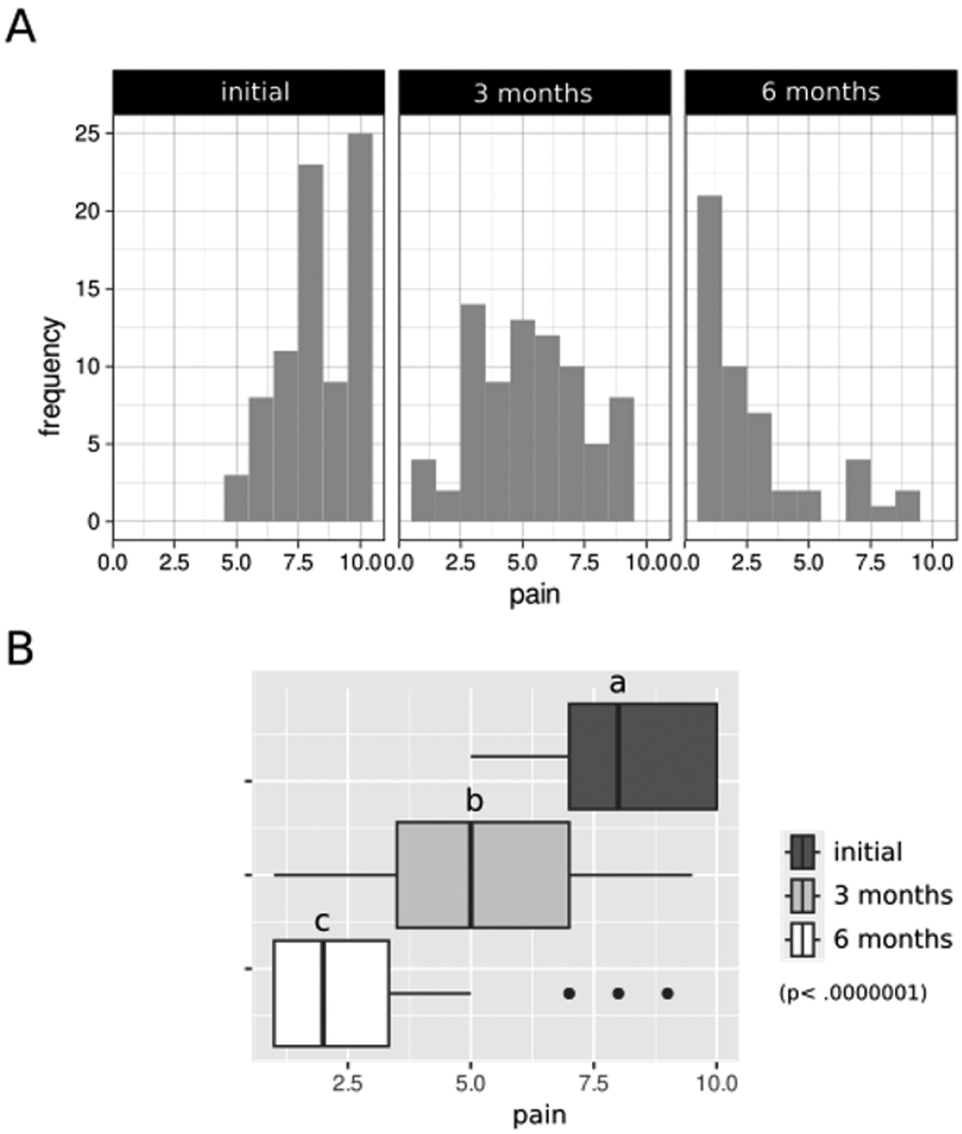

Figure 1. Distribution and summary statistics of variable "pain" over time. A- Histograms showing the distribution of the variable at three time points: initial, 3 months, and 6 months. The x axis represents symptom strength (pain) according to Visual Analogue Scale. The y axis represents frequency measured as counts. B- Boxplots summarizing the variable distribution at the same time points. Different letters above the boxes (a, b, c) indicate statistically significant differences between groups ($p < 0.05$, Friedman's Test followed by pairwise comparisons).

order to minimize this possibility, patients received the adjuvant treatment for six months. Participants were recruited among patients who usually attended the city's primary care units or clinics and data was collected in a decentralized way. Participating GPs registered their patients' responses, and the hospital pharmacy registered dosing information and any observations respecting herbal preparations. This could explain the study's dropout rate. However our clinical results are similar to those found in a real world setting and therefore could be classified as real world evidence (27). For instance, socio-economic conditions and access to health-care facilities, situations often found in developing countries, can be considered as factors affecting the drop-out rate. In this regard, we suggest using socio-economic status indicators as covariates in future studies.

In this study 65% of the patients showed a pain reduction of more than 50% at the end of the trial. These results are consistent with previous similar studies (19,20,26,28–34). These studies however, tested inhaled cannabis (smoked or vaporized) rather than oral oil extracts at fixed strengths. So far, studies combining herbal preparations along with known, fixed ratios for THC and CBD are scarce. By

using standardized herbal preparations and strengths we minimize potential differences due to administration route and secondary compounds composition whilst maintaining the benefits of whole flower extracts.

Participants showed a similar tendency in reduction of anxiety, insomnia and other life quality parameters studied, except for appetite. This is also consistent with previous studies (19) and shows a potential for further investigation regarding the effects that cannabis has on overall life quality, and how this can positively affect certain symptoms such as chronic pain.

There were differences in the effective doses required to reach pain reduction among patients, which could indicate interindividual variability (19) and therefore require titration. Individual titration could also be a key to reducing adverse effects, by starting low, slowly increasing dosage and instructing participants to reduce dosage if any side effects appear. Our findings showed mild, dose-related, and short-lasting adverse effects, such as nausea, headache, drowsiness, palpitations, insomnia and increased appetite. None of these required hospitalization and they disappeared within hours with dose reduction. It must be noted that no symptoms compatible with psychoactive effects were reported during this study. This is likely due to the presence of CBD in the full spectrum preparations, which acts as a modulator of possible psychoactive side effects associated with THC (4–8).

No participants increased nor added analgesic or anti-inflammatory drugs during the course of the study. Moreover, one in four patients reduced or discontinued analgesic and or anti inflammatory drugs, such as NSAIDs, opioids, corticoids and pregabalin during the study. Unfortunately this data was only collected in a qualitative manner due to the decentralized nature of this study. Further studies should address this issue as chronic use of these drugs increases risk of ulcers, gastritis, renal and bowel dysfunction, cognitive decline and hospitalization, especially in older adults, as reported elsewhere (35,36). Considering cannabis herbal preparations for the treatment of chronic pain may not only benefit patients from a safe and effective therapeutic option but health care systems could increase sustainability and reduce hospitalization due to adverse effects.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

Funding for the present study was granted by the CONICET (National Scientific and Technological Research Council) and the Health Ministry of the province of Chubut, Argentina.

References

1. Pertwee R, editor. Handbook of Cannabis. London, England: Oxford University Press; 2014.
2. Pisanti S, Bifulco M. Medical Cannabis: a plurimillennial history of an evergreen: PISANTI and BIFULCO. J Cell Physiol. 2019;234(6):8342–51. doi:10.1002/jcp.27725.
3. Russo E, Iversen L, Petro DJ, Grotenhermen F, Campbell FA, Moore A, et al. Cannabinoids in pain management. BMJ. 2001;323(7323):1249– doi:10.1136/bmj.323.7323.1249.
4. SEIC. Guía Básica sobre los Cannabinoides. Madrid, Spain: ediciones de la Universidad Complutense de Madrid; 2002.
5. Pazos Rodríguez MRG. Cannabinoides y sistema endocannabinoide. In: EFECTOS-TERAPÉUTICOS-DE-LOS-CANNABINOIDES. Madrid, Spain: Ediciones de la Universidad Complutense de Madrid. 2017. p. 7–23.
6. Navarini L, Margiotta DPE, Afflitto GG, Afeltra A. Cannabinoids in autoimmune and rheumatic diseases. In Mosaic of Autoimmunity. Elsevier; 2019. p. 417–29.
7. Nabbout R, Thiele EA. The role of cannabinoids in epilepsy treatment: a critical review of efficacy results from clinical trials. Epileptic Disord. 2020;22(S1):23–8. doi:10.1684/epd.2019.1124.
8. Cannabis scheduling review: part 1. Gov.uk. 2018. https://www.gov.uk/government/publications/cannabis-scheduling-review-part-1
9. Russo EB. Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. Br J Pharmacol. 2011;163(7):1344–64. doi:10.1111/j.1476-5381.2011.01238.x.
10. Pamplona FA, da Silva LR, Coan AC. Potential clinical benefits of CBD-rich cannabis extracts over purified CBD in treatment-resistant epilepsy: observational data meta-analysis. Front Neurol. 2018;9:1050. doi:10.3389/fneur.2018.00759.
11. McPartland JM, Russo EB. Cannabis and cannabis extracts: greater than the sum of their parts? J Cannabis Therapeutics. 2001;1(3-4):103–32. doi:10.1300/J175v01n03_08.
12. McPartland JM, Pruitt PL. Side effects of pharmaceuticals not elicited by comparable herbal medicines: the case of tetrahydrocannabinol and marijuana. Altern Ther Health Med. 1999;5(4):57–62.

13. Anand U, Pacchetti B, Anand P, Sodergren MH. Cannabis-based medicines and pain: a review of potential synergistic and entourage effects. Pain Manag. 2021;11(4):395–403. doi:10.2217/pmt-2020-0110.
14. Sarzi-Puttini P, Batticciotto A, Atzeni F, Bazzichi L, Di Franco M, Salaffi F, Marotto D, Ceribelli A, Ablin JN, Hauser W, et al. Medical cannabis and cannabinoids in rheumatology: where are we now? Expert Rev Clin Immunol. 2019;15(10): 1019–32. doi:10.1080/1744666X.2019.1665997.
15. Shin S, Mitchell C, Mannion K, Smolyn J, Meghani SH. An integrated review of cannabis and cannabinoids in adult oncologic pain management. Pain Manag Nurs. 2019;20(3):185–91. doi:10.1016/j.pmn.2018.09.006.
16. Maayah ZH, Takahara S, Ferdaoussi M, Dyck JRB. The molecular mechanisms that underpin the biological benefits of full-spectrum cannabis extract in the treatment of neuropathic pain and inflammation. Biochim Biophys Acta Mol Basis Dis. 2020;1866(7):165771. https://www.sciencedirect.com/science/article/pii/S0925443920301162 doi:10.1016/j.bbadis.2020.165771.
17. Maayah ZH, Takahara S, Ferdaoussi M, Dyck JRB. The anti-inflammatory and analgesic effects of formulated full-spectrum cannabis extract in the treatment of neuropathic pain associated with multiple sclerosis. Inflamm Res. 2020;69(6):549–58. doi:10.1007/s00011-020-01341-1.
18. Vigil JM, Montera MA, Pentkowski NS, Diviant JP, Orozco J, Ortiz AL, Rael LJ, Westlund KN. The therapeutic effectiveness of full spectrum hemp oil using a chronic neuropathic pain model. Life. 2020;10(5):69. https://www.mdpi.com/2075-1729/10/5/69 doi:10.3390/life10050069.
19. Haroutounian S, Ratz Y, Ginosar Y, Furmanov K, Saifi F, Meidan R, Davidson E. The effect of medicinal cannabis on pain and quality-of-life outcomes in chronic pain: a prospective open-label study. Clin J Pain. 2016;32(12):1036–43. https://journals.lww.com/clinicalpain/Abstract/2016/12000/The_Effect_of_Medicinal_Cannabs_on_Pain_and.3.aspx
20. Aragón F, Lozada M, McCarthy I, Bigatti G. Fitopreparados de variedades medicinales de cannabis como coadyuvantes en medicina general: composición química, eficacia y dosificación. 2021.
21. Parolin ML, Toscanini UF, Velázquez IF, Llull C, Berardi GL, Holley A, Tamburrini C, Avena S, Carnese FR, Lanata JL, et al. Genetic admixture patterns in Argentinian Patagonia. PLoS One. 2019;14(6):e0214830. doi:10.1371/journal.pone.0214830.
22. ICD-11 for mortality and morbidity statistics. 2022. Who.int. https://icd.who.int/browse/2024-01/mms/en
23. Vicente Herrero MT, Delgado Bueno S, Bandrés Moyá F, Ramírez Iñiguez de la Torre MV, Capdevila García L. Valoración del dolor. Revisión Comparativa de Escalas y Cuestionarios. Rev Soc Esp Dolor. 2018;25(4):2024–36. 228–https://scielo.isciii.es/scielo.php?script=sci_arttext&pid=S1134-80462018000400228
24. Pardo C, Muñoz T, Chamorro C. Monitorización del dolor: recomendaciones del grupo de trabajo de analgesia y sedación de la SEMICYUC. Med Intensiva. 2006;30(8):379–85. https://scielo.isciii.es/scielo.php?script=sci_arttext&pid=S0210-56912006000800004 doi:10.1016/S0210-5691(06)74552-1.
25. Nhs.uk. 2022. https://www.england.nhs.uk/wp-content/uploads/2022/12/Short-form-12-health-survey-questionnaire.pdf.
26. Abrams DI, Jay CA, Shade SB, Vizoso H, Reda H, Press S, Kelly ME, Rowbotham MC, Petersen KL. Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial. Neurology. 2007;68(7):515–21. doi:10.1212/01.wnl.0000253187.66183.9c.
27. Chodankar D. Introduction to real-world evidence studies. Perspect Clin Res. 2021;12(3):171–4. doi:10.4103/picr.picr_62_21.
28. Wallace MS, Marcotte TD, Umlauf A, Gouaux B, Atkinson JH. Efficacy of inhaled cannabis on painful diabetic neuropathy. J Pain. 2015;16(7):616–27. doi:10.1016/j.jpain.2015.03.008.
29. Wilsey B, Marcotte T, Deutsch R, Gouaux B, Sakai S, Donaghe H. Low-dose vaporized cannabis significantly improves neuropathic pain. J Pain. 2013;14(2):136–48. doi:10.1016/j.jpain.2012.10.009.
30. Wilsey B, Marcotte T, Tsodikov A, Millman J, Bentley H, Gouaux B, Fishman S. A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain. J Pain. 2008;9(6):506–21. doi:10.1016/j.jpain.2007.12.010.
31. Dose-dependent effects of smoked cannabis on capsaicin-induced pain and hyperalgesia in healthy volunteers. Anesthesiology. 2007;107(5):785–96. doi:10.1097/01.anes.0000286986.92475.b7.
32. Ellis RJ, Toperoff W, Vaida F, van den Brande G, Gonzales J, Gouaux B, Bentley H, Atkinson JH. Smoked medicinal cannabis for neuropathic pain in HIV: a randomized, crossover clinical trial. Neuropsychopharmacology. 2009;34(3):672–80. doi:10.1038/npp.2008.120.
33. Ware MA, Wang T, Shapiro S, Robinson A, Ducruet T, Huynh T, Gamsa A, Bennett GJ, Collet J-P. Smoked cannabis for chronic neuropathic pain: a randomized controlled trial. CMAJ. 2010;182(14):E694–701. doi:10.1503/cmaj.091414.
34. Corey-Bloom J, Wolfson T, Gamst A, Jin S, Marcotte TD, Bentley H, Gouaux B. Smoked cannabis for spasticity in multiple sclerosis: a randomized, placebo-controlled trial. CMAJ. 2012;184(10):1143–50. doi:10.1503/cmaj.110837.
35. Marcum ZA, Hanlon JT. Recognizing the risks of chronic nonsteroidal anti-inflammatory drug use in older adults. The annals of long-term care. Ann Longterm Care. 2010;18(9):24–7.
36. Brunton L, Knollmann B. Goodman and Gilman's the pharmacological basis of therapeutics. 14th ed. Columbus, OH: mcGraw-Hill Education; 2022.