

CUIDADO É FUNDAMENTAL

Escola de Enfermagem Alfredo Pinto – UNIRIO

INTEGRATIVE REVIEW OF THE LITERATURE

DOI: 10.9789/2175-5361.rpcfo.v14.11627

THERAPEUTIC BENEFITS OF CANNABINOIDS IN THE TREATMENT OF CHRONIC PAIN IN CANCER PATIENTS

*Benefícios terapêuticos dos canabinoides no tratamento da dor crônica em pacientes com câncer**Beneficios terapéuticos del cannabinoideos en el tratamiento del dolor crónico en pacientes con cáncer*Roni Robson da Silva¹ Leandro Andrade da Silva² Andréa Ferreira Leite Inácio³ Eliseu da Costa Campos¹ Diego Ferreira da Silva¹ Tatiana Silva⁴ 

ABSTRACT

Objective: to present the state of the art of publications expressed in the world scientific literature on the subject, as well as to identify the therapeutic benefits of medicinal cannabis in the treatment of pain. **Method:** this is an integrative literature review, whose data search was performed in virtual libraries. Web of Science, Scopus, Medline, IBECs, Lilacs, Cochrane Library, Emerald Insight and Scielo from August to October 2021. **Results:** 367 articles were found. Forty-three articles were selected to be read in full and 15 met the criteria of this review. **Conclusion:** evidence shows that although increasingly prescribed or authorized, medical cannabis or Cannabinoids for chronic pain remain controversial for many physicians.

DESCRIPTORS: Cannabis; Cannabinoids; Medical marijuana; Chronic pain; Câncer pain.

¹ Universidade de São Paulo, São Paulo, São Paulo, Brazil

² Universidade do Estado do Rio de Janeiro, Rio de Janeiro, Rio de Janeiro, Brazil

³ Comissão de Controle de Infecção Hospitalar, Mato Grosso do Sul, Brazil

⁴ Universidade Federal do Triângulo Mineiro, Uberaba, Minas Gerais, Brazil

Received: 01/09/2022; Accepted: 02/08/2022; Published online: 10/24/2022

Corresponding Author: Roni Robson da Silva, E-mail: rr.roni1@gmail.com

How cited: Silva RR, Silva LA, Inácio AFL, Campos EC, Silva DF, Silva T. Therapeutic benefits of cannabinoids in the treatment of chronic pain in cancer patients. *R Pesq Cuid Fundam* [Internet]. 2022 [cited year month day];14:e11627. Available from: <https://doi.org/10.9789/2175-5361.rpcfo.v14.11627>



RESUMO

Objetivo: apresentar o estado da arte das publicações expressas na literatura científica mundial sobre a temática, bem como identificar os benefícios terapêuticos da Cannabis medicinal no tratamento da dor. **Método:** trata-se de uma revisão integrativa da literatura, cuja busca de dados foi realizada nas bibliotecas virtuais. Web of Science, Scopus, Medline, IBECs, Lilacs, Cochrane Library, Emerald Insight e Scielo no período de agosto a outubro de 2021. **Resultados:** foram encontrados 367 artigos. Quarenta e três artigos foram selecionados para serem lidos na íntegra e 15 atenderam aos critérios desta revisão. **Conclusão:** as evidências mostram que embora cada vez mais prescritos ou autorizados, a cannabis medicinal ou os Canabinóides para a dor crônica continuam a ser controversos para muitos médicos.

DESCRITORES: Cannabis; Canabinoides; Maconha medicinal; Dor crônica; Dor do câncer.

RESUMEN

Objetivo: presentar el estado del arte de las publicaciones expresadas en la literatura científica mundial sobre el tema, así como identificar los beneficios terapéuticos del cannabis medicinal en el tratamiento del dolor. **Método:** se trata de una revisión integradora de la literatura, cuya búsqueda de datos se realizó en bibliotecas virtuales. Web of Science, Scopus, Medline, IBECs, Lilacs, Cochrane Library, Emerald Insight y Scielo de agosto a octubre de 2021. **Resultados:** se encontraron 367 artículos. Se seleccionaron 43 artículos para ser leídos en su totalidad y 15 cumplieron con los criterios de esta revisión. **Conclusión:** la evidencia muestra que, aunque cada vez más se prescribe o autoriza, el cannabis medicinal o los cannabinoides para el dolor crónico siguen siendo controvertidos para muchos médicos.

DESCRIPTORES: Cannabis; Canabinoides; Marihuana medicinal; Dolor crónico; Dolor de cáncer.

INTRODUCTION

The use of cannabis for medicinal purposes is longstanding, as this plant has been used for therapeutic purposes for over 4000 years.¹ However, cannabis has a high risk profile and its use for medicinal purposes is highly controversial, even for therapeutic reasons.² Medicinal cannabis (CM) refers to the use of cannabis or cannabinoids for the treatment of a medical condition or to alleviate symptoms associated with it.³ The spectrum of substances classified as CM includes: 1) Phytocannabinoids, which are found in cannabis herb and resins.¹ The main cannabinoids are Tetrahydrocannabinol (THC) and Cannabidiol (CBD); 2) Purified cannabinoids that originate from cannabis extracts (e.g. Nabiximols and purified Cannabidiol); and 3) Synthetic cannabinoids e.g. Dronabinol and Nabilone.³

THC is considered the main psychoactive component of cannabinoids, with potential benefits that may include pain control, improved nausea and muscle relaxation and potential side effects including psychosis, sedation and intoxication.⁴ CBD has shown some benefits in controlling anxiety, psychosis, inflammation, epilepsy and demonstrated neuroprotective effects.³⁻⁴

Cancer is the leading public health problem in the world and is already among the four leading causes of premature death (before the age of 70) in most countries,⁵ according to data from the National Cancer Institute (INCA).⁵ Cancer incidence and mortality have been increasing worldwide, in part due to population aging and growth, changes in the distribution and prevalence of risk factors, and especially those associated with socioeconomic development.⁶ Brazil is expected to register 625,000 new cases of cancer for each year from 2020 to 2022 according to data from the Brazilian Ministry of Health's 2020 Estimation of Cancer Incidence in Brazil.⁵⁻⁶

Cancer-related pain is common, occurring in up to 70% of patients undergoing chemotherapy and 90% of those with advanced disease.⁷ There is growing interest in cannabinoids for pain control worldwide, along with more permissive legislative changes in many countries.⁸ Currently, possible medical applications of the plant or its pharmacologically active natural or synthetic agents are strongly restricted, both for ethical and legal reasons.^{4,8}

The medicinal use of cannabis is already legal in 40 countries. In 2018, a total of 31 states in the United States passed laws allowing access to CM.⁹ Cancer is a qualifying condition for almost all medical cannabis programs in these countries.⁶⁻⁷ The WHO guidelines for the pharmacological and radiotherapy management of cancer pain in adults and adolescents suggest analyzing data on cannabinoids for cancer pain.⁸⁻⁹

Chronic pain is a problem of global magnitude. According to the International Association for the Study of Pain, (IASP),¹⁰ pain is always subjective and personal.¹⁰ Data with the National Cancer Institute (INCA)⁵ the incidence of moderate or severe pain occurs in 30% of cancer patients receiving treatment and in 60% to 90% of patients with advanced cancer.¹¹

Estimates of the prevalence of chronic pain are likely to vary depending on the sample population surveyed and the method of assessment.¹⁰⁻¹¹ Therapies for the treatment of chronic pain include various pharmacological agents¹² such as: tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, and opioid analgesics¹¹. However, these drugs offer limited pain relief and are associated with adverse effects. There is growing interest in the scientific community in the use of cannabis-based medications.¹³

This study is relevant to science since cancer patients turn to cannabis for symptomatic relief because of its reported ability

to decrease pain, nausea, and anorexia from cancer or its treatments. There is some evidence that cannabinoids appear to have an emerging therapeutic role, especially in chronic diseases and as an adjunct to cancer treatment.¹⁴

Increasing evidence supports cannabinoids in controlling chemotherapy-induced nausea and vomiting and in pain control. Studies in this field are limited because of difficulties associated with standardized dosage estimates and the inability to accurately assess the biological activities of cannabis compounds and derived products.¹⁴

However, despite increasing access by cancer patients, there are still limited data on their benefits and risks for cancer-related symptom control, largely due to federal regulations, larger-scale studies on their use patterns are lacking, especially with regard to THC and CBD dosing.¹¹⁻¹²

Although cannabinoids may have potential clinical benefits, their use is not without potential adverse effects and more research is needed to define their role in medical practice.^{5,9-10} The purpose of this study is to present the state of the art of the publications expressed in the worldwide scientific literature on the topic, as well as to identify the therapeutic benefits of medicinal cannabis in pain management.

METHODS

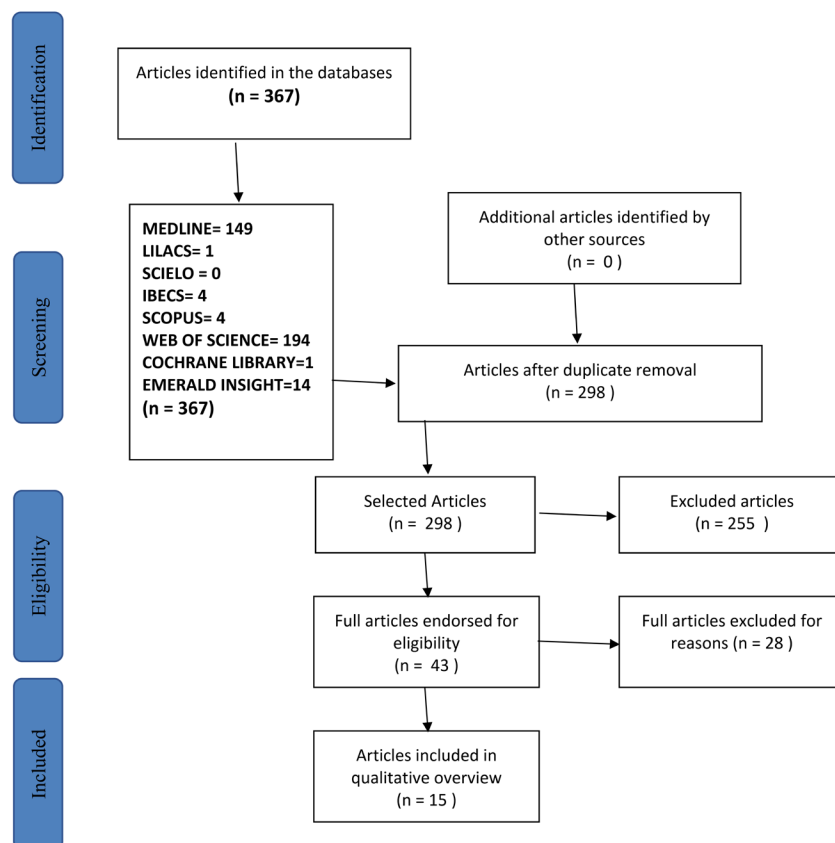
This is an integrative literature review study. The research question was defined from the PICO strategy. It is intended to answer the guiding question: Are Cannabinoids (I) effective (O) in treating chronic pain symptoms (C) in cancer patients (P)? The keywords “Cannabis” AND “Cannabinoids” AND “Medical Marijuana” AND “Chronic pain” AND “Cancer pain” were defined from the Health Sciences Descriptors (DeCS) vocabulary.

These were combined using the Boolean operator AND in the electronic libraries: Web of Science, Scopus, Cochrane Library, Emerald Insight, Medline, IBECs, LILACS, and SciELO. Inclusion criteria: publications of studies from the period 2017 to 2021, with abstracts and texts available in full in the databases cited.

Opinion articles, editorials, letters to the editor, duplicate articles, and publications that did not address the topic were excluded. A total of 367 studies were identified, of which 15 were selected for this review, presented through the PRISMA flowchart,¹⁵ Figure 1. A form was prepared consisting of variables related to the identification of the article: Author/year/country and; characterization of the studies; research subjects, synthesis of results and level of evidence.

Critical analysis of the selected papers, comparing theoretical knowledge, identification of conclusions and implications

Figure 1 – Selection of articles by descriptors in the databases Rio de Janeiro, RJ, Brazil, 2021



Source: The authors, 2021.

resulting from this review, which enabled the understanding of the state of the art of knowledge production on the impact of cannabis in the treatment of pain in cancer patients.

The level of evidence identified in the analyzed articles was classified according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.¹⁶ In this system, the quality of evidence is described in four levels: high, moderate, low, and very low, Chart 1.

Evidence from randomized clinical trials can be downgraded by lack of allocation confidentiality, lack of blinding, incomplete follow-up, selective reporting of outcomes, and other limitations such as early termination of the study for benefit and insufficient information to assess whether there is significant risk of bias.¹⁶

For each of these domains, the risk of bias is assessed, being classified as high risk, uncertain, and low risk of bias.

RESULTS

A total of 367 studies were identified in these databases, as illustrated in Figure 1, which followed the PRISMA¹⁵ recommendations to describe the literature search process. Of these, 69 duplicate articles were excluded, leaving 298 unique articles. Then, the titles and abstracts were read, observing the inclusion and exclusion criteria. As a result, 255 articles were excluded, and another 43 articles met the eligibility criteria. We then started the full, in-depth reading of these studies by two reviewers, independently. Any disagreements between reviewers that arose during this stage were worked out and resolved by consensus, resulting in a final sample of 15 articles. The articles included in this synthesis, Table 1, were developed in eight different countries: United States (n= seven), Spain (n= one), Italy (n= one), Australia (n= one), Canada (n= two), Israel (n= one), Colombia (n= one) and England (n= one). As for the method, most researchers used

Chart 1 – Levels of evidence. Rio de Janeiro, RJ, Brazil, 2021

Level	Definition	Implications
High	There is strong confidence that the true effect is close to the one estimated	It is unlikely that further work will modify the confidence in the estimate of the effect
Moderate	There is moderate confidence in the estimated effect	Future work may modify the confidence in the effect estimate, with the possibility of even modifying the estimate
Low	Confidence in the effect is limited	Future work is likely to have an important impact on our confidence in the effect estimate
Very Low	The confidence in the effect estimate is very limited. There is an important degree of uncertainty in the findings	Any estimate of effect is uncertain

Source: The authors, 2021

Table 1 – Categorization of the scientific production included in the review. Rio de Janeiro, RJ, Brazil, 2021

Title	Author/Country Year	Goal	Method	Result	Level of Evidence
Revisione sistematica sull'efficacia terapeutica e la sicurezza della cannabis per i pazienti affetti da sclerosi multipla, dolore neuropatico cronico e pazienti oncologici che assumono chemioterapie	Amato L et al, 2017 / Italia	Provide evidence of the benefits and harms of cannabis treatment.	Systematic Review	It is not certain whether cannabis, including extracts and tinctures, compared to placebo or other antiemetic drugs, reduces nausea and vomiting in cancer patients requiring chemotherapy,	Moderate
Provider perspectives on use of medical marijuana in children with cancer	Ananth P et al., 2017 / USA	Investigate physician perspectives on the legal use of MM in children with cancer.	Quantitative cross-sectional study	Most pediatric oncology providers are willing to consider the use of MM in children with cancer and receive frequent inquiries	Low
Oral medicinal cannabinoids to relieve symptom burden in the palliative care of patients with advanced cancer	Good P et al., 2019 / USA	This study aims to define the role of cannabidiol (CBD) in symptom burden management in patients with advanced cancer in standard palliative care	Randomized Clinical Trial	The primary endpoint is a change from baseline in total ESAS TSDS on the day. The clinically significant change is determined as an improvement in TSDS of ≥ 6	Low

Tabela I – Cont.

Living with a hope of survival is challenged by a lack of clinical evidence:	Buchwald et al., 2019 / USA	To collect information from experienced cancer patients on treatment with CBM receiving palliative care regarding the rationale and outcomes of the treatment decision.	Qualitative observational study	Most patients reported relief of symptoms, such as insomnia, anxiety, nausea, and pain, after starting treatment with CBM, but this outcome was perceived as less of a focus compared to hope for cure.	Very low
Cannabis surveillance with twitter data: emerging topics and social bots	Allem; Escobedo; Dharmapuri, 2020 / USA	Use publicly accessible data from people posting on Twitter to quickly capture and describe the public's recent experiences with cannabis.	Qualitative observational study	The predominant topics of posts included cannabis use with mentions of cannabis initiation, processed cannabis products, and health and medical with posts suggesting that cannabis can help with cancer, sleep, pain, anxiety, depression, trauma, and post-traumatic stress disorder.	Low
Cannabinoids for adult cancer-related pain	Boland EG et al., 2019 / England	To determine the beneficial and adverse effects of cannabis/cannabinoids compared to placebo/ other active agents for the treatment of cancer-related pain in adults.	Systematic review and meta-analysis	There was no difference between cannabinoids and placebo for the difference in the change in mean pain scores on the High Numeric Rating Scale	
The efficacy of medical marijuana in the treatment of cancer-related pain	Ian M et al., 2019 / USA	to characterize the role of MMJ in symptomatic relief and opioid consumption in the oncology population	Cohort study	ESAS scores for pain, physical, emotional and total scores improved in severe MMJ (-) and MMJ (+); opioid consumption was reduced by 22% in MMJ (-) (135-106 mg / day MME, $p = 0.124$) and 33% in MMJ (+) (90-60 mg / day MME, $p = 0.421$)	Moderate
Therapeutic use of cannabis and cannabinoids: an evidence mapping and appraisal	Montero-Oleas et al., 2020 / Spain	Identify, characterize, evaluate, and organize the current available evidence around the therapeutic use of cannabis and cannabinoids, using evidence maps	Systematic review	The evidence on the medical use of cannabis is ample. However, due to methodological limitations, conclusions were weak in most of the comparisons evaluated	Moderate
Cannabis: A Toxin-producing Plant with potential Therapeutic uses	Breijyeh et al., 2021 / Israel	Highlight the potential therapeutic effects of cannabis and cannabinoids, as well as the acute and chronic toxic effects of cannabis use on various body systems	Systematic review	Between the promising therapeutic advantages, high abuse tendency and safety concerns, additional research efforts are still needed to better understand the interactions of cannabinoids within the human body and to explore the potential medical applications of cannabis	Low
Opioid-sparing effects of medical cannabis or cannabinoids for chronic pain	Noori A et al., 2020 / Canada	To evaluate the efficacy and harms of adding medical cannabis to prescription opioids among people living with chronic pain.	Systematic review	Opioid dose reduction, pain relief, sleep disturbance, physical and emotional functioning, and adverse events.	Very low

Tabela I – Cont.

Medicinal cannabis: knowledge, beliefs, and attitudes of Colombian psychiatrists	Orjuela-Rojas et al., 2021 / Colombia	To describe the results of a survey of Colombian psychiatrists on aspects of medical cannabis, such as attitudes towards its potential use, perceived knowledge and beliefs around its regulation and safety	Cross-sectional quali-quant study	Eighty-two percent of psychiatrists agreed that medical cannabis should be available for different medical conditions and 73.1% said they would like to prescribe it.	Moderate
Gaps in evidence for the use of medically authorized cannabis: Ontario and Alberta, Canada	Lee et al., 2021 / Canada	Provide new and relevant demographic and clinical data from one of the largest databases of patients seeking cannabis as a medical therapy in Ontario (ON) and Alberta (AB), Canada,	Cohort study	In both AB and ON, most of the reasons for authorizing medical cannabis are not supported by clinical evidence to fully support its effectiveness for long-term use.	Moderate
Patterns of Medical cannabis use among cancer patients from a medical cannabis dispensary in New York State	Kim et al., 2019 / USA	Describe the patterns of medical cannabis use by patients with cancer and how the patterns differ from patients without cancer.	Cohort study	There was an increase in the daily THC dose by a factor of 0.20 mg / week, resulting in a corresponding increase in the daily THC: CBD ratio. Compared to patients without cancer, these trends were not different in the cancer group for the daily THC dose among cancer patients.	Low
Knowledge and attitudes of Australian general practitioners towards medicinal cannabis: a cross-sectional survey	Karanges et al., 2018 / Australia	To examine the knowledge and attitudes of Australian general practitioners (GPs) towards medical cannabis, including patient demand, GPs' perceptions of therapeutic effects and potential harms, perceived knowledge and willingness to prescribe	Quantitative cross-sectional research	Support for medical cannabis use was condition-specific, with strong support for use in cancer pain, palliative care, and epilepsy, and much lower support for use in depression and anxiety.	Low
Medical oncologists' beliefs, practices, and knowledge regarding marijuana used therapeutically:	Braun et al., 2018 / USA	Identify whether Oncologists would be sufficiently informed about MM, reticent to discuss or recommend therapeutic marijuana clinically, and skeptical about the usefulness of MM in cancer treatment given the limited evidence base.	Observational study	Our results identify a relative discrepancy between oncologists' self-reported knowledge base and their beliefs and practices regarding MM	Moderate

Source: The authors, 2021.

the quali-quantitative approach to describe and analyze in depth the different dimensions of the therapeutic process.

DISCUSSION

In recent decades, the endocannabinoid system has been the object of study, arousing considerable interest of physicians and scientists¹⁷ with potential therapeutic target in numerous pathological conditions.¹⁸ Its involvement in various physiolo-

gical processes is well known, such as energy balance, appetite stimulation, blood pressure, pain modulation, embryogenesis, control of nausea and vomiting, memory, learning, and immune response, among others.^{17,19} It was reported in the study by Amato L et al²⁰ that alterations in endocannabinoid levels may be related to neurological diseases such as Parkinson's disease, Huntington's disease, Alzheimer's disease, and multiple sclerosis, as well as anorexia and irritable bowel syndrome.^{17,20} This evidence is in line with the study by Ananth P et al,²¹ which highlights the alterations in the endocannabinoid system associating them with growth, migration, and the invasion of some tumors.²¹ Cannabinoids have been tested in several types of cancer, including brain, breast, and prostate cancer.^{6,17-18} The study by Braun et al²² reports that cannabinoids have shown promise as analgesics for the treatment of inflammatory and neuropathic pain.²³ In research by Good P et al²⁴ there is also evidence of a control of emotional states, and cannabinoids may be useful in reducing and palliating symptoms of post-traumatic stress disorder and anxiolytic disorders.²³⁻²⁴ In addition, some cannabinoid-based medications have already been approved in several countries, including Nabilone and Dronabinol capsules for the treatment of nausea and vomiting associated with chemotherapy.²¹ Most studies on cannabis use patterns among cancer patients are limited to a single site lacking large-scale studies.²⁵ This result corroborates with the work of Noori A et al,²⁶ which showed that Colombian psychiatrists have a favorable attitude toward prescribing medical cannabis; however, there is a serious lack of legal knowledge.²³⁻²⁶

An interesting finding in the study by Kaufmann et al,⁸ was that most physicians agreed with the use of (CM) to combat chronic cancer-related pain receiving the highest approval with 87.6%.²⁴⁻²⁵

The systematic review by Montero-Oleas²⁸ identified all randomized clinical trials (RCTs) of cannabinoids compared to placebo or other active agents for the treatment of cancer-related pain in adults to determine the efficacy of cannabinoids and evaluated the tolerability and safety of medical cannabis and cannabis-based medications for cancer pain, reported very low quality evidence for a non-significant 50% reduction in pain ($p = 0.82$).²⁵ The systematic review by Amato et al²⁰ shows us the absolute change in mean pain intensity, which is a more sensitive outcome than a dichotomous outcome, for example the proportion of participants reporting pain relief of 50% or more from the beginning to the end of the study.²⁶ The study by Silva et al⁵ was conducted on five international databases and showed a higher risk of adverse events when compared to placebo, mainly drowsiness (OR 2.69 (1.54 to 4.71), $p < 0.001$) and dizziness (OR 1.58 (0.99 to 2.51), $p = 0.05$).²⁴ No treatment-related deaths were reported. The dropout and mortality rates were high.²⁵

CONCLUDING REMARKS

Many chronic pain patients rely on potent painkillers and tend to relapse into a cyclical situation of pain, inactivity, and

depression. Legislation surrounding cannabis and its derivatives is increasingly being considered for medicinal use in several countries.

Chronic cancer-related pain is the most common indication for cannabinoid therapy. From the legal point of view, there is no jurisprudence in Brazil on the subject, the prescription is indicated in case of severe disease, with established therapeutic approaches and if there is a prospect of improvement of the disease or its symptoms. The evidence is of low quality, and the knowledge about the use of cannabis-based drugs to treat cancer pain symptoms is insufficient.

Cannabinoids are considered as an emerging treatment for chronic pain, it is important that physicians are aware of the positive and negative aspects related to their use. The most commonly prescribed oral products are: oils, sprays, and capsules. They can be administered in a more controlled and socially acceptable manner than inhaled products, although they have a slower onset. It should be recognized that the long-term effects of medical cannabis, potential drug interactions, and effectiveness in different types of pain remain only partially understood.

High quality studies are needed for physicians to provide evidence-based advice to patients interested in using cannabis as a complementary treatment. However, more large-scale research is needed to truly understand the completeness of cannabinoid benefits. A limitation of this study was the small number of studies conducted worldwide.

REFERENCES

1. Silva RR da, Silva LA da. Psychosocial load and burnout syndrome in healthcare professionals in the fight against COVID-19 pandemic. *Rev. Pesqui. (Univ. Fed. Estado Rio J., Online)*. [Internet]. 2021 [cited 2021 nov 18];13. Available from: <https://doi.org/10.9789/2175-5361.rpcfo.v13.11097>.
2. Silva RR da, Neves MP das, Silva LA da, Silva MVG, Hipólito RL, Marta CB. Consumo de drogas psicoativas em contexto de sexual entre homens gays como fator de risco para transmissão de HIV/Aids. *Glob Acad Nurs*. [Internet]. 2020 [acesso em 18 de novembro 2021];1(3). Disponível em: <https://doi.org/10.5935/2675-5602.20200057>.
3. Silva RR da, Silva LA da, Souza MVL de, Silva MVG da, Neves MP das, Vargas D, et al. Minority gender stress and its effects on mental health as a risk factor for depression in transgender persons: Literature review. *Res Soc Dev*. [Internet]. 2021 [cited 2021 nov 18];10(12): e51610313693. Available from: <https://doi.org/10.33448/rsd-v10i13.13693>.
4. Orjuela-Rojas JM, Orjuela XG, Serna SO. Medicinal cannabis: knowledge, beliefs, and attitudes of colombian psychiatrists. *J cannabis Res*. 2021 [cited 2021 nov 18];3(1). Available from: <https://doi.org/10.1186/s42238-021-00083-z>.
5. Silva IN de CJAG da. Estimativa 2020: incidência de câncer no Brasil TT - estimate/2020 - cancer incidence in Brazil

- TT. [Internet]. 2020. p. 120. Disponível em: <https://www.inca.gov.br/sites/ufu.sti.inca.local/files//media/document//estimativa-2020-incidencia-de-cancer-no-brasil.pdf>.
6. Fowler CJ. The endocannabinoid system - current implications for drug development. *J. intern. med.* [Internet]. 2021 [cited 2021 nov 18];290(1). Available from: <https://dx.doi.org/10.1111/joim.13229>.
 7. Boland EG, Bennett MI, Allgar V, Boland JW. Cannabinoids for adult cancer-related pain: systematic review and meta-analysis. *BMJ support. palliat. care* (Online). [Internet]. 2020 [cited 2021 nov 18];10(1). Available from: <http://dx.doi.org/10.1136/bmjspcare-2019-002032>.
 8. Kaufmann CN, Kim A, Miyoshi M, Han BH. Patterns of medical cannabis use among older adults from a cannabis dispensary in New York State. *Cannabis Cannabinoid Res.* [Internet]. 2020 [cited 2021 nov 18];0(0). Available from: <http://doi.org/10.1089/can.2020.0064>.
 9. Chapman EJ, Edwards Z, Boland JW, Maddocks M, Fettes L, Malia C, et al. Practice review: evidence-based and effective management of pain in patients with advanced cancer. *Palliat. med.* [Internet]. 2020 [cited 2021 nov 18];34(4). Available from: <https://doi.org/10.1177/0269216319896955>.
 10. Daris B, Verboten MT, Knez Z, Ferik P. Cannabinoids in cancer treatment: Therapeutic potential and legislation. *Bosn. j. basic med. sci.* (Print). [Internet]. 2019 [cited 2021 nov 18];19(1). Available from: <https://doi.org/10.17305/bjbs.2018.3532>.
 11. Tran T, Kavuluru R. Social media surveillance for perceived therapeutic effects of cannabidiol (CBD) products. *Int. j. drug policy.* [Internet]. 2020 [cited 2021 nov 18];77. Available from: <https://doi.org/10.1016/j.drugpo.2020.102688>.
 12. Lowe H, Toyang N, Steele B, Bryant J, Ngwa W, Nedamat K. The current and potential application of medicinal cannabis products in dentistry. *Dent. j.* [Internet]. 2021 [cited 2021 nov 18]; 9(9). Available from: <https://doi.org/10.3390/dj9090106>.
 13. Fehniger J, Brodsky AL, Kim A, Pothuri B. Medical marijuana utilization in gynecologic cancer patients. *Gynecol. Oncol. Rep.* [Internet]. 2021 [cited 2021 nov 18];37. Available from: <https://doi.org/10.1016/j.gore.2021.100820>.
 14. Argueta DA, Ventura CM, Kiven S, Sagi V, Gupta K. A balanced approach for cannabidiol use in chronic pain. *Front. pharmacol.* [Internet]. 2020 [cited 2021 nov 18];11. Available from: <https://doi.org/10.3389/fphar.2020.00561>.
 15. Moher D. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *Ann. intern. med.* [Internet]. 2009 [cited 2021 nov 18];151(4). Available from: <https://doi.org/10.7326/0003-4819-151-4-200908180-00135>.
 16. Granholm A, Alhazzani W, Møller MH. Use of the GRADE approach in systematic reviews and guidelines. *Br. j. anaesth.* [Internet]. 2019 [cited 2021 nov 18];123(5). Available from: <https://doi.org/10.1016/j.bja.2019.08.015>.
 17. Dzierzanowski T. Prospects for the use of cannabinoids in oncology and palliative care practice: a review of the evidence. *Cancers.* [Internet]. 2019 [cited 2021 nov 18];11(2). Available from: <https://doi.org/10.3390/cancers11020129>.
 18. Bolshakova M, Bluthenthal R, Sussman S. Opioid use and misuse: health impact, prevalence, correlates and interventions. *Psychol. health.* [Internet]. 2019 [cited 2021 nov 18];34(9). Available from: <https://doi.org/10.1080/08870446.2019.1622013>.
 19. Noori A, Miroshnychenko A, Shergill Y, Atefeh N, Miroshnychenko A, Shergill Y, et al. Opioid-sparing effects of medical cannabis or cannabinoids for chronic pain: a systematic review and meta-analysis of randomised and observational studies. *BMJ Open.* [Internet]. 2021 [cited 2021 nov 18];11: e047717. Available from: <https://doi.org/10.1136/bmjopen-2020-047717>.
 20. Amato L, Minozzi S, Mitrova Z, Parmelli E, Saule R, Cruciani F, et al. Systematic review of safety and therapeutic efficacy of cannabis in patients with multiple sclerosis, neuropathic pain, and in oncological patients treated with chemotherapy. *Epidemiol. prev.* [Internet]. 2017 [cited 2021 nov 18];41(5-6). Available from: <https://doi.org/10.19191/EP17.5-6.AD01.069>.
 21. Ananth P, Ma C, Al-Sayegh H, Kroon L, Klein V, Wharton C, et al. Provider perspectives on use of medical marijuana in children with cancer. *Pediatrics* [Internet]. 2018 [cited 2021 nov 18];141(1): e20170559. Available from: <https://doi.org/10.1542/peds.2017-0559>.
 22. Braun IM, Wright A, Peteet J, Meyer FL, Yuppa DP, Bolcic-Jankovic D, et al. Medical oncologists' beliefs, practices, and knowledge regarding marijuana used therapeutically: a nationally representative survey study. *J. clin. oncol.* [Internet]. 2018 [cited 2021 nov 18];36(19). Available from: <https://doi.org/10.1200/JCO.2017.76.1221>.
 23. Kim A, Kaufmann CN, Ko R, Li Z, Han BH. Patterns of medical cannabis use among cancer patients from a medical cannabis dispensary in New York State. *J. palliat. med.* [Internet]. 2019 [cited 2021 nov 18];22(10). Available from: <https://doi.org/10.1089/jpm.2018.0529>.
 24. Good P, Haywood A, Gogna G, Martin J, Yates P, Greer R, et al. Oral medicinal cannabinoids to relieve symptom burden in the palliative care of patients with advanced cancer: a double-blind, placebo controlled, randomised clinical trial of efficacy and safety of cannabidiol (CBD). *BMC palliat. care.* [Internet]. 2019 [cited 2021 nov 18];18(1). Available from: <https://dx.doi.org/10.1186/s12904-019-0494-6>.

25. Lee C, Round JM, Klarenbach S, Hanlon JG, Hyshka E, Dyck JRB, et al. Gaps in evidence for the use of medically authorized cannabis: Ontario and Alberta, Canada. *Harm reduct. =j.* [Internet]. 2021 [cited 2021 nov 18];18(1). Available from: <https://doi.org/10.1186/s12954-021-00509-0>.
26. Noori A, Busse JW, Sadeghirad B, Siemieniuk RA, Wang L, Couban R, et al. Individual opioids, and long-versus short-acting opioids, for chronic noncancer pain Protocol for a network meta-analysis of randomized controlled trials. *Medicine (Baltimore)*. [Internet]. 2019 [cited 2021 nov 18];98(43). Available from: <http://dx.doi.org/10.1097/MD.00000000000017647>.